Synthesis of γ-Lactones and Ascorbic Acid Analogues by Diastereoselective Hydrogenation of α-Hydroxy-γ-alkylidenebutenolides

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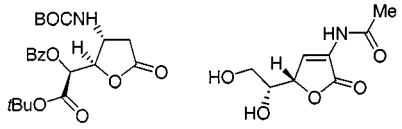
Keywords: Butenolides / Hydrogenations / Lactones / Silyl enol ethers / Stereoselectivity

The cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with oxalyl chloride afforded functionalized γ-alkylidene-α-hydroxybutenolides, which were transformed into *cis*-configured γ-lactones by diastereoselective hydrogenation.

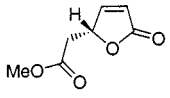
Introduction

Saturated γ-lactones are present in a variety of biologically relevant natural products.[1] Examples include goniofufurone,[2a,2b] a styryl lactone that proved cytotoxic to human tumour cells, aplasmomycin,[2c] boromycin,[2d] muscarine,[2e,2f] palytoxin,[2g] *C*-glycosides,[2h] and erythroskyrine.[2i] In addition, functionalized γ-lactones represent useful precursors for the synthesis of polyketide structures.[3] Unsaturated γ-lactones (butenolides) are also present in many biologically relevant ring systems:[4] lactone A, for example, was isolated from the marine sponge *Xestospongia*,[5] (+)-leptosphaerin is a metabolite of the marine ascomycete *Leptosphaeria oraemaris*,[6a] and compound WF-3681 is an aldose reductase inhibitor produced by *Chaetomella raphigera*.[6b] Ascorbic acid analogues[7] have been used as key intermediates in the synthesis of (+)- and (−)-eldanolide,[8] the antileukaemic lignans (+)-*trans*-burseran,[9] (−)-isostegane,[9] (+)- and (−)-steganacin,[10] (−)-verrucarinolactone,[11] and chrysanthemic acid analogues.[12]

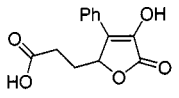


Lactone A

(+)-Leptosphaerin



Marine Sponge from *Xestospongia*

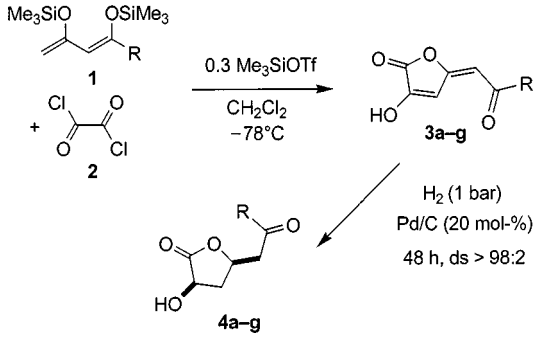


WF-3681

Although a number of syntheses of γ-lactones and butenolides are known,[13] they are in many cases limited to specific substitution patterns. The development of alternative strategies for the preparation of these important heterocycles is therefore of considerable importance. We have recently reported a new synthesis of γ-alkylidene-α-hydroxybutenolides by means of a Lewis acid catalysed cyclization of 1,3-bis(trimethylsilyoxy)-1,3-butadienes with oxalyl chloride.[14] Here we report an efficient approach to racemic γ-lactones, based on diastereoselective hydrogenation of γ-alkylidene-α-hydroxybutenolides.[15]

Results and Discussion

The Pd/C-catalysed hydrogenation[16] of γ-alkylidenebutenolide **3a**, which was efficiently prepared by Me_3SiOTf-catalysed cyclization of bis(silyl enol ether) **1a** with oxalyl chloride,[14b] afforded the γ-lactone **4a** in good yield and with very good *cis* diastereoselectivity. Treatment of dienes **1b**−**g** with oxalyl chloride afforded the novel butenolides **3b**−**g** in good yields. Hydrogenation of **3b**−**e** gave the *cis*-



Scheme 1. Synthesis of γ-butyrolactones **4a**−**g**

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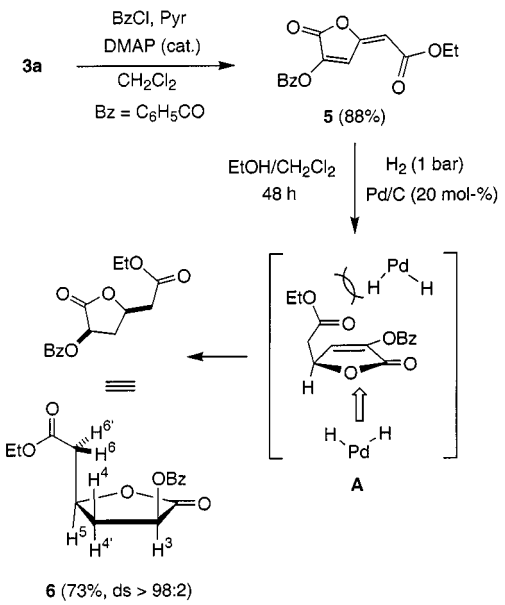
Table 1. Synthesis of butenolides **3** and lactones **4**

3/4	R	Yield of **3** (%)[a]	[a] Yield of **4** (%)[a]
a	OEt	74	74
b	OMe	72	72
c	O(*t*Bu)	73	85
d	O(*i*Bu)	56	87
e	OCH_2CH_2OMe	55	82
f	OCH_2Ph	50	0
g	*t*Bu	84	63

[a] Isolated yield.

configured γ-lactones **4b**−**e** with very good diastereoselectivities (Scheme 1, Table 1). A complex mixture was obtained in the hydrogenation of benzyl ester **3f**, whilst hydrogenation of the ketone-derived butenolide **3g** once more afforded the γ-lactone **4g** with very good *cis* diastereoselectivity.

The *cis* diastereoselectivity can be explained by the following observation: only the exocyclic double bond was hydrogenated when (a) the reaction time was shortened to 1 h, (b) the partial hydrogen pressure was reduced, or (c) the solution was not properly flushed with hydrogen. These results suggest that the exocyclic double bond was hydrogenated first,[17] to give intermediate **A**, and this was diastereoselectively hydrogenated from the sterically less encumbered side of the molecule (Scheme 2).



Scheme 2. Synthesis and structure elucidation of lactone **6**

The relative configurations of the γ-lactones were studied spectroscopically. In fact, the benzoyl-protected derivative **6** proved to be an excellent candidate for NMR experiments, due to the absence of any signal overlap. Lactone **6** was prepared in good yield and with very good diastereoselectivity from γ-alkylidenebutenolide **5**, which was obtained by protection of **3a** with benzoyl chloride. The ^{1}H NMR signals were assigned by H,H- and C,H-COSY experiments. Protons 6-H and 6-H′ both coupled with two protons (AB system), two signals were detected for the diastereotopic protons 4-H (δ = 3.06) and 4-H′ (δ = 2.16), which coupled with each other ($^2J_{4',4}$ = 12.8 Hz) and with hydrogen atoms 3-H and 5-H. The greater chemical shift for 4-H than for 4-H′ can be explained by the influence of the neighbouring ester groups. As was to be expected, high values were observed for the coupling constants $^3J_{3,4'}$ (10.3 Hz) and $^3J_{4',5}$ (10.3 Hz), indicating a *cis* relationship between the respective hydrogen atoms. In contrast, lower values were observed for $J_{4,5}$ (5.6 Hz) and $J_{3,4}$ (8.5 Hz). Related chemical shifts and coupling constants were observed for the corresponding resonances of lactones **4** (Table 2). In addition, NOESY experiments were helpful in establishing the relative configuration independently.

