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Diastereo- and Enantioselective Synthesis of 4- and 3,4-Substituted 2-Acetoxy-butyrolactones

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Abstract: An efficient asymmetric synthesis of 4-mono- and 3,4-disubstituted 2-acetoxy-butyrolactones **2** has been developed, based on a hydrazone-mediated asymmetric aldol reaction, an intramolecular lactonization and a stereoselective hydrogenation of the resulting butenolides **1**. An application of this process in the synthesis of the natural hunger substance **3** (ee = 90%) is also presented. © 1999 Elsevier Science Ltd. All rights reserved.

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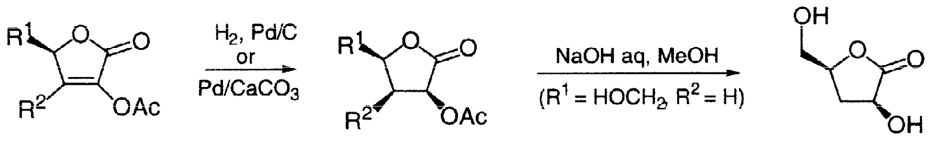
2-Hydroxylated butyrolactones are common structural features of many natural and synthetic biologically active compounds and are also versatile synthetic building blocks [1]. For example, some 4-alkyl-2-hydroxy-butyrolactones are excellent food intake-control substances [1a]. (2*S*,4*S*)-2-hydroxy-4-hydroxymethyl-butyrolactone **3** (3-DPA lactone) is a natural hunger substance [1b,2a]. Racemic butyrolactone **2a** has been used as a key intermediate in the total synthesis of racemic nonactin [1c]. Moreover, this class of lactones have been used as precursors to 1,3-diols, which are structural fragments frequently found in many natural products [1d,e].



1a $R^1 = Me, R^2 = H$
1b $R^1 = BnOCH_2, R^2 = H$
1c $R^1 = Me_2CHCH_2, R^2 = H$
1d $R^1 = n\text{-}Bu, R^2 = H$
1e $R^1 = Ph, R^2 = H$
1f $R^1 = Me, R^2 = Me$
1g $R^1 = Me, R^2 = Bn$

2a $R^1 = Me, R^2 = H$
2b $R^1 = HOCH_2, R^2 = H$
2c $R^1 = Me_2CHCH_2, R^2 = H$
2d $R^1 = n\text{-}Bu, R^2 = H$
2f $R^1 = Me, R^2 = Me$
2g $R^1 = Me, R^2 = Bn$
2h $R^1 = BnOCH_2, R^2 = H$

(*S*,*S*)-3
natural hunger substance
(3-DPA lactone)

Scheme 1

Due to the wide range of its utilities, the stereoselective synthesis of this class of compounds has received considerable attention [2]. To the best of our knowledge, access to enantiomerically highly enriched 2-oxygenated butyrolactone derivatives has been dominated by carbohydrate approaches. Using carbohydrates as "chiral pool" is attractive due to its appropriate functionalization and predictive power.

However, the limited availability of suitable carbohydrates and the difficulty in obtaining the intended stage of deoxygenation and stereochemical control with a certain target molecule has promoted the necessity to develop a flexible non-carbohydrate approach. We envisaged that an extension of our previous work [3] on the enantioselective synthesis of silyl protected isotetronic acids readily permits the enantioselective synthesis of

