Asymmetric Synthesis of 2-Aryl-5-oxotetrahydrofuran-2-carboxylic Acids

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Received 7 April 2006; revised 1 June 2006

Abstract: 3-Aryl-2-hydroxycyclopent-2-en-1-ones, when subjected to asymmetric oxidation, result in enantiomerically enriched 2-aryl-5-oxotetrahydrofuran-2-carboxylic acids. Electron-donating substituents in the *para* position of the phenyl ring increase the yield and decrease the enantioselectivity of the process.

Key words: tertiary γ-lactones, oxotetrahydrofuran-2-carboxylic acids, asymmetric oxidations, stereoselectivity

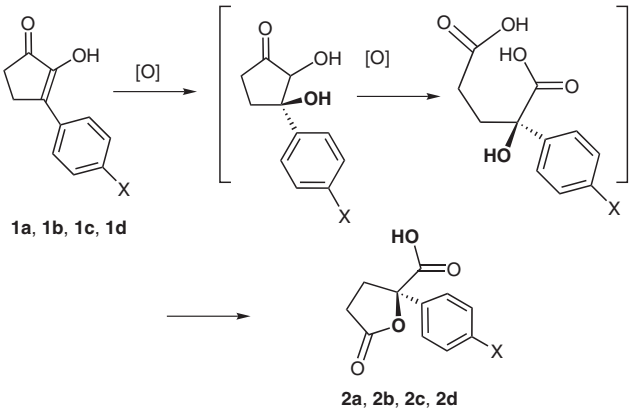
Various substituted tertiary lactones are valuable precursors for bioactive compounds.[1] On the other hand, these structures themselves bear different biological activities;[2] for example, the derivatives of the title compound – 2-aryl-5-oxotetrahydrofuran-2-carboxylic acids – exhibit depressive action on the central nervous system.[3]

There are limited methods for the synthesis of 2-aryl-5-oxotetrahydrofuran-2-carboxylic acids.[3,4] No convenient methods for the asymmetric synthesis of these compounds have been described. The aim of the present study was to elaborate a method for the asymmetric synthesis of 2-aryl-5-oxotetrahydrofuran-2-carboxylic acids from achiral 3-aryl-2-hydroxycyclopent-2-en-1-ones.

We have recently developed a short and highly enantioselective method for the synthesis of 2-alkyl-substituted 2-hydroxyglutaric acid γ-lactones from 3-alkylcyclopentane-1,2-diones by asymmetric oxidation using the Ti(O*i*-Pr)$_4$/diethyl tartrate/*t*-BuOOH complex.[5] We expected that achiral 3-aryl-2-hydroxycyclopent-2-en-1-ones **1** (enol tautomers of 3-arylcyclopentane-1,2-diones) might also be substrates for the asymmetric oxidation complex and afford 2-aryl-5-oxotetrahydrofuran-2-carboxylic acids **2** (Scheme 1).

For the synthesis of the starting compounds, aryl-substituted cyclopentane-1,2-diones, we used the coupling of benzaldehydes with 1-acetoxybut-3-en-2-one (**6**) (according to the Stetter reaction[6]), followed by an intramolecular base-induced cyclization. Thus, 3-aryl-2-hydroxycyclopent-2-en-1-ones **1a–d** were prepared from the corresponding benzaldehydes **7a–d** and 1-acetoxybut-3-en-2-one (**6**) [prepared in a 53% yield from but-2-yne-1,4-diacetate (**5**)[7]] (Scheme 2).

In order to find appropriate asymmetric oxidation conditions, the reaction was carried out with **1a** (X = H) as a model compound at different molar ratios of **1a**, Ti(O*i*-Pr)$_4$, (+)-diethyl tartrate and *t*-BuOOH. The results obtained are presented in Table 1.



[O] = Ti(O*i*-Pr)$_4$/(+)-diethyl tartrate/*t*-BuOOH

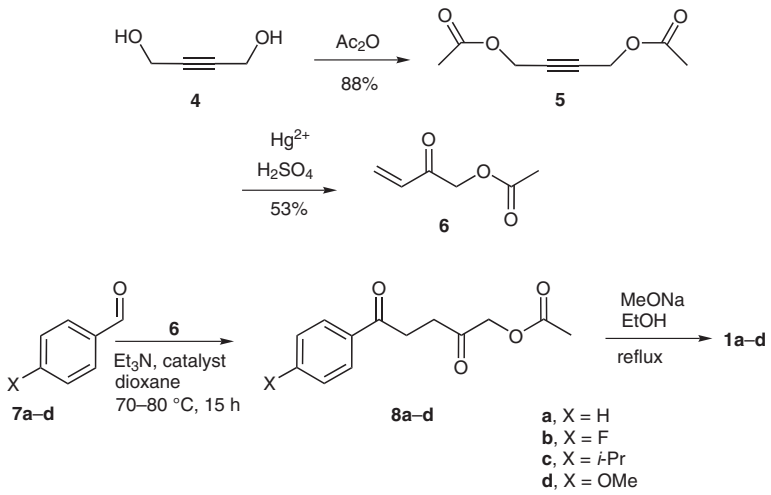
a, X = H; **b**, X = F; **c**, X = *i*-Pr; **d**, X = OMe

Scheme 1 Synthesis of 2-aryl-5-oxotetrahydrofuran-2-carboxylic acids **2a–d** from achiral 3-aryl-2-hydroxycyclopent-2-en-1-ones **1a–d** by asymmetric oxidation.

