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Enantioselective Synthesis of Pyranofuranone Moieties of Manoalide and Cacospongionolide B by Enzymatic and Chemical Approach

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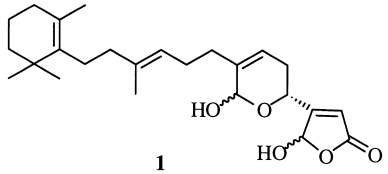
Abstract—Two synthetic sequences leading to the pyranofuranone moieties of Manoalide and Cacospongionolide B in enantiomerically enriched forms are reported. The key steps involve either an enantioselective aldol condensation or an enzymatic resolution.

Manoalide[1] (**1**) and cacospongionolide B[2] (**2**) are the most representative compounds of a class of anti-inflammatory sesterterpenes isolated from soft sponges. From a structural point of view, they are characterised by the presence of pyranofuranone residues, differing from each other by the substitution in the dihydropyran ring.



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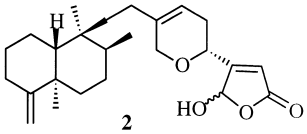

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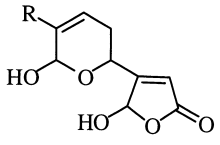
Pharmacological tests performed on both **1** and **2** have revealed very interesting biological activities: manoalide is a potent, irreversible inhibitor of phospholipase A_2 (PLA_2) while cacospongionolide B has shown a comparable activity on recombinant human synovial PLA_2 in vitro.[3] These results stimulated the elaboration of synthetic sequences for the preparation of **1** and analogues of type **3** and **4** whose availability has allowed additional information on structure–activity relationship to be obtained. However, it has to be noted that all the established synthetic procedures lead to the products **1**,[4] **3** and **4**[5,6] as racemic mixtures.



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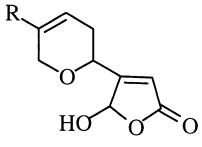

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Since the pyranofuranone system is considered the pharmacophoric group of **1** and **2** we decided that access to chiral non-racemic subunits of type **3** and **4** (R=H) could be conveniently exploited for the acquisition of additional data concerning biological activities. An approach to chiral non-racemic pyranones, which can be conveniently elaborated to **3** and **4**, was already reported by us as a preliminary communication.[7] We report here full experimental details on the above-mentioned procedure, which was based on an enantioselective aldol reaction, as well as an alternative approach based on enzymatic resolution of an intermediate of the synthetic sequence leading to **3** and **4**.

Results and Discussion

Enzymatic approach

In the first strategy of synthesis (±)-*anti*-4-acetoxy-6-(furan-3-yl)-2-oxo-tetrahydro-pyran **10** was chosen as a possible intermediate to be resolved by enantioselective enzymatic hydrolysis (Scheme 1).

Key intermediate **10** was prepared through the synthetic sequence reported in Scheme 2 following the approach

Keywords: aldol reaction; asymmetric synthesis; enzyme catalysis; 1,3-dioxin-4-ones.

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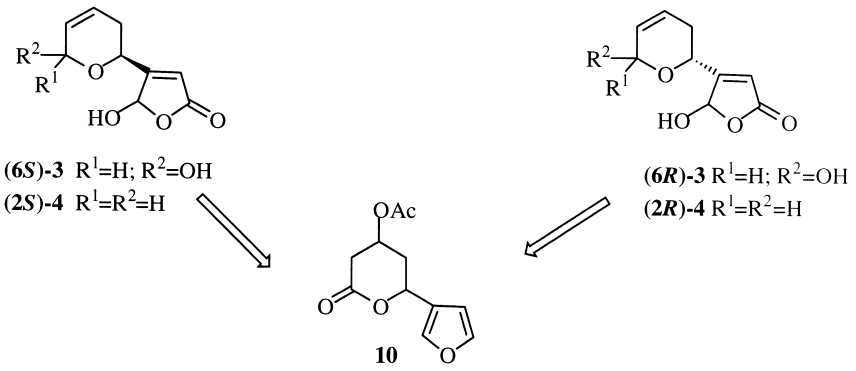
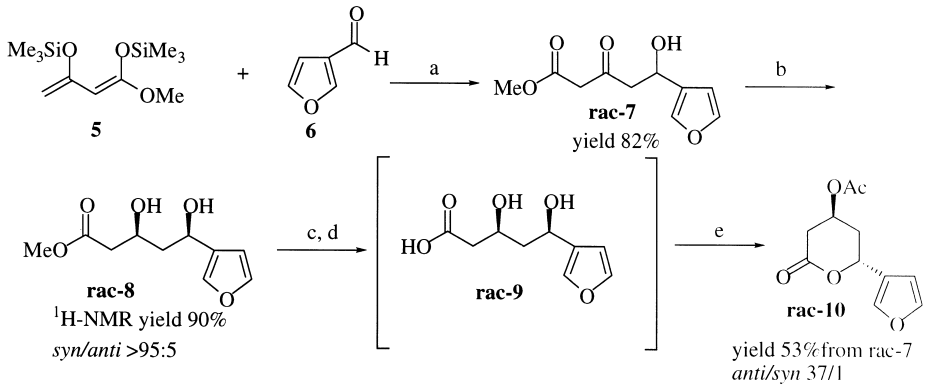


Scheme 1.



Scheme 2. (a) BF_3Et_2O, Et_2O, −78°C; (b) $Et_2BOMe/NaBH_4$, THF, −70°C; (c) 1N, NaOH, EtOH; (d) 6N, HCl; (e) Ac_2O/Py, room temperature.