Inversion of configuration at the C-3 carbon atoms in lactones **4a** and **4b** was studied next. Treatment of the mesylate of **4a** with KOH resulted in decomposition. Treatment of **4a** with sodium benzoate afforded the desired products, but with only moderate stereoselectivity. We eventually found that application of the Mitsunobu procedure[18] with benzoic acid resulted in complete inversion of the configuration and formation of the *trans*-configured lactones **7a** and **7b** in good yields (Scheme 3). The configurations of the products were established by comparison of the spectroscopic data with those of lactone **6** (vide infra).

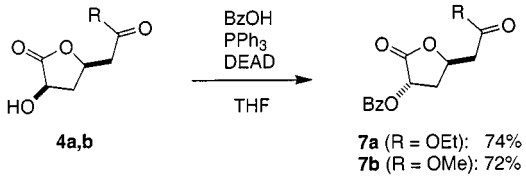
The hydroxy group at carbon atom C-3 allowed an efficient functionalization of the γ-lactone through SN_2 reactions with non-oxygen nucleophiles. Lactone **4a** was converted in high yield under standard conditions[19] into the mesylate **8** (Scheme 4). Treatment of **8** with sodium azide afforded lactone **9** with complete inversion of configuration.[19] Treatment of **8** with lithium bromide gave the bromide **10a** in high yield.[20] Unfortunately, the stereoselectivity here was rather low (*ds* = 2:1) and could not be improved by modification of the conditions. A slightly better selectivity (*ds* = 3:1) was observed on treatment of **8** with sodium iodide, which afforded the corresponding lactone **10b** in good yield. Treatment of **10a** with DBU resulted in the formation of the open-chain ester **11** rather than in the formation of a butenolide.[21] Product **11** was presumably formed by initial deprotonation of the CH_2 group adjacent to the ester, cleavage of the C5−O bond and subsequent elimination of HBr. The configuration of **11** was established by comparison of the ^{1}H NMR spectroscopic data with those reported in the literature.[22]

It seems appropriate to briefly compare the ^{1}H NMR spectroscopic features of lactones **4**, **6**, **7**, and **8** (Table 2). Thanks to the identical relative configurations of their substituents, lactones **4** all exhibited similar chemical shifts for protons 4-H, 4-H′, 3-H, and 5-H. Hydrogen atoms 4-H and 4-H′ were assigned on the basis of the observed coupling constants (vide supra). Hydrogen atoms 4-H were deshielded relative to 4-H′, due to through-space electronic effects of the adjacent hydroxy and ester groups. Because of the enhanced electron-withdrawing effect of the benzoyl group, larger chemical shifts were observed for protons 4-

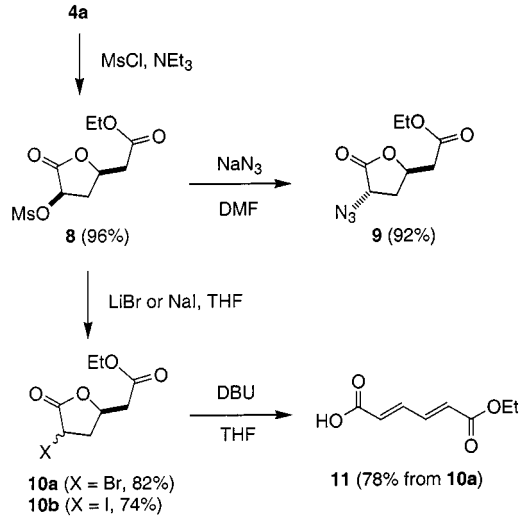
Table 2. Characteristic chemical shifts (^{1}H NMR)

Compd.	δ (4-H′)[a]	δ (4-H)[a]	δ (3-H)	δ (5-H)
4a	2.00 (ddd, 12.5, 10.6, 10.6)	2.90 (m)	4.58	4.82
4b	1.98 (ddd, 12.5, 10.5, 10.5)	2.82 (m)	4.58	4.82
4c	1.96 (ddd, 12.5, 10.5, 10.5)	2.80 (ddd, 12.5, 8.5, 5.5)	4.57	4.77
4d	1.95 (m)	2.60−2.95 (m)	4.55	4.80
4e	1.98 (ddd, 12.5, 10.5, 10.5)	2.80 (m)	4.60	4.80
4g	1.86 (ddd, 12.6, 10.4, 10.4)	2.82 (ddd, 12.6, 8.4, 5.4)	4.57	4.86
6	2.16 (ddd, 12.8, 10.3, 10.3)	3.06 (ddd, 12.8, 8.5, 5.6)	5.73	4.94
7a	2.60 (dd, 8.0, 7.8)	2.60 (dd, 8.0, 7.8)	5.67	5.12
7b	2.57 (dd, 8.0, 7.6)	2.57 (dd, 8.0, 7.6)	5.65	4.58
8	1.86 (ddd, 12.5, 10.5, 10.5)	2.95 (ddd, 12.5, 8.5, 5.5)	5.36	4.83
9	2.32 (t, 7.0)	2.32 (t, 7.0)	4.40	4.95

[a]Chemical shifts ($CDCl_3$) in ppm and coupling constants in Hz.



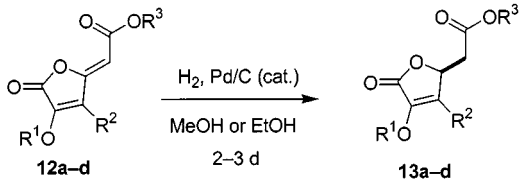
Scheme 3. Mitsunobu reactions of **4a** and **4b**



Scheme 4. Functionalization reactions of lactone **4a**

H, 4-H′, 3-H, and 5-H in **6** than for their counterparts in lactones **4**. In particular, the resonance of hydrogen atom 3-H was shifted downfield by more than 1 ppm, since it was directly influenced by the benzoyl group. In the case of the benzoyl derivatives **7a** and **7b**, similar shifts were observed for 3-H. Because of the inversion of configuration in the latter compound, the chemical shifts and coupling constants of 4-H, 4-H′, and 5-H differed significantly from those of lactones **4** and **6**. The hydrogen atoms 4-H′ and 4-H were deshielded and shielded, respectively, relative to the respective atoms of lactone **6**. This can be explained by the fact that both hydrogen atoms were both located next to a hydrogen atom (3-H or 5-H) and next to the ester or the benzoyloxy group. Therefore, dd signals were observed for both 4-H′ and 4-H, with coupling constants in the range of ca. 8 Hz. For mesylate **8** and lactones **4**, similar spectroscopic features were observed, except for a significant deshielding of hydrogen atom 3-H, located next to the mesylate group. The relative *trans* configuration of the substituents in azide **9** was supported by the deshielding and shielding of hydrogen atoms 4-H′ and 4-H, respectively.

Hydrogenation reactions of γ-alkylidenebutenolides containing an additional substituent were studied next (Scheme 5, Table 3). The Pd/C-catalysed hydrogenation of methoxy-substituted γ-alkylidenebutenolide **12a**[14b] afforded the ascorbic acid analogue **13a**. Only the exocyclic double bond was hydrogenated, with very good chemoselectivity. The product was isolated in 58% yield when the reaction was carried out under a hydrogen pressure of $p = 75$ bar. A better yield (70%) was obtained with hydrogen at atmospheric pressure. The yield could be further improved from 70 to 82% by use of the less polar, benzoyl-protected derivative **12b**, which was prepared from **12a** in good yield. The hydrogenation of the methyl- and ethyl-substituted derivatives **12c** and **12d** was equally efficient, and afforded the butenolides **13c** and **13d**, respectively, in good yields.



Scheme 5. Hydrogenation of butenolides **12a−d**

Table 3. Synthesis of ascorbic acid analogues **13a−d**

13	R^1	R^2	R^3	*p* [bar]	Solvent	Yield (%)[a]
a	H	OMe	Me	75	MeOH	58
a	H	OMe	Me	1	MeOH	70
b	Bz	OMe	Me	1	CH_2Cl_2	82
c	H	Me	Me	1	MeOH	71
d	H	Et	Et	1	EtOH	61

[a] Isolated yields.

