Pergamon

Tetrahedron 57 (2001) 9597–9605

TETRAHEDRON

# Stereoselective syntheses of *syn* 5-[1-hydroxy-2-(2-bromo-phenyl)-ethyl]-5-methyl-5*H*-furan-2-one and *syn* 5-[1-hydroxy-2-(2-methoxy-phenyl)-ethyl]-5-methyl-5*H*-furan-2-one

Elena Redero, Celso Sandoval and Francisco Bermejo*

*Departamento de Química Orgánica, Facultad de Químicas, Universidad de Salamanca, Pza de la Merced s.n., 37008 Salamanca, Spain*

Received 13 July 2001; revised 6 September 2001; accepted 5 October 2001

**Abstract**—The aldol condensation of 2-(*tert*-butyldimethylsilyloxy)-5-methyl-furan **4** with several phenylacetaldehydes led stereoselectively to the *syn* or the *anti* aldols under fluoride- or Lewis-acid-promoted conditions. However low yields are obtained due to the formation of the double condensation products or aldols at C-3 site. An alternative six-step synthetic sequence was developed to access the target molecules starting from 2-bromo-phenyl acetaldehyde **20** and 2-methoxy-phenyl acetaldehyde **21**. Structural assessment of the aldol products was achieved by stereospecific transformations and $^1$H NMR nOe experiments. 

## 1. Introduction

Silyloxy furans are ambident carbon nucleophiles with which many densely functionalized molecules have been synthesized. Aldol-type addition of 2-(trimethylsilyloxy)-furan (TMSOF) **1** and 2-(*tert*-butyldimethylsilyloxy)furan (TBSOF) **3** to different acceptors is essential for the assembly of carbon chains with adjacent oxygen functionalities and has been reviewed extensively.[1–6] In fact, the Lewis acid-promoted nucleophilic reactivity of silyloxy furans is restricted to the C-5 site and many contributions to this field have been based on this particular type of chemical behavior.

In contrast to this reactivity, however, 5-methyl-2-trimethylsiloxy-furan **2** undergoes a competitive reaction at C-3 when reacted with *ortho*-carboxylic esters. Under Lewis acid catalysis, the reaction takes place mainly at the C-3 site and the reaction product at C-5 has only been detected as a minor product. This has been explained considering the steric repulsion between the methyl group at C-5 and the electrophile.[7] However, to our knowledge there is no complete study on the condensations of either **2** or **4** with aldehydes that offers a full account of the issues of the regio- and stereoselectivity of the aldol process.

As a part of a project aiming to synthesize eleuthoside analogs[8] we were interested in preparing *syn* 5-(1-hydroxy-2-phenyl-ethyl)-5-methyl-dihydro-furan-2-ones of the type **5**, valuable intermediates in our synthetic strategy. We therefore decided to explore the synthetic potential of

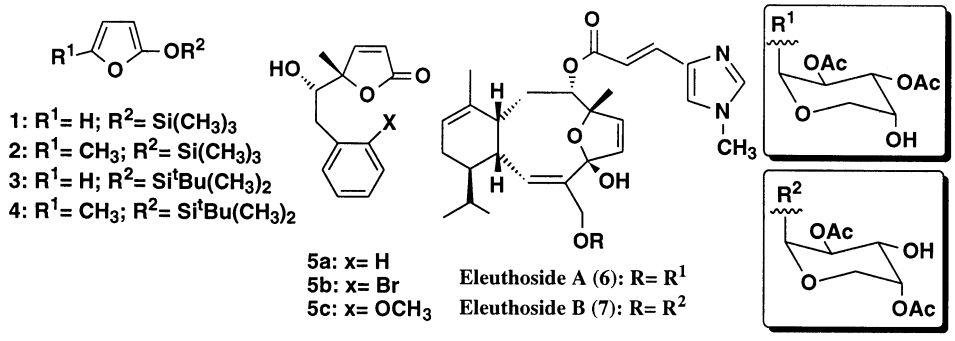
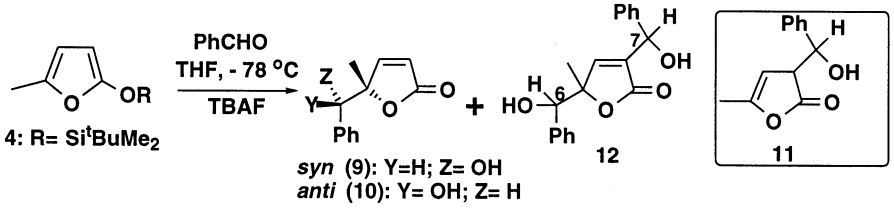



**Figure 1.**

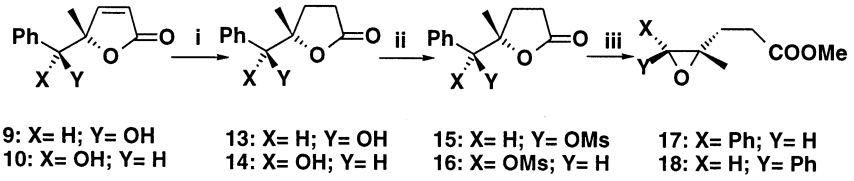
*Keywords*: aldol reactions; furanones; stereoselection; stereospecifity.

* Corresponding author. Tel.: +34-923-294481; fax: +34-923-294574; e-mail: fcobmjo@gugu.usal.es

0040–4020/01/$ - see front matter 
PII: S0040-4020(01)00975-9




**Scheme 1.**




**Scheme 2.** (i) $H_2$, Pd/C (5%), EtOH, rt; (ii) MsCl, pyr, DMAP, $CH_2Cl_2$, rt; (iii) NaMeO, MeOH, rt.

the aldol condensation of silyloxyfuran **4** with several phenyl-acetaldehydes (Fig. 1).

## 2. Results and discussion

We first studied the fluoride-promoted aldol condensation between the silyloxy furan **4** with benzaldehyde **8** at −78°C (Scheme 1). Under these conditions, the double-condensation product **12** was isolated with 65% yield. We assumed that the formation of **12** occurred through iterative condensation induced by fluoride basic catalysis after the aldol product at the C-3 site **11** had been formed. However, condensation at the C-5 site followed the normal behavior of silyloxy furans[9,10] since it took place stereoselectively (**9**–**10**=2:98) and the *anti* aldol **10** was isolated by flash chromatography with 25% yield.

Under Lewis acid promotion ($SnCl_4$, $TiCl_4$ and $F_3B{\cdot}Et_2O$) at −78°C, the reaction led mainly to the aldol product at the C-3 site **11** as a mixture of diastereoisomers; these were isolated by flash chromatography with 49, 45 and 51% yields, respectively. Nevertheless, the formation of the *syn* aldol **9** took place at the C-5 site with excellent steroselectivity (**9**–**10**>98:2), but again with rather modest yields (15, 16 and 16%, respectively). No trace of the double condensation product **12** was detected by $^1$H NMR when the reaction was run under these conditions.

Structural assessment of the aldols **9** and **10** required further synthetic effort since analysis of the $^1$H NMR spectra lacked the information provided by the coupling of the proton geminal to the hydroxy function due to the presence of the methyl group at the butenolide moiety.

The aldol products **9** and **10** were stereospecifically transformed into epoxides **17** and **18**, with 70 and 65% overall yields, respectively, by application of a three-step synthetic sequence (catalytic hydrogenation, mesylation and methanolysis followed by mesylate displacement) as depicted in Scheme 2.[11]

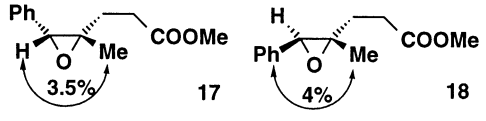



**Figure 2.** Some nOe difference increments observed for **17** and **18**.

Structural assignments of epoxides **17** and **18** are based on $^1$H NMR nOe studies, whose results are represented by double arrows in Fig. 2. Thus, for **17**, there is a sizeable nOe effect (3.5%) at the methyl group ($\delta$: 1.45 ppm) upon irradiation at the proton in *cis*-position ($\delta$: 3.89 ppm). The configuration of the epoxide **18** was confirmed by a nOe experiment, which revealed a positive effect (4%) between the methyl ($\delta$: 1.04 ppm) and the phenyl group ($\delta$: 7.30 ppm).