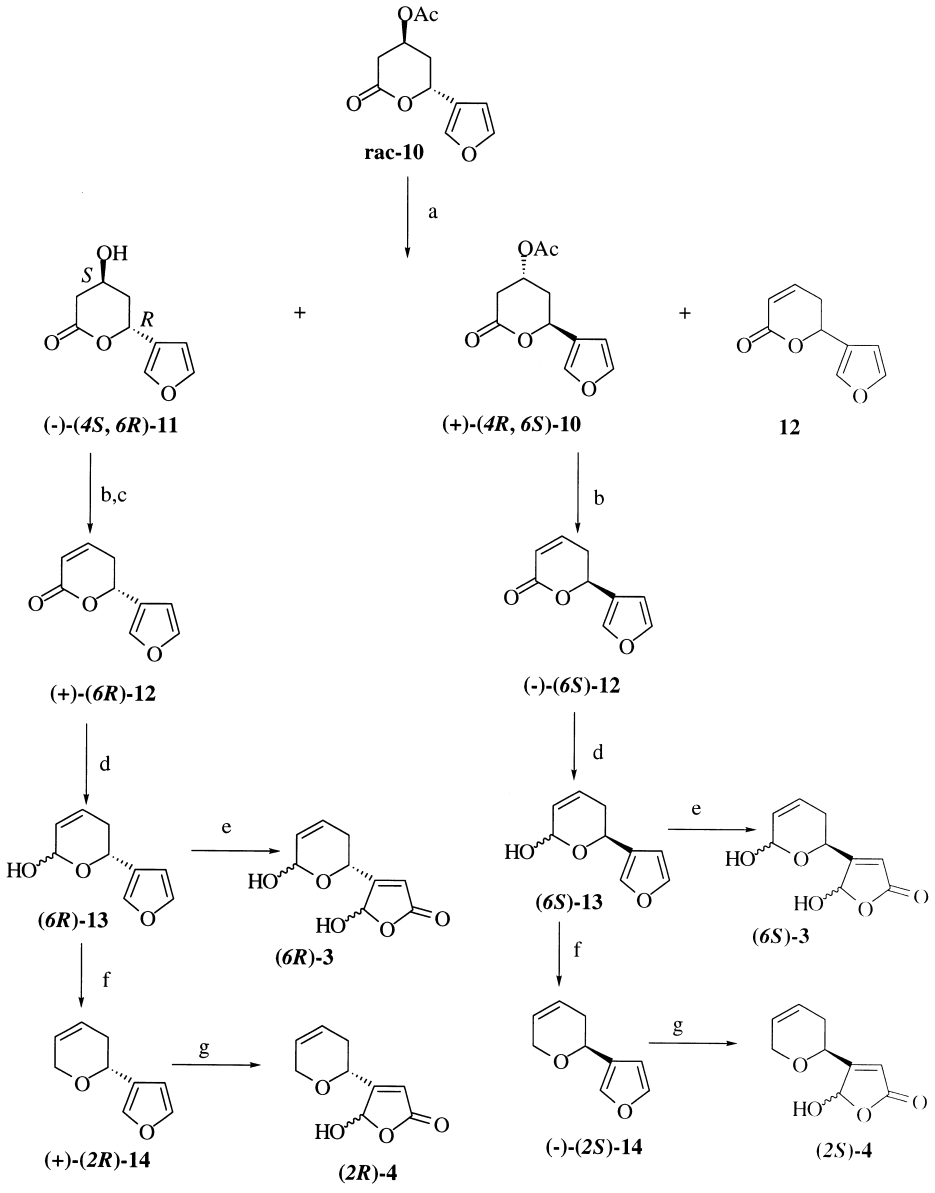
previously set up for the synthesis of racemic analogues[4,5] with minor modifications.

The first step, involving an aldol-type condensation between 3-formyl furan **6** and diene[8] **5**, afforded compound **7** in good yield, which was converted with very high diastereoselectivity into 3,5-dihydroxy-ester **8** by reduction with $Et_2BOMe/NaBH_4$ system according to the Prasad procedure.[9] *Syn* relationship of –OH groups was confirmed both by comparison of spectroscopic data (^{1}H NMR and ^{13}C NMR) with literature data[9] and Rychnovsky methodology.[10] Hydrolysis of **8** and acidification under carefully controlled conditions, in order to avoid side-processes of H_2O elimination or furan ring opening, led to dihydroxy-acid **9**, which was converted without purification into the key intermediate **10** by treatment with Ac_2O/Py. In the reactions **b**, **c** and **d** no appreciable stereochemical modification of C(4) and C(6) atoms took place since **10** was obtained as a 37/1 *anti/syn* mixture as indicated by ^{1}H NMR data.

A set of experiments, performed in acetone/water mixture at room temperature in the presence of lipase from *Pseudomonas fluorescens* (PFL), resulted in approximately 40% conversion of **rac-10** after 7 h (Scheme 3). Chromatographic purification afforded **(−)-11** (33% yield), while the unchanged acetyl-lactone **(+)-10** proved to be contaminated by variable amounts of the corresponding elimination product **12** (60% overall yield). The *S* configuration at C(4) of **(−)-11** was assigned by means of the modified Mosher procedure.[11]

Because the C(4) and C(6) originate from the *syn*-diol **9**, the absolute configuration at C(6) in **11** should be *R*.

In spite of several attempts, the efficient chromatographic separation of the components of the mixture **(+)-10** and **12** failed because of the tendency of **10** to suffer AcOH elimination in the course of the laborious purification procedure. In every case, the enzymatic hydrolysis was shown to occur with a high degree of enantioselectivity: in fact, **(−)-11** was obtained with 91% ee, determined through ^{1}H NMR analysis on the corresponding (*S*)-MTPA ester. Lactone **(+)-(6*R*)-12** was then easily prepared by base-catalysed elimination performed on **(−)-(4*S*, 6*R*)-10** (80% overall yield, calculated on **(−)-(4*S*, 6*R*)-11**). The unresolved mixture **(+)-(4*R*, 6*S*)-10** and **12** was submitted to the same treatment to give **(−)-(6*S*)-12** ($[\alpha]_D^{20}=-36.7$, *c* 1.7, $CHCl_3$) whose enantiomeric excess (33%) was determined on the grounds of the molecular rotation of **(+)-(6*R*)-12** ($[\alpha]_D^{20}=+108.0$, *c* 1.7, $CHCl_3$, 91% ee). This very low value of ee could be reasonably attributed to the occurrence of a competitive process of AcOH elimination, suffered by **rac-10** during the enzymatic hydrolysis. The following conversion of **(+)-12** and **(−)-12** into the chiral non racemic pyranofuranone subunits **3** and **4** was achieved through the exploitation of the synthetic sequence previously proposed for racemic **12**.[5]