According to the data obtained, unsubstituted 2-hydroxy-3-phenyl-2-cyclopenten-1-one (**1a**) gets oxidized like alkyl-substituted substrates – the main isolated reaction product (after lactonization) was lactone acid **2a**. In all of the cases, the yield of the lactone acid was lower (32–43%) than that for alkyl substituted substrates (up to 83%).[5] Also, the enantioselectivity of the asymmetric oxidation was considerably lower than that for alkyl-substituted substrates (ee ≥95%). The best yield (43%, ee 78%) was obtained at the molar ratio of 1.0:1.0:1.6:2.5 of the components of the **1a** and Ti complex when a dilute reaction mixture was used (Table 1, entry 4). The best enantioselectivity for phenyl-substituted substrate **2a** (ee 86%) was obtained using ordinary reaction conditions for alkyl-substituted substrates (with a yield of 36 and 38%; Table 1, entries 1 and 2). An increase in the substrate/Ti-complex ratio caused the reduction of both, the yield and ee (Table 1, entry 3). In all the experiments the formation of keto acid **3a** in 16–21% yields was also observed, the amount of which is considerably higher than that for alkyl-substituted substrates.

It is also noteworthy that in all the experiments, a considerable amount of substrate **1a** remained unreacted and was isolated from the reaction mixture (36–42%). However,

SYNTHESIS 2006, No. 18, pp 3031–3036
Advanced online publication: 15.08.2006
DOI: 10.1055/s-2006-950193; Art ID: T06306SS

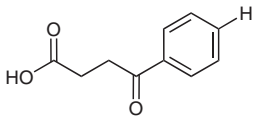


Scheme 2 Synthesis of 3-aryl-2-hydroxycyclopent-2-en-1-ones **1a–d**.

Table 1 Asymmetric Oxidation of **1a** under Different Conditions

Entry	Reaction time (h)	Concn **1a** (mg/mL)	Complex ratio: **1a**/Ti(O*i*-Pr)$_4$/(+)-diethyl tartrate/*t*-BuOOH	Lactone acid **2a**, yield (%) (ee%)[a]	Keto acid **3a** (%)[b]
1[c]	66	22	1:1:1.6:2.5	36 (86)	16
2	113	22	1:1:1.6:2.5	38 (86)	18
3	115	22	1:3:3.6:4.0	32 (65)	17
4	114	11	1:1:1.6:2.5	43 (78)	21

[a] Enantiomeric purity of **2a** was determined from ^{1}H NMR-spectra of its (1*R*,2*S*,5*R*)-(–)-menthyl ester.
[b] Keto acid **3a**:



[c] The best conditions for the oxidation of alkyl substrates.[5]

our attempts to achieve a better conversion of the substrate and an increase in the yield were unsuccessful.

Asymmetric oxidation of different 3-aryl-2-hydroxy-2-cyclopenten-1-ones **1b–d** was carried out under oxidation conditions found for substrate **1a** (Table 1, entry 2). The results obtained are presented in Table 2.

According to the data, the *p*-substituent influences both the yield of the products and the enantioselectivity of the process. Thus, the yield varies from 38 to 52%, while the enantioselectivity (ee %) changes in the range of 50 to 86%. It can be mentioned that the 4-fluoro group behaves similarly to the unsubstituted phenyl substrates (yield: 38% vs 43%; ee % 86% vs 86%; Table 2, entries 1 and 2), while the strongest electron-donating methoxy group causes the highest yield of **2d** (52%) and the lowest stereoselectivity (ee 50%; Table 2, entry 4). In all of the cases above, a higher extent of the decarboxylation reaction

Table 2 Lactone Acids **2a–d** from 3-Aryl-2-hydroxycyclopent-2-en-1-ones **1a–d**[a]

Entry	Substrate **1**	X	Isolated lactone acid **2** yield (%) (ee %)[b]	Keto acid **3** yield (%)
1	**1a**	H	38 (86)	16
2	**1b**	F	43 (86)	24
3	**1c**	*i*-Pr	42 (72)	23
4	**1d**	OMe	52 (50)	34

[a] All the reactions were carried out under the same conditions: **1a–d**/Ti(O*i*-Pr)$_4$/(+)-diethyl tartrate/*t*-BuOOH ratio: 1:1:1.6:2.5; concn **1** = 22 mg/mL in CH_2Cl_2 at –20 °C, reaction time = 114 h.
[b] Enantiomeric purities of (*R*)-2-aryl-5-oxotetrahydrofuran-2-carboxylic acids were determined by HPLC, using the Daicel Chiralcel ODH column.

(according to the formation of by-product **3**) was observed for stronger electron-donating groups.

When correlating the yield of the products and the stereoselectivity of the process with σ^+ constants[8] of the substituents, we observed a clear dependence of those values on the electron-donating abilities of the groups. The enantioselectivity of the process (presented as ee % of **2a–d**) correlates best with σ^+ constants ($R^2 = 0.989$). Interestingly enough, the yields of the main product **2a–d** and by-product **3a–d** reflect the same tendency of the σ^+ constants of the *para*-substituted groups (Figure 1).