In conclusion, we report a new approach to racemic *cis*-configured γ-lactones by diastereoselective hydrogenation of functionalized γ-alkylidenebutenolides. Our current work is directed towards the development of an enantioselective version of this methodology.

Experimental Section

General: See ref.[14b]

General Procedure for the Preparation of γ-Alkylidenebutenolides by Reaction of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with Oxalyl Chloride: A CH_2Cl_2 solution (7 mL) of Me_3SiOTf (0.45 mmol) was added at −78 °C to a CH_2Cl_2 solution (30 mL) of oxalyl chloride (1.5 mmol, 0.13 mL) and the 1,3-bis(trimethylsiloxy)-1,3-butadiene **3** (1.5 mmol). The temperature was allowed to rise to 20 °C over 6 h. After the mixture had been stirred for 2−6 h at 20 °C, a saturated solution of NaCl was added, the organic layer was separated, and the aqueous layer was repeatedly extracted with ether. The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel; ether/petroleum ether, 1:10 → 1:3).

Ethyl [4-Hydroxy-5-oxofuran-2(5*H*)-ylidene]acetate (3a): The synthesis of **3a** has been reported previously.[14b]

Methyl [4-Hydroxy-5-oxofuran-2(5*H*)-ylidene]acetate (3b): Starting from methyl acetoacetate (175 mg, 1.50 mmol), **3b** was isolated as a colourless solid (184 mg, 72%). ^{1}H NMR ([D$_6$]acetone, 250 MHz): δ = 3.81 (s, 3 H, OCH_3), 5.79 (s, 1 H, C*H*CO_2Me), 7.24 (s, 1 H, ring-CH). ^{13}C NMR ([D$_6$]acetone, 62.5 MHz): δ = 51.00 (OCH_3), 97.59 (*C*HCO_2Me), 108.00 (ring-CH), 149.53, 160.05, 163.40, 165.75 (C). IR (KBr): $\tilde{\nu}$ = 3230 cm^{-1}, 3147, 3080, 2983, 1775, 1696, 1382, 1146, 1088, 1038. MS (EI, 70 eV): *m*/*z* (%) = 170 (15) [M$^+$], 142 (10); the exact molecular mass *m*/*z* = 170.0215±2 mD [M$^+$] for $C_7H_6O_5$ was confirmed by HRMS (EI, 70 eV).

***tert*-Butyl [4-Hydroxy-5-oxofuran-2(5*H*)-ylidene]acetate (3c):** The synthesis of **3c** has been reported previously.[14b]

Isobutyl [4-Hydroxy-5-oxofuran-2(5*H*)-ylidene]acetate (3d): Starting from **1d** (1.00 g, 3.30 mmol), **3d** was isolated as a colourless solid (390 mg, 56%). ^{1}H NMR ([D$_6$]acetone, 250 MHz): δ = 0.94 (d, *J* = 7.0 Hz, 6 H, CH_3), 2.04 [nonuplet, *J* = 7.0 Hz, 1 H, C*H*$(CH_3)_2$], 3.93 (d, *J* = 7.0 Hz, 2 H, CH_2), 5.70 (d, *J* = 1.0 Hz, 1 H, C*H*CO_2), 7.24 (d, *J* = 1.0 Hz, 1 H, ring-CH). ^{13}C NMR ([D$_6$]acetone, 62.5 MHz): δ = 19.25 (CH_3), 28.44 [*C*H$(CH_3)_2$], 70.98 (CH_2), 98.74 (*C*HCO_2), 108.83 (ring-CH), 150.34, 160.74, 164.19, 166.14 (C). IR (KBr): $\tilde{\nu}$ = 3238 (br) cm^{-1}, 3084 (w), 2965 (m), 1777 (s), 1692 (s), 1632 (s), 1621 (s), 1408 (m), 1275 (m), 1092 (m). MS (EI, 70 eV): *m*/*z* (%) = 212 (4) [M$^+$], 157 (49), 139 (100); the exact molecular mass *m*/*z* = 212.0684±2 mD [M$^+$] for $C_{10}H_{12}O_5$ was confirmed by HRMS (EI, 70 eV). $C_{10}H_{12}O_5$ (212.2): calcd. C 56.60, H 5.70; found C 56.77, H 5.74.

2-Methoxyethyl [4-Hydroxy-5-oxofuran-2(5*H*)-ylidene]acetate (3e): Starting from methoxyethyl acetoacetate (1.00 g, 3.28 mmol), **3e** was isolated as a colourless solid (386 mg, 55%). ^{1}H NMR ([D$_6$]acetone, 250 MHz): δ = 3.31 (s, 3 H, OCH_3), 3.60, 4.26 (2 × t, *J* = 5.0 Hz, 2 × 2 H, OCH_2), 5.66 (d, *J* = 1.0 Hz, 1 H, C*H*CO_2), 7.13 (d, *J* = 1.0 Hz, 1 H, ring-CH). ^{13}C NMR ([D$_6$]acetone, 62.5 MHz): δ = 58.65 (OCH_3), 64.03, 70.90 (OCH_2), 98.53 (*C*HCO_2), 108.82 (ring-CH), 150.38, 160.93, 164.18, 166.01 (C). IR (KBr): $\tilde{\nu}$ = 3141 (br) cm^{-1}, 3097 (w), 3001 (w), 2963 (w), 1811 (s), 1716 (s), 1652 (m), 1620 (s), 1394 (m), 1228 (m), 1208 (m), 1140 (m), 1056 (s). MS (EI, 70 eV): *m*/*z* (%) = 214 (2) [M$^+$], 184 (3), 139 (100); the exact molecular mass *m*/*z* = 214.0477±2 mD [M$^+$] for $C_9H_{10}O_6$ was confirmed by HRMS (EI, 70 eV).

Benzyl [4-Hydroxy-5-oxofuran-2(5*H*)-ylidene]acetate (3f): Starting from **1f** (2.00 g, 5.94 mmol), **3f** was isolated as a colourless solid (726 mg, 50%). ^{1}H NMR ([D$_6$]acetone, 250 MHz): δ = 5.20 (s, 2 H, OCH_2), 5.74 (s, 1 H, C*H*CO_2), 7.15 (s, 1 H, ring-CH), 7.25−7.50 (Ph). ^{13}C NMR ([D$_6$]acetone, 62.5 MHz): δ = 66.61 (OCH_2), 98.43 (*C*HCO_2), 108.74 (ring-CH), 128.83, 128.88, 129.19 (CH, Ph), 136.98 (C, Ph), 150.34, 161.03, 164.09, 165.91 (C). IR (KBr): $\tilde{\nu}$ = 3222 (br) cm^{-1}, 3148 (m), 1776 (s), 1694 (s), 1631 (s), 1621 (s), 1402 (m), 1269 (s), 1244 (m), 1090 (m). MS (EI, 70 eV): *m*/*z* (%) = 246 [M$^+$] (22), 201 (19), 140 (60), 91 (100); the exact molecular mass *m*/*z* = 246.0528±2 mD [M$^+$] for $C_{13}H_{10}O_5$ was confirmed by HRMS (EI, 70 eV).