Since the transformation of butenolides **9** and **10** into epoxides **17** and **18** were, respectively, achieved through stereospecific reactions we proposed the *syn* and *anti* relative configurations for **9** and **10**, respectively. The results of the aldol condensations between **4** and benzaldehydes **19**–**21** are shown in Table 1.

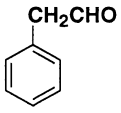
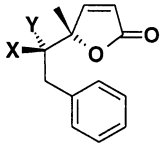
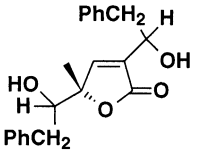
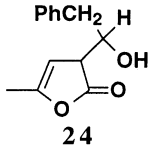
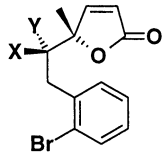
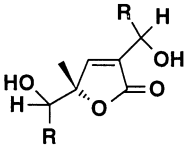
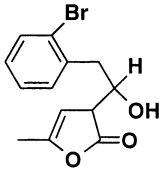
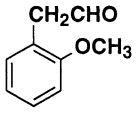
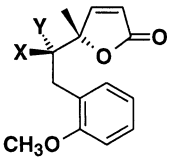
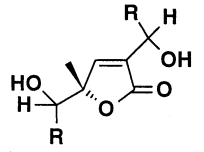
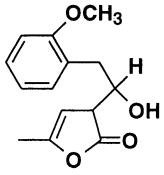
Under fluoride promotion, the main products of the aldol condensation at −78°C proved to be the double-condensation products at the C-3 and C-5 sites **25** (45%), **29** (47%) and **33** (45%). However, condensation at C-5 took place stereoselectively (*anti*–*syn*≥97:3) although with rather modest yields (15–20%).

Under Lewis acid promotion ($SnCl_4$, $TiCl_4$ and $BF_3{\cdot}Et_2O$) the condensation led mainly to the aldols at the C-3 site as mixtures of diastereoisomers **24**, **28** and **32** with yields ranging from 35 to 60%. Nevertheless, the condensation at the C-5 site took place with excellent stereoselectivity (*syn*–*anti*≥98:2) although again with low yields (ranging from 15 to 20%).

Alternatively, the synthesis of *syn* aldols **26** and **30** was achieved by application of stereocontrolled six-step sequences to the *ortho*-substituted benzaldehydes **20** and **21**, respectively, with quite acceptable overall yields (32 and 35%) (Scheme 3).[12]

Since all the transformations are stereospecific, this alternative synthetic route allowed us to assign the relative stereochemistry of the *syn* aldols **26** and **30** unequivocally.

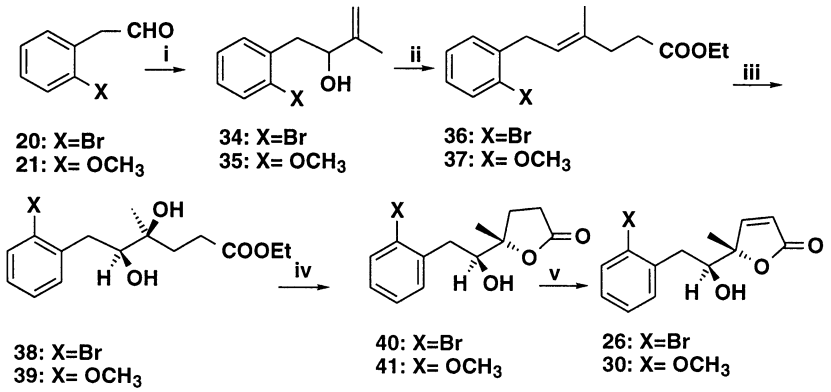
**Table 1.** Aldol condensations of silyloxyfuran **4** with aldehydes **19–21**

| Entry | Aldehyde | Fluoride-promoted condensation | | Lewis acid promotion |
|---|---|---|---|---|
| | | Aldol at C-5 (yield); **a/b** ratio (by $^1$H NMR) | Aldol at C-3 and C-5 (yield) | Aldols at C-3 and C-5 (yields) |
| 1 |  (**19**) |  ***syn*** **22: X=H; Y= OH** ***anti*** **23: X= OH; Y= H** (18%) **22 : 23**= 3:97 |  **25** (45%) |  **24** A: **24** (47); **22** (15.0); **23** (0.2) B: **24** (35); **22** (16.5); **23** (0.3) C: **24** (50); **22** (17.6); **23** (0.3) |
| 2 |  (**20**) |  ***syn*** **26: X=H; Y= OH** ***anti*** **27: X= OH; Y= H** (15%) **26 : 27**= 2: 98 |  **29:** R= *o*-BrPh (47%) |  **28** A: **28** (45); **26** (16.7); **27** (0.3) B: **28** (38); **26** (18.0); **27** (0.2) C: **28** (47); **26** (19.6); **27** (0.3) |
| 3 |  (**21**) |  ***syn*** **30: X=H; Y= OH** ***anti*** **31: X= OH; Y= H** (20%) **30 : 31**= 2:98 |  **33**: R= *o*-$CH_3$OPh (45%) |  **32** A: **32** (47); **30** (18.0); **23** (0.4) B: **32** (40); **30** (18.0); **23** (0.2) C: **32** (60); **30** (19.6); **23** (0.4) |

Fluoride-promoted reactions were run in THF by dropwise addition of the silyloxyfuran **4** (1.1 equiv.) to the solution of the aldehyde (1 equiv.) in THF at −78°C followed by addition of $Bu_4NF$ (1.1 equiv.). The reaction mixture was stirred for 15 h at that temperature and quenched by addition of aq. $NH_4Cl$. The standard work-up procedure was followed by flash chromatography on silica gel. Lewis acid-promoted reactions: to a solution of the silyloxyfuran **4** (1 equiv.) and the aldehyde (1 equiv.) in dry dichloromethane at −78°C, 1 equiv. of the Lewis acid (A: $SnCl_4$; B: $TiCl_4$; C: $BF_3{\cdot}Et_2O$) was added and the reaction mixture was stirred for 6 h at that temperature under an argon atmosphere. The reaction was then quenched by addition of aq. $NaHCO_3$ and, after rt had been reached, the mixture was extracted with $CH_2Cl_2$. The organic extracts were combined, washed with water, dried ($Na_2SO_4$), and concentrated in vacuo. The crude reaction product was fractionated by flash chromatography on silica gel.

## 3. Conclusion

In conclusion, the fluoride-promoted aldol condensation between silyloxy furan **4** and the carboxaldehydes **19**, **20** and **21** led to the formation of the double-condensation products **25**, **29** and **33**, respectively, as the major products. However, condensation at the C-5 site took place stereoselectively and allowed us to isolate the *anti* aldols **23**, **27** and **31** with 18, 15 and 20% yields, respectively. Under Lewis acid promotion, the *syn* aldols **22**, **26** and **30** were




**Scheme 3.** (i) $CH_2{=}C(CH_3)MgBr$, THF, −78°C; (ii) $CH_3C(OEt)_3$, 2,4-DNP, 145°C; (iii) $OsO_4$, NMO, acetone, $H_2O$=8:1; rt; (iv) PPTS, THF, reflux; (v) (a) LDA, THF, −78°C, HMPA, $Ph_2Se_2$; (b) $H_2O_2$, AcOH, THF, rt, 1 h.

obtained with excellent stereoselectivity (*syn*–*anti*≥98:2) but rather modest yields (15–20%). An alternative synthetic route was opened to prepare the *syn* aldols **26** and **30** from phenylacetaldehydes **20** and **21** by application of a six-step synthetic sequence with 32 and 35% overall yields, respectively.