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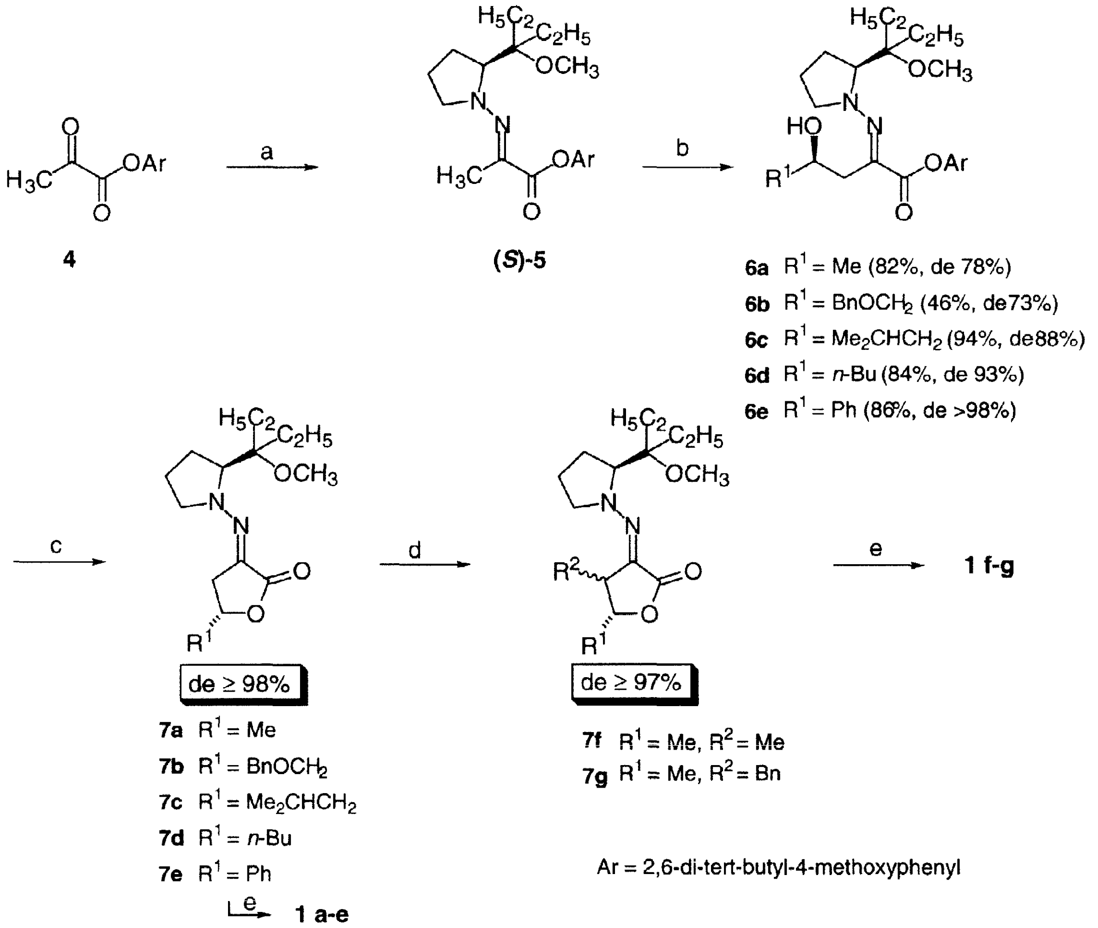
the 2-acetoxy-butyrolactones **2** via stereoselective hydrogenation of the corresponding butenolides **1** (Scheme 1). Herein we report a novel approach to enantiomerically enriched 4- and 3,4-substituted 2-acetoxy-butyrolactones **2** employing our hydrazone methodology and an application of this process in the asymmetric synthesis of a natural hunger substance **3** is also presented.



6a R^1 = Me (82%, de 78%)
6b R^1 = $BnOCH_2$ (46%, de73%)
6c R^1 = Me_2CHCH_2 (94%, de88%)
6d R^1 = *n*-Bu (84%, de 93%)
6e R^1 = Ph (86%, de >98%)

7a R^1 = Me
7b R^1 = $BnOCH_2$
7c R^1 = Me_2CHCH_2
7d R^1 = *n*-Bu
7e R^1 = Ph

7f R^1 = Me, R^2 = Me
7g R^1 = Me, R^2 = Bn

Ar = 2,6-di-tert-butyl-4-methoxyphenyl

Scheme 2

Reagents and conditions: a) SAEP, c-hexane, TsOH, reflux, 83%; b) 1. LDA, LiBr, THF, –78°C; 2. R^1CHO, –90°C → –78°C; c) 1. *t*-BuOK, THF, –30°C ± 5°C; 2. 1 M citric acid solution; 3. flash chromatography. d) 1. LDA, LiBr, THF, –78°C; 2. CH_3I or BnBr, –100°C → –78°C; 3. 1M citric acid solution; e) 1. O_3, CH_2Cl_2, –78°C; 2. Ac_2O, cat. pyridine, r.t.

For the purpose of flexibility and convenience, the sequence described in our previous paper [3d] was modified in order to prepare a series of butenolides **1**. As depicted in Scheme 2, the chiral auxiliary is introduced by condensation of the 2-oxoester **4** with the enantiopure hydrazine (*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP) [4] to give the hydrazone (*S*)-**5** exclusively as (*E*)-isomer. The lithium azaenolate of hydrazone **5** was prepared with lithium diisopropylamide (LDA) in the presence of lithium bromide in THF and allowed to react at –90 C° with a variety of aldehydes to afford the aldol adducts **6a-e** (yields: 46 - 94%; de = 73 - ≥ 98% determined by NMR spectroscopy). The configuration of the major aldol adducts were assigned in the case of the aldols **6a-e** based on the stereochemical model for aldol reactions via SAMP/RAMP hydrazones [5]. Furthermore, the structure of aldol **6c** has been unambiguously determined by single-crystal X-ray analysis of its corresponding benzyloxymethyl ether [3d]. In addition, the structure of aldol adduct **6b** was further proven by the following chemical conversion to the natural product **3** of known absolute configuration.

