Synthesis of (+)- and (−)-Phaseolinic Acid by Combination of Enzymatic Hydrolysis and Chemical Transformations with Revision of the Absolute Configuration of the Natural Product

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Introduction

(−)-Phaseolinic acid (**1**),[1] a metabolite of a fungus, *Macrophomina phaseolina,* and (−)-methylenolactocin (**2**),[2] an antitumoral antibiotic from *Penicillum sp.* (Chart 1), have recently received considerable attention, and a few formal and total syntheses of these compounds have been published.[3]

In the course of our studies aimed at the synthesis of enantiomerically pure γ-butyrolactones[4] we focused our attention on the synthesis of both enantiomers of phaseolinic acid (**1**) and on the determination of their absolute configuration by means of chemical and spectroscopic correlations. The strategy was to correlate (−)-phaseolinic acid (**1**) with (−)-methylenolactocin (**2**) through the butenolide (−)-**3** (Chart 1).

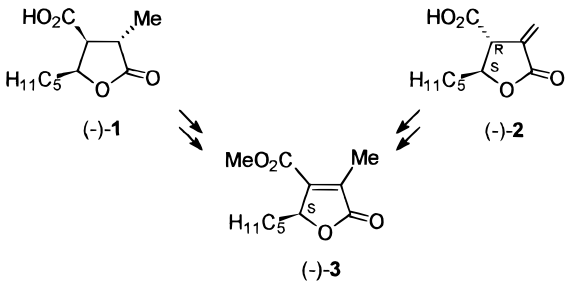
Results and Discussion

(−)-Phaseolinic acid (**1**) and (−)-methylenolactocin (**2**) were prepared starting from two diastereomeric lactones, **5** and **6,** respectively (Scheme 1). These latter compounds were obtained from the keto diester **4**,[5] as already proposed[6] by Johnson and co-workers for the synthesis of racemic protolichesterinic acid. The diastereomeric ratio **5**:**6** was 4:1 in favor of the less stable isomer **5** when the reduction of the keto carbonyl group was performed at −15 °C.

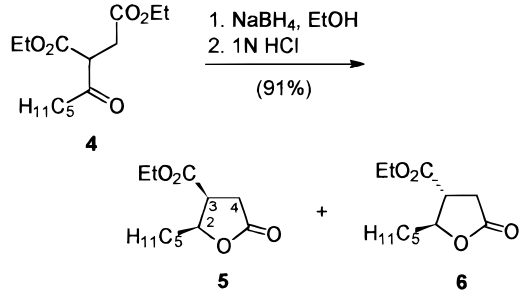
The enantiomers of phaseolinic acid were synthesized as shown in Scheme 2. The ethoxycarbonyl group of the racemic *cis*-lactone **5** was chemically hydrolyzed to the acid lactone **7,** which was transformed into racemic phaseolinic acid **1** by stereocontrolled α-methylation.[7,8] This latter compound was then esterified to **8** with ethyl iodide in the presence of DBU at room temperature.[9]

The resulting racemic lactone **8** was then kinetically resolved by means of pig liver esterase (PLE) at room

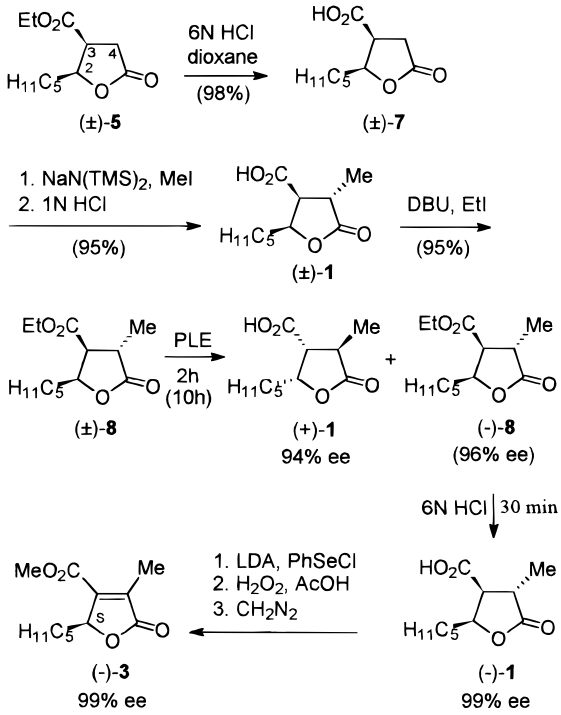
Chart 1



Scheme 1



Scheme 2



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(9) Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn*. **1978**, *51*, 2401.