## 4. Experimental

All reactions were carried out using dry solvents under a nitrogen or argon atmosphere. All the solvents and chemicals were commercially available and, unless otherwise indicated, were used as received. Tetrahydrofuran, diethyl ether and toluene were dried over sodium benzophenone ketyl. Methylene chloride was dried over $CaH_2$ under argon and kept over molecular sieves. $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker WP-200-SY spectrometer operating at 200 and 50.3 MHz, respectively; chemical shifts are reported in ppm ($\delta$), and the coupling constants are indicated in Hz. $^1H$ NMR spectra were referenced to either the residual proton in the deuterated solvent or TMS. $^{13}C$ NMR spectra are referenced to the chemical shifts of the deuterated solvent. IR spectra were determined on a Bomen MB-100 IR-FT spectrophotometer as indicated in each case; the frequencies in the IR spectra are indicated in $cm^{-1}$. Microanalyses were performed by Dr Benigno Macías–Sánchez (Department of Inorganic Chemistry, University of Salamanca) on a Perkin–Elmer 240-B analyzer. Unless otherwise indicated, preparative chromatography was performed with silica gel (40–63 mm) using the technique of flash chromatography.[13]

*Materials*: benzaldehyde and phenylacetaldehyde were purchased from Aldrich and vacuum-distilled prior to use. 2-bromophenyl-acetaldehyde **20** and 2-methoxyphenyl-acetaldehyde **21** were obtained from 2-bromophenethyl alcohol and 2-allylphenol, respectively. 2-(*tert*-Butyldimethylsiloxy)-5-methylfuran (**4**) was obtained from α-angelicalactone following a known procedure.[14]

### 4.1. Fluoride-promoted aldol condensation of silyloxyfuran (4) with aldehydes. General procedure

A 0.5 M solution of 2-(*tert*-butyldimethylsiloxy)-5-methylfuran (**4**) (1.1 equiv.) in freshly distilled THF was added dropwise to a 0.5 M solution of the aldehyde in dry THF at −78°C under argon atmosphere. Then, tetrabutyl ammonium fluoride (1.1 equiv.) was added to the reaction mixture and this was stirred overnight at that temperature. Aqueous saturated ammonium chloride was added and the reaction mixture was allowed to warm to room temperature. The reaction was extracted with ethyl acetate and the organic layers were washed with brine and dried over $Na_2SO_4$. Evaporation of the solvent at reduced pressure afforded a crude product that was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (7:3) led to the isolation of the following products.

### 4.2. Reaction with benzaldehyde

**4.2.1. (5*S**,1′*S**)-5-(1′-Hydroxy-phenylmethyl)-5-methyl-5*H*-furan-2-one (9).** 0.5%; mp 115°C (di-isopropyl ether); IR (neat) $\nu$ 3479, 2360, 1732, 1109, 965, 729; $^1H$ NMR ($CDCl_3$): $\delta$ 1.47 (s, 3H); 4.75 (s, 1H); 6.02 (d, $J$=5.6 Hz, 1H); 7.31 (d, $J$=5.6 Hz, 1H); 7.34 (m, 5H); 7.31 (d, $J$=5.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 19.46 ($CH_3$); 77.80 (CH); 90.82 (C); 121.40 (CH); 128.13 (CH); 158.47 (CH); 172.16 (C); EIMS *m*/*z* (relative intensity) 205 (M+1, 26); 154 (50); 107 (100); 91 (19); 69 (24). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58, H, 5.92; found: C, 70.49, H, 5.87.

**4.2.2. (5*S**,1′*R**)-5-(1′-Hydroxy-phenylmethyl)-5-methyl-5*H*-furan-2-one (10).** 24.5%; mp 132–134°C (di-isopropyl ether); IR (neat) $\nu$ 3405, 1727, 1059, 829, 702; $^1H$ NMR ($CD_3OD$): $\delta$ 1.39 (s, 3H); 4.86 (s, 1H); 5.98 (d, $J$=5.6 Hz, 1H); 7.32 (m, 5H); 7.64 (d, $J$=5.6 Hz, 1H); $^{13}C$ NMR ($CD_3OD$) $\delta$ 20.48 ($CH_3$); 78.08 (CH); 92.75 (C); 122.11 (CH); 128.97 (CH); 140.87 (C); 161.19 (CH); 174.98 (C); EIMS *m*/*z* (relative intensity): 205 (M+1, 33); 154 (39); 137 (37); 107 (100); 99 (39); 89 (13); 77 (21). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58, H, 5.92; found: C, 70.41, H, 5.83.

**4.2.3. 3,5-Bis-(hydroxy-phenylmethyl)-5-methyl-5*H*-furan-2-one (12).** 65%; mp 148°C (di-isopropyl ether); IR (neat) $\nu$ 3346, 1738, 1454, 1050, 715; $^1H$ NMR ($CDCl_3$): $\delta$ 1.32 (s, 3H); 4.83 (s, 1H); 5.55 (s, 1H); 7.05 (s, 1H); 7.34 (m, 10H); $^{13}C$ NMR ($CD_3OD$): $\delta$ 20.57 ($CH_3$); 69.90 (CH); 78.23 (CH); 90.55 (C); 128.88 (CH); 138.42 (C); 140.89 (C); 142.46 (C); 153.21 (CH); 173.08 (C); EIMS *m*/*z* (relative intensity): 311 (M+1, 8); 203 (2); 187 (100); 154 (87); 136 (73); 107 (58); 89 (26); 77 (36). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53, H, 5.85; found: C, 73.48, H, 5.76.

### 4.3. Reaction with phenylacetaldehyde

**4.3.1. (5*S**,1′*S**)-5-(1′-Hydroxy-2′-phenyl-ethyl)-5-methyl-5*H*-furan-2-one (22).** 0.5%; IR (neat) $\nu$ 3350, 1750, 1472, 835; $^1H$ NMR ($CDCl_3$): $\delta$ 1.38 (s, 3H); 2.85 (dd, 1H, $J$=12, 11 Hz); 3.05 (dd, 1H, $J$=12, 3 Hz); 3.85 (dd, 1H, $J$=11, 3 Hz); 6.03 (d, 1H, $J$=6 Hz); 7.20 (m, 5H); 7.43 (d, 1H, $J$=6 Hz); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.80 ($CH_3$); 38.50 ($CH_2$); 77.23 (CH); 88.70 (C); 120.88 (CH); 126.70 (CH); 128.70 (CH); 128.28 (CH); 128.30 (CH); 128.32 (CH); 139.40 (C); 158.12 (CH); 171.80 (C); EIMS *m*/*z* (relative intensity): 219 (M+1, 5); 153 (25); 136 (10); 98 (100); 77 (50). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47; found: C, 71.47, H, 6.39.

**4.3.2. (5*S*′*,1′*R**)-5-(1′-Hydroxy-2′-phenyl-ethyl)-5-methyl-5*H*-furan-2-one (23).** 17.5%; IR (neat) $\nu$ 3350, 1750, 1472, 835; $^1H$ NMR ($CDCl_3$): $\delta$ 1.53 (s, 3H); 2.63 (dd, 1H, $J$=10, 12 Hz); 3.01 (dd, 1H, $J$=12, 3 Hz); 3.74 (dd, 1H, $J$=10, 3 Hz); 6.05 (d, 1H, $J$=6 Hz); 7.23 (m, 5H); 7.50 (d, 1H, $J$=6 Hz); $^{13}C$ NMR ($CDCl_3$): $\delta$ 19.03 ($CH_3$); 38.65 ($CH_2$); 76.39 (CH); 90.17 (C); 121.15 (CH); 126.90 (CH); 128.73 (CH); 128.75 (CH); 129.30 (CH); 129.32 (CH); 137.51 (C); 159.10 (CH); 172.28 (C) ppm; EIMS *m*/*z* (relative intensity): 219 (M+1, 5); 153 (25); 136 (10); 121 (25); 98 (100); 77 (50); 65 (15%). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47; found: C, 71.46, H, 6.37.