Lactonization of aldol adducts **6a-e** to the lactones **7a-e** was easily achieved by treating **6a-e** with potassium-*t*-butoxide in THF at –30 °C. After flash column chromatography the diastereomerically pure lactones **7a-e** were obtained in good yields (Table 1). The 3,4-disubstituted-hydrazonelactones **7f-g** were conveniently prepared in good yields with high diastereomeric excesses (de > 97%) via alkylation of the lithium azaenolate of lactone **7a** at –100°C to –70°C with methyl iodide and benzyl bromide, respectively. The configuration of the newly formed stereogenic centers, which are destroyed by tautomerism in the subsequent conversion to butenolides **1f-g**, was not determined.

Table 1. Asymmetric synthesis of 2-acetoxy-butyrolactones **2a-d,f,h** and the natural hunger substance **3**

7a-g	yield(%)	de(%)[a]	**1a-g**	yield(%)[b]	ee(%)	**2a-d,f,h** and **3**	yield(%)	ee(%)[c]	$[\alpha]_D^{RT}$ (c, $CHCl_3$)	confg.
7a	86	>98	**1a**	33	91[d]	**2a**	75	91	79.8 (0.1)	2*S*,4*R*
7b	66	>98	**1b**	48	90	**2b**	62	90	33.5 (1.0)	2*S*,4*S*
7c	80	≥98	**1c**	56	90[e]	**2c**	77	90	42.7 (0.75)	2*S*,4*R*
7d	87	≥98	**1d**	56	89[e]	**2d**	88	89	38.3 (0.6)	2*S*,4*R*
7e	72	≥98	**1e**	12	n.d.	**2f**	57	94	67.1 (0.35)	2*S*,3*S*,4*R*
7f	66	>98	**1f**	61	94[d]	**2h**	10[f]	n.d	n.d.	2*S*,4*S*
7g	51	>97	**1g**	62	n.d.	**3**	87	90	10 (0.4)	2*S*,4*S*

[a] Determined by NMR spectroscopy. [b] Yield for two steps. [c] Based on the ee value of compounds **1**. [d] Determined by GC (Chirasil dex, 25M). [e] Determined by GC (Lipodex E, 25M). [f] Isolated as a product from the hydrogenation reaction mixture of **1b**. n.d. = not determined.

Cleavage of hydrazonelactones **7a-g** was most satisfatorily carried out at –78°C by ozonolysis to furnish the unstable α-keto lactones, which were immediately acetylated (Ac_2O, pyridine) to give butenolides **1a-g** in reasonable yields. Only in the case of the conversion of **7e** to **1e** was the reaction complex and the chemical yield was significantly lower. The racemization at C-4 was observed but was very limited, due to the use of a catalytic amount of pyridine as a base. The ee values of **1a**, **1c**, **1d** and **1f** were determined by capillary gas chromatography on chiral stationary phases.

Hydrogenation of the butenolides **1a-d** and **1f** over palladium on carbon in ethanol proceeded smoothly with the expected high cis-stereoselectivity yielding **2a-d** and **2f**, respectively [5]. This specific *cis*-stereochemistry was attributed to the steric hinderance of the side chain at C-4, which led to the *cis*-addition of hydrogen from the least hindered face of the 2,3-double bond to produce *cis*-**2a-d**, **f**. The NMR spectra of these were fully consistent with *cis*-stereochemistry [6]. The ee values of **2a**, **2c**, **2d** and **2f** refer to the ee values of corresponding **1a**, **1c**, **1d** and **1f**, which were determined by GC. It was found that in some cases (e.g. **2a**, **2c**, and **2d**), palladium on calcium carbonate was more effective in inducing high cis-stereoselection than palladium on carbon. In the case of the hydrogenation of **1b**, **2h** was also isolated as a product. If the reaction time was longer, e.g. 48 h, the benzyl group of **2h** could be removed by further hydrogenolysis to give **2b**.

Catalytic hydrogenation of **1e** over palladium on carbon, however, did not give a satisfactory result to yield the corresponding 2-acetoxy-4-phenyl-butyrolactone. One product was identified as 2-acetoxy-4-phenylbutyric acid, obviously produced by the reduction of the 2,3-double bond and hydrogenolysis of the C (4)-O single bond. In addition, hydrogenation of **1g** over palladium on carbon was not a clean reaction either, and if palladium on calcium carbonate was employed as the catalyst, the hydrogenation reaction did not take place. This may be due to the steric hindrance of the benzyl group at C-3.