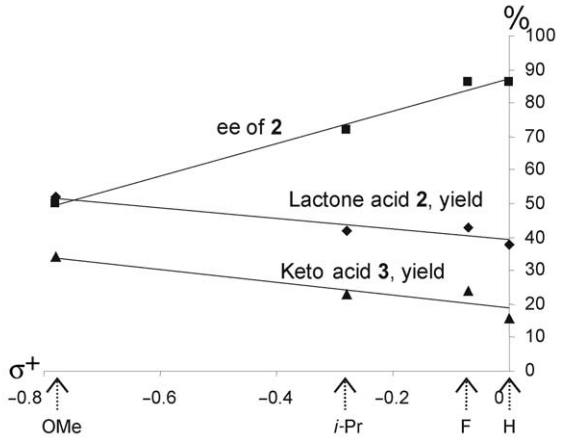


Figure 1 Correlation of yields of γ-lactone acids **2a–d**, keto acids **3a–d** and enantiopurity of **2a–d** with s+ constants of the *para* substituents.[8]

The effects of the *para*-substitution in phenyl allylic alcohols have been previously investigated in the asymmetric epoxidation reaction using the same Ti-complex. The authors have observed also a substantial influence from the electronic properties of the substituents – faster reaction with electron-donating groups.[9]

To determine the enantiopurity of the 3-aryl-5-oxotetrahydrofuran-2-carboxylic acids **2**, both *R*- and *S*-enantiomers were synthesized. The (*R*)-**2** enantiomer was obtained with the use of (+)-diethyl tartrate and the (*S*)-**2** enantiomer from (–)-diethyl tartrate (the absolute configuration of different γ-lactone acids has repeatedly been confirmed by us by comparing the optical rotation values of the different newly synthesized compounds with those from the literature[10]). The ee values of compounds **2b–d** were determined by using chiral phase HPLC. In the case of 5-oxo-3-phenyltetrahydrofuran-2-carboxylic acid (**2a**), the compound was converted into the corresponding esters with (1*R*,2*S*,5*R*)-(–)-menthol.[10b] The presence of diastereomeric esters is clearly seen nearly on all ^{13}C and several ^1H chemical shifts in the NMR spectra. To determine enantiomeric purity, integration of high-field isopropyl methyl doublets of menthol part in the 0.5–0.6 ppm area was used (Figure 2).

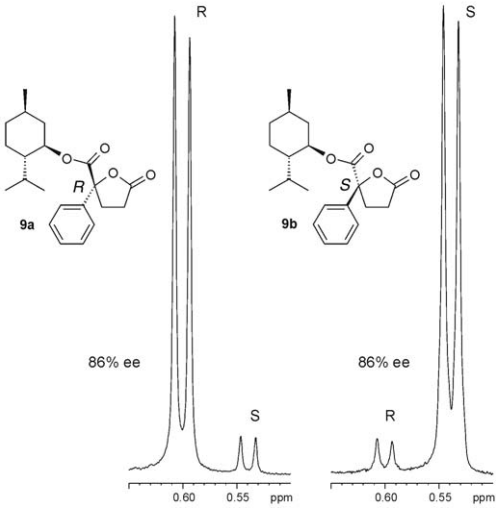


Figure 2 A part of ^1H NMR spectrum of diastereomers of 5-oxo-3-phenyltetrahydrofuran-2-carboxylic acid menthyl esters **9a** and **9b**.

Commercial reagents (Aldrich) were generally used without purification. CH_2Cl_2 for asymmetric oxidation was distilled from CaH_2 and stored over 3Å molecular sieve pellets. Petroleum ether (PE) fraction used had boiling range 40–60 °C. TLC analysis was performed using DC-Alufolien Kieselgel 60 F254 (Merck) and Silufol® UV 254 silica gel plates. Merck Silica gel 60 (0.063–0.200 mm) and Chemapol silica gel L 40/100 were used for column chromatography. Melting points were determined by VEB Nombinat Nagema K8 (Germany) apparatus. Optical rotations were obtained using an A. Krüss Optronic GmbH polarimeter P 3002. Enantiomeric purity was determined on a LKB liquid chromatograph with a Uvicord UV detector, using a Daicel Chiracel ODH chiral column. IR spectra were recorded on a PerkinElmer Spectrum BX FTIR spectrometer. ^1H and ^{13}C NMR spectra were determined using deuterated solvents ($CDCl_3$, δ = 7.27 and 77.00, CD_3OD, δ = 3.30 and 49.00, or DMSO-d_6, δ = 2.50 and 39.50) on a Bruker AMX-500 spectrometer. 2D FT methods were used for the analysis of synthesized compounds. Mass spectra were measured on a Hitachi M80B spectrometer in the EI (70 eV) and CI (isobutane) mode. Elemental analyses were performed on a PerkinElmer C, H, N, S-Analyzer 2400.

Acetic Acid 5-Aryl-2,5-dioxopentyl Esters 8a–d

Compounds **8a–d** were synthesized from the corresponding *para*-substituted benzaldehydes **7a–d** and 1-acetoxy-3-buten-2-one according to the literature.[6]

Acetic Acid 2,5-Dioxo-5-phenylpentyl Ester (8a)

Compound **8a** was obtained from 1-acetoxy-3-buten-2-one (**6**) and benzaldehyde (**7a**) in 71% yield as colorless crystals; mp 61–62 °C (Lit.[6] mp 62–64 °C).

Acetic Acid 5-(4-Fluorophenyl)-2,5-dioxopentyl Ester (8b)

Compound **8b** was obtained from 1-acetoxybut-3-en-2-one (**6**) and 4-fluorobenzaldehyde (**7b**) in 68% yield as colorless crystals; mp 77–78 °C.