(5*E*)-5-(3,3-Dimethyl-2-oxobutylidene)-3-hydroxyfuran-2(5*H*)-one (3g): The synthesis of **3g** has previously been reported.[14b]

Ethyl (4-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (4a): A suspension of Pd/C (20 mol %) in EtOH/CH_2Cl_2 (1:1; 35 mL) was saturated with hydrogen (1 bar). To this suspension was added a solution of **3a** (185 mg, 1.00 mmol). After stirring for 72 h, the solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by filtration through a short pad of silica gel to give **4a** as a colourless solid (139 mg, 74%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.00 (ddd, $J_{4,4'}$ = 12.5 Hz, $J_{4,3}$ = $J_{4,5}$ = 10.6 Hz, 1 H, 4-H′), AB signal (δ_A = 2.70, δ_B = 2.85, $J_{A,B}$ = 17.6 Hz, $J_{A,5}$ = $J_{B,5}$ = 6.5 Hz, 2 H, 6-H, 6-H′), partly overlapped by 2.90 (m, 1 H, 4-H), 4.18 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.58 (dd, $J_{3,4}$ = 10.5 Hz, $J_{3,4'}$ = 8.5 Hz, 1 H, 3-H), 4.82 (dddd, $J_{5,4}$ = 10.5 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.5 Hz, $J_{5,4'}$ = 5.5 Hz, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 13.92 (CH_3), 36.33, 39.75 (CH_2), 61.01 (OCH_2), 68.09, 72.76 (CH), 169.47, 177.16 (C). IR (neat): $\tilde{\nu}$ = 3437 (br) cm^{-1}, 2984 (m), 2938 (m), 1779 (s), 1732 (s), 1651 (m), 1449 (s), 1409 (m), 1388 (s), 1371 (s), 1316 (s), 1284 (s), 1262 (s), 1189 (s), 1130 (s), 1026 (s). MS (DCI): *m*/*z* (%) = 394 (22) [2 M + NH_4^+], 206 [M + NH_4^+] (100).

Methyl (4-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (4b): Methylidenefuranone **3b** (170 mg, 1.00 mmol) was treated with hydrogen (1 bar) and Pd/C (20 mol %) in 5 mL of EtOH/CH_2Cl_2 (1:1). The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by filtration through a short pad of silica gel to give **4b** as a colourless oil (125 mg, 72%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.98 (ddd, $J_{4,4'}$ = 12.5 Hz, $J_{4,3}$ = $J_{4,5}$ = 10.5 Hz, 1 H, 4-H′), AB signal (δ_A = 2.70, δ_B = 2.90, $J_{A,B}$ = 17.5 Hz, $J_{A,5}$ = $J_{B,5}$ = 6.5 Hz, 2 H, 6-H, 6-H′), partly overlapped by 2.82 (m, 1 H, 4-H), 3.73 (s, 3 H, OCH_3), 4.58 (dd, $J_{3,4}$ = 10.5 Hz, $J_{3,4'}$ = 8.5 Hz, 1 H, 3-H), 4.82 (dddd, $J_{5,4}$ = 10.5 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.5 Hz, $J_{5,4'}$ = 5.5 Hz, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 36.41, 39.59 (CH_2), 52.05 (OCH_3), 68.16, 72.75 (CH), 169.89, 177.02 (C). MS (DCI): *m*/*z* (%) = 192 (100) [M + NH_4^+].

***tert*-Butyl (4-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (4c):** Methylidenefuranone **3c** (210 mg, 0.99 mmol) was treated with hydrogen (1 bar) and Pd/C (20 mol %) in 36 mL of CH_2Cl_2 (1:1). The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by filtration through a short pad of silica gel to give **4c** as a colourless solid (182 mg, 85%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.45 (s, 9 H, CH_3), 1.96 (ddd, $J_{4,4'}$ = 12.5 Hz, $J_{4,3}$ = $J_{4,5}$ = 10.5 Hz, 1 H, 4-H′), AB signal (δ_A = 2.60, δ_B = 2.78, $J_{A,B}$ = 17.5 Hz, $J_{A,5}$ = $J_{B,5}$ = 6.5 Hz, 2 H, 6-H, 6-H′),

partly overlapped by 2.80 (ddd, $J_{4',4}$ = 12.5 Hz, $J_{4',3}$ = 8.5 Hz, $J_{4',5}$ = 5.5 Hz, 1 H, 4-H), 4.57 (dd, $J_{3,4}$ = 10.5 Hz, $J_{3,4'}$ = 8.5 Hz, 1 H, 3-H), 4.77 (dddd, $J_{5,4}$ = 10.5 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.5 Hz, $J_{5,4'}$ = 5.5 Hz, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 27.99 (CH_3), 36.48, 41.10 (CH_2), 68.28, 73.14 (CH), 81.85 [$OC(CH_3)_3$], 168.63, 177.23 (C). IR (neat): $\tilde{\nu}$ = 3436 (br) cm^{-1}, 2980 (m), 2933 (m), 1779 (s), 1729 (s), 1476 (m), 1457 (m), 1395 (m), 1370 (s), 1315 (m), 1288 (m), 1257 (m), 1159 (s), 1026 (m). MS (DCI): *m/z* (%) = 450 (6) [2 M + NH_4^+], 234 (100) [M + NH_4^+].

Isobutyl (4-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (4d): Methylidenefuranone **3d** (163 mg, 0.77 mmol) was treated with hydrogen (1 bar) and Pd/C (20 mol %) in 24 mL of CH_2Cl_2. The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by filtration through a short pad of silica gel to give **4d** as a colourless oil (144 mg, 87%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.90 (d, *J* = 7.0 Hz, 6 H, CH_3), 1.95 [m, 2 H, 4-H′, C*H*(CH_3)$_2$], 2.60−2.95 (m, 3 H, 6-H, 6-H′, 4-H), 3.88 (d, *J* = 7.0 Hz, 2 H, OCH_2), 4.55 (m, 1 H, 3-H), 4.80 (m, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 18.92 (CH_3), 27.49 [*C*H(CH_3)$_2$], 36.48, 39.85 (CH_2), 68.23 (CH), 71.14 (OCH_2), 72.86 (CH), 169.47, 177.11 (C). IR (neat): $\tilde{\nu}$ = 3441 (br) cm^{-1}, 2963 (s), 2896 (m), 2876 (m), 1780 (s), 1735 (s), 1471 (m), 1408 (s), 1390 (m), 1371 (m), 1315 (m), 1284 (m), 1255 (m), 1188 (s), 1130 (s). MS (DCI): *m/z* (%) = 450 (40) [2 M + NH_4^+], 234 (100) [M + NH_4^+]. $C_{10}H_{16}O_5$ (216.2): calcd. C 55.55, H 7.46; found C 55.59, H 7.32.

2-Methoxyethyl (4-Hydroxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (4e): Methylidenefuranone **3e** (126 mg, 0.59 mmol) was treated with hydrogen (1 bar) and Pd/C (20 mol %) in 18 mL of CH_2Cl_2. The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by filtration through a short pad of silica gel to give **4e** as a colourless oil (105 mg, 82%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.98 (ddd, $J_{4,4'}$ = 12.5 Hz, $J_{4,3}$ = $J_{4,5}$ = 10.5 Hz, 1 H, 4-H′), AB signal (δ_A = 2.75, δ_B = 2.89, $J_{A,B}$ = 17.5 Hz, $J_{A,5}$ = $J_{B,5}$ = 6.5 Hz, 2 H, 6-H, 6-H′), overlapped by 2.80 (m, 1 H, 4-H), 3.39 (s, 3 H, OCH_3), 3.60, 4.25 (2 × t, *J* = 5.0 Hz, 2 × 2 H, OCH_2), 4.60 (dd, $J_{3,4}$ = 10.5 Hz, $J_{3,4'}$ = 8.5 Hz, 1 H, 3-H), 4.80 (dddd, $J_{5,4}$ = 10.5 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.5 Hz, $J_{5,4'}$ = 5.5 Hz, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 36.29, 39.63 (CH_2), 58.81 (OCH_3), 63.84 (OCH_2), 68.17 (CH), 70.06 (OCH_2), 72.68 (CH), 169.40, 177.00 (C). IR (neat): $\tilde{\nu}$ = 3404 (br) cm^{-1}, 2929 (m), 2854 (m), 1778 (s), 1737 (s), 1658 (m), 1454 (m), 1412 (m), 1378 (m), 1316 (m), 1284 (m), 1259 (m), 1184 (s), 1128 (s), 1100 (s), 1030 (s). MS (DCI): *m/z* (%) = 454 (8) [2 M + NH_4^+], 236 (100) [M + NH_4^+].