**4.3.3. 3,5-Bis-(1′-hydroxy-2-phenyl-ethyl)-5-methyl-5*H*-furan-2-one (25).** 45%; IR (neat) $\nu$ 3434, 3030, 1750, 1497, 1456, 1262, 1080; $^1H$ NMR ($CDCl_3$): $\delta$ 1.38 (s, 3H); 2.48 (dd, 1H, $J$=10, 12 Hz); 2.85 (m, 1H); 3.12 (dd,

1H, $J$=12, 4 Hz); 3.35 (m, 2H); 3.68 (dd, 1H, $J$=10, 4 Hz); 4.65 (m, 1H); 7.14 (s, 1H); 7.22 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 19.24 ($CH_3$); 38.41 ($CH_2$); 41.71 ($CH_2$); 67.53 (CH); 76.41 (CH); 88.75 (C); 126.60 (CH); 126.61 (CH); 128.26 (CH); 128.27 (CH); 128.44 (CH); 128.45 (CH); 129.20 (CH); 129.21 (CH); 129.60 (CH); 129.62 (CH); 135.96 (C); 136.94 (C); 137.83 (C); 151.92 (CH); 171.58 (C); EIMS *m/z* (relative intensity): 338 (M, 5); 246 (25); 200 (50); 157 (22); 127 (72); 91 (100); 77 (22). Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54, H, 6.55; found: C, 74.46, H, 6.49.

### 4.4. Reaction with 2-bromo-phenylacetaldehyde

**4.4.1. (5*S*′*,1′*S**)-5-[2′-(2-Bromophenyl)-1′-hydroxy-ethyl]-5-methyl-5*H*-furan-2-one (26).** 0.3%; IR (neat) $\nu$ 3425, 2950, 1750, 1470, 1442, 1260, 1110, 1080, 1030, 740; $^1$H NMR ($CDCl_3$): $\delta$ 1.59 (s, 3H); 2.75 (m, 1H); 3.22 (m, 1H); 3.12 (m, 1H); 3.95 (m, 1H); 6.12 (d, 1H, $J$=6 Hz); 7.20 (m, 4H); 7.52 (d, 1H, $J$=6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.62 ($CH_3$); 41.85 ($CH_2$); 79.70 (CH); 90.50 (C); 120.93 (CH); 127.38 (CH); 127.51 (CH); 126.61 (CH); 128.26 (CH); 137.06 (C); 158.20 (C); 173.22 (C); EIMS *m/z* (relative intensity): 298 (M+1, 5); 201 (25); 169 (20); 149 (25); 98 (100); 91 (50); 77 (100). Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55, H, 4.41; found: C, 52.46, H, 4.32.

**4.4.2. (5*S*′*,1′*R**)-5-[2′-(2-Bromophenyl)-1′-hydroxy-ethyl]-5-methyl-5*H*-furan-2-one (27).** 14.7%; IR (neat) $\nu$ 3420, 2950, 1751, 1474, 1443, 1265, 1109, 1080, 1028, 822, 739; $^1$H NMR ($CDCl_3$): $\delta$ 1.59 (s, 3H); 2.75 (dd, 1H, $J$=10, 12 Hz); 3.17 (dd, 1H, $J$=12, 3 Hz); 3.90 (dd, 1H, $J$=10, 3 Hz); 6.12 (d, 1H, $J$=6 Hz); 7.20 (m, 3H); 7.52 (d, 2H, $J$=6 Hz) ppm; $^{13}$C NMR ($CDCl_3$): $\delta$ 19.73 ($CH_3$); 38.66 ($CH_2$); 74.56 (CH); 90.47 (C); 121.61 (CH); 127.53 (CH); 128.58 (CH); 131.98 (CH); 132.96 (CH); 137.06 (C); 158.20 (CH); 172.10 (C); EIMS *m/z* (relative intensity): 298 (M+1, 5); 199 (10); 171 (16); 153 (32); 98 (70); 77 (100). Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55, H, 4.41; found: C, 52.48, H, 4.37.

**4.4.3. 3,5-Bis-[2′-(2-bromo-phenyl)-1′-hydroxy-ethyl]-5-methyl-5*H*-furan-2-one (29).** 47%; IR (neat) $\nu$ 3441, 1751, 1474, 1441, 1265, 1028, 739; $^1$H NMR ($CDCl_3$): $\delta$ 1.57 (s, 3H); 2.55 (dd, 1H, $J$=12, 10 Hz); 3.10 (dd, 1H, $J$=12, 3 Hz); 3.28 (m, 1H); 3.90 (dd, 1H, $J$=10, 3 Hz); 4.90 (m, 1H); 7.20 (m, 6H); 7.23 (s, 1H); 7.54 (d, 2H, $J$=7 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 19.58 ($CH_3$); 38.58 ($CH_2$); 41.67 (CH); 66.33 (CH); 74.44 (CH); 89.03 (C); 124.47 (C); 125.00 (C); 127.23 (CH); 127.34 (CH); 128.37 (CH); 128.39 (CH); 132.00 (CH); 132.03 (CH); 132.72 (CH); 132.75 (CH); 136.40 (C); 136.46 (C); 137.12 (C); 151.18 (CH); 171.50 (C); EIMS *m/z* (relative intensity): 497 (M+1, 10); 324 (10); 279 (8); 199 (30); 171 (50); 127 (100). Anal. Calcd for $C_{21}H_{20}Br_2O_4$: C, 50.83, H, 4.06; found: C, 50.76, H, 3.98.

### 4.5. Reaction with 2-methoxy-phenylacetaldehyde

**4.5.1. (5*S**,1′*S**)-5-[1′-Hydroxy-2′-(2-methoxy-phenyl)-ethyl]-5-methyl-5*H*-furan-2-one (30).** 0.5%; IR (neat) $\nu$ 3470, 2935, 1750, 1028, 740; $^1$H NMR ($CDCl_3$): $\delta$ 1.57 (s, 3H); 2.85 (m, 1H); 3.05 (m, 1H); 3.85 (m, 1H); 3.86 (s, 3H); 6.10 (d, 1H, $J$=6 Hz); 7.20 (m, 4H); 7.58 (d, 1H, $J$=6 Hz); $^{13}$C NMR ($CD_3OD$): $\delta$ 18.78 ($CH_3$); 34.20 ($CH_2$); 55.65 ($CH_3$); 77.20 (CH); 90.50 (C); 110.80 (CH); 121.36 (CH); 121.50 (CH); 126.60 (C); 128.60 (CH); 135.25 (CH); 157.70 (C); 159.80 (CH); 173.22 (C); EIMS *m/z* (relative intensity): 249 (M+1, 5); 150 (100); 120 (50) 90 (45). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50; found: C, 67.66, H, 6.42.

**4.5.2. (5*S**,1′*R**)-5-[1′-Hydroxy-2′-(2-methoxy-phenyl)-ethyl]-5-methyl-5*H*-furan-2-one (31).** 19.5%; IR (neat) $\nu$ 3470, 3150, 1750, 1600, 1495, 1240, 945, 754; $^1$H NMR ($CDCl_3$): $\delta$ 1.55 (s, 3H); 2.90 (m, 2H); 3.75 (m, 1H); 3.84 (s, 3H); 6.06 (d, 1H, $J$=6 Hz); 7.10 (m, 4H); 7.54 (d, 1H, $J$=6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.88 ($CH_3$); 33.86 ($CH_2$); 55.67 ($CH_3$); 76.61 (CH); 90.66 (C); 110.73 (CH); 121.12 (CH); 121.39 (CH); 126.41 (C); 128.55 (CH); 131.60 (CH); 157.45 (C); 159.80 (CH); 172.81 (C); EIMS *m/z* (relative intensity): 249 (M+1, 15); 150 (100); 120 (60); 98 (35); 90 (40). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50; found: C, 67.68, H, 6.40.

**4.5.3. 3,5-Bis-[1′-hydroxy-2′-(methoxy-phenyl)-ethyl]-5-methyl-5*H*-furan-2-one (33).** 45%; IR (neat) $\nu$ 3440, 1750, 1474, 1440, 1265, 1028; $^1$H NMR ($CDCl_3$): $\delta$ 1.60 (s, 3H); 2.60 (m, 1H); 3.15 (m, 1H); 3.30 (m, 2H); 3.95 (m, 1H); 4.95 (m, 1H); 7.20 (m, 8H); 7.25 (s, 1H); $^{13}$C NMR ($CD_3OD$): $\delta$ 19.56 ($CH_3$); 38.56 ($CH_2$); 41.68 (CH); 55.60 ($CH_3$); 66.35 (CH); 74.50 (CH); 89.00 (C); 125.40 (C); 126.50 (C); 127.34 (CH); 128.37 (CH); 128.42 (CH); 128.60 (CH); 132.00 (CH); 132.03 (CH); 132.72 (CH); 132.75 (CH); 151.20 (CH); 157.35 (C); 157.60 (C); 171.50 (C). Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33, H, 6.58; found: C, 69.26, H, 6.47.