As an application of the above process in natural product synthesis, 3-DPA lactone **3**, known as a natural hunger substance, was synthesized. Treatment of **2b** with aqueous sodium hydroxide in methanol and subsequent acidification gave (*S*,*S*)-2-hydroxy-4-hydroxymethyl-butyrolactone (*S*,*S*)-**3** in 87% yield, which was spectroscopically consistent with the reported one [2a].

In summary, a flexible approach to highly enantiomerically enriched 4-mono- and 3,4-disubstituted 2-acetoxybutyrolactones **2** has been achieved, based on an asymmetric aldol reaction and a stereoselective hydrogenation of butenolides **1** as key steps. An application of this process led to the asymmetric synthesis of lactone **3**, a natural hunger substance.

Experimental Section

General: Solvents were dried immediately prior to use. Dry THF was distilled from potassium/benzophenone under argon. Dichloromethane was distilled from $\mathrm{CaH_2}$. Ether and petroleum ether were distilled prior to use. Commercial reagents were used directively as received. All reaction were carried out under anhydrous conditions under argon, unless otherwise stated. Yields refer to chromatographically and spectroscopically homogeneous materials.

Optical rotations were measured on a Perkin-Elmer P241 polarimeter and solvents of UVASOL quality (Merck). Microanalyses were obtained with a CHN-O-RAPID elemental analyser. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 (300 and 75 MHz) with TMS as the internal standard. IR spectra were recorded on a 1720 X and 1750 spectrophotometer. Mass spectra were obtained on a Varian MAT 212. High-resolution mass spectra were recorded on a Finnigan MAT 95. Melting points were measured on a Büchi apparatus and are uncorrected.

General procedure for aldol reactions with SAEP-hydrazone 5: A solution of LDA/LiBr was prepared by addition of n-BuLi in n-hexane (1.6 M, 0.90 mL, 1.44 mmol) to a solution of diisopropylamine (217 µl, 1.57 mmol) and LiBr (124 mg, 1.44 mmol) in THF (3 mL) at 0 °C. To this LDA/LiBr solution was added dropwise a solution of hydrazone **5** [3]. (621 mg, 1.31 mmol) in THF (5 mL) at –78 °C. The reaction mixture was stirred at this temperature for 1h and then cooled to –90°C. The aldehyde (1.44 mmol) was added dropwise by syringe. The reaction solution was kept at –90 °C for 1h, warmed to –78 °C, and kept for 1h. The reaction was quenched by the addition of saturated $\mathrm{NH_4Cl}$ solution and diluted with ether. The organic layer was seperated, washed with water, buffer solution (PH 7), brine and dried over $\mathrm{MgSO_4}$. The solvent was removed in vacuo and the aldol product **6** was obtained after flash column chromatography .

(*S*,*R*)-(+)-1-[3-Hydroxy-1-(2,6-di-tert-butyl-4-methoxy-1-phenoxycarbonyl)-1-butylideneamino]-2-(1-ethyl-1-methoxypropyl)pyrrolidine (6a): The general aldol procedure was followed with acetaldehyde as a reactant. Purification by flash column chromatography (silica gel, petroleum ether /diethyl ether 1 : 2) provided **6a** as a highly viscous yellow oil (82%), de = 78% (^{1}H NMR); $[\alpha]_D^{22}$ = 516 (c 1.25, $\mathrm{CHCl_3}$); ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 0.84-0.88 (m, 6H, $\mathrm{(CH_2C}\mathit{H}_3)_2$), 1.30, 1.35 (2s, 2 x 9 H, 2 x $\mathrm{C(C}\mathit{H}_3)_3$), 1.54-1.74 (m, 4H, 2 x $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 1.90-2.05 (m, 4 H, $\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2$), 2.72 (dd, J = 14.78, J = 4.02, 1H, $\mathrm{C}\mathit{H}_2\mathrm{C{=}N}$), 2.75 (br, 1H, OH), 2.88 (dd, J =14.78, J = 8.4, 1H, $\mathrm{C}\mathit{H}_2\mathrm{C{=}N}$), 3.26 (s, 3H, $\mathrm{COC}\mathit{H}_3$), 3.37 (m, 1H, $\mathrm{C}\mathit{H}_2\mathrm{N}$), 3.65 (m, 1H, $\mathrm{C}\mathit{H}_2\mathrm{N}$), 3.81 (s, 3H, $\mathrm{ArOC}\mathit{H}_3$), 3.98 (m, 1H, $\mathrm{C}\mathit{H}\mathrm{N}$), 4.16 (m,1H, $\mathrm{C}\mathit{H}\mathrm{OH}$), 6.87 (m,2H, 2ArH); ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 7.97, 8.19 (2x$\mathrm{CH_2}\mathit{C}\mathrm{H_3}$), 23.78, 23.92 (2x$\mathit{C}\mathrm{H_2CH_3}$), 24.11 ($\mathit{C}\mathrm{H_3CHOH}$), 25.25 ($\mathrm{NCH_2}\mathit{C}\mathrm{H_2}$), 26.84 ($\mathrm{NCH}\mathit{C}\mathrm{H_2}$), 31.09, 31.51 (2x $\mathrm{C(}\mathit{C}\mathrm{H_3)_3}$), 35.61, 35.74 (2x $\mathit{C}\mathrm{(CH_3)_3}$), 39.53 ($\mathit{C}\mathrm{H_2C{=}N}$), 50.34 ($\mathrm{CO}\mathit{C}\mathrm{H_3}$), 55.25 ($\mathrm{N}\mathit{C}\mathrm{H_2}$), 56.66 ($\mathrm{ArO}\mathit{C}\mathrm{H_3}$), 65.66 ($\mathrm{N}\mathit{C}\mathrm{H}$), 72.89 ($\mathit{C}\mathrm{HOH}$), 80.38 ($\mathit{C}\mathrm{OCH_3}$), 111.52, 111.59 (2 arom C), 133.07 ($\mathit{C}\mathrm{O_2Ar}$), 142.40 (arom C), 143.57, 143.72 (2 arom C), 156.09 (arom C),168.30 (C=N); IR ($\mathrm{CHCl_3}$): ν = 3432, 2968, 1710, 1589, 1562, 1456, 1430, 1365, 1303, 1268, 1106, 757 cm^{-1}; MS (CI): m/z (%) = 519 (100, M$^+$); Anal. Calcd for $\mathrm{C_{30}H_{50}N_2O_5}$ (518.74): 69.46, H 9.71, N 5.40; Found: C 69.51, H 9.87, N 5.75.