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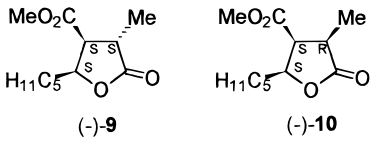
Chart 2



(-)-**9** (-)-**10**

temperature. After 2 h (20% conversion), the acid (+)-**1** was obtained in 15% yield and 94% ee,[10] while the unreacted ester (−)-**8** (59%) was found to have 32% ee.

When the reaction time was prolonged for 10 h, the unreacted ester (−)-**8** was obtained in 35% yield and 96% ee, while the remaining acid (+)-**1** (35% yield) was found to have an ee of 47%.[10] Hydrolysis of (−)-**8**, carried out in refluxing dioxane under acidic conditions for 30 min furnished pure phaseolinic acid (−)-(**1**) with 99% ee,[10] after crystallization. In this manner both enantiomers of phaseolinic acid (**1**) were available in good enantiomeric purity.

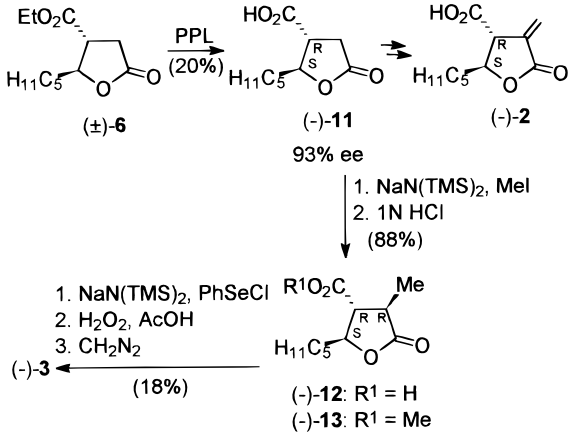
Other enzymes such as *Candida cylindracea* lipase (CRL) and porcine pancreatic lipase (PPL) were uneffective, whereas porcine liver acetone powder (PLAP) afforded the acid (+)-**1** in 10% yield and 88% ee, at 25% conversion, and the ester (−)-**8** in 25% yield and 97% ee, at 75% conversion.

(−)-Phaseolinic acid (**1**) thus obtained was converted into the corresponding butenolide (−)-**3** (Scheme 2). The sequence of reactions involved α-phenylselenenylation in the presence of LDA as a base with HMPA added, oxidation, and syn elimination of the phenylselenyloxide intermediate, in accordance with the procedure by Grieco and Miyashita.[7,11] Since the reaction did not go to completion, the crude mixture was eventually treated with diazomethane to esterify the carboxy groups present and to allow separation of the products. Besides the butenolide (−)-**3** (99% ee), in fact, also the methyl ester of the unreacted phaseolinic acid (−)-**9**[12] and the *all-cis*-lactone (−)-**10**[13] were isolated by chromatography (Chart 2). The three lactones (−)-**3**, (−)-**9**, and (−)-**10** were in the ratio 75:15:10.

The same butenolide (−)-**3** was arrived at starting from the lactone (−)-**11** (Scheme 3), whose configuration is known[3k,4b] to be 2*S*,3*R*, being a direct precursor of (−)-methylenolactocin (**2**).