### 4.6. Lewis acid-promoted aldol condensation of silyloxyfuran (4) with aldehydes

A 0.5 M solution of the aldehyde (1 equiv.) and 2-(*tert*-butyldimethylsilyloxy)-5-methyl furan **4** (1 equiv.) in dry $CH_2Cl_2$ was cooled at −78°C under argon. Then, the Lewis acid (1 equiv.) was added dropwise and the reaction mixture was stirred for 6 h at the same temperature. The reaction was then quenched by the addition of an aq. $NaHCO_3$ solution and after ambient temperature had been reached, the mixture was extracted with $CH_2Cl_2$ and the organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was flash-chromatographed on silica gel. Elution with hexane–ethyl acetate (7:3) led to the isolation of the following products.

### 4.7. Reaction with benzaldehyde

**4.7.1. 3-(1′-Hydroxy-phenylmethyl)-5-methyl-3*H*-furan-2-one (11).** 51% as a mixture of diastereoisomers. The following spectroscopic properties for the major isomer are given: IR (neat) $\nu$ 3479, 1735, 1112, 968, 726; $^1$H NMR ($CDCl_3$): $\delta$ 1.98 (s, 3H); 3.50 (m, 1H); 4.94 (m, 1H); 5.25 (m, 1H); 7.35 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.40 ($CH_3$); 54.06 (CH); 72.36 (CH); 103.21 (CH); 127.30 (CH); 127.35 (CH); 127.40 (CH); 128.70 (CH); 128.72 (CH); 140.90 (C); 142.95 (C); 168.0 (C). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58, H, 5.92; found: C, 70.49, H, 5.87. (**9**): (15.7%) and (**10**): (0.3%).

### 4.8. Reaction with phenylacetaldehyde

**4.8.1. 3-(1′-Hydroxy-2′-phenyl-ethyl)-5-methyl-3*H*-furan-2-one (24).** 47% as a mixture of diastereoisomers. The following spectroscopic properties for the major isomer are given: IR (neat) $\nu$ 3480, 1735, 1110, 965, 725; $^1$H NMR ($CDCl_3$): $\delta$ 1.98 (s, 3H); 2.72 (m, 2H); 3.08 (m, 1H); 4.28 (m, 1H); 5.25 (m, 1H); 7.35 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.40 ($CH_3$); 40.68 ($CH_2$); 51.70 (CH); 72.00 (CH); 103.85 (CH); 125.80 (CH); 128.30 (CH); 128.35 (CH); 128.60 (CH); 128.65 (CH); 138.85 (C); 142.25 (C); 168.20 (C). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47; found: C, 71.47, H, 6.39. (**22**) (15%) and (**23**) (0.2%).

### 4.9. Reaction with 2-bromo-phenylacetaldehyde

**4.9.1. 3-[2′-(2-Bromo-phenyl)-1′-hydroxy-ethyl]-5-methyl-3*H*-furan-2-one (28).** 45% as a mixture of diastereoisomers. The following spectroscopic properties for the major isomer are given: IR (neat) $\nu$ 3475, 1738, 1115, 950, 725; $^1$H NMR ($CDCl_3$): $\delta$ 1.97 (s, 3H); 2.78 (m, 2H); 3.15 (m, 1H); 4.30 (m, 1H); 5.05 (m, 1H); 7.30 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.35 ($CH_3$); 32.85 ($CH_2$); 51.45 (CH); 70.50 (CH); 103.85 (CH); 122.85 (CH); 127.60 (CH); 128.00 (CH); 130.50 (CH); 132.00 (CH); 142.10 (C); 142.30 (C); 168.10 (C). Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55, H, 4.41; found: C, 52.49, H, 4.37. (**26**) (16.7%) and (**27**) (0.3%).

### 4.10. Reaction with 2-methoxy-phenylacetaldehyde

**4.10.1. 3-[1′-Hydroxy-2-(2-methoxy-phenyl)-ethyl]-5-methyl-3*H*-furan-2-one (32).** 47% as a mixture of diastereoisomers. The following spectroscopic properties for the major isomer are given: IR (neat) $\nu$ 3470, 1740, 1112, 945; $^1$H NMR ($CDCl_3$): $\delta$ 1.98 (s, 3H); 2.69 (m, 2H); 3.10 (m, 1H); 3.75 (s, $CH_3$); 4.28 (m, 1H); 5.03 (m, 1H); 6.98 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.39 ($CH_3$); 30.78 ($CH_2$); 51.48 (CH); 56.3 ($CH_3$); 71.50 (CH); 103.90 (CH); 114.20 (CH); 120.90 (CH); 124.38 (CH); 126.75 (CH); 129.30 (CH); 142.28 (C); 162.00 (C); 168.08 (C). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50; found: C, 67.69, H, 6.42. (**30**) (18%) and (**31**) (0.4%).

### 4.11. (5*S**,1′*S**)-5-(1′-Hydroxy-phenylmethyl)-5-methyl-dihydro-5*H*-furan-2-one (13)

A suspension of **9** (163 mg, 0.80 mmol) and 60 mg of Palladium on charcoal (5%) in 10 ml of EtOH was stirred for 5 h at room temperature. Then, the catalyst was filtered and the solvent evaporated to give 140 mg of a crude which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (8:2) and evaporation of the solvent at reduced pressure afforded **13** (125 mg, 76%). IR (neat) $\nu$ 3460, 2980, 1770, 1452, 1200, 1053, 943 and 737; $^1$H NMR ($CDCl_3$): $\delta$ 1.27 (s, 3H); 1.72 (m, 2H); 2.43 (m, 2H); 4.55 (s, 1H); 7.26 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 23.53 ($CH_3$); 29.17 ($CH_2$); 30. 26 ($CH_2$); 78.93 (CH); 87.72 (C); 127.3 (CH); 127.5 (CH); 128.14 (CH) 128.3 (CH); 128.5 (CH); 138.95 (C); 177.12 (C). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89, H, 6.84; found: C, 69.79, H, 6.80. EIMS *m/z* (relative intensity): 206 (M+1, 10); 178 (15); 107 (45); 99 (100); 77 25).

### 4.12. (5*S**,1′*R**)-5-(1′-Hydroxy-phenylmethyl)-5-methyl-dihydro-5*H*-furan-2-one (14)

An analogous procedure to that followed for the preparation of **13** applied to **10** (140 mg, 0.68 mmol) afforded **14** (125 mg, 88%) IR (neat) $\nu$ 3461, 2982, 1771, 1454, 1418, 1381, 1200, 1053, 943; $^1$H NMR ($CDCl_3$): $\delta$ 1.32 (s, 3H); 1.70 (m, 2H); 2.55 (m, 2H); 4.30 (s, 1H); 7.33 (m, 5H); $^{13}$C NMR ($CD_3OD$): $\delta$ 23.54 ($CH_3$); 27.82 ($CH_2$); 29.32 ($CH_2$); 78.07 (CH); 88.61 (C); 127.27 (CH); 127.29 (CH); 127.59 (CH); 128.43 (CH); 128.45 (CH); 138.83 (C); 177.13 (C). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89, H, 6.84; found: C, 69.81, H, 6.78. EIMS *m/z* (relative intensity): 206 (M+1, 15); 178 (10); 107 (45); 99 (100); 77 (15).