(*S*,*S*)-(+)-1-[4-Benzyloxy-3-hydroxy-1-(2,6-di-tert-butyl-4-methoxy-1-phenoxycarbonyl)-1-butylideneamino]-2-(1-ethyl-1-methoxypropyl)pyrrolidine (6b): The general aldol procedure was followed with benzyloxyacetaldehyde as a reactant. Purification by flash column chromatography (silica gel, petroleum ether/diethyl ether 1 : 1) provided **6b** as a highly viscous yellow oil (46%), de = 73% (^{1}H NMR); $[\alpha]_D^{22}$ = 422.2 (c 0.5, CHCl$_3$); ^{1}H NMR(300 MHz, CDCl$_3$): δ = 0.83-0.85 (m, 6H, 2CH$_2$C*H*$_3$), 1.31, 1.34 (2s, 2x9H, 2xC(C*H*$_3$)$_3$), 1.54-1.80 (m, 4H, 2xCH$_2$CH$_3$), 1.85-2.03 (m, 4H, C*H*$_2$C*H*$_2$), 2.84 (d, J = 6.04, 2H, C*H*$_2$C=N), 3.22 (s, 3H, COC*H*$_3$), 3.46-3.51 (m, 3H, C*H*$_2$CHOH, N-HC*H*), 3.69-3.72 (m, 1H, N-*H*CH), 3.80 (s, 3H, ArOC*H*$_3$), 3.93-3.95 (m, 1H, C*H*N), 4.12-4.16 (m, 1H, C*H*OH), 4.53 (d, J = 1.64, 2H, PhC*H*$_2$O), 6.87 (m, 2H, ArH), 7.28-7.36 (m, 5H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 8.02, 8.04 (2xCH$_2$*C*H$_3$), 23.72, 23.75 (2x*C*H$_2$CH$_3$), 25.17 (NCH$_2$*C*H$_2$), 26.87 (NCH*C*H$_2$), 31.132, 31.53 (2x C(*C*H$_3$)$_3$), 34.01 (*C*H$_2$C=N), 35.62, 35.77 (2x *C*(CH$_3$)$_3$), 50.39 (CO*C*H$_3$), 55.30 (O*C*H$_2$CHOH), 55.32 (N*C*H$_2$), 56.40 (ArO*C*H$_3$), 68.35 (N*C*H), 73.01(*C*HOH), 74.48 (*C*OCH$_3$), 80.44 (Ph*C*H$_2$), 111.59 (arom C), 127.71 (arom C), 127.78 (arom C), 128.47 (arom C), 138.20 (arom C), 143.76, 143.78 (arom C),156.10 (arom C), 168.50 (*C*=N); IR (film): ν = 3433, 3089, 2966, 1712, 1589, 1565, 1496, 1455, 1304, 1218, 1174, 755 cm^{-1}; MS (CI): m/z (%) = 625(44, M$^+$),389 (18), 237(100); Anal. Calcd for $C_{37}H_{56}N_2O_6$(624.86): C 71.12, H 9.03, N 4.48; Found: C 70.99, H 9.37, N 4.42.