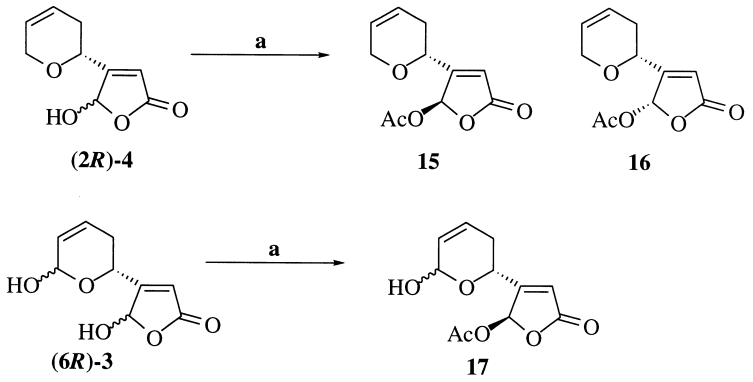
Scheme 3. (a) PFL/Acetone (pH=7.3); (b) DBU/$CHCl_3$; (c) Ac_2O/Py; (d) DIBAL/−78°C; (e) $^1O_2/CH_2Cl_2$/−78°C; (f) Et_3SiH/BF_3Et_2O; (g) $^1O_2/CH_2Cl_2$/−78°C.

The appropriate elaboration of the pyran nucleus, involving partial or complete reduction of the carbonyl functionality of (+)-**(6*R*)-12**, according to the Kraus methodology,[12] furnished, respectively, **(6*R*)-13** and (+)-**(2*R*)-14**. Finally, the γ-hydroxybutenolide system was generated by photooxidation with $^1O_2$ and regioselective decomposition of the resulting endoperoxide in the presence of diisopropylethyl amine to give the target compounds **3** and **4**, characterised by *R* absolute configuration at the pyran stereogenic center. The opposite stereochemical outcome was obviously obtained starting from the unsaturated lactone (−)-**(6*S*)-12**. Since the proton and carbon NMR spectra of **3** and **4** were somewhat complicated for the presence of mixtures of diastereomers, the structures were confirmed by treatment with acetic anhydride and pyridine, followed by HPLC purification of the corresponding acetates. In the case of **(2*R*)-4** the above treatment afforded the two expected acetates **15** and **16**, while in the case of **(6*R*)-3,** the monoacetate **17** was obtained as far predominant product (Scheme 4). The stereochemistry at C-5 in the 5-membered ring has been determined on the ground of the chemical shift values in the ^1H NMR spectra of the acetates **15** and **16** as reported in Ref. 13. The stereochemistry of **17** has been analogously determined.

On the grounds of these results we concluded that the enzymatic approach has disclosed the access to enantiomerically enriched pyranofuranones, but its main limitation is represented by the low yields and the low ee of the unsaturated lactone (−)-**(6*S*)-12**.

Chemical approach

The attempt to circumvent the above limitation stimulated the elaboration of a new strategy involving a chemical approach to key intermediates (−)-**11** and (+)-**11**, as

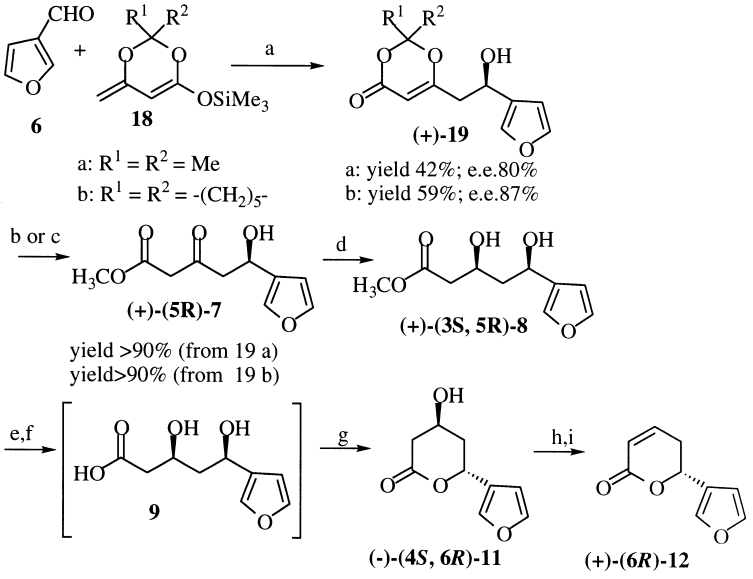


Scheme 4. (a) Ac_2O, Pyridine.

depicted in Scheme 5.[7] The first stereogenic centre was generated in an enantioselective way by an aldol-type condensation between 3-formyl furan **6** and masked acetoacetates[14,15] **18** in the presence of $Ti(OiPr)_4$ as metal catalyst and *R*-(+)-binaphthol as chiral auxiliary. Two silyloxydienes were tested and **18b** gave the best results both in terms of yield and enantioselectivity. Ee's of aldols **(+)-19** were determined through ^1H NMR analysis on the corresponding (*S*)-MTPA esters. The same methods previously employed for the compound **(−)-11** allowed to assign the *R* configuration to the stereogenic centre of **(+)-19**.

A known methodology,[16] involving treatment of **(+)-19** with 2 equiv. of MeOH in refluxing toluene for 16 h, led to **(+)-(5*R*)-7** in 70% of yield. However, a noticeable improvement was obtained by submitting the same methanol–toluene solution of **(+)-19** to microwave (MW) irradiation so that **(+)-(5*R*)-7** was isolated in >90% yield in only 15 min. Usual reduction of **(+)-(5*R*)-7** with Et_2BOMe/$NaBH_4$ system gave dihydroxyester **(+)-(3*S*, 5*R*)-8** in nearly quantitative yield and high diastereoselectivity (*syn*/*anti* ratio >95/5, based on ^1H NMR data).