The acid lactone (−)-**11**,[4b] having 93% ee, was α-methylated under the stereocontrolled conditions by Grieco.[7,8] The resulting lactone (−)-**12** (88% yield) was transformed into the butenolide (−)-**3** through the same sequence of reactions reported above for the conversion of (−)-**1** into (−)-**3**[14] (Scheme 3). The butenolide (−)-**3** was isolated in 18% yield and 94% ee after chromatographic separation

Scheme 3

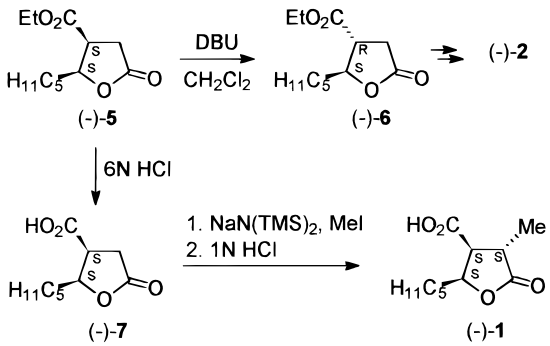


(±)-**6** (-)-**11** (-)-**2**

93% ee

(-)-**3** (-)-**12**: R[1] = H (-)-**13**: R[1] = Me

Scheme 4



(-)-**5** (-)-**6** (-)-**2** (-)-**7** (-)-**1**

from the methyl ester of the unreacted lactone (−)-**13**[15] (35% yield, 93% ee).

The butenolide (−)-**3** isolated from lactone (−)-**11** was the same enantiomer as that previously obtained from phaseolinic acid (−)-(**1**). Since its C-2 does not enter in any of the above reactions, it seems reasonable to assign the *S* configuration also to C-2 of phaseolinic acid (−)-**1**. Further experiments were performed to settle the absolute configuration of phaseolinic acid (−)-**1**, as shown in Scheme 4.

The ester lactone (−)-**5** having 92% ee[16] isomerized to (−)-**6** by treatment with DBU in refluxing dichloromethane. Since it is unlikely that inversion of configuration occurs at C-2 and because lactone (−)-**6** is the ethyl ester of the lactone (−)-**11**, a direct precursor of (−)-methylenolactocin (**2**) (Scheme 3), the configuration of C-2 in (−)-**6** and hence in (−)-**5** must be *S*.

The ethoxycarbonyl group in (−)-**5** was then chemically hydrolyzed and the resulting acid lactone (−)-**7** (62% ee) was α-methylated with methyl iodide in excess and NaN(SiMe$_3$)$_2$ as the base, furnishing phaseolinic acid (−)-**1**, with 63% ee (Scheme 4). Therefore, the configuration at C-2 must be the same both in (−)-phaseolinic acid (**1**) and (−)-methylenolactocin (**2**). A further support to this conclusion came from the analysis of the CD spectra of phaseolinic acid (−)-**1** and the butenolide (−)-**3**.

Phaseolinic acid (−)-**1** exhibited a positive Cotton effect ($\Delta\epsilon_{216} = +2.2$, dioxane, lit.[1] $\Delta\epsilon = +1.76$). Interestingly,

(10) Determined by chiral HRGC of either its methyl or ethyl ester.

(11) The reaction yield was satisfactory only when phenylselenyl chloride was used in large excess (twelvefold).

(12) The geometry of (−)-**9** was confirmed by means of DIFNOE measurements. Irradiation of H-2 doublet of double doublet at 4.65 ppm enhanced H-3 doublet of doublets (10%), while irradiating the methyl doublet at 1.30 ppm, the signals relative to H-2 (2%), H-3 (3%) and H-4 (4%) were enhanced.

(13) The geometry of (−)-**10** was established by means of DIFNOE measurements. Irradiation of H-2 doublet triplet at 4.34 ppm enhanced both H-3 doublet of doublets (6%) and H-4 double quartet (4%), while irradiating H-3 at 3.25 ppm, the signals of H-2 (6%) and H-4 (3%) were enhanced. Finally, an enhancement of H-2 (3%) and H-3 (4%) was observed by irradiating H-4 signal at 2.83 ppm.

(14) NaN(SiMe$_3$)$_2$ was used in place of LDA, which gave no results.