General procedure for lactonization of aldol adducts 6a-e to hydrazonelactones 7a-e: To a solution of the aldol adduct **6** (1 mmol) in THF (10 mL) was added *t*-BuOK (1.1 mmol) at –30 °C under argon. The reaction mixture was stirred at this temperature until TLC indicated complete reaction. The reaction was quenched by the addition of citric acid solution (1M, 1 mL) and diluted with ether. After warming to room temperature, the organic layer was separated, washed with water, saturated NaHCO$_3$ solution, brine, and dried over MgSO$_4$. The solvent was removed in vacuo and the hydrazonelactone **7** was obtained after flash column chromatography.

(*S*,*R*)-(+)-N-[2-(1-Ethyl-1-methoxypropyl)pyrrolidine]-3-imino-5-methyl-dihydro-2-furanone (7a): The aldol adduct **6a** was cyclized as outlined above. After flash column chromatography (silica gel, petroleum ether/diethyl ether 1:2), the furanone **7a** was obtained as a colourless solid (86%), m.p. 90-92 °C; de > 98% (^{1}H NMR); $[\alpha]_D^{22}$ = 1056 (c 0.7, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.87, 0.90 (2t, J = 7.38, 6H, C(CH$_2$C*H*$_3$)$_2$), 1.48 (d, J = 6.04, 3H, C*H*$_3$CHO), 1.53-1.74 (m, 4H, C(C*H*$_2$CH$_3$)$_2$), 1.90-2.10 (m, 4H, C*H*$_2$C*H*$_2$), 2.75(dd, J = 16.78, J = 6.71, 1H, C*H*$_2$C=N), 3.07 (dd, J = 16.78, J = 7.72, 1H, C*H*$_2$C=N), 3.19 (m, 1H, NC*H*$_2$CH$_2$), 3.27 (s, 3H, OC*H*$_3$), 3.70 (m, 1H, NC*H*$_2$CH$_2$), 4.01 (m, 1H, NC*H*CH$_2$), 4.62 (m, 1H, CH$_3$C*H*O); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 8.0, 8.27 (2CH$_2$*C*H$_3$), 22.46 (*C*H$_3$CHO), 23.92, 24.01 (2 *C*CH$_2$CH$_3$), 24.74 (NCH$_2$*C*H$_2$), 26.49 (NCH*C*H$_2$), 35.88 (*C*H$_2$C=N), 50.49 (CO*C*H$_3$), 53.69 (N*C*H$_2$), 71.76 (N*C*H), 72.47 (O*C*H), 80.47 (*C*OCH$_3$), 127.35 (*C*=N), 168.80 (*C*=O); IR (KBr): ν = 2968, 2880, 1765, 1686, 1655, 1508, 1498, 1386, 1291 1049 cm^{-1}; MS (70 eV, EI): m/z (%) = 282 (0.2, M$^+$), 181 (69), 137 (39), 101 (84), 70 (100); Anal. Calcd for $C_{15}H_{26}N_2O_3$ (282.382): C 63.80, H 9.28, N 9.92; Found: C 63.61, H 9.31, N 9.85.

(*S*,*S*)-(+)-5-Benzyloxymethyl-N-[2-(1-ethyl-1-methoxypropyl)pyrrolidine]-3-imino-dihydro-2-furanone (7b): The aldol adduct **6b** was cyclized as outlined above. After flash column chromatography (silica gel, petroleum ether/diethyl ether 1:2), the furanone **7a** was obtained as a colourless oil (66%), de > 98% (^{1}H NMR); $[\alpha]_D^{22}$ = 457.4 (c 1.35, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.87, 0.89 (2t, J = 7.72, 6H, 2xCH$_2$C*H*$_3$), 1.50-1.75 (m, 4H, 2xC*H*$_2$CH$_3$), 1.88-2.30 (m, 4H, C*H*$_2$C*H*$_2$), 2.91 (dd, J = 17.1, J = 8.39, 1H, C*H*$_2$C=N), 3.07 (dd, J = 17.1, J = 5.7, 1H, C*H*$_2$C=N), 3.16-3.22 (m, 1H, C*H*$_2$N), 3.26 (s, 3H, OC*H*$_3$), 3.69 (m, 2H, OC*H*$_2$CHO), 3.70-3.73 (m, 1H, C*H*$_2$N), 4.02 (m, 1H, C*H*N), 4.61 (d, J = 1.1, 2H, PhC*H*$_2$O), 4.64-4.69 (m, 1H, C*H*O), 7.29 (m, 5H, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ =8.0, 8.30 (2CH$_2$*C*H$_3$), 23.88, 24.0 (2 *C*H$_2$CH$_3$), 24.80 (NCH$_2$*C*H$_2$), 26.49 (NCH*C*H$_2$), 30.27 (*C*H$_2$C=N), 50.50 (CO*C*H$_3$), 53.68 (N*C*H$_2$), 71.33 (O*C*H$_2$CHO), 71.79 (N*C*H), 73.73 (O*C*H), 74.32 (Ph*C*H$_2$O), 80.49 (*C*OCH$_3$), 127.79, 127.92, 128.52 (arom C), 168.53 (*C*=O); IR (CHCl$_3$): ν = 3064, 2971, 1757, 1657, 1579, 1496, 1455, 1345, 1215, 1183, 1029, 699 cm^{-1}; MS (70 eV, EI): m/z (%) = 388 (0.35, M$^+$), 287 (95), 101 (33), 91 (100), 70 (85); Anal. Calcd for $C_{22}H_{32}N_2O_4$(388.51): C 68.01, H 8.30, N 7.21; Found: C 67.87, H 8.34, N 7.39.