5-(3,3-dimethyl-2-oxobutyl)-3-hydroxyfuran-2(5*H*)-one (4g): (5*E*)-5-(3,3-Dimethyl-2-oxobutylidene)-3-hydroxyfuran-2(5*H*)-one (**3g**) (50 mg, 0.26 mmol) was treated with hydrogen (1 bar) and Pd/C (20 mol %) in 5 mL of EtOH/CH_2Cl_2 (1:1). The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1:4) to give **4g** as a colourless solid (33 mg, 63%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.14 [s, 9 H, $C(CH_3)_3$], 1.86 (ddd, $J_{4,4'}$ = 12.6 Hz, $J_{4,3}$ = $J_{4,5}$ = 10.4 Hz, 1 H, 4-H′), AB signal (δ_A = 2.76, δ_B = 3.15, $J_{A,B}$ = 17.7 Hz, $J_{A,5}$ = $J_{B,5}$ = 6.4 Hz, 2 H, 6-H, 6-H′), partly overlapped by 2.82 (ddd, $J_{4',4}$ = 12.6 Hz, $J_{4',3}$ = 8.4 Hz, $J_{4',5}$ = 5.4 Hz, 1 H, 4-H), 4.57 (dd, $J_{3,4}$ = 10.6 Hz, $J_{3,4'}$ = 8.4 Hz, 1 H, 3-H), 4.86 (dddd, $J_{5,4}$ = 10.4 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.4 Hz, $J_{5,4'}$ = 5.4 Hz, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 25.99 [$C(CH_3)_3$], 36.85, 42.03 (C-4, C-6), 44.17 [$C(CH_3)_3$], 68.27, 73.21 (C-3, C-5), 177.27 (C-2), 212.16 (O=C*t*Bu). MS (70 eV, DCI): *m/z* (%) = 418 (12) [2 M + NH_4^+], 235 (24), 218 (100) [M + NH_4^+].

Ethyl (4-Benzyloxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (5): A CH_2Cl_2 (70 mL) solution of **3a** (591 mg, 3.21 mmol), benzoyl chloride (0.41 mL, 1.1 equiv.), pyridine (0.39 mL, 1.5 equiv.), and DMAP (catalytic amount) was stirred at 0 °C for 24 h. Water was added to the solution, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether, 1:1) to give **5** as a colourless solid (820 mg, 88%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.35 (t, *J* = 7.0 Hz, 3 H, CH_3), 4.30 (q, *J* = 7.0 Hz, 2 H, OCH_2), 6.00 (s, 1 H, C*H*CO_2Me), 8.55 (t, *J* = 8.0 Hz, 2 H, Ph), 8.65 (t, *J* = 8.0 Hz, 1 H, Ph), 8.20 (d, *J* = 8.0 Hz, 2 H, Ph), 8.40 (s, 1 H, ring-CH).

Ethyl [4-(Benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl]acetate (6): Compund **5** (426 mg, 1.5 mmol) was treated with hydrogen (1 bar) and Pd/C (20 mol %) in EtOH/CH_2Cl_2 (1:1, 50 mL). The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1:5) to give **6** as a colourless solid (315 mg, 73%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.16 (ddd, $J_{4',4}$ = 12.8 Hz, $J_{4',5}$ = $J_{4',3}$ = 10.3 Hz, 1 H, 4-H′), AB signal (δ_A = 2.75, δ_B = 2.94, $J_{A,B}$ = 16.4 Hz, $J_{A,5}$ = 6.2 Hz, $J_{B,5}$ = 6.8 Hz, 2 H, 6-H, 6-H′), 3.06 (ddd, $J_{4,4'}$ = 12.8 Hz, $J_{4,3}$ = 8.5 Hz, $J_{4,5}$ = 5.6 Hz, 1 H, 4-H), 4.20 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2), 4.94 (m, not completely resolved dddd, $J_{5,4'}$ = 10.3 Hz, $J_{5,6(B)}$ = 6.8 Hz, $J_{5,6(A)}$ = 6.2 Hz, $J_{5,4}$ = 5.6 Hz, 1 H, 5-H), 5.73 (dd, $J_{3,4'}$ = 10.3 Hz, $J_{3,4}$ = 8.5 Hz, 1 H, 3-H), 7.43−8.09 (m, 5 H, Ar). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 14.11 (CH_3), 34.76, 40.07 (C-4, C-6), 61.25 (CH_2O), 68.80, 72.80 (C-3, C-5), 128.53 (CH, Ph), 130.01, 130.08 (CH, Ph; C, Ph), 133.79 (CH, Ph), 165.35, 168.98, 171.59 ($PhCO_2$, C-2, CO_2Et). MS (70 eV, EI): *m/z* (%) = 292 (25) [M^+]; the exact molecular mass *m/z* = 292.0947±2 mD [M^+] for $C_{15}H_{16}O_6$ was confirmed by HRMS (EI, 70 eV).

Synthesis of γ-Lactones 7a and 7b: A toluene solution (1 mL) of DEAD (0.133 mL, 0.85 mmol) was added at 0 °C to a degassed toluene solution (10 mL) of **4a** (154 mg, 0.82 mmol), benzoic acid (104 mg, 0.85 mmol), and PPh_3 (322 mg, 1.23 mmol). The solution was stirred at 20 °C for 14 h. The solvent was removed in vacuo, and the residue was purified by chromatography (silica gel; ether/petroleum ether, 1:3) to give **7a** as a slightly yellow oil (172 mg, 72%).

Ethyl [4-(Benzyloxy)-5-oxotetrahydrofuran-2-yl]acetate (7a): Starting from **4a** (154 mg, 0.82 mmol), **7a** was isolated as a slightly yellow oil (177 mg, 74%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.28 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.60 (dd, *J* = 8.0, *J* = 7.8, 2 H, 4-H, 4-H′), 2.80 (m, 2 H, 6-H, 6-H′), 4.20 (q, *J* = 7.0 Hz, 2 H, OCH_2), 5.12 (quint, *J* = 6.8 Hz, 5-H), 5.67 (t, *J* = 8.0 Hz, 1 H, 3-H), 7.40−7.60 (m, 3 H, Ph), 8.07 (dt, *J* = 6.3, *J* = 1.2, 2 H, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 13.98 (CH_3), 33.40, 39.36 (CH_2), 61.00 (OCH_2), 68.41, 73.96 (CH), 128.37 (CH, Ph), 128.48 (C, Ph), 129.80, 133.61 (CH, Ph), 165.22, 169.09, 172.16 (C). IR (neat): $\tilde{\nu}$ = 3441 (br) cm^{-1}, 2963 (s), 2896 (m), 2876 (m), 1780 (s), 1735 (s), 1471 (m), 1408 (s), 1390 (m), 1371 (m), 1315 (m), 1284 (m), 1255 (m), 1188 (s), 1130 (s). MS (EI, 70 eV): *m/z* (%) = 292 (4) [M^+], 105 (100); the exact molecular mass *m/z* = 292.0946±2 mD [M^+] for $C_{15}H_{16}O_6$ was confirmed by HRMS (EI, 70 eV).