(15) The geometry of (−)-**13** was established by means of DIFNOE measurements. Irradiation of H-2 produced enhancement of H-4 doublet quartet (4%), while irradiation of H-3 at 2.64 ppm enhanced the methyl doublet at 1.31 ppm (4%)

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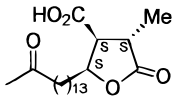
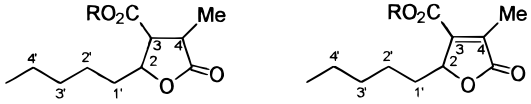
Chart 3



(-)-**14**

Chart 4



pertusarinic acid (−)-**14**[17] (Chart 3), possessing the same 2*S*,3*S*,4*S* configuration, although a different aliphatic chain at C-2, showed a positive Cotton effect at 221 nm ($\Delta\epsilon_{221} = +1.38$, CH_3CN) due to the n → π* transition.

The butenolide (−)-**3** exhibited in its CD spectrum a weak negative n → π* Cotton effect at 256 nm ($\Delta\epsilon_{256} = -0.6$) and a strong positive π → π* Cotton effect at 229 nm ($\Delta\epsilon_{229} = +2.5$), which are consistent with the *S* configuration of its stereocenter.[18] This attribution follows from the studies initially made by Uchida[18a] and more recently by Gawronski[18b] and Kirby[18c] on a series of natural and synthetic substituted α-butenolides. They found that the sign of the Cotton effect of both transitions are correlated with the absolute configuration of the γ-carbon atom of the α,β-unsaturated γ-lactone.

Since all our results are nonconflicting, the conclusion can be drawn that the configuration of natural phaseolinic acid having negative specific rotation is 2*S*,3*S*,4*S* and not 2*R*,3*R*,4*R*, as reported in the literaure.[1,3a,3b]

Experimental Section

Tetrahydrofuran was distilled from sodium benzophenone ketyl. Lipase from porcine pancreas (type II, crude, no. L-3126) and from *Candida cylindracea* (no. L-1754), esterase from pig liver in 3.2 M $(NH_4)_2SO_4$ suspension (no. E−2884), and porcine liver acetone powder (no. L-8251) were supplied from Sigma Chemicals Co. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ glass-backed silica gel plates with visualization by UV light (254 nm) or iodine. Flash chromatography (FC) purifications were carried out on silica gel (Merck 60, 230−400 mesh). NMR spectra were recorded in $CDCl_3$ and referenced to residual $CHCl_3$ at 7.26 ppm (^{1}H) and 77.0 ppm (^{13}C). Mass spectra were obtained at 70 eV. Chiral HRGC analyses were obtained using a CHIRALDEX type G-TA, trifluoroacetyl-γ-cyclodextrin, 40 m × 0.25 mm, column.

All reactions leading to enantiomerically pure compounds were also repeated on racemic mixtures, to evaluate the enantiomeric excess by chiral HRGC.

Numbering of butanolide and butenolide is given in Chart 4.

Synthesis of Racemic Phaseolinic Acid (±)-(1). Lactone (±)-**5** (0.6 g, 2.6 mmol) was refluxed in 50 mL of a 2:1 mixture of dioxane and 6 N HCl for 30 min. Evaporation of the solvent left the acid (±)-**7** (0.52 g, 98% yield, after crystallization from 9:1 light petroleum−ethyl acetate). A solution of (±)-**7** (0.150 g, 0.75 mmol) in 1.4 mL of anhydrous THF was added to sodium bis(trimethylsilyl)amide (1.65 mL, 1.65 mmol) (1.0 M solution in THF) at −78 °C under Ar over 30 min.[7] The mixture was stirred at −78 °C for 1 h, then methyl iodide (0.45 mL, 7.2 mmol) was slowly added and the mixture was stirred for additional 2 h. Then the mixture was allowed to warm until −20 °C, 2 N HCl (8 mL) was added, the mixture was extracted three times with ether, and the organic phases were washed with brine and dried on Na_2SO_4. After removal of the solvent, racemic phaseolinic acid (±)-**1** (0.152 g, 95% yield) was isolated in mixture with the unreacted lactone (±)-**7** (5%). Separation of the two lactones was accomplished by transformation into the corresponding ethyl esters (±)-**5** and (±)-**8** with ethyl iodide and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)[9] and separation by flash chromatography (eluent, ethyl acetate−light petroleum, gradient from 0% to 20%). Phaseolinic acid (±)-**1** was then recovered by acidic hydrolysis in dioxane of compound (±)-**8**.