General procedure for preparation of 4,5-disubstituted hydrazonefuranone 7f-g: A solution of LDA/LiBr was prepared by addition of n-BuLi in n-hexane (1.6 M, 908 µl, 1.47 mmol) to a solution of diisopropylamine (216 µl, 1.58 mmol) and LiBr (108 mg, 1.24 mmol) in THF (2 mL) at 0 °C. To this LDA/LiBr solution was added dropwise a solution of hydrazone **7a** (320 mg, 1.13 mmol) in THF (5 mL) at –78 °C. The reaction mixture was stirred at this temperature for 2 h and then cooled to –100°C. CH_3I (1.44 mmol) or BnBr (1.24 mmol) was added dropwise by syringe. The reaction solution was kept at –100 °C for 1h, warmed to –78 °C, and kept for 5 h. The reaction was quenched by the addition of citric acid solution (1M, 1.5 mL) and diluted with ether. After warming to room temperature, the organic layer was separated, washed with water, saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. The solvent was removed in vacuo and the hydrazonefuranones **7f-g** were obtained after flash column chromatography (silica gel, petroleum ether /diethyl ether 1 : 1).

(*S*,*R*,*S)-(+)-4,5-Dimethyl-N-[2-(1-ethyl-1-methoxypropyl)pyrrolidine]-3-iminodihydro-2-furanone (7f)**: The hydrazonefuranone **7a** was alkylated with CH_3I as outlined above to give **7f** as colourless solid(66%), m.p. 85.5-87 °C; de > 98% (^{1}H NMR); $[\alpha]_D^{22}$ = 1012.5 (c 0.2, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.87, 0.89 (2t, J = 7.32, 6H, $2xCH_2CH_3$), 1.19 (d, J = 7.02, 3H, $CH_3CHC{=}N$), 1.41 (d, J = 6.40, 3H, CH_3CHO), 1.45-1.70 (m, 4H, $2xCH_2CH_3$), 1.91-2.13 (m, 4H, CH_2CH_2), 2.88 (dq, J = 2.44, J = 7.02, 1H, $CH_3CHC{=}N$), 3.04-3.07 (m, 1H, CH_2N), 3.24 (s, 3H, OCH_3), 3.57-3.62 (m, 1H, CH_2N), 4.01-4.03 (m, 1H, CHN),4.28 (dq, J = 2.44, J = 6.40, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.97, 8.27 ($2CH_2CH_3$), 17.25 ($CH_3CHC{=}N$), 22.21 (CH_3CHO), 23.65, 23.99 (2 CH_2CH_3), 24.75 (NCH_2CH_2), 26.67 ($NCHCH_2$), 40.29 ($CHC{=}N$), 50.48 ($COCH_3$), 53.85 (NCH_2), 72.40 (NCH), 79.62 (CH_3CHO), 80.62 ($COCH_3$); IR (KBr): ν = 2970, 1747, 1583, 1451, 1345, 1211, 1145, 1035, 924 cm^{-1}; MS (70 eV, EI): m/z (%) = 296 (1.6, M$^+$), 195 (100), 181 (9), 101 (19); Anal. Calcd for $C_{16}H_{28}N_2O_3$: C 64.83, H 9.52, N 9.45; Found: C 64.52, H 9.62, N 9.49.