### 4.13. (5*S**,1′*S**)-5-(1′-Methanesulfonyloxy-phenyl-methyl)-5-methyl-dihydro-5*H*-furan-2-one (15)

To a solution of **13** (125 mg, 0.6 mmol) and pyridine (0.6 ml, 7.2 mmol) in 10 ml of methylene chloride were successively added methanesulfonyl chloride (89.3 mg, 0.78 mmol) and dimethyl aminopyridine (11 mg). The reaction was stirred for 30 h at room temperature and was then quenched by the addition of 5 ml of water. The reaction was extracted with methylene chloride, washed with HCl (10%) and sat. $NaHCO_3$ solutions and dried over $Na_2SO_4$. Evaporation of the solvent at reduced pressure afforded a crude product which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (8:2) afforded **15** (154.4 mg, 90%) IR (neat) $\nu$ 2986, 1778, 1497, 1456, 1362, 1227, 1177, 1099, 959, 855, 735, 704; $^1$H NMR ($CDCl_3$): $\delta$ 1.29 (s, 3H); 2.06 (m, 2H); 2.54 (m, 2H); 2.64 (s, 3H); 5.37 (s, 1H); 7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$): $\delta$ 24.04 ($CH_3$); 28.71 ($CH_2$); 31.01 ($CH_2$); 39.13 ($CH_3$); 85.62 (C); 87.04 (CH); 128.31 (CH); 128.60 (CH); 128.62 (CH) 128.64 (CH); 129.56 (CH); 133.51 (C); 175.97 (C). Anal. Calcd for $C_{13}H_{16}O_5S$: C, 54.92, H, 5.67; found: C, 54.88, H, 5.59. EIMS *m/z* (relative intensity): 285 (M+1, 5); 189 (32); 154 (100); 107 (28); 91 (35); 77 (33).

### 4.14. (5*S**,1′*R**)-5-(1′-Methanesulfonyloxy-phenyl-methyl)-5-methyl-dihydro-5*H*-furan-2-one (16)

A procedure analogous to the previously described for the collection of **15** applied to **14** (212 mg, 1 mmol) afforded **16** (275 mg, 94%) IR (neat) $\nu$ 2938, 1784, 1454, 1497, 1454, 1416, 1354, 1096, 856, 802, 706; $^1$H NMR ($CDCl_3$): $\delta$ 1.42 (s, 3H); 1.95 (m, 2H); 2.58 (m, 2H); 2.83 (s, 3H); 5.47 (s, 1H); 7.40 (m, 5H); $^{13}$C NMR ($CD_3OD$): $\delta$ 24.11 ($CH_3$); 28.54 ($CH_2$); 28.96 ($CH_2$); 38.98 (CH); 85.88 (C); 86.33 (CH); 127.90 (CH); 128.52 (CH); 128.54 (CH); 128.80 (CH); 128.85 (CH); 133.90 (C); 175.58 (C). Anal. Calcd for $C_{13}H_{16}O_5S$: C, 54.92, H, 5.67; found: C, 54.85, H, 5.58. EIMS *m/z* (relative intensity): 285 (M+1, 5); 278 (2); 167 (15); 149 (35); 130 (10); 99 (100); 77 (20).

### 4.15. (4*S**,5*R**)-4,5-Epoxy-6-phenyl-4-methyl-pentanoic methyl ester (17)

Sodium methoxide (32 mg, 0.6 mmol) was added to a solution of **15** (154.4 mg, 0.5 mmol) in 10 ml of anhydrous methanol. The reaction was stirred for 6 h and the solvent was evaporated at reduced pressure to give a solid which

was subjected to column chromatography, eluting with hexane–ethyl acetate (8:2) to afford **17** (96 mg, 80%). IR (neat) $\nu$ 2955, 1738, 1497, 1456, 1192, 1071, 791, 750, 702; $^1$H NMR ($CDCl_3$): $\delta$ 1.45 (s, 3H); 1.64 (t, $J$=4 Hz, 2H); 2.32 (dt, $J$=4, 1 Hz, 2H); 3.59 (s, 3H); 3.69 (s, 1H); 7.29 (m, 5H); $^{13}$C NMR ($CD_3OD$): $\delta$ 21.78 ($CH_3$); 26.93 ($CH_2$); 29.77 ($CH_2$); 51.47 (CH); 62.55 (C); 64.95 (CH); 126.33 (CH); 126.35 (CH); 127.54 (CH); 128.10 (CH); 128.12 (CH); 135.85 (C); 173.18 (C). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89, H, 7.32; found: C, 70.78, H, 7.24. EIMS *m/z* (relative intensity): 221 (M+1, 11); 189 (15); 153 (17); 91 (100); 77 (65).

### 4.16. (4*S**,5*S**)-4,5-Epoxy-6-phenyl-4-methyl-pentanoic methyl ester (18)

An analogous procedure to that followed for the preparation of **17**, applied to **16** (275 mg, 1 mmol) afforded **18** (185 mg, 87%) IR (neat) $\nu$ 2953, 1738, 1198, 1073, 790, 750, 702, 566; $^1$H NMR ($CDCl_3$): $\delta$ 1.05 (s, 3H); 2.06 (t, $J$=7.7 Hz, 2H); 2.50 (t, $J$=7.7 Hz, 2H); 3.70 (s, 3H); 3.89 (s, 1H); 7.31 (m, 5H); $^{13}$C NMR ($CD_3OD$): $\delta$ 15.92 ($CH_3$); 29.78 ($CH_2$); 33.25 ($CH_2$); 51.71 (CH); 62.45 (C); 63.59 (CH); 126.41 (CH); 126.42 (CH); 127.50 (CH); 128.08 (CH); 128.10 (CH); 136.20 (C); 173.40 (C). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89, H, 7.32; found: C, 70.80, H, 7.26 EIMS *m/z* (relative intensity): 221 (M+1, 11); 189 (10); 147 (10); 133 (10); 114 (30); 91 (100); 77 (28).

### 4.17. 1-(2-Bromo-phenyl)-3-methyl-but-3-en-2-ol (34)

A suspension of dry cerium(III) chloride (1.8 g, 7.3 mmol) in 15 ml of dry THF was stirred for 2 h at room temperature. Then, a solution of bromobenzaldehyde **20** (1.1 g, 5.5 mmol) in 12 ml of THF was added at 0°C and the reaction mixture was stirred for 1 h. The reaction mixture was chilled at −78°C and 15 ml (7.4 mmol) of a 0.5 M solution of isopropenyl magnesium bromide in THF was added dropwise. The reaction was stirred for 1 h and then quenched by the addition of 25 ml of AcOH (10%). The reaction was extracted with ethyl ether and the organic layers were washed with NaOH (10%), brine and dried over anhydrous sodium sulfate. Evaporation of the solvent at reduced pressure afforded a crude product, which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (9:1) afforded **34** (0.72 g, 55%) IR (neat) $\nu$ 3408, 1742, 1028, 903 and 748; $^1$H NMR ($CDCl_3$): $\delta$1.85 (s, 3H); 2.81 (dd, 1H, $J$=12, 9 Hz); 3.12 (dd, 1H, $J$=12, 4 Hz); 4.39 (m, 1H); 4.87 (s, 1H); 5.00 (s, 1H); 7.2 (m, 3H); 7.56 (d, 1H, $J$=8 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.38 ($CH_3$); 42.64 ($CH_2$); 74.94 (CH); 111.34 ($CH_2$); 125.04 (C); 127.54 (CH); 128.43 (CH); 132.20 (CH); 133.11 (CH) 138.30 (C); 147.22 (C). Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79, H, 5.43; found: C, 54.68, H, 5.38. EIMS *m/z* (relative intensity): 241 (M+1, 5); 170 (70); 153 (20); 136 (10); 107 (10); 91 (55); 71 (100).

### 4.18. 1-(2-Methoxy-phenyl)-3-methyl-but-3-en-2-ol (35)

A procedure analogous to the previously described for bromobenzaldehyde (**20**) applied to 2-methoxy-phenyl-acetaldehyde (**21**) (2.4 g, 29 mmol) led to a residue (2.5 g) which was flash-chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) yielded **35** (2.2 g, 74%) as a colorless oil IR (neat) $\nu$ 3439, 2926, 1726, 1600, 1495, 1464, 1244, 1115, 1051, 1030, 899 and 752; $^1$H NMR ($CDCl_3$): $\delta$ 1.63 (s, 3H); 2.37 (s, 1H); 2.80 (dd, 1H, $J$=14, 9 Hz); 3.00 (dd, 1H, $J$=14, 4 Hz); 3.84 (s, 3H); 4.35 (dd, 1H, $J$=9, 4 Hz); 4.84 (s, 1H); 4.97 (s, 1H); 6.92 (m, 2H); 7.25 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 18.00 ($CH_3$); 37.24 ($CH_2$); 55.26 ($CH_3$); 75.54 (CH); 110.32 ($CH_2$); 110.46 (CH); 120.63 (CH); 127.03 (C); 127.74 (CH) 131.18 (CH); 147.34 (C); 157.59 (C). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13, H, 7.92; found: C, 74.08, H, 7.87. EIMS *m/z* (relative intensity): 192 (M+1, 5); 153 (10); 137 (10); 122 (10); 107 (18); 91 (52); 69 (38).