Methyl [4-(Benzyloxy)-5-oxotetrahydrofuran-2-yl]acetate (7b): Starting from **4a** (174 mg, 1.00 mmol), **7b** was isolated as a slightly yellow oil (200 mg, 72%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.57 (dd, *J* = 8.0, *J* = 7.6, 2 H, 4-H, 4-H′), 2.78 (m, 2 H, 6-H, 6-H′), 3.69 (s, 3 H, OCH_3), 4.58 (quint, *J* = 6.3 Hz, 5-H), 5.65 (t, *J* = 7.7 Hz, 1 H, 3-H), 7.35−7.60 (m, 3 H, Ph), 8.02 (d, *J* = 7.4 Hz, 2 H, Ph). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 33.45, 39.14 (CH_2),

51.98 (OCH_3), 68.42, 73.93 (CH), 128.40 (CH, Ph), 128.48 (C, Ph), 129.83, 133.64 (CH, Ph), 165.24, 169.57, 172.14 (C). IR (KBr): $\tilde{\nu}$ = 3441 (br) cm^{-1}, 2953 (s), 1781 (s), 1724 (s), 1450 (m), 1439 (m), 1362 (m), 1340 (m), 1328 (m), 1285 (s), 1188 (m), 1126 (s). MS (EI, 70 eV): *m*/*z* (%) = 278 (16) [M^+], 105 (100); the exact molecular mass *m*/*z* = 278.0790±2 mD [M^+] for $C_{14}H_{14}O_6$ was confirmed by HRMS (EI, 70 eV).

Ethyl {4-[(Methylsulfonyl)oxy]-5-oxotetrahydrofuran-2-yl}acetate (8): A CH_2Cl_2 solution (40 mL) of **4a** (130 mg, 0.69 mmol), NEt_3 (0.143 mL, 1.03 mmol), and mesyl chloride (0.080 mL, 1.03 mmol) was stirred at 0 °C for 1 h. Water was added to the solution, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo to give **8** as a colourless solid (176 mg, 96%). ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.21 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.86 (ddd, $J_{4,4'}$ = 12.5 Hz, $J_{4,3}$ = $J_{4,5}$ = 10.5 Hz, 1 H, 4-H′), AB signal (δ_A = 2.65, δ_B = 2.80, $J_{A,B}$ = 17.5 Hz, $J_{A,5}$ = $J_{B,5}$ = 6.5 Hz, 2 H, 6-H, 6-H′), 2.95 (ddd, $J_{4',4}$ = 12.5 Hz, $J_{4',3}$ = 8.5 Hz, $J_{4',5}$ = 5.5 Hz, 1 H, 4-H), 3.10 (s, 3 H, SCH_3), 4.11 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.83 (dddd, $J_{5,4}$ = 10.5 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.5 Hz, $J_{5,4'}$ = 5.5 Hz, 1 H, 5-H), 5.36 (dd, $J_{3,4}$ = 10.5 Hz, $J_{3,4'}$ = 8.5 Hz, 1 H, 3-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 13.87 (CH_3), 34.48 (CH_2), 39.32 (SCH_3), 39.37 (CH_2), 61.02 (OCH_2), 72.93, 73.74 (CH), 168.77, 170.69 (C). IR (neat): $\tilde{\nu}$ = 3334 (br) cm^{-1}, 3027 (m), 2985 (m), 2942 (m), 1793 (s), 1732 (s), 1656 (m), 1449 (m), 1411 (s), 1361 (s), 1290 (m), 1264 (s), 1178 (s), 1097 (s), 1061 (s), 1029 (s), 1003 (s). MS (DCI): *m*/*z* (%) = 550 (100) [2 M + NH_4^+], 284 (87) [M + NH_4^+].

Ethyl (4-Azido-5-oxotetrahydrofuran-2-yl)acetate (9): A DMF solution (1 mL) of **8** (105 mg, 0.39 mmol) and NaN_3 (38 mg, 0.59 mmol) was stirred for 12 h at 20 °C. The solution was filtered, and the filtrate was concentrated in vacuo to give **9** as a colourless oil (76 mg, 92%). ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.28 (t, *J* = 6.3 Hz, 3 H, CH_3), 2.32 (t, *J* = 7.0 Hz, 2 H, 4-H, 4-H′), 2.73 (m, 2 H, 6-H, 6-H′), 4.15 (q, *J* = 6.3 Hz, 2 H, OCH_2), 4.40 (t, *J* = 7.2 Hz, 1 H, 3-H), 4.95 (quint, *J* = 6.5 Hz, 5-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 14.02 (CH_3), 33.33, 39.18 (CH_2), 56.88 (CH, C-3), 61.16 (OCH_2), 74.52 (CH, C-5), 169.02, 172.66 (C). MS (DCI): *m*/*z* (%) = 231 (100) [M + NH_4^+].

Ethyl (4-Bromo-5-oxotetrahydrofuran-2-yl)acetate (10a): A THF solution (2.5 mL) of **8** (106 mg, 0.40 mmol) and LiBr (69 mg, 0.80 mmol) was stirred for 20 h at 20 °C. The solution was filtered, and the filtrate was concentrated in vacuo to give **10a** as a colourless oil (82 mg, 82%, *ds* = 2:1). ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.25 (t, *J* = 6.5 Hz, 3 H, CH_3), 2.25−3.25 (m, 4 H, 4-H, 6-H), 4.15 (q, *J* = 6.5 Hz, 2 H, OCH_2), 4.45 (dd, *J* = 6.6, *J* = 1.0, 3-H, major isomer), 4.55 (t, *J* = 7.0 Hz, 3-H, minor isomer), 4.92 (quint, *J* = 6.5 Hz, 5-H, minor isomer), 5.10 (m, 5-H, major isomer). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 14.01 (CH_3, both isomers), 37.03, 38.07 (CH, C-3), 38.28, 38.62, 38.92, 39.53 (CH_2), 61.12 (OCH_2), 74.93, 75.18 (CH, C-5), 168.93, 168.97 (C), 172.66 (C, both isomers). MS (DCI): *m*/*z* (%) = 251, 249 (4) [M^+], 204, 206 (25), 162, 164 (25); the exact molecular mass *m*/*z* = 249.9840±2 mD [M^+] for $C_8H_{11}O_4Br$ was confirmed by HRMS (EI, 70 eV).

Ethyl (4-Iodo-5-oxotetrahydrofuran-2-yl)acetate (10b): A THF solution (2.5 mL) of **8** (105 mg, 0.40 mmol) and NaI (120 mg, 0.80 mmol) was stirred for 20 h at 20 °C. The solution was filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1:3) to give **10b** as a colourless oil (88 mg, 74%, *ds* = 3:1). ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.25 (t, *J* = 6.5 Hz, 3 H, CH_3), 2.30−3.20 (m, 4 H, 4-H, 6-H), 4.20 (q, *J* = 6.5 Hz, 2 H, OCH_2), 4.58 (dd, *J* = 6.6, *J* = 1.0, 3-H, major isomer), 4.72 (t, *J* = 7.0 Hz, 3-H, minor isomer), 5.05 (m, 1 H, 5-H, both isomers). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 7.45, 10.40 (CH, C-3), 14.01 (CH_3, both isomers), 38.58, 39.31, 39.80, 40.67 (CH_2), 61.324 (OCH_2, both isomers), 75.33, 76.09 (CH, C-5), 169.04, 169.09, 173.80, 173.91 (C). IR (neat): $\tilde{\nu}$ = 3521 (br) cm^{-1}, 2983 (m), 2936 (m), 1780 (s), 1732 (s), 1630 (m), 1465 (m), 1403 (s), 1386 (s), 1349 (m), 1325 (s), 1314 (s), 1283 (s), 1264 (s), 1173 (s), 1097 (s). MS (DCI): *m*/*z* (%) = 298 (44) [M^+], 253 (41), 210 (42), 171 (100); the exact molecular mass *m*/*z* = 297.9702±2 mD [M^+] for $C_8H_{11}O_4I$ was confirmed by HRMS (EI, 70 eV).