IR (KBr): 1759, 1727, 1690, 1594, 1506, 1227, 1160, 1074, 1026, 834 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 5.3, 8.6 Hz, 2 H_{arom}, *o*-CH), 7.11 (t, *J* = 8.6 Hz, 2 H_{arom}, *m*-CH), 4.79 (s, 2 H, CH_2OCO), 3.30 (t, *J* = 6.2 Hz, 2 H, CH_2COPh), 2.83 (t, *J* = 6.2 Hz, 2 H, $COCH_2$), 2.15 (s, 3 H, CH_3CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.8 (C-2), 196.3 (C-5), 170.2 (C=O, ester), 165.8 (FC_{arom}, J = 254.9 Hz), 132.7 (C_{arom}, J = 2.9 Hz), 130.6 (*o*-CH_{arom} J = 9.4 Hz), 115.6 (*m*-CH_{arom} J = 21.9 Hz), 68.0 (C-1), 32.3 (C-3), 32.0 (C-4), 20.4 (CH_3, ester).

MS (EI, 70 eV): *m*/*z* (%) = 253 (0.1, [M + H$^+$]), 179 (100), 151 (13), 123 (98), 109 (3), 95 (44), 75 (14).

Anal. Calcd for $C_{13}H_{13}FO_4$: C, 61.90; H, 5.19. Found: C, 61.86; H, 4.98.

Acetic Acid 5-(4-Isopropylphenyl)-2,5-dioxopentyl Ester (8c)
Compound **8c** was obtained from 1-acetoxybut-3-en-2-one (**6**) and 4-isopropylbenzaldehyde (**7c**) in 53% yield as colorless crystals; mp 45–47 °C.

IR (KBr): 2966, 1737, 1687, 1606, 1572, 1384, 1357, 1232, 1179, 1026, 1070, 824 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, J = 8.4 Hz, 2 H_{arom}, *o*-CH), 7.30 (d, J = 8.4 Hz, 1 H_{arom}, *m*-CH), 4.79 (s, 2 H, CH_2OCO), 3.32 (t, J = 6.2 Hz, 2 H, CH_2COPh), 2.95 [sept, J = 7.0 Hz, 1 H, CH(CH_3)$_2$], 2.82 (t, J = 6.2 Hz, 2 H, $COCH_2$), 2.15 (s, 3 H, CH_3CO), 1.25 [d, J = 7.0 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.0 (C-2), 197.6 (C-5), 170.2 (C=O, ester), 154.7 (*i*-PrC_{arom}), 134.2 (C_{arom}), 128.2 (*o*-CH_{arom}), 126.6 (*m*-CH_{arom}), 68.1 (C-1), 34.1 [CH(CH_3)$_3$], 32.4 (C-3), 32.0 (C-4), 23.5 [CH(CH$_3$)$_3$], 20.4 (CH_3, ester).

MS (CI): *m*/*z* (%) = 277 (34, [M + H$^+$]), 235 (4), 203 (100), 147 (64), 115 (3), 91 (9).

HRMS-EI: *m*/*z* calcd for [M – $CH_3CO_2CH_2$]$^+$ $C_{13}H_{15}O_2$: 203.1071; found: 203.1073.

Acetic Acid 5-(4-Methoxyphenyl)-2,5-dioxopentyl Ester (8d)
Compound **8d** was obtained from 1-acetoxybut-3-en-2-one (**6**) and 4-methoxybenzaldehyde (**7d**) in 48% yield as colorless crystals; mp 81–82 °C.

IR (KBr): 2847, 1758, 1727, 1669, 1601, 1574, 1512, 1243, 1176, 1071, 1030, 830 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.8 Hz, 2 H_{arom}, *o*-CH), 6.90 (d, J = 8.8 Hz, 2 H_{arom}, *m*-CH), 4.78 (s, 2 H, CH_2OCO), 3.83 (s, 3 H, ArOCH_3), 3.27 (t, J = 6.2 Hz, 2 H, CH_2COPh), 2.79 (t, J = 6.2 Hz, 2 H, $COCH_2$), 2.14 (s, 3 H, CH_3CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.0 (C-2), 196.4 (C-5), 170.1 (C=O, ester), 163.5 (MeOC_{arom}), 130.2 (*o*-CH_{arom}), 129.4 (C_{arom}), 113.6 (*m*-CH_{arom}), 68.0 (C-1), 55.3 (ArOCH$_3$), 32.4 (C-3), 31.7 (C-4), 20.3 (CH_3, ester).

MS (EI, 70 eV): *m*/*z* (%) = 264 (2, [M$^+$]), 191 (71), 163 (4), 135 (100), 107 (7), 92 (15), 77 (18).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.64; H, 6.10.

2-Hydroxy-3-phenylcyclopent-2-en-1-ones 1a–d; General Procedure
To a solution of **8** (0.012 mol) in EtOH (70 mL), was added a solution of NaOMe (0.814 g, 0.015 mol) in EtOH (70 mL) in one portion at r.t. After the addition, the color of the solution turned red-brown. The mixture was stirred for 15 min at r.t. and refluxed for 10 min. After cooling, AcOH (4.0 mL) was added to the mixture. EtOH and AcOH were evaporated under vacuum and H_2O (50 mL) was added to the residue. The product was extracted with CH_2Cl_2 (3–5 ×). The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and solvents were removed on a rotary evaporator. The residue was purified by column chromatography on silica gel (Merck silica gel 60) using petroleum ether–acetone gradient from 20:1 to 10:5.

2-Hydroxy-3-phenylcyclopent-2-en-1-one (1a)
Compound **1a** was obtained from **8a** in 40% yield as a colorless solid; mp 192–193 °C (Lit.[6] mp 187–189 °C).