### 4.19. 6-(2-Bromo-phenyl)-4-methyl-hex-4-en-oic acid ethyl ester (36)

Into a 10 ml round-bottomed flask, equipped with thermometer, a micro-distilling head and condenser, were successively placed 1-(2-bromo-phenyl)-3-methyl-but-3-en-2-ol **34** (3.6 g, 15.2 mmol), ethyl orthoacetate (20 ml, 109 mmol) and 2,4-dinitro-phenol (50 mmol). The reaction mixture was heated to 145°C (internal value) under an argon atmosphere. After 5 h, a total of 1.75 ml (30.4 mmol) of ethanol was distilled. Then, the excess of ethyl orthoacetate was distilled under vacuum to yield a crude (3.5 g), which was fractionated by flash chromatography on silica gel. By elution with hexane–ethyl acetate (95:5) **36** (3 g, 65) was obtained as a yellow oil, IR (neat) $\nu$ 2980, 1763, 1441, 1159, 1026, 750; $^1$H NMR ($CDCl_3$): $\delta$ 1.22 (t, 3H, $J$=7 Hz); 1.73 (s, 3H); 2.40 (m, 4H); 3.42 (d, 2H, $J$=7 Hz); 4.11 (q, 2H, $J$=7 Hz); 5.32 (t, 1H, $J$=7 Hz); 7.05 (m, 1H); 7.25 (m, 2H); 7.52 (d, 1H, $J$=8 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 14.16 ($CH_3$); 16.19 ($CH_3$); 33.10 ($CH_2$); 34.56 ($CH_2$); 34.61 ($CH_2$); 60.16 ($CH_2$); 122.18 (CH); 125.86 (C); 127.37 (CH) 127.44 (CH); 129.92 (CH); 132.62 (CH); 135.48 (C); 140.55 (C); 173.09 (C). Anal. Calcd for $C_{15}H_{19}BrO_2$: C, 57.89, H, 6.15; found: C, 57.78, H, 6.08. EIMS *m/z* (relative intensity): 312 (M+1, 11); 223 (25); 185 (49); 143 (100); 128 (49); 115 (23); 77 (14).

### 4.20. 6-(2-Methoxy-phenyl)-4-methyl-hex-4-en-oic acid ethyl ester (37)

An analogous procedure to the previously described for the 6-(2-bromo-phenyl)-4-methyl-hex-4-en-oic ethyl ester (**36**) applied to (2-methoxy-phenyl)-3-methyl-but-3-en-2-ol (**35**) (2.6 g, 13.54 mmol) led to a residue (3 g) which was flash-chromatographed on silica gel. Elution with hexane–ethyl acetate (95:5) yielded **37** (2.85 g, 80%) as a colorless oil IR (neat) $\nu$ 2980, 2938, 2837, 1736, 1599, 1493, 1464, 1371, 1290, 1244, 1159, 1111, 1032 and 754; $^1$H NMR ($CDCl_3$): $\delta$ 1.24 (t, 3H, $J$=7 Hz); 1.74 (s, 3H); 2.43 (m, 4H); 3.35 (d, 2H, $J$=7 Hz); 3.83 (s, 3H); 4.11 (q, 2H, $J$=7 Hz); 5.38 (t, 1H, $J$=7 Hz); 6.88 (m, 2H); 7.14 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 14.11 ($CH_3$); 15.85 ($CH_3$); 28.22 ($CH_2$); 33.21 ($CH_2$); 34.71 ($CH_2$); 55.20 ($CH_3$); 60.05 ($CH_2$); 110.24 (CH); 120.39 (CH) 123.39 (CH); 126.84 (CH); 129.18 (CH); 129.69 (C); 134.17 (C); 157.29 (C); 173.19 (C). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25, H, 8.45; found: C, 73.18, H, 8.36. EIMS *m/z* (relative intensity): 263 (M+1, 20); 217 (20); 177 (85); 135 (100); 99 (75); 77 (55).

### 4.21. (4*S**,5*S**)-6-(2-Bromo-phenyl)-4,5-dihydroxy-4-methyl-hexanoic acid ethyl ester (38)

To a solution of ethyl ester **36** (3 g, 10 mmol) in 15 ml of acetone–water (8:1) were successively added at 0°C under an argon atmosphere *N*-methyl morpholine oxide (2.7 g, 19 mmol) and 5 ml of a 0.1 M $OsO_4$ solution in $^t$BuOH (0.5 mmol). The reaction mixture was stirred at room temperature for 15 h. Then, 25 ml of an aqueous (10%) $NaHSO_3$ solution was added, the reaction mixture was saturated with solid NaCl, and extracted with ethyl acetate. The organic layers were washed with brine and dried over $Na_2SO_4$ to afford 3 g of a crude which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (7:3) afforded **38** (2.7 g, 89%) as a colorless oil IR (neat) $\nu$ 3337, 2982, 1724, 1181, 1030 and 752; $^1$H NMR ($CDCl_3$): $\delta$ 1.24 (s, 3H); 1.25 (t, 3H, $J$=7 Hz); 1.96 (m, 2H); 2.55 (t, 2H, $J$=7 Hz); 2.68 (dd, 2H, $J$=10, 14 Hz); 3.10 (dd, 1H, $J$=2, 14 Hz); 3.71 (dd, 1H, $J$=10, 2 Hz); 4.13 (q, 2H, $J$=7 Hz); 7.25 (m, 1H); 7.30 (m, 2H); 7.55 (d, 1H, $J$=7 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 14.73 ($CH_3$); 21.53 ($CH_3$); 29.70 ($CH_2$); 33.96 ($CH_2$); 38.65 ($CH_2$); 61.19 ($CH_2$); 74.56 (C); 76.33 (CH); 125.28 (C) 128.09 (CH); 128.72 (CH); 132.75 (C); 133.41 (CH); 138.97 (C); 175.24 (C). Anal. Calcd for $C_{15}H_{21}BrO_4$: C, 52.19, H, 6.13; found: C, 52.10, H, 6.07. FABMS *m*/*z* (relative intensity): 345 (M+1, 10); 283 (10); 89 (30).

### 4.22. (4*S**,5*S**)-6-(2-Methoxy-phenyl)-4,5-dihydroxy-4-methyl-hexanoic acid ethyl ester (39)

An analogous procedure to the previously described for the preparation of 6-(2-bromo-phenyl)-4,5-dihydroxy-4-methyl-hexanoic acid ethyl ester **38** applied to 6-(2-methoxy-phenyl)-4-methyl-hex-4-en-oic acid ethyl ester **37** (2.75 g, 1.9 mmol) led to a residue (3.2 g) which was flash-chromatographed on silica gel. Elution with hexane–ethyl acetate (75:25) yielded **39** (3 g, 96%) as a colorless oil IR (neat) $\nu$ 3476, 2980, 2938, 1730, 1603, 1495, 1466, 1375, 1244, 1182, 1117, 1032, 922, 866, and 754; $^1$H NMR ($CDCl_3$): $\delta$ 1.19 (s, 3H); 1.24 (t, 3H, $J$=7 Hz); 1.91 (m, 2H); 2.55 (dd, 1H, $J$=12, 10 Hz); 2.60 (t, 2H, $J$=7 Hz); 2.95 (dd, 2H, $J$=12, 2 Hz); 3.65 (dt, 1H, $J$=10, 2 Hz); 3.82 (s, 3H); 4.12 (q, 2H, $J$=7 Hz); 6.89 (m, 2H); 7.18 (m, 2H); $^{13}$C NMR ($CDCl_3$): $\delta$ 13.99 ($CH_3$); 20.97 ($CH_3$); 28.55 ($CH_2$); 32.89 ($CH_2$); 33.26 ($CH_2$); 55.07 ($CH_3$); 60.13 ($CH_2$); 73.60 (C); 76.35 (CH); 110.29 (CH); 120.57 (CH); 127.34 (C); 127.60 (CH); 131.10 (CH); 157.28 (C); 174.23 (C). Anal. Calcd for $C_{16}H_{24}O_5$: C, 68.84, H, 8.16; found: C, 68.76, H, 8.08. EIMS *m*/*z* (relative intensity): 296 (M, 5); 250 (10); 233 (12); 145 (50); 121 (50); 99 (100); 77 (20).