(2*R,3*R**,4*R**)-4-Methyl-5-oxo-2-pentyl-tetrahydro-3-furancarboxylic Acid (1):** mp 150−1 °C (from light petroleum−ethyl acetate): ^{1}H NMR (400 MHz) δ 5.8 (1 H, bs, OH), 4.64 (1 H, dt, *J* = 8.3, 8.3, 5.4, H-2), 3.25 (1 H, dd, *J* = 9.3, 8.3, H-3), 2.90 (1 H, dq, *J* = 9.3, 6.8, H-4), 1.54 (2 H, m, 2 H-1′), 1.44 (1 H, m, H-2′), 1.34 (1 H, m, H-2′), 1.25 (4 H, m, 2 H-3′, 2 H-4′), 1.16 (3H, d, *J* = 6.8, Me at C-3), 0.81 (3 H, bt, Me of the chain); ^{13}C NMR (100.4 MHz) δ 178.4 (s), 172.1 (s), 78.5 (d, C-2), 52.4 (d, C-3), 37.8 (d, C-4), 32.6 (t, C-3′), 32.3 (t, C-1′), 26.7 (t, C-2′), 23.6 (t, C-4′), 15.0 (q, Me at C-4), 14.7 (q, Me of the chain). (Found: C, 61.80, H, 8.42. $C_{11}H_{18}O_4$ requires: C, 61.66, H, 8.47.)

(2*R,3*R**,4*R**)-4-Methyl-5-oxo-2-pentyltetrahydro-3-furancarboxylic Acid Ethyl Ester (8).** The ester (±)-**8** was isolated as an oil: IR (neat) 1782, 1736 (C=O), 1200 (O−CO); ^{1}H NMR (400 MHz) δ 4.66 (1 H, ddd, *J* = 10.0, 8.3, 3.4, H-2), 4.23 (2 H, q, *J* = 7.3, OCH_2CH_3), 3.17 (1 H, dd, *J* = 9.8, 8.3, H-3), 3.05 (1 H, dq, *J* = 9.8, 7.3, H-4), 1.52 (2 H, m, H-1′, H-2′), 1.42 (1 H, m, H-1′), 1.40−1.20 (11 H, d, t, m, 2 Me, H-2′, 2 H-3′, 2 H-4′), 1.30 (t, *J* = 7.3, OCH_2CH_3), 1.29 (d, *J* = 7.3, Me at C-4), 0.88 (3 H, bt, Me of the chain); ^{13}C NMR (100.4 MHz) δ 177.6 (s), 169.5 (s), 77.4 (d, C-2), 61.2 (t, OCH_2CH_3), 51.6 (d, C-3), 36.2 (d, C-4), 31.2 (t, C-3′), 30.9 (t, C-1′), 25.1 (t, C-2′), 22.2 (t, C-4′), 14.3 (q, Me at C-4), 14.0 (q, OCH_2CH_3), 13.7 (q, Me of the chain); mass spectrum (EI) *m*/*z* 243 (MH^+, 0.8), 242 ($M^{+\cdot}$, 0.5), 214 ($[M - C_2H_5]^+$, 0.8), 196 (14), 195 (13), 183 (13), 171 (77), 169 (40), 143 (100), 142 (27), 127 (18), 115 (60), 99 (34), 97 (79), 95 (20), 87 (55), 83 (23), 81 (19), 71 (23), 69 (98), 55 (70).

Kinetic Resolution of Phaseolinic Acid Ethyl Ester (±)-8. To a solution of the lactone (±)-**8** (0.460 g, 1.9 mmol), in a buffer solution (0.1 M KH_2PO_4/Na_2HPO_4, 5.0 mL), was added PLE (170 units/mg, Sigma, 0.10 mL). The pH value was mantained at 7.5 by continuous addition of 1 N NaOH. After 2 h (20% conversion), the crude reaction mixture was extracted with diethyl ether. After the usual workup, the lactone (−)-**8** (0.271 g, 59% yield) in 32% ee was obtained. The aqueous phase was acidified to pH 2 with 1 N HCl and extracted several times with diethyl ether. The usual workup furnished the acid (+)-**1** (0.061 g, 15% yield): mp 141−2 °C (from light petroleum−ethyl acetate); $[\alpha]^{25}_D = +111.4$ (*c* 0.22, $CHCl_3$); $\Delta\epsilon_{220} = -2.0$, dioxane; 94% ee.