3-(4-Fluorophenyl)-2-hydroxycyclopent-2-en-1-one (1b)
Compound **1b** was obtained from **8b** in 72% yield as a colorless solid; mp 177–178 °C.

IR (KBr): 3217, 1708, 1637, 1599, 1512, 1396, 1271, 1243, 1160, 1136, 824 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD): δ = 7.87 (dd, J = 5.5, 8.8 Hz, 2 H_{arom}, *o*-CH), 7.04 (t, J = 8.8 Hz, 2 H_{arom}, *m*-CH), 3.99 (s, 1 H, OH), 2.76 (m, 2 H, H-4), 2.45 (m, 2 H, H-5).

^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD): δ = 203.6 (C-1), 162.8 (FC_{arom}, J = 250.5 Hz), 148.7 (C-2), 137.9 (C-3), 130.4 (C_{arom}, J = 3.1 Hz), 129.3 (*o*-CH_{arom}, J = 8.4 Hz), 115.2 (*m*-CH_{arom}, J = 21.5 Hz), 31.0 (C-5), 23.1 (C-4).

MS (EI, 70eV): *m*/*z* (%) = 192 (100, [M$^+$]), 163 (17), 149 (11), 135 (26), 121 (39), 107 (19), 75 (11).

HRMS-EI: *m*/*z* calcd for [M]$^+$ $C_{11}H_9FO_2$: 192.0586; found: 192.0574.

2-Hydroxy-3-(4-isopropylphenyl)cyclopent-2-en-1-one (1c)
Compound **1c** was obtained from **8c** in 54% yield as a colorless solid; mp 180–181 °C.

IR (KBr): 3235, 2952, 1699, 1634, 1607, 1514, 1394, 1274, 1209, 1133, 817 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.75 (s, 1 H, OH), 7.83 (d, J = 7.6 Hz, 2 H_{arom}, *o*-CH), 7.29 (d, J = 7.6 Hz, 2 H_{arom}, *m*-CH), 2.89 [sept, J = 6.9 Hz, 1 H, CH(CH_3)$_3$], 2.73 (m, 2 H, H-4), 2.40 (m, 2 H, H-5), 1.20 [d, J = 6.9 Hz, 6 H, CH(CH_3)$_3$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 202.4 (C-1), 149.3 (C-2), 149.1 (*i*-PrC_{arom}), 137.1 (C-3), 132.3 (C_{arom}), 127.1 (*o*-CH_{arom}), 126.3 (*m*-CH_{arom}), 33.3 [CH(CH_3)$_3$], 31.0 (C-5), 23.6 [CH(CH$_3$)$_3$], 22.7 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 216 (62, [M$^+$]), 201 (100), 173 (4), 145 (9), 128 (9), 115 (16), 91 (9), 77 (7).

HRMS-EI: *m*/*z* calcd for [M]$^+$ $C_{14}H_{16}O_2$: 216.1149; found: 216.1143.

2-Hydroxy-3-(4-methoxyphenyl)cyclopent-2-en-1-one (1d)
Compound **1d** was obtained from **8d** in 38% yield as a colorless solid; mp 200–201 °C.

IR (KBr): 3212, 2839, 1703, 1636, 1603, 1514, 1399, 1254, 1240, 1180, 1134, 1026, 818 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.66 (s, 1 H, OH), 7.87 (d, J = 7.6 Hz, 2 H_{arom}, *o*-CH), 7.01 (d, J = 7.6 Hz, 2 H_{arom}, *m*-CH), 3.79 (s, 3 H, ArOCH_3), 2.73 (m, 2 H, H-4), 2.40 (m, 2 H, H-5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 202.1 (C-1), 159.6 (MeOC_{arom}), 148.5 (C-2), 137.4 (C-3), 128.6 (*o*-CH_{arom}), 127.3 (C_{arom}), 113.9 (*m*-CH_{arom}), 55.1 (ArOCH$_3$), 30.9 (C-5), 22.8 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 204 (100) [M$^+$], 189 (6), 175 (4), 161 (4), 147 (7), 133 (34), 108 (8), 91 (8), 77 (11).

HRMS-EI: *m*/*z* calcd for [M]$^+$ $C_{12}H_{12}O_3$: 204.0785; found: 204.0785.

Asymmetric Oxidation of 2-Hydroxy-3-phenylcyclopent-2-en-1-ones 1a–d; General Procedure
Ti(O*i*-Pr)$_4$ (0.3 mL, 1 mmol) was added to a suspension of CH_2Cl_2 (6 mL) and 4Å powdered molecular sieves (100 ± 5 mg) under argon and the flask was cooled to –20 to –25 °C using solid CO_2/CCl_4 during the whole process. (+)-DET (0.27 mL, 1.6 mmol) was added and the mixture was stirred for 15 min. A suspension of 3-aryl-2-hy-

droxycyclopent-2-en-1-one **1** (1 mmol) in CH_2Cl_2 (2.0 mL) was added and the mixture was stirred for 60 min. TBHP (0.4 mL, 2.5 mmol, 6.25 M solution in decane) was then added and the reaction was kept at –20 °C for 114 h. After that, H_2O (6.0 mL) was added and the mixture was intensively stirred for 1 h at r.t. Then, a solution (1.2 mL) prepared from NaOH (1.5 g) and NaCl (0.25 g) in H_2O (4.5 mL) was added to the mixture and it was again intensively stirred at r.t. for an additional 1 h. CH_2Cl_2 layer was removed and the mixture acidified with aq 1 M HCl until pH 2 and extracted with EtOAc (3–5 ×). The combined organic extracts were dried ($MgSO_4$) and the solvents were evaporated on a rotary evaporator. The residue was dissolved in CH_2Cl_2 (20 mL) and conc. HCl (0.2 mL) was added and the mixture was stirred for 2 h at r.t. Then H_2O (10 mL) was added and the CH_2Cl_2 layer was separated. The aqueous layer was extracted with EtOAc (3–4 ×) and the combined extracts were dried ($MgSO_4$). After evaporation of the solvents, the residue was purified by flash chromatography (Chemapol silica gel L40/100), using petroleum ether–acetone (10:2) to give the corresponding γ-lactone acid **2** and keto acid **3**.