Key intermediate **(−)-(4*S*, 6*R*)-11** was then accessible by a new procedure employing MW irradiation of a toluene suspension of dihydroxyacid **9**, available after carefully controlled hydrolysis of **(+)-(3*S*, 5*R*)-8** (58% overall yield starting from **7**). No appreciable stereochemical modification of the stereogenic centres took place in this three-step sequence as showed by ^1H NMR data: in fact, hydroxylactone **(−)-(4*S*, 6*R*)-11** was obtained as a 37/1 *anti*/*syn* mixture and in 95% ee. The hydroxylactone **(−)-(4*S*, 6*R*)-11** was transformed into the lactone **(+)-12** and finally into the target compounds **(6*R*)-3** and **(2*R*)-4** according to the procedure used for the lactone in the enzymatic approach. The same synthetic sequence with the exception of the employment in the first step of (*S*)-(−)-binaphthol as chiral auxiliary, has allowed to obtain the enantiomeric key intermediate **(−)-(3*R*, 5*S*)-8** with comparable yield and 80% enantiomeric excess.



Scheme 5. a=$Ti(OiPr)_4$/(R)-(+)-binaphthol; b=toluene, MeOH (12 equiv.), MW (*P*=250 W), 15 min; c=MeOH, toluene, Δ; d=Et_2BOMe, $NaBH_4$; e=NaOH/EtOH; f=6N HCl; g=toluene, MW (*P*=300 W), 45 min; h=Ac_2O/Py; i=DBU/$CHCl_3$.

Conclusion

In conclusion both enantiomerically enriched pyranofuranone moieties of manoalide and cacospongionolide B are now accessible through two different approaches: in particular, the use of MW irradiation in the chemical one has led to the elaboration of a more rapid sequence with no appreciable loss of efficiency and selectivity.

Experimental

General remarks

All reactions involving air-sensitive materials were performed using oven dried glassware under an atmosphere of dry nitrogen. Anhydrous Et_2O, toluene and CH_2Cl_2 were freshly distilled from CaH_2; THF was distilled from $LiAlH_4$ and then from sodium and benzophenone. *i*-Pr_2NH was distilled from CaH_2, MeOH from KOH. NMR spectra were recorded on a Bruker DRX 400 (400.135 MHz for ^1H and 100.03 MHz for ^{13}C) and on a Bruker AM 250 (250.13 MHz for ^1H and 62.89 MHz for ^{13}C) spectrometers. Chemical shifts are given in ppm (δ) scale; for the spectra in $CDCl_3$, the $CHCl_3$ signal was used as internal standard (δ 7.26 ^1H, δ 77.0 ^{13}C). *J* values are given in Hz. MS(EI): VG TRIO 2000. Column chromatographic separations were carried out using Silica gel 60 (70–230 mesh and 230–400 mesh, Merck). Optical rotations were measured at the sodium D line (589 nm) at room temperature with a JASCO DIP 1000 polarimeter.

5-[Furan-3-yl]-5-hydroxy-3-oxo-pentanoic acid methyl ester (*rac*-7). To a solution of **5**[8] (2.5 g, 10 mmol) in 58 ml of dry Et_2O under argon at −78°C were added 3-furylaldehyde (1.44 g, 15 mmol) and BF_3Et_2O (1.42 g, 10 mmol). The reaction mixture was stirred for 1 h in the dark, then saturated aqueous $NaHCO_3$ was slowly added, the mixture was allowed to warm to room temperature and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated to give crude *rac*-**7**. Purification of the crude product by silica gel column chromatography (30% $Et_2O/CHCl_3$) gave the *title compound rac*-**7** (1.7 g, 82%) as a pale yellow oil; [Found: C 56.5; H 5.79. $C_{10}H_{12}O_5$ requires C, 56.60; H, 5.70%]; R_f (30% $Et_2O/CHCl_3$) 0.45; ν_{max} (liquid film) 3480, 1740, 1713 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.34 (1H, s, *H*-furan), 7.32 (1H, d, *J*=1.5 Hz, *H*-furan), 6.33 (1H, s, *H*-furan), 5.09 (1H, dd, *J*=8.7, 3.6 Hz, C*H*OH), 3.66 (3H, s, OMe), 3.46 (2H, s, COCH_2CO), 2.96 (1H, dd, *J*=17.2, 8.7 Hz, CH_aH$_b$CHOH), 2.85 (1H, dd, *J*=17.2, 3.6 Hz, CH_bH$_a$CHOH); δ_C (62.89 MHz, $CDCl_3$) 202.5, 167.2, 143.4, 139.0, 127.2, 108.3, 62.8, 52.5, 50.2, 49.5; *m/z* (EIMS) 212 (M^+).

5-[Furan-3-yl]-3,5-dihydroxy-pentanoic acid methyl ester (*rac*-8). A solution of Et_2BOMe (5.2 ml of 1 M solution in THF) was added dropwise to a solution of rac-**7** (844 mg, 3.99 mmol) in dry THF (32 ml, 0.125 M) and dry MeOH (8 ml), under argon at −70°C. After stirring for 15 min $NaBH_4$ (196 mg, 5.18 mmol) was added, and the mixture was stirred for 5 h, until TLC analysis judged the reaction to be complete. The reaction mixture was diluted with ethyl acetate and quenched with acetic acid (4.7 ml). The organic phase was washed with saturated aqueous $NaHCO_3$, with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was azeotroped a few times with methanol until boron-containing compounds were removed. The reaction afforded 754 mg of rac-**8** in >95/5 *syn/anti* ratio and 90% yield, on the grounds of spectroscopic data (^1H NMR and ^{13}C NMR). Purification of crude rac-**8** (100 mg) by silica gel chromatography (20% MeOH/$CHCl_3$) gave the pure major *syn* isomer (87.5 mg, 87% yield) as a colourless oil; [Found: C 56.2; H 6.5. $C_{10}H_{14}O_5$ requires C, 56.07; H, 6.59%]; R_f (40% $Et_2O/CHCl_3$) 0.32; ν_{max} ($CHCl_3$) 3480, 1730 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, s, *H*-furan), 7.37 (1H, s, *H*-furan), 6.39 (1H, s, *H*-furan), 4.95 (1H, dd, *J*=9.6, 3.2 Hz, C*H*OH), 4.33–4.27 (1H, m, C*H*OHCH$_2$CO), 3.71 (3H, s, OMe), 2.57–2.46 (2H, m, CH_2CO), 1.94 (1H, dt partially overlapped, *J*=14.0, 10.0 Hz, CH_aH$_b$CHOH), 1.78 (1H, dt, *J*=14.0, 9.2 Hz, CH_bH$_a$CHOH); δ_C (100.03 MHz, $CDCl_3$) 172.8, 143.3, 138.9, 128.6, 108.3, 68.4, 66.9, 51.8, 43.3, 41.3; *m/z* (EIMS) 214 (<1%, M^+); 196 (M^+-H_2O).