The kinetic resolution of (±)-**8** (0.460 g, 1.9 mmol), carried out under the same conditions as above for 10 h, furnished the acid (+)-**1** (0.142 g, 35% yield) with 47% ee and the ester (−)-**8** (0.161 g, 35% yield) with 96% ee: $[\alpha]^{25}_D = -90.4$ (*c* 0.23, $CHCl_3$), $\Delta\epsilon_{219} = +2.3$, dioxane; $[\alpha]^{25}_D = -98.3$ (*c* 0.24, CH_3CN), $\Delta\epsilon_{218} = +1.8$, CH_3CN.

Hydrolysis of (−)-**8** (0.100 g, 0.40 mmol) was carried out in refluxing dioxane (4.5 mL) in the presence of 6 N HCl (2.2 mL) for 30 min. After elimination of dioxane the mother liquors were treated with a solution of $NaHCO_3$ and extracted with ether. The basic solution was treated with 6 N HCl until pH 2 and extracted with ether. After the usual workup, evaporation of the solvent left a solid (0.080 g, 91% yield) which was crystallized with light petroleum−ethyl acetate, (−)-**1**: mp 140−1 °C; $[\alpha]^{25}_D = -112.3$ (*c* 0.26, $CHCl_3$); $\Delta\epsilon_{219} = +2.2$, dioxane; 99% ee [lit.[1] mp 139−40 °C, $[\alpha]_D = -150$ (*c* 0.2, $CHCl_3$); lit.[3a] mp 138−40 °C, $[\alpha]^{25}_D = -142$ (*c* 0.22, $CHCl_3$); lit.[3b] mp 137−8 °C, $[\alpha]^{26}_D = -147$ (*c* 0.37, $CHCl_3$)].

Conversion of (−)-Phaseolinic Acid (1) to the Butenolide (−)-3. To a stirred solution of LDA (1.8 mmol) (1.5 M solution in cyclohexane) in anhydrous THF (2 mL) at −78 °C under Ar was added (−)-phaseolinic acid (**1**) (0.15 g, 0.7 mmol) in THF (1.6 mL) slowly. The mixture was stirred at −78 °C for 3 h, then a solution of HMPA (1.5 mL) and phenylselenyl chloride (1.60 g, 8.3 mmol) in THF (27 mL) was added and the

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reaction was set aside for 2 h. The mixture was stirred for further 1.5 h at −78 °C, then the temperature was allowed to raise to −20 °C and 2 N HCl was added. The solution was extracted four times with ether. The organic phases were washed with brine and extracted four times with a saturated solution of $NaHCO_3$. The basic solution was acidified with 6 N HCl and extracted four times with diethyl ether. Evaporation of the solvent left a semisolid crude reaction mixture (0.140 g) which was dissolved in THF and stirred at 0 °C. Glacial acetic acid (4 drops) and 30% hydrogen peroxide (2.0 mL) were added. After stirring at 0 °C for 1 h, 2 N HCl was added and the mixture extracted three times with ether. Esterification of the resulting reaction mixture with diazomethane gave an oil (0.140 g) which was a mixture of the butenolide (−)-**3** (75%), the methyl ester of the unreacted lactone (−)-**9** (15%), and a small amount of the *all-cis*-lactone (−)-**10** (10%). Separation by flash chromatography (eluent, ethyl acetate−light petroleum gradient from 0% to 10%) afforded the butenolide (−)-**3** (0.060 g, 37% yield), the methyl ester of the parent lactone (−)-**9,** and the *all-cis*-lactone (−)-**10**.