(*R*)-5-Oxo-2-phenyltetrahydrofuran-2-carboxylic Acid (2a)
Compound **2a** was obtained in 36% yield as a colorless powder; mp 154–155 °C; $[\alpha]_D^{22}$ –9.1 (*c* = 1.71, MeOH); ee 86%.

IR (KBr): 1744, 1498, 1451, 1405, 1243, 1219, 1177, 1042, 866, 756, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$ + CD_3OD): δ = 7.46 (m, 2 H_{arom}, *o*-CH), 7.33 (m, 2 H_{arom}, *m*-CH), 7.30 (m, 1 H_{arom}, *p*-CH), 3.02 and 2.53 (m, 2 H, H-3), 2.64 and 2.51 (m, 2 H, H-4).

^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD): δ = 175.8 (C-5), 172.0 (C=O, acid), 137.9 (C_{arom}), 128.5 (CH_{arom}, *para* to C_{arom}), 128.4 (*m*-CH_{arom}), 125.0 (*o*-CH_{arom}), 87.0 (C-2), 33.1 (C-3), 28.0 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 191 (0.2), 179 (0.5), 161 (100), 133 (40), 117 (14), 105 (67), 91 (6), 77 (45).

HRMS-EI: *m*/*z* calcd for $[M - CO_2H]^+$ $C_{10}H_9O_2$: 161.0602; found: 161.0599.

4-Oxo-4-phenylbutyric Acid (3a)
Compound **3a** was obtained in 16% yield as a colorless powder; mp 110–113 °C.

IR (KBr): 1685, 1595, 1449, 1401, 1260, 1240, 1172, 947, 765, 689 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.99 (m, 2 H_{arom}, *o*-CH), 7.58 (t, *J* = 7.4 Hz, 1 H_{arom}, *p*-CH), 7.47 (m, 2 H_{arom}, *m*-CH), 5.15 (s, 1 H, OH), 3.32 (t, *J* = 6.5 Hz, 2 H, H-3), 2.82 (t, *J* = 6.5 Hz, 2 H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8 (C-4), 178.6 (C-1), 136.4 (C_{arom}), 133.3 (CH_{arom}, *para* to C_{arom}), 128.6 (*m*-CH_{arom}), 128.0 (*o*-CH_{arom}), 33.1 (C-3), 28.0 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 178 (7, $[M^+]$), 105 (100), 77 (79).

(*R*)-2-(4-Fluorophenyl)-5-oxotetrahydrofuran-2-carboxylic Acid (2b)
Compound **2b** was obtained in 43% yield as a colorless powder; mp 131–138 °C; $[\alpha]_D^{22}$ –14.0 (*c* = 1.71, MeOH); ee 86%.

IR (KBr): 1785, 1713, 1600, 1509, 1413, 1272, 1242, 1182, 1154, 1068, 905, 841 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.56 (dd, *J* = 5.2, 8.9 Hz, 2 H_{arom}, *o*-CH), 3.05 and 2.61 (m, 2 H, H-3), 2.68 and 2.60 (m, 2 H, H-4).

^{13}C NMR (125 MHz, CD_3OD): δ = 177.5 (C-5), 173.4 (C=O, acid), 164.2 (FC_{arom}, *J* = 246.5 Hz), 136.0 (C_{arom}, *J* = 2.6 Hz), 128.7 (*o*-CH_{arom}, *J* = 8.3 Hz), 116.3 (*m*-CH_{arom}, *J* = 22.0 Hz), 88.0 (C-2), 34.2 (C-3), 29.0 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 224 (0.4, $[M^+]$), 179 (100), 151 (9), 123 (78), 109 (6), 95 (31), 75 (13).

Anal. Calcd for $C_{11}H_9FO_4$: C, 58.93; H, 4.05. Found: C, 58.83; H, 4.01.

4-(4-Fluorophenyl)-4-oxobutyric Acid (3b)
Compound **3b** was obtained in 24% yield as a colorless powder; mp 95–99 °C.

IR (KBr): 1697, 1679, 1597, 1508, 1401, 1236, 1183, 1163, 941, 828 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 8.08 (dd, *J* = 5.4, 8.8 Hz, 2 H_{arom}, *o*-CH), 7.22 (t, *J* = 8.8 Hz, 2 H_{arom}, *m*-CH), 3.30 (t, *J* = 6.5 Hz, 2 H, H-3), 2.71 (t, *J* = 6.5 Hz, 2 H, H-2).