4-Acetoxy-6-(furan-3-yl)-2-oxo-tetrahydro-pyran (*rac*-10). An EtOH solution (15 ml) of crude rac-**8** and 0.1N NaOH (35 ml) was stirred at room temperature for 1 h. The reaction solution was acidified with 6N HCl, diluted with H_2O, and extracted with AcOEt (3×70 ml). The combined organic extracts was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford a mixture of acid **9** and racemic lactone **11** (717 mg).

To a solution of this mixture in pyridine (2.87 ml, 35.8 mmol) acetic anhydride (1.70 ml, 17.9 mmol) was added, and the solution was stirred until TLC analysis indicated the reaction to be complete. The reaction mixture was then diluted with AcOEt (12 ml), and 1N HCl (10 ml) was added. The organic layer was washed with saturated $NaHCO_3$ and brine. Drying over anhydrous Na_2SO_4 and evaporation gave crude acetylated lactone rac-**10**. The product was chromatographed (10% $Et_2O/CHCl_3$) to afford rac-**10** (474 mg, 53% yield from rac-**7**) as a yellow oil; [Found: C 59.0; H 5.3. $C_{11}H_{12}O_5$ requires C, 58.93; H, 5.39%]; R_f (10% $Et_2O/CHCl_3$) 0.55; ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.49 (1H, s, *H*-furan), 7.43 (1H, s, *H*-furan), 6.43 (1H, s, *H*-furan), 5.60 (1H, dd, *J*=10.8, 3.2 Hz, C*H*O), 5.33–5.29 (1H, m, C*H*OAc), 2.87 (1H, dd, *J*=18.2, 5.3 Hz, CH_aH$_b$CO), 2.79 (1H, dd, *J*=18.2, 3.6 Hz, CH_bH$_a$CO), 2.34–2.29 (1H, m, CH_aH$_b$CHO), 2.19 (1H, ddd, *J*=14.4, 10.8, 3.4 Hz, CH_bH$_a$CHO); 2.11 (3H, s, OMe); δ_C (62.89 MHz, $CDCl_3$) 169.8, 168.3, 143.8, 139.7, 124.0, 108.3, 70.7, 65.3, 35.2, 33.4, 20.9.

6-[Furan-3-yl]-4-hydroxy-tetrahydro-pyran-2-one ((−)-11). To a solution of rac-**10** (308 mg, 1.37 mmol) in acetone (3.9 ml) and phosphate buffer 82.9 ml, pH=7) was added lipase from *Pseudomonas fluorescens* (24 mg, 3560 U/mg). The pH was maintained at 8 by adding 0.1N NaOH. The reaction was monitored by TLC and stopped at approximately 40% conversion (7 h) by adding AcOEt. The mixture was extracted with AcOEt, and the organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by column

chromatography (SiO_2, $CHCl_3/Et_2O$ 8/2) affording 82 mg (0.45 mmol, 33% yield, 91% ee) of **(−)-11** as a yellow ochre oil and a mixture of **(+)-10** and of the elimination product **12** (184 mg, 60% yield); [Found: C 59.2; H 5.7. $C_9H_{10}O_4$ requires C, 59.34; H, 5.53%]; R_f (30% Et_2O/$CHCl_3$) 0.24**;** $[\alpha]_D^{20}=-14.6$ (*c* 2.5, $CHCl_3$); ν_{max} (liquid film) 3439, 1730 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, s, *H*-furan), 7.42 (1H, s, *H*-furan), 6.42 (1H, s, *H*-furan), 5.74 (1H, dd, *J*=10.8, 3.4 Hz, C*H*OCO), 4.48–4.44 (1H, m, C*H*OH), 2.83 (1H, dd, *J*=17.6, 4.8 Hz, CH_aH_bCO), 2.70 (1H, dd, *J*=17.6, 3.2 Hz, CH_bH_aCO), 2.23–2.08 (2H, m, CH_2CHO); δ_C (100.03 MHz, $CDCl_3$) 169.8, 143.8, 139.7, 124.5, 108.5, 70.5, 62.7, 38.7, 36.6; *m/z* (EIMS) 182 (M^+).

Mosher esters of (−)-11. To a solution of **(−)-11** (5 mg, 0.027 mmol) and pyridine (22 μl) 4-dimethylaminopyridine (catalytic quantity) and (*S*)-MTPACl (5.5 μl) were added. The mixture was stirred at room temperature until TLC analysis indicated the reaction to be complete. The mixture was directly chromatographed on silica gel (40% AcOEt/30–50° light petroleum) to afford 9.6 mg (0.024 mmol) of (*R*)-MTPA ester (92% yield) as a pale yellow oil;. δ_H (250 MHz, $CDCl_3$) 7.50–7.36 (7H, m, Ph+*H*-furan), 6.40 (1H, d, *J*=1.7 Hz, *H*-furan), 5.57–5.53 (1H, m, C*H*OMTPA), 5.43 (1H, dd, *J*=9.8, 4.5 Hz, C*H*O), 3.51 (3H, s, OMe), 2.96 (1H, dd, *J*=18.3, 5.5 Hz, CH_aH_bCO), 2.79 (1H, dd, *J*=18.3, 3.9 Hz, CH_bH_aCO), 2.35–2.27 (2H, m, CH_2CHO). The (*S*)-MTPA ester was prepared according to the previous procedure starting from (*R*)-MTPACl. δ_H (250 MHz, $CDCl_3$) 7.50–7.37 (7H, m, Ph+*H*-furan), 6.34 (1H, s, *H*-furan), 5.60–5.54 (1H, m, C*H*OMTPA), 5.21 (1H, dd, *J*=16.3, 6.2 Hz, C*H*O), 3.57 (3H, s, OMe), 2.95 (1H, dd, *J*=18.1, 5.0 Hz, CH_aH_bCO); 2.89–2.70 (1H, m, CH_bH_aCO), 2.31–2.19 (2H, m, CH_2CHO).