(2*S*)-(−)-2,5-Dihydro-4-methyl-5-oxo-2-pentyl-3-furancarboxylic Acid Methyl Ester (3). The ester was isolated as an oil. IR (neat) 1767, 1722, 1664, 1228; ^{1}H NMR (400 MHz) δ 5.07 (1 H, ddq, J = 2.2, 2.2, 7.8, H-2), 3.86 (3 H, s, OMe), 2.16 (3 H, d, J = 2.2, Me at C-4), 2.05 (1 H, m, H-1′), 1.53 (1 H, m, H-1′), 1.37 (2 H, m, 2 H-2′), 1.23 (4 H, m, 2 H-3′, 2 H-4′), 0.85 (3 H, bt, Me of the chain); ^{13}C NMR (100.4 MHz) δ 172.8 (s), 162.6 (s), 147.5 (s), 137.3 (s), 81.3 (d, C-2), 52.2 (q, OMe), 32.69 (t C-1′), 31.3 (t, C-3′), 24.3 (t, C-2′), 22.3 (t, C-4′), 13.8 (q, Me of the chain), 10.7 (q, Me at C-4); mass spectrum (EI) m/z 227 (MH^+, 0.4), 226 ($M^{+\cdot}$, 0.5), 197 ($[M - C_2H_5]^+$, 60), 156 ($[M-C_5H_{10}]^{+\cdot}$, 100), 128 (45), 127 (37), 124 (52), 123 (31), 99 (36), 71 (31), 67 (43), 55 (23), 43 (62); $[\alpha]^{25}_D = -47.5$ (c 0.12, CH_3CN); $\Delta\epsilon_{256} = -0.6$; $\Delta\epsilon_{225} = +2.5$, CH_3CN; 94% ee. The retention time was 33.55 min for (−)-**3** and 30.13 min for (+)-**3** (120 °C for 2 min, 3 °C/min up to 150 °C within 40 min).

(2*S*,3*S*,4*S*)-(−)-4-Methyl-5-oxo-2-pentyltetrahydro-3-furancarboxylic Acid Methyl Ester (9). The ester (−)-**9** was isolated as an oil. IR (neat) 1780, 1735 (C=O), 1205 (O−CO); ^{1}H NMR (400 MHz) δ 4.65 (1 H, ddd, J = 10.5, 8.3, 3.4, H-2), 3.68 (3H, s, OMe), 3.17 (1 H, dd, J = 9.8, 8.3, H-3), 3.04 (1 H, dq, J = 9.8, 7.3, H-4), 1.45 (2 H, m, H-1′, H-2′), 1.32 (2 H, m, H-1′, H-2′), 1.25−1.15 (7 H, m and d, Me, 2 H-3′, 2 H-4′), 1.30 (d, J = 7.3, Me at C-4), 0.90 (3 H, bt, Me of the chain); ^{13}C NMR (100.4 MHz) δ 177.6 (s), 170.2 (s), 77.5 (d, C-2), 52.3 (q, OMe), 51.7 (d, C-3), 36.3 (d, C-4), 31.3 (t, C-3′), 31.2 (t, C-1′), 25.2 (t, C-2′), 22.4 (t, C-4′), 14.4 (q, Me at C-4), 13.9 (q, Me of the chain); $[\alpha]^{25}_D = -81.7$ (c 0.30, CH_3CN).

(2*S*,3*S*,4*R*)-(−)-4-Methyl-5-oxo-2-pentyltetrahydro-3-furancarboxylic Acid Methyl Ester (10). The ester (−)-**10** was isolated as an oil. IR (neat) 1780, 1730; ^{1}H NMR (400 MHz) δ 4.34 (1H, dt, J = 5.4, 5.4, 7.8 Hz, H-2), 3.68 (3 H, s, OMe), 3.25 (1H, dd, J = 5.4, 7.8, H-3), 2.83 (1 H, apparent quintet, J = 7.3, H-4), 1.70 (1 H, m, H-1′), 1.50 (2 H, m, H-1′, H-2′), 1.35 (1 H, m, H-2′), 1.25 (4 H, m, 2 H-3′, 2 H-4′), 1.18 (3 H, d, J = 7.3, Me at C-4), 0.83 (3 H, bd, Me of the chain); ^{13}C NMR (100.4 MHz) δ 177.0 (s), 170.0 (s), 78.1 (d, C-2), 51.7 (q, OMe), 50.7 (d, C-3), 39.1 (d, C-4), 31.4 (t, C-3′), 30.9 (t, C-1′), 25.5 (t, C-2′), 22.4 (t, C-4′), 13.9 (q, Me of the chain), 10.3 (q, Me at C-4); $[\alpha]^{25}_D = -45.3$ (c 0.23, CH_3CN); $\Delta\epsilon_{219} = -0.93$; 99% ee.