^{13}C NMR (125 MHz, CD_3OD): δ = 198.8 (C-4), 176.5 (C-1), 167.2 (FC_{arom}, *J* = 253.0 Hz), 134.7 (C_{arom}, *J* = 2.7 Hz), 131.9 (*o*-CH_{arom}, *J* = 8.3 Hz), 116.6 (*m*-CH_{arom}, *J* = 22.3 Hz), 34.3 (C-3), 28.9 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 196 (9, $[M^+]$), 179 (6), 151 (1), 123 (100), 95 (80), 75 (28).

(*R*)-2-(4-Isopropylphenyl)-5-oxotetrahydrofuran-2-carboxylic Acid (2c)
Compound **2c** was obtained in 42% yield as a colorless powder; mp 131–139 °C; $[\alpha]_D^{22}$ –12.2 (*c* = 1.72, MeOH); ee 72%.

IR (KBr): 2960, 1785, 1758, 1714, 1612, 1514, 1419, 1385, 1365, 1293, 1255, 1173, 1064, 898, 832 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.43 (m, 2 H_{arom}, *o*-Ph), 7.26 (m, 2 H_{arom}, *m*-Ph), 3.00 and 2,60 (m, 2 H, H-3), 2.86 [sept, *J* = 6.9 Hz, 1 H, C*H*$(CH_3)_3$], 2.62 and 2.54 (m, 2 H, H-4), 1.22 [d, *J* = 6.9 Hz, 6 H, CH(CH_3)$_3$].

^{13}C NMR (125 MHz, CD_3OD): δ = 177.7 (C-5), 173.6 (C=O, acid), 150.7 (*i*-PrC_{arom}), 137.2 (C_{arom}), 127.6 (*m*-CH_{arom}), 126.4 (*o*-CH_{arom}), 88.5 (C-2), 35.0 [*C*H$(CH_3)_3$], 34.0 (C-3), 29.0 (C-4), 24.3 [CH(*C*H_3)$_3$].

MS (EI, 70 eV): *m*/*z* (%) = 248 (2, $[M^+]$), 233 (0.5), 220 (0.2), 203 (100), 161 (6), 147 (37), 133 (6), 115 (8), 91 (12), 77 (8).

HRMS-EI: *m*/*z* calcd for $[M - CO_2H]^+$ $C_{13}H_{15}O_2$: 203.1071; found: 203.1069.

4-(4-Isopropylphenyl)-4-oxobutyric Acid (3c)
Compound **3c** was obtained in 23% yield as a colorless powder; mp 139–143 °C.

IR (KBr): 2962, 1713, 1687, 1607, 1572, 1399, 1364, 1350, 1239, 1176, 942, 826 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 7.92 (d, *J* = 8.2 Hz, 2 H_{arom}, *o*-CH), 7.35 (d, *J* = 8.2 Hz, 2 H_{arom}, *m*-CH), 3.28 (t, *J* = 6.4 Hz, 2 H, H-3), 2.95 [sept, *J* = 6.9 Hz, 1 H, C*H*$(CH_3)_3$], 2.68 (t, *J* = 6.4 Hz, 2 H, H-2), 1.25 [d, *J* = 6.9 Hz, 6 H, CH(CH_3)$_3$].

^{13}C NMR (125 MHz, CD_3OD): δ = 200.1 (C-4), 176.6 (C-1), 156.1 (*i*-PrC_{arom}), 135.9 (C_{arom}), 129.4 (*o*-CH_{arom}), 127.7 (*m*-CH_{arom}), 35.5 [*C*H$(CH_3)_3$], 34.3 (C-3), 28.9 (C-2), 24.0 [CH(*C*H_3)$_3$].

MS (EI, 70 eV): *m*/*z* (%) = 220 (6, $[M^+]$), 203 (9), 147 (100), 133 (3), 119 (3), 104 (11), 91 (14), 77 (11).

(*R*)-2-(4-Methoxyphenyl)-5-oxotetrahydrofuran-2-carboxylic Acid (2d)
Compound **2d** was obtained in 52% yield as a colorless powder; mp 117–130 °C; $[\alpha]_D^{22}$ –18.6 (*c* = 1.75, MeOH); ee 52%.

IR (KBr): 2845, 1744, 1612, 1512, 1410, 1264, 1235, 1221, 1180, 1045, 1028, 927, 833 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.42 (d, *J* = 8.9 Hz, 2 H_{arom}, *o*-CH), 6.93 (d, *J* = 8.9 Hz, 2 H_{arom}, *m*-CH), 3.78 (s, 3 H, ArOCH_3), 2.98 and 2,63 (m, 2 H, H-3), 2.59 and 2.55 (m, 2 H, H-4).

^{13}C NMR (125 MHz, CD_3OD): δ = 177.8 (C-5), 173.8 (C-1), 161.4 (MeOC_{arom}), 131.6 (C_{arom}), 127.8 (*o*-CH_{arom}), 114.9 (*m*-CH_{arom}), 88.4 (C-2), 55.8 (ArOCH_3), 33.9 (C-3), 29.1 (C-4).

MS (EI, 70 eV): *m*/*z* (%) = 236 (7, [M$^+$]), 208 (3), 191 (94), 163 (4), 135 (93), 121 (4), 98 (13), 83 (42), 77 (24).

HRMS-EI: *m*/*z* calcd for [M – CO_2H]$^+$ $C_{11}H_{11}O_3$: 191.0707; found: 191.0699.

4-(4-Methoxyphenyl)-4-oxobutyric Acid (3d)

Compound **3d** was in 32% yield as a colorless powder; mp 140–143 °C.