(+)-(6*R*)-6-[Furan-3-yl-5,6-dihydro-pyran-2-one ((+)-12). The acetyl lactone **(−)-11** (184 mg, 1.0 mmol) was dissolved in $CHCl_3$ (5 ml), and DBU (three drops) was added. The solution was allowed to stand at room temperature for 1 h, and then acidified with 2N HCl and extracted with Et_2O. The ethereal layer was washed with H_2O and dried (Na_2SO_4). The solvent was removed under vacuum, and the product was chromatographed (SiO_2, $CHCl_3$) to afford **(+)-12** in 80% yield from **(−)-11** as a pale yellow oil; [Found: C 65.7; H 4.8. $C_9H_8O_3$ requires C, 65.85; H, 4.91%]; R_f (10% $Et_2O/CHCl_3$) 0.62**;** $[\alpha]_D^{20}=+108.0$ (*c* 1.7, $CHCl_3$);[17] ν_{max} (neat) 1720, 1645 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.49 (1H, d, *J*=0.9 Hz, *H*-furan), 7.42 (1H, t, *J*=1.6 Hz, *H*-furan), 6.99–6.91 (1H, m, C*H*CH_2), 6.46–6.45 (1H, m, *H*-furan), 6.12–6.07 (1H, m, C*H*CO), 5.45 (1H, dd, *J*=9.7, 5.7 Hz, C*H*O), 2.75–2.24 (2H, m, CH_2CHO); δ_C (62.89 MHz, $CDCl_3$) 163.7, 144.7, 143.6, 139.9, 123.8, 121.5, 108.5, 72.3, 30.0; *m/z* (EIMS) 164 (M^+).

The unresolved mixture **(+)-(4*R*, 6*S*)-10** and **12** was submitted to the same treatment to give **(−)-(6*S*)-12** in 32% yield from rac-**10**; $[\alpha]_D^{20}=-36.7$ (*c* 2.5, $CHCl_3$); ee 33%.

(6*R*)-6-[Furan-3-yl-5,6-dihydro-2H-pyran-2-ol (13). To a toluene solution (0.3 M) of unsaturated lactone **(−)-11** (476 mg, 2.9 mmol) cooled to −78°C was added dropwise DIBAL (1 M in CH_2Cl_2, 2.9 ml). The solution was stirred until TLC analysis indicated the reaction to be complete. The mixture was then poured into a stirred mixture of ice (9.5 g) and acetic acid (3.0 ml). $CHCl_3$ (20 ml) was added and the mixture was stirred vigorously for 10 min. An additional portion (39 ml) of $CHCl_3$ was then added, and the stirring continued until two distinct layers were formed when the stirring was stopped. The mixture was extracted with $CHCl_3$, and the organic layer was washed with bicarbonate and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, the residue was purified by column chromatography (SiO_2, $CHCl_3$) affording 470 mg (2.84 mmol, 98% yield) of **(6*R*)-13** as a pale yellow oil; [Found: C 65.2; H 6.0. $C_9H_{10}O_3$ requires C, 65.05; H, 6.07%]; R_f (30% $Et_2O/CHCl_3$) 0.52; ν_{max} ($CHCl_3$) 3420, 1610 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.44 (1H, d, *J*=0.6 Hz, *H*-furan), 7.40 (1H, t, *J*=1.7 Hz, *H*-furan), 6.45–6.43 (1H, m, *H*-furan), 6.12–6.06 (1H, m, CH=C*H*CH_2), 5.88–5.81 (1H, m, CH=C*H*CHOH), 5.47 (1H, bs, C*H*OH), 5.00 (1H, dd, *J*=10.8, 3.7 Hz, C*H*O), 2.41–2.14 (2H, m, CH_2CHO); δ_C (62.89 MHz, $CDCl_3$) 143.3, 139.4, 128.7, 126.10, 123.8, 108.8, 89.4, 61.6, 31.0.

(+)-(2*R*)-2-(Furan-3-yl)-3,6-dihydro-2H-pyran (14). A dry methylene chloride (18.9 ml) solution of the crude lactol **13** (235 mg, 1.42 mmol) and triethylsilane (247.1 mg, 2.13 mmol, 0.34 ml) was cooled under argon at −78°C. BF_3Et_2O (0.2 ml, 1.5 mmol) was added and the solution was stirred until TLC indicated the disappearance of the lactol and then quenched by addition of saturated $NaHCO_3$ (10 ml). The mixture was warmed to room temperature and extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ and brine. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated affording oil, which was purified by chromatography (SiO_2, $CHCl_3$) yielding 110.5 mg of **(+)-(2*R*)-14** (52% yield from **11**); [Found: C 71.9; H 6.8. $C_9H_{10}O_2$ requires C, 71.98; H, 6.71%]; R_f (5% $Et_2O/CHCl_3$) 0.63**;** $[\alpha]_D^{20}=+60.0$ (*c* 1.3, $CHCl_3$); ν_{max} (neat) 1640; 861 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, s, *H*-furan), 7.39 (1H, d, *J*=1.4 Hz, *H*-furan), 6.43 (1H, s, *H*-furan), 5.90–5.76 (1H, m, C*H*=C*H*), 4.57 (1H, dd, *J*=9.8, 3.6 Hz, C*H*O), 4.31 (1H, dd, *J*=15, 3.6 Hz, CH_aH_bO), 4.27 (1H, dd, *J*=15, 3.6 Hz, CH_bH_aO), 2.39–2.27 (2H, m, CH_2CHO); δ_C (100.03 MHz, $CDCl_3$) 143.1, 139.2, 126.9, 126.4, 123.9, 108.9, 68.5, 65.8, 31.4; *m/z* (EIMS) 150 (M^+).