Conversion of the *trans*-Lactone (−)-11 to the Butenolide (−)-3. The lactone (−)-**11**[4b] (0.100 g, 0.5 mmol) was methylated following the procedure described for the methylation[7] of the *cis*-lactone **7.** The crude reaction mixture obtained (0.096 g, 96% yield) contained the unreacted lactone (−)-**11** (8%) and the methyl lactone (−)-**12** (92%). Since they could not be separated, the subsequent reactions were carried out on the mixture of (−)-**11** and (−)-**12**. This mixture (0.096 g) in anhydrous THF (1.0 mL) was added to a stirred solution of sodium bis(trimethylsilyl)amide (0.8 mL, 0.8 mmol) (1.0 M solution in THF) at −78 °C under Ar. After 1 h, phenylselenyl chloride (0.70 g, 3.6 mmol) in THF (12 mL) was added and the reaction set aside for 2 h. The mixture was stirred for further 1.5 h at −78 °C, then the temperature was allowed to raise to −20 °C and 2 N HCl was added. The solution was extracted four times with ether. The organic phases were washed with brine and extracted four times with a saturated solution of $NaHCO_3$. The basic solution was acidified to pH 2 and extracted four times with diethyl ether. The solvent was evaporated, and to the crude reaction mixture (0.095 g) dissolved in THF (5 mL) were added glacial acetic acid (2 drops) and 30% hydrogen peroxide (1.0 mL). Esterification of the resulting mixture with diazomethane gave an oil (0.060 g) which was a 1:2 mixture of (−)-**3** and (−)-**13**, while only traces of the parent lactone (−)-**11** were found in the ^{1}H NMR spectrum of the crude reaction mixture. Separation by flash chromatography (eluent, ethyl acetate-light petroleum gradient from 0% to 6%) afforded the saturated lactone (−)-**13** (0.040 g, 35% yield) and the unsaturated lactone (−)-**3** (0.020 g, 18% yield).

(2*S*,3*R*,4*R*)-(−)-4-Methyl-5-oxo-2-pentyltetrahydro-3-furancarboxylic Acid Methyl Ester (13). The ester (−)-**13** was isolated as an oil. IR (neat) 1782, 1736; ^{1}H NMR (400 MHz) δ 4.35 (1H, ddd, J = 3.9, 8.3, 9.3 Hz, H-2), 3.77 (3 H, s, OMe), 2.94 (1 H, dq, J = 6.8, 11.2, H-4), 2.64 (1H, dd, J = 9.3, 11.2, H-3), 1.70 (1 H, m, H-1′), 1.61 (1 H, m, H-1′), 1.52 (1H, m, H-2′), 1.38 (1H, m, H-2′), 1.33−1.17 (7 H, m and d, 2 H-3′, 2 H-4′, Me at C-4), 1.31 (d, J = 6.8, Me at C-4), 0.88 (3 H, bd, Me of the chain); ^{13}C NMR (100.4 MHz) δ 176.8 (s), 171.2 (s), 79.6 (d, C-2), 54.2 (d, C-3), 52.6 (q, OMe), 39.9 (d, C-4), 34.8 (t, C-1′), 31.3 (t, C-3′), 24.9 (t, C-2′), 22.4 (t, C-4′), 14.4 (q, Me at C-4), 13.9 (q, Me of the chain); mass spectrum (EI) m/z 229 (MH^+, 0.7), 197 (6), 157 (45), 129 (77), 102 (100), 97 (45), 69 (90); $[\alpha]^{25}_D = -36.7$ (c 0.15, CH_3CN); $\Delta\epsilon_{220} = -1.1$, CH_3CN; 94% ee.

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