6-Ethoxy-6-oxohexa-2,4-dienoic Acid (11): A THF solution (5 mL) of lactone **10** (80 mg, 0.32 mmol) and DBU (100 mg, 0.66 mmol) was stirred at 20 °C for 24 h. The solution was worked up in the usual way. Product **11** was isolated by chromatography (silica gel; ether); yield: 43 mg, 78%. The configuration of **11** was established by comparison of its ^1H NMR spectroscopic data with those reported in the literature for the (*E*,*Z*) and (*Z*,*Z*) isomers.[22] The product was obtained as a 2.5:1 mixture of (*E*,*E*) and (*E*,*Z*) isomers. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.30 (t, *J* = 6.5 Hz, 3 H, CH_3 both isomers), 4.25 (q, *J* = 6.5 Hz, 2 H, OCH_2 both isomers), 6.01 (d, *J* = 14.0 Hz, 1 H, CH minor isomer), 6.18 (d, *J* = 16.0 Hz, 1 H, CH minor isomer), 6.22 (m, 2 H, CH major isomer), 6.75 (t, *J* = 14.0 Hz, 1 H, CH minor isomer), 7.35 (m, 2 H, CH major isomer), 8.35 (dd, *J* = 14.0, *J* = 16.0 Hz, 1 H, CH minor isomer). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 14.17 (CH_3, both isomers), 60.90, 60.99 (OCH_2), 123.72, 127.41, 129.32, 129.90, 138.15, 140.33, 142.56, 142.90 (CH), 165.76, 166.03, 170.04, 170.59 (C). MS (DCI): *m*/*z* (%) = 170 (19) [M^+], 152 (19), 125 (63), 97 (100).

Synthesis of γ-Alkylidenebutenolides 12a, 12c, and 12d: The synthesis of these compounds has been reported.[14b]

Methyl [4-(Benzyloxy)-3-methoxy-5-oxofuran-2(5*H*)-ylidene]acetate (12b): A CH_2Cl_2 (40 mL) solution of **12a** (200 mg, 1.00 mmol), benzoyl chloride (0.13 mL, 1.1 equiv.), pyridine (0.12 mL, 1.5 equiv.), and DMAP (catalytic amount) was stirred at 0 °C for 24 h. Water was added to the solution, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1:1) to give **12b** as a colourless solid (255 mg, 84%). ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.81 (s, 3 H, OCH_3), 4.13 (s, 3 H, OCH_3), 5.72 (s, 1 H, C*H*CO_2Me), 7.40−7.75 (m, 3 H, Ph), 8.12 (m, 2 H, Ph). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 51.16, 59.49 (OCH_3), 97.80 (*C*HCO_2Me), 126.97 (C), 128.90, 130.61 (CH, Ph), 133.68 (C), 134.75 (Ph, CH), 149.71, 153.23, 161.78, 163.31, 163.44 (C). MS (EI, 70 eV): *m*/*z* (%) = 305 (3) [M^+ + 1], 304 [M^+], 105 (100); the exact molecular mass *m*/*z* = 304.0583±2 mD [M^+] for $C_{15}H_{12}O_7$ was confirmed by HRMS (EI, 70 eV).

Methyl (4-Hydroxy-3-methoxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (13a): Pd/C (20 mol %) was added to a methanol solution (10 mL) of **12a** (100 mg, 0.50 mmol). The solution was treated with hydrogen (75 bar) for 48 h at 20 °C. The solution was filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1:3) to give **14a** as a colourless solid (58 mg, 58%). The product was isolated in 70% yield (70 mg) when the reaction was carried out under a hydrogen pressure of 1 bar. ^1H NMR ($CDCl_3$, 250 MHz): δ = AB signal (δ_A = 2.53, δ_B = 2.87, $J_{A,B}$ = 16.4 Hz, $J_{A,5}$ = 8.8 Hz, $J_{B,5}$ = 3.7 Hz, 2 H, 6-H), 3.73 (s, 3 H, OCH_3), 4.18 (s, 3 H, CO_2CH_3), 5.07 (dd,

$J_{5,6H(A)}$ = 8.8 Hz, $J_{5,6H(B)}$ = 3.7 Hz, 1 H, 5-H), 5.67 (s, 1 H, OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 37.10 (C-6), 52.19, 59.53 (H_3COC=C, CO_2CH_3), 72.62 (C-5), 118.63, 151.67 (C-3, C-4), 169.52, 171.07 (C-2, CO_2Me). $C_8H_{10}O_6$ (202.2): calcd. C 47.53, H 4.99; found C 47.67, H 5.02.

Methyl [4-(Benzyloxy)-3-methoxy-5-oxo-2,5-dihydrofuran-2-yl]acetate (13b): Pd/C (20 mol %) was added to a CH_2Cl_2 solution (10 mL) of **12b** (80 mg, 0.26 mmol). The suspension was treated with hydrogen (1 bar) for 48 h at 20 °C and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1:3) to give **13b** as a colourless solid (66 mg, 82%). ^{1}H NMR ([D$_6$]acetone, 250 MHz): δ = AB signal (δ_A = 2.70, δ_B = 3.08, $J_{A,B}$ = 16.5 Hz, $J_{A,5}$ = 8.7 Hz, $J_{B,5}$ = 3.6 Hz, 2 H, 6-H), 3.65 (s, 3 H, OCH_3), 4.18 (s, 3 H, CO_2CH_3), 5.27 (dd, $J_{5,6H(A)}$ = 8.8 Hz, $J_{5,6H(B)}$ = 3.6 Hz, 1 H, 5-H), 7.50−7.60 (m, 2 H, Ph), 7.70−7.80 (m, 1 H, Ph), 8.12 (m, 2 H, Ph). ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 37.35 (C-6), 52.19, 60.33 (CH_3), 73.21 (CH, C-5), 114.50, 128.83 (C), 129.82, 130.98, 135.23 (CH, Ph), 163.90, 164.44, 166.81, 169.75 (C). MS (EI, 70 eV): *m*/*z* (%) = 306 (3) [M$^+$], 105 (100); the exact molecular mass *m*/*z* = 306.0740±2 mD [M$^+$] for $C_{15}H_{14}O_7$ was confirmed by HRMS (EI, 70 eV).

Methyl (4-Hydroxy-3-methyl-5-oxo-2,5-dihydrofuran-2-yl)acetate (13c): A methanol suspension (5 mL) of Pd/C (20 mol %) was repeatedly flushed with hydrogen (1 bar). Methyl (2*Z*)-[4-hydroxy-3-methyl-5-oxofuran-2(5*H*)-ylidene]acetate (**12c**; 63 mg, 0.34 mmol) was added, and the suspension was again flushed with hydrogen. The reaction mixture was stirred for 48 h at 20 °C (1 bar) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel; ether/petroleum ether, 1:3) to give **13c** as a colourless solid (45 mg, 71%). ^{1}H NMR ([D$_6$]acetone, 250 MHz): δ = 1.90 (s, 3 H, 4-CH_3), AB signal (δ_A = 2.46, δ_B = 2.98, $J_{A,B}$ = 16.2 Hz, $J_{A,5}$ = 8.8 Hz, $J_{B,5}$ = 3.5 Hz, 2 H, 6-H), 3.66 (s, 3 H, CH_3O), 5.09−5.18 (m, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 9.25 (CH_3), 37.52 (C-6), 52.29 (CH_3O), 77.73 (C-5), 130.53, 137.88 (C-3, C-4), 169.70, 169.89 (C-2, CO_2Me). MS (70 eV, EI): *m*/*z* (%) = 186 (22) [M$^+$]; the exact molecular mass *m*/*z* = 186.0528±2 mD [M$^+$] for $C_8H_{10}O_5$ was confirmed by HRMS (EI, 70 eV).