5-Hydroxy-4-((6*R*)-2-hydroxy-3,6-dihydro-2H-pyran-6-yl)-5H-furan-2-one ((6*R*)-3). To a solution of **(6*R*)-13** (49.7 mg, 0.30 mmol) in dry CH_2Cl_2 (15.0 ml) *N*,*N*-diisopropylethylamine (0.22 ml) and polymer-bound rose bengal catalyst (7.5 mg, 15% by weight) were added. The solution was cooled to −78°C and oxygen gas was bubbled through the solution for 10 min. The solution was stirred at −78°C under an atmosphere of oxygen and irradiated with a 500 W tungsten incandescent lamp for 6 h. The reaction mixture was allowed to warm to room temperature, the photosensitizer was removed by filtration, and aqueous oxalic acid (1.3 mmol) was added and the solution was stirred for 45 min. The mixture was extracted with CH_2Cl_2/MeOH, the organic extracts were dried over Na_2SO_4 and the solvent was evaporated under vacuum. The reaction mixture was

purified by chromatography (SiO_2, $CHCl_3$/MeOH 95/5) to obtain the γ-hydroxybutenolide **(6*R*)-3** (6.5 mg, 11% yield) as a pale yellow oil. [Found: C 54.7; H 5.0. $C_9H_{10}O_5$ requires C, 54.55; H, 5.09%]; R_f (10% MeOH/ $CHCl_3$) 0.32; ν_{max} ($CHCl_3$) 3360; 1760 cm^{-1}; ^1H and ^{13}C NMR were identical to those previously described for the enantiomeric mixture of (6*R*)- and (6*S*)-**3**[6]; *m/z* (EIMS) 181 (M^+-OH^-), 135 ($M^+-OH^--HCOOH$).

5-Hydroxy-4-[(2*R*)-(3,6-dihydro-2H-pyran-2-yl)]-5H-furan-2-one ((2*R*)-4). To a solution of (+)-**(2*R*)-14** (16 mg, 0.11 mmol) in dry CH_2Cl_2 (5.4 ml) *N,N*-diisopropylethylamine (0.08 ml) and polymer-bound rose bengal catalyst (2.6 mg, 15% by weight) were added. The solution was cooled to −78°C and oxygen gas was bubbled through the solution for 10 min. The solution was stirred at −78°C under an atmosphere of oxygen and irradiated with a 500 W tungsten incandescent lamp for 6 h. The reaction mixture was allowed to warm to room temperature, the photosensitizer was removed by filtration, aqueous oxalic acid (0.50 mmol) was added and the solution was stirred for 45 min. The mixture was extracted with CH_2Cl_2, the organic extracts were dried over Na_2SO_4 and the solvent was evaporated under vacuum. The reaction mixture was purified by chromatography (SiO_2, $CHCl_3$/MeOH 95/5) to obtain the γ-hydroxybutenolide **(2*R*)-4** (9.8 mg, 49% yield) as a pale yellow oil. [Found: C 59;4; H 5.5. $C_9H_{10}O_4$ requires C, 59.34; H, 5.53%]; R_f (5% MeOH/$CHCl_3$) 0.44; ν_{max} ($CHCl_3$) 3330; 1760 cm^{-1}; the ^1H and ^{13}C NMR spectra were identical to those previously described for the enantiomer mixture of (2*R*)- and (2*S*)-**4**[6]; *m/z* (EIMS) 183 (M^++1), 182 (M^+), 164 (M^+-H_2O), 136 ($M^+-HCOOH$).

6-[(2*R*)-2-(Furan-3-yl)-2-hydroxy-ethyl]-2,2-dimethyl-1,3-dioxin-4-one (19a) and 4-[(2*R*)-2-(furan-3-yl)-2-hydroxy-ethyl]-1,5-dioxa-spiro[5.5]undec-3-en-2-one (19b). A mixture of (+)-1,1′-bi-2-naphthol (2 mmol, 579 mg), titanium tetraisopropoxide (2 mmol, 0.6 ml) and molecular sieves 3 Å (9.7 g, activated under vacuum at 200°C overnight) in dry THF (20 ml) was stirred for 1 h at room temperature under an argon atmosphere. The mixture was cooled to −78°C and the 3-furylaldehyde **6** (9.52 mmol, 0.8 ml) was added. After 20 min the diene **18a**[14] or **18b**[14,15] (11.4 mmol) was added, the mixture was stirred for 1 h at −78°C and then allowed to warm to room temperature. After stirring overnight at that temperature the mixture was poured into saturated $NaHCO_3$ solution and stirred for 30 min. The product was extracted with Et_2O, the organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude product was purified by chromatography (SiO_2, $CHCl_3$/Et_2O 95/5) affording (+)-**19a** or (+)-**19b** as a yellow oil. (+)-**19a**: yield 42%, [Found: C 60.6; H 5.8. $C_{12}H_{14}O_5$ requires C, 60.50; H, 5.92%]; R_f (5% Et_2O/$CHCl_3$) 0.21; $[\alpha]_D^{20}=+22.3$ (*c* 1.15, $CHCl_3$), ee 80%; ν_{max} (liquid film) 3424; 1718, 1630 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.39 (2H, m, *H*-furan), 6.40 (1H, s, *H*-furan), 5.30 (1H, s, C*H*CO), 4.96 (1H, dd, *J*=8.2, 5.0 Hz, C*H*OH), 2.68 (1H, dd, *J*=14.6, 8.2 Hz, CH_aH_bCHOH), 2.61 (1H, dd, *J*=14.6, 5.0 Hz, CH_bH_aCHOH), 2.45 (1H, bs, O*H*), 1.66 (3H, s, CH_3), 1.65 (3H, s, CH_3); δ_C ^{13}C NMR (100.03 MHz, $CDCl_3$) 168.2; 161.1; 143.7; 139.1; 127.7; 108.1; 106.7; 95.3; 63.7; 42.0; 25.2; 24.6. (+)-**19b**: yield 59%, [Found: C 64.8; H 6.4. $C_{15}H_{18}O_5$ requires C, 64.74; H, 6.52%]; R_f (10% Et_2O/$CHCl_3$) 0.34; $[\alpha]_D^{20}=+23.0$ (*c* 1.15, $CHCl_3$), ee 87%; ν_{max} ($CHCl_3$) 3450; 1730, 1643 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39–7.38 (2H, m, *H*-furan), 6.40 (1H, s, *H*-furan), 5.25 (1H, s, C*H*CO), 4.96 (1H, dd, *J*=7.4, 5.2 Hz, C*H*OH), 2.70– 2.61 (2H, m, CH_2CHOH), 2.00–1.43 (10H, m, $(CH_2)_5$); δ_C (100.03 MHz, $CDCl_3$) 167.6, 160.9, 143.8, 139.2, 127.6, 108.1, 107.4, 95.6, 64.0; 42.1, 34.1, 33.4, 24.6, 22.2.