IR (KBr): 2842, 1698, 1667, 1602, 1574, 1514, 1426, 1270, 1247, 1174, 1028, 943, 834 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD): δ = 7.96 (d, *J* = 8.8 Hz, 2 H_{arom}, *o*-CH), 6.98 (d, *J* = 8.8 Hz, 2 H_{arom}, *m*-CH), 3.85 (s, 3 H, OCH_3), 3.24 (t, *J* = 6.4 Hz, 2 H, H-3), 2.67 (t, *J* = 6.4 Hz, 2 H, H-2).

^{13}C NMR (125 MHz, CD_3OD): δ = 199.1 (C-4), 176.7 (C-1), 165.3 (MeOC_{arom}), 131.4 (*o*-CH_{arom}), 130.9 (C_{arom}), 114.8 (*m*-CH_{arom}), 56.0, (ArOCH_3), 34.0 (C-3), 29.0 (C-2).

MS (EI, 70 eV): *m*/*z* (%) = 208 (9, [M$^+$]), 135 (100), 123 (7), 107 (8), 92 (10), 77 (15).

γ-Phenyl-γ-lactone Acid Menthol Esters 9a and 9b

Diastereomeric esters were synthesized separately from *R*- and *S*-enantiomers of γ-lactone acids **1a** with (1*R*,2*S*,5*R*)-(–)-menthol according to the known procedure.[10b] Enantiomeric purity of diastereomers was determined from ^{1}H NMR spectra in the 0.5–0.6 ppm area.

(*R*)-5-Oxo-2-phenyltetrahydrofuran-2-carboxylic Acid (1*R*,2*S*,2*R*)-2-Isopropyl-5-methylcyclohexyl Ester (9a)

Lactone acid menthyl ester **9a** was obtained according to the known procedure.[10b]

^{1}H NMR (500 MHz, $CDCl_3$): δ (acid part) = 7.50 (m, 2 H_{arom}, *o*-CH), 7.39 (m, 2 H_{arom}, *m*-CH), 7.36 (m, 1 H_{arom}, *p*-CH), 3.05 and 2.57 (m, 2 H, H-4), 2.61 (m, 2 H, H-3); δ (menthyl part) = 4.68 (dt, *J* = 4.5, 2 × 10.9 Hz, H-1), 1.86 and 0.92 (m, 2 H, H-6), 1.66 and 0.82 (m, 2 H, H-4), 1.63 and 0.99 (m, 2 H, H-3), 1.47 (m, 1 H, H-8), 1.45 (m, 1 H, H-5), 1.36 (m, 1 H, H-2), 0.86 (d, *J* = 6.5 Hz, 3 H, H-7), 0.76 (d, *J* = 7.0 Hz, 3 H, H-10), 0.60 (d, *J* = 7.0 Hz, 3 H, H-9).

^{13}C NMR (125 MHz, $CDCl_3$): δ (acid part) = 175.0 (C-5), 169.9 (C-1), 137.9 (C_{arom}), 128.7 (CH_{arom}, *para* to C_{arom}), 128.5 (*m*-CH_{arom}), 125.2 (*o*-CH_{arom}), 33.0 (C-4), 28.2 (C-3); δ (menthyl part) = 76.8 (C-1), 46.8 (C-2), 40.2 (C-6), 34.0 (C-4), 31.3 (C-5), 25.9 (C-8), 23.1 (C-3), 21.9 (C-7), 20.6 (C-10), 15.9 (C-9).

(*S*)-5-Oxo-2-phenyltetrahydrofuran-2-carboxylic Acid (1*R*,2*S*,2*R*)-2-Isopropyl-5-methylcyclohexyl Ester (9b)

Lactone acid menthyl ester **9b** was obtained according to the known procedure.[10b]

^{1}H NMR (500 MHz, $CDCl_3$): δ (acid part) = 7.49 (m, 2 H_{arom}, *o*-CH), 7.39 (m, 2 H_{arom}, *m*-CH), 7.36 (m, 1 H_{arom}, *p*-CH), 3.10 and 2.55 (m, 2 H, H-4), 2.65 and 2.55 (m, 2 H, H-3); δ (menthyl part) = 4.67 (dt, *J* = 4.5, 2 × 10.9 Hz, H-1), 1.90 and 0.97 (m, 2 H, H-6), 1.65 and 0.83 (m, 2 H, H-4), 1.62 and 0.98 (m, 2 H, H-3), 1.45 (m, 1 H, H-8), 1.45 (m, 1 H, H-5), 1.38 (m, 1 H, H-2), 0.88 (d, *J* = 6.5 Hz, 3 H, H-7), 0.74 (d, *J* = 7.0 Hz, 3 H, H-10), 0.54 (d, *J* = 7.0 Hz, 3 H, H-9).

^{13}C NMR (125 MHz, $CDCl_3$): δ (acid part) = 175.1 (C-5), 169.7 (C-1), 138.2 (C_{arom}), 128.6 (CH_{arom}, *para* to C_{arom}), 128.5 (*m*-CH_{arom}), 124.9 (*o*-CH_{arom}), 33.1 (C-4), 28.2 (C-3); δ (menthyl part) = 76.8 (C-1), 46.8 (C-2), 40.3 (C-6), 34.0 (C-4), 31.3 (C-5), 25.9 (C-8), 23.2 (C-3), 21.9 (C-7), 20.5 (C-10), 15.9 (C-9).

Acknowledgment

The authors thank the Estonian Ministry of Education and Research for grant 0142725s06, Estonian Science Foundation for financial support (Grant No: 5628 and 6778) and Competence Centre for Cancer Research for support.

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