Ethyl (3-Ethyl-4-hydroxy-5-oxo-2,5-dihydrofuran-2-yl)acetate (13d): Methylidenefuranone **12d** (56 mg, 0.26 mmol) was treated with hydrogen (1 bar) and Pd/C (20 mol %) in 5 mL of EtOH. The solution was filtered, the filtrate was concentrated in vacuo, and the residue was purified by chromatography (silica gel; ether/petroleum ether, 1:3) to give **13d** as a colourless solid (35 mg, 61%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.27 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$CH$_2$O), 1.67 (t, *J* = 7.6 Hz, 3 H, C*H*$_3$CH$_2$C=C), AB signal (δ_A = 2.13, δ_B = 2.18, $J_{A,B}$ = 7.6 Hz, $J_{A,X}$ = $J_{B,X}$ = 7.6 Hz, 2 H, CH$_2$C=C), AB signal (δ_A = 2.48, δ_B = 2.80, $J_{A,B}$ = 16.1 Hz, $J_{A,5}$ = 8.6 Hz, $J_{B,5}$ = 3.9 Hz, 2 H, 6-H), 4.18 (q, *J* = 7.1 Hz, 2 H, CH$_3$C*H*$_2$O), 5.26 (dd, $J_{5,6H(A)}$ = 8.6 Hz, $J_{5,6H(B)}$ = 3.9 Hz, 1 H, 5-H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.55, 14.09 (*C*H$_3$CH$_2$C=C, *C*H$_3$CH$_2$O), 17.80 (*C*H$_2$C=C), 37.94 (C-6), 61.31 (CH$_2$O), 76.78 (C-5), 134.82, 137.27 (C-3, C-4), 169.25, 169.89 (C-2, CO_2Et). MS (70 eV, EI): *m*/*z* (%) = 214 (32) [M$^+$]. A small amount of an unknown impurity could not be separated.

[1] For a review, see: U. Ravid, R. M. Silverstein, L. R. Smith, *Tetrahedron* **1978**, *34*, 1449.

[2] [2a] C. Cagnolini, M. Ferri, P. R. Jones, P. J. Murphy, B. Ayres, B. Cox, *Tetrahedron* **1997**, *53*, 4815. [2b] P. J. Murphy, *J. Chem. Soc., Chem. Commun.* **1992**, 1096. [2c] E. J. Corey, D. H. Hua, B.-C. Pan, S. P. Seitz, *J. Am. Chem. Soc.* **1982**, *104*, 6818. [2d] M. A. Avery, S. C. Choudhry, O. P. Dhingra, M. Kang, J. D. White, A. J. Whittle, *J. Am. Chem. Soc.* **1983**, *105*, 6517. [2e] R. Amouroux, B. Gerin, M. Chastrette, *Tetrahedron Lett.* **1982**, 4341. [2f] M. Chmielewski, P. Guzik, *Heterocycles* **1984**, *22*, 7. [2g] Y. Kishi, S. S. Ko, L. L. Klein, K.-P. Pfaff, *Tetrahedron Lett.* **1982**, 4415. [2h] M. Lakhrissi, Y. Chapleur, *Angew. Chem.* **1996**, *108*, 833; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 750−752. [2i] L. Herrera, M. S. Pino Gonzalez, M. Nieto Sampedro, R. M. Dominguez Aciego, *Tetrahedron* **1989**, *45*, 269.

[3] [3a] S. Hanessian, P. J. Murray, S. P. Sahoo, *Tetrahedron Lett.* **1985**, 5623. For hydrogenations of butenolides, see: [3b] G. Stork, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1987**, *109*, 1564.

[4] Reviews: [4a] Y. S. Rao, *Chem. Rev.* **1976**, *76*, 625. [4b] G. Pattenden, *Prog. Chem. Nat. Prod.* **1978**, *35*, 133. [4c] D. W. Knight, *Contemp. Org. Synth.* **1994**, *1*, 287.

[5] E. Quinoà, E. Kho, L. V. Manes, P. Crews, G. Bakus, *J. Org. Chem.* **1986**, *51*, 4260.

[6] [6a] A. J. Pallenberg, J. D. White, *Tetrahedron Lett.* **1986**, 5591. [6b] T. Namiki, M. Nishikawa, Y. Itoh, I. Uchida, M. Hashimoto, *Tetrahedron Lett.* **1987**, 1400.

[7] J. A. J. M. Vekemans, G. A. M. Franken, C. W. M. Dapperens, E. F. G. Godefroi, *J. Org. Chem.* **1988**, *53*, 627.

[8] J. P. Vigneron, R. Meric, M. Larcheveque, A. Debal, J. Y. Lallemand, G. Kunesch, P. Zagetti, M. Gallois, *Tetrahedron* **1984**, *40*, 3521.

[9] K. Tomioka, T. Ishiguro, K. Koga, *J. Chem. Soc., Chem. Commun.* **1979**, 652.

[10] K. Tomioka, T. Ishiguro, Y. Iitaka, K. Koga, *Tetrahedron* **1984**, *40*, 1303.

[11] K. Tomioka, F. Sato, K. Koga, *Heterocycles* **1982**, *17*, 311.

[12] J. Mann, A. Thomas, *J. Chem. Soc., Chem. Commun.* **1985**, 737.

[13] For recent syntheses, see: C. Harcken, R. Brückner, *Angew. Chem.* **1997**, *109*, 2866; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2750, and references cited therein.

[14] [14a] P. Langer, M. Stoll, *Angew. Chem.* **1999**, *111*, 1919; *Angew. Chem. Int. Ed.* **1999**, *38*, 1803. [14b] P. Langer, T. Schneider, M. Stoll, *Chem. Eur. J.* **2000**, *6*, 3204.

[15] For related hydrogenations of butenolides, see: [15a] C. Marino, O. Varela, R. M. de Lederkremer, *Carbohydr. Res.* **1990**, *220*, 145. [15b] L. O. Jerocic, O. J. Varela, A. F. Cirelli, R. M. de Lederkremer, *Tetrahedron* **1984**, *40*, 1425.

[16] A. J. Poss, M. S. Smyth, *Tetrahedron Lett.* **1988**, *29*, 5723.

[17] This assumption is also supported by the selective hydrogenation of the exocyclic double bond of 3-(benzoyloxy)-5-ethylidene-2(5*H*)-furanone with Pd/$BaSO_4$ as the catalyst: [17a] O. J. Varela, A. F. Cirelli, R. M. de Lederkremer, *Carbohydr. Res.* **1982**, *100*, 424. [17b] C. Marino, O. Varela, R. M. de Lederkremer, *Carbohydr. Res.* **1991**, *220*, 145.

[18] [18a] J. Mulzer, N. Salimi, *Liebigs Ann. Chem.* **1986**, 1172. [18b] O. Mitsunobu, *Synthesis* **1981**, 1.

[19] J. A. J. M. Vekemans, R. G. M. de Bruyn, R. C. H. M. Caris, A. J. P. M. Kokx, J. J. H. G. Konings, E. F. Godefroi, *J. Org. Chem.* **1987**, *52*, 1093.

[20] [20a] J. Gharbi-Benarous, M. S. Morales-Rios, G. Dana, *Can. J. Chem.* **1985**, *63*, 2384. [20b] C. Herdeis, J. Telser, *Eur. J. Org. Chem.* **1999**, 1407.

[21] S. Kanemasa, N. Nakagawa, H. Suga, O. Tsuge, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 171.

[22] [22a] B. J. Adger, C. Barrett, J. Brennan, P. McGuigan, M. A. McKervey, B. Tarbit, *J. Chem. Soc., Chem. Commun.* **1993**, 1220. [22b] M. M. Rogic, T. R. Demmin, *J. Am. Chem. Soc.* **1978**, *100*, 5472. [22c] A. Funke, P. Karrer, *Helv. Chim. Acta* **1949**, *32*, 1017.

Received November 19, 2001
[O01539]