(5*R*)-5-(Furan-3-yl)-5-hydroxy-3-oxo-pentanoic acid methyl ester ((+) 7). A solution of (+) **19-b** (150 mg, 0.54 mmol) and absolute MeOH (0.15 ml) in dry toluene (1.8 ml, 0.3 M) was subjected to MW irradiation (*P*=250 W, *t*=15 min) in a kitchen oven. The solvent was removed under vacuum giving compound (+)-**(5*R*)-7** in high yield (>90%); $[\alpha]_D^{20}=+33.0$ (*c* 1.33, $CHCl_3$). ^1H and ^{13}C NMR (400 MHz, $CDCl_3$) identical to **rac-7**.

(−)-(4*S*, 6*R*)-6-(Furan-3-yl)-4-hydroxy-tetrahydro-pyran-2-one (11). A suspension of acid **9** (100 mg, 0.5 mmol), obtained according the previously procedure for rac-**7**, in toluene (5 ml, 0.1 M) was subjected to MW irradiation (*P*=300 W, *t*=45 min). The solvent was removed under vacuum and the crude product was purified by chromatography (SiO_2, $CHCl_3$/MeOH 95/5) affording (−)-**11** in 58% yield from (+)**(5*R*)-7**. ee >95%, $[\alpha]_D^{20}=-15.4$ (*c* 1.0, $CHCl_3$). For ^1H NMR and ^{13}C NMR data see (−)-**11**.

4-[(*2R*)-3,6-Dihydro-2H-pyran-2-yl]-5-acetoxy-5H-furan-2-one (15 and 16). The compounds **15** and **16** were prepared from **(2*R*)-4** by standard acetylation with Ac_2O and pyridine. After the usual work-up, the diastereomeric mixture was separated by HPLC analysis on a SW5 Spherisorb analytical column (20% AcOEt/*n*-hexane, 2 ml/min.) affording compounds **15** and **16** (ca. 3:1) as yellow oils; **(15)**: R_f (50% Et_2O/30–50° light petroleum) 0.72; δ_H (400 MHz, $CDCl_3$) 6.96 (1H, s, C*H*OAc), 6.18–6.17 (1H, m, C*H*CO), 5.88–5.79 (2H, m, C*H*=C*H*), 4.41 (1H, ddd, *J*=8.5, 2.8, 1.4 Hz, C*H*O), 4.31–4.29 (2H, m, CH_2O), 2.34–2.15 (2H, m, CH_2CHO), 2.17 (3H, s, CH_3CO); δ_C (100.03 MHz, $CDCl_3$) 168.9, 166.1, 160.5, 126.5, 122.5, 118.1, 92.2, 69.3, 65.9, 29.4, 20.7. (16): δ_H (400 MHz, $CDCl_3$) 7.06 (1H, s, C*H*OAc), 6.11–6.10 (1H, m, C*H*CO), 5.89–5.78 (2H, m, C*H*=C*H*), 4.38 (1H, ddd, *J*=7.4, 3.2, 1.2 Hz, C*H*O), 4.25–4.24 (2H, m, CH_2O), 2.37–2.32 (2H, m, CH_2CHO), 2.17 (3H, s, CH_3CO); δ_C (100.03 MHz, $CDCl_3$) 168.8, 166.2, 160.3, 126.4, 122.4, 119.0, 92.8, 68.3, 65.9, 28.8, 20.6; *m/z* (EIMS) 164 (M^+-CH_3COOH).

5-Acetoxy-4-[(*6R*)-2-hydroxy-3,6-dihydro-2H-pyran-6-yl]-5H-furan-2-one (17). Acetylation of **(6*R*)-3** gave a complex mixture of products. The mixture was separated by HPLC on a Spherisorb ODS2 analytical column (acetonitrile, 2 ml/min.) to yield **17**; (17): R_f (50% Et_2O/30–50° light petroleum) 0.51; δ_H (400 MHz, $CDCl_3$) 6.96 (1H, s, C*H*OAc, 5-membered ring), 6.20–6.07 (2H, m, C*H*CO and CH_2CH=CH), 5.88–5.85 (1H, m, CH_2CH=C*H*), 5.41 (1H, bs, C*H*OH), 4.79–4.74 (1H, m, C*H*O, 6-membered ring), 2.31–2.15 (2H, m, CH_2CH=CH), 2.13 (3H, s, CH_3CO); δ_C (100.03 MHz, $CDCl_3$) 168;7, 165.2, 160.3, 127.5, 125.5, 118.4, 94.2, 91.8, 63.6, 28.8, 20.6; *m/z* (EIMS) 164 (M^+-CH_3COOH).

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17. This value represents a correction of $[\alpha]_D$ reported for compounds (+)-**12** and (−)-**12** in Ref. 7.