### 4.23. (5*S**,1′*S**)-5-[2′-(2-Bromo-phenyl)-1′-hydroxy-ethyl]-5-methyl-dihydro-furan-2-one (40)

Pyridinium *para*-toluenesulfonate (PPTS) (150 mg, 0.6 mmol) was added to a solution of diol **38** (229 mg, 0.6 mmol) in THF (20 ml) under an argon atmosphere. The reaction mixture was heated under reflux conditions for 2 h. Then, the reaction was cooled to room temperature and the mixture diluted by the addition of ethyl acetate (20 ml). The organic layers were washed with aqueous sat. $NaHCO_3$ and brine and dried over $Na_2SO_4$ to afford a residue (175 mg) which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (8:2) afforded the lactone **40** (123 mg, 63%) IR (neat) $\nu$ 3447, 1769, 1265 and 743; $^1$H NMR ($CDCl_3$): $\delta$ 1.52 (s, 3H); 2.01 (m, 2H); 2.47 (m, 1H); 2.68 (m, 1H); 2.72 (dd, 1H, $J$=14, 10 Hz); 3.17 (dd, 1H, $J$=14, 2 Hz); 3.88 (dd, 2H, $J$=10, 2 Hz); 7.12 (dt, 1H, $J$=8, 2 Hz); 7.28 (m, 2H); 7.56 (dd, 1H, $J$=8, 1 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ 21.67 ($CH_3$); 29.26 ($CH_2$); 30.86 ($CH_2$); 37.84 ($CH_2$); 75.73 (CH); 88.23 (C); 124.49 (C); 127.52 (CH); 128.55 (CH); 132.20 (CH); 132.95 (CH); 137.21 (C); 176.71 (C). Anal. Calcd for $C_{13}H_{15}BrO_3$: C, 52.19, H, 5.05; found: C, 52.12, H, 4.85. EIMS *m*/*z* (relative intensity): 300 (M+1, 5); 201 (5); 171 (5); 120 (15); 99 (100); 91 (40); 77 (30).

### 4.24. (5*S**,1′*S**)-5-[2′-(2-Methoxy-phenyl)-1′-hydroxy-ethyl]-5-methyl-dihydro-furan-2-one (41)

A procedure analogous to the previously described for 5-[2-(2-bromo-phenyl)-1-hydroxy-ethyl]-5-methyl-dihydro-furan-2-one **40** applied to 6-(2-methoxy-phenyl)-4,5-dihydroxy-4-methyl-hexanoic acid ethyl ester **39** (2.23 g, 7.5 mmol) led to a residue (2.5 g) which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (9:1) afforded **41** (1.99 g, 100%) mp 71°C IR (neat) $\nu$ 3459, 2936, 1767, 1730, 1603, 1588, 1495, 1464, 1383, 1240, 945, 804 and 756; $^1$H NMR ($CDCl_3$): $\delta$ 1.47 (s, 3H); 1.98 (m, 2H); 2.42 (m, 1H); 2.60 (m, 1H); 2.65 (dd, 1H, $J$=14, 10 Hz); 2.98 (dd, 1H, $J$=14, 2 Hz); 3.78 (dd, 2H, $J$=10, 2 Hz); 3.83 (s, 3H); 6.95 (m, 2H); 7.28 (m, 2H); 7.12 (m, 1H); $^{13}$C NMR ($CDCl_3$): $\delta$ 22.36 ($CH_3$); 29.29 ($CH_2$); 30.72 ($CH_2$); 32.60 ($CH_2$); 55.28 ($CH_3$); 76.97 (CH); 88.05 (C); 110.46 (C); 120.83 (CH); 126.52 (C); 128.00 (CH); 131.14 (CH); 157.36 (C); 177.20 (C). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18, H, 7.25; found: C, 67.12, H, 7.16. EIMS *m*/*z* (relative intensity): 250 (M, 22); 151 (100); 121 (45); 99 (38); 77 (10); 65 (8).

### 4.25. Dehydrogenation of 40: (5*S**,1′*S**)-5-[2′-(2-bromo-phenyl)-1′-hydroxy-ethyl]-5-methyl-5*H*-furan-2-one (26)

A solution of **40** (123 mg, 0.4 mmol) in THF (5 ml) was added dropwise to a solution of LDA (1.3 mmol) in THF (5 ml) at −78°C under argon. After 1 h, a solution of $Ph_2Se_2$ (400 mg, 1.3 mmol) and HMPA (180 μl) in THF (5 ml) was added. After 15 min, the mixture was allowed to warm to −40°C and, after 90 min poured into aq. $NH_4Cl$ (25 ml). The residue obtained after the work-up was dissolved in THF (5 ml) and $H_2O_2$ aq. (30%, 0.20 ml, 2.3 mmol) and acetic acid (0.04 ml) were added. After 1 h, the reaction was quenched with sat $NaHCO_3$ aq. and extracted with ethyl acetate. The organic layers were washed with $NaHSO_3$ (10%), brine and dried over $Na_2SO_4$ to give a crude (150 mg) which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (8:2) afforded **26** (93 mg, 76%) with identical spectroscopic properties to those described above.

### 4.26. Dehydrogenation of 41: (5*S**,1′*S**)-5-[1′-hydroxy-2′-(2-methoxy-phenyl)-ethyl]-5-methyl-5*H*-furan-2-one (30)

An analogous procedure to that previously described for **26**

applied to 5-[2-(2-methoxy-phenyl)-1-hydroxy-ethyl]-5-methyl-dihydro-furan-2-one **41** (0.5 g, 2 mmol) led to a residue (550 mg) which was fractionated by flash chromatography on silica gel. Elution with hexane–ethyl acetate (7:3) afforded **30** (382 mg, 77%) with identical spectroscopic properties to those described above.

## Acknowledgements

We thank the 'Dirección General de Investigación del Ministerio de Ciencia y Tecnología', Spain. (CICYT, Grant 1FD1997-1640) for financial support. We are gratefully acknowledged to Professor G. Casiraghi (University of Parma, Italy) for providing us with reprints related to the topic. Thanks are given to Dr Jesus Angel de la Fuente, Instituto Biomar S.A., Polígono Industrial de Onzonilla, Edificio CEI, 24231 Onzonilla, León, Spain, for technical assistance.

## References

1. Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607–626.
2. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677–1716.
3. Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333–1350.
4. Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; Jai, 1998; Vol. 3, pp. 113–189 and references therein.
5. Casiraghi, G.; Zanardi, F. *Chem. Rev*. **2000**, *100*, 1929–1972.
6. Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109–118.
7. Asaoka, M.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn* **1979**, *52*, 1953–1956.
8. Ketnizel, S.; Rudi, A.; Schleyer, M.; Benayahi, Y.; Kashman, Y. *J. Nat. Prod.* **1996**, *59*, 873–875.
9. Brown, D. W.; Campbell, M. M.; Taylor, A. P.; Zhang, X-A. *Tetrahedron Lett.* **1987**, *28*, 985–988.
10. Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037–4040.
11. Barlett, P. A. *Tetrahedron* **1980**, *36*, 3–72.
12. All new compounds were characterized by spectroscopic methods. Correct microanalytical data have been obtained for all of them.
13. Still, W. C.; Kahn, M. A. *J. Org. Chem.* **1978**, *11*, 114–120.
14. Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168–180.