(*S*,*R*,*S)-(+)-4-Benzyl-N-[2-(1-ethyl-1-methoxypropyl)pyrrolidine]-3-imino-5-methyl-dihydro-2-furanone (7g)**: The hydrazonefuranone **7a** was alkylated with BnBr as outlined above to give **7g** as a colourless solid (51%), m.p. 107.5-108 °C; de > 97% (^{1}H NMR); $[\alpha]_D^{22}$ = 733.3 (c 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90, 0.93 (2t, J = 7.69, 6H, $2xCH_2CH_3$), 1.20 (d, J = 6.32, 3H, CH_3CHO), 1.50-1.74 (m, 4H, $2xCH_2CH_3$),1.93-2.20 (m, 4H, CH_2CH_2), 2.46 (m, 1H, $CHC{=}N$), 3.12-3.22 (m, 3H, HCHN, $PhCH_2$), 3.26 (s, 3H, OCH_3), 3.79-3.82 (m, 1H, CH_2N), 4.06-4.10 (dd, J = 3.57, J = 8.52, 1H, CHN), 4.43 (dq, J = 1.1, J = 6.32, 1H, CHO), 7.18-7.36 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.10, 8.39 ($2CH_2CH_3$), 22.97 (CH_3CHO), 23.88, 23.89 (2 CH_2CH_3), 24.87 (NCH_2CH_2), 26.65 ($NCHCH_2$), 36.20 ($PhCH_2$), 46.90 ($CHC{=}N$), 50.56 ($COCH_3$), 54.36 (NCH_2), 72.60 (NCH), 76.31 (CHO), 80.60 ($COCH_3$), 125.20 (C=N), 127.06, 128.93, 129.43, 129.80, 137.60 (arom C), 168.0 (C=O); IR ($CHCl_3$): ν = 2973, 1749, 1574, 1496, 1454, 1320, 1216, 1183, 755 cm^{-1}; MS (70 eV, EI): m/z (%) = 372 (1.9, M$^+$), 271 (100), 101 (16), 91 (42); Anal. Calcd for $C_{22}H_{32}N_2O_3$: C 70.94, H 8.66, N 7.52; Found: C 70.83, H 8.71, N 7.49.

General procedure for ozonolysis of the hydrazonelactones 7a-g and subsequent acylation, to afford butenolides 1a-g: The hydrazonelactone **7** was dissolved in CH_2Cl_2 (50 mL) and cooled to –78°C. Ozone was passed through the solution at this temperature until the reaction was complete (TLC). The solvent was removed in vacuo and to the residue was added Ac_2O (5 mL) and a catalytic amount of pyridine under argon. The reaction mixture was stirred at room temperature under argon for 24 h. The reaction solution was poured into ice-cold aqueous $NaHCO_3$, stirred for 1h, and was then extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (silica gel) yielded **1a-g.**

(*R*)-(–)-3-Acetoxy-5-methyl-2(5H)-furanone (1a): The hydrazone **7a** was treated with ozone and Ac_2O as described above. Flash column chromatography (silica gel, petroleum ether/diethyl ether 2 : 1) yielded

1a as colourless oil (33%), ee = 91% (GC, chiral stationary phase); $[\alpha]_D^{22}$ = –16 (c 0.5, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.50 (d, J = 6.71, 3H, C*H*$_3$CHO), 2.31 (s, 3H, C*H*$_3$C=O), 5.14 (dq, J = 1.68, J = 6.72, *H*-5), 7.27 (d, J = 1.68, 1H, *H*-4); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.42 (*C*H$_3$CHO), 20.93 (*C*H$_3$C=O), 75.68 (*C*-5), 134.73 (*C*-4), 137.88 (*C*-3), 167.20 (CH$_3$*C*=O), 216.50 (*C*-2); IR (film): ν = 2981, 1774, 1666, 1648, 1447, 1374, 1196, 1110, 1089, 879 cm^{-1}; MS (CI): m/z (%) = 157 (100, M$^+$ + 1). Anal. Calcd for $C_7H_8O_4$ (156.14): C 53.85, H 5.16; Found: C 53.57, H 5.51.

(*S*)-(–)-3-Acetoxy-5-benzyloxymethyl-2(5H)-furanone (1b): The hydrazone **7b** was treated with ozone and Ac$_2$O as described above. Flash column chromatography (silica gel, petroleum ether/diethyl ether 2 : 1) yielded **1b** as a colourless oil (48%), $[\alpha]_D^{22}$ = –28.6 (c 1.05, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.31 (s, 3H, C*H*$_3$C=O), 3.71 (d, J = 5.04, 2H, OC*H*$_2$CHO), 4.58 (br, 2H, PhC*H*$_2$), 5.16 (dt, J = 5.04, J = 2.02, 1H, *H*-5), 7.28 (d, J = 2.02, 1H, *H*-4), 7.30-7.36 (m, 5H, Ar*H*); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 20.92 (*C*H$_3$CO), 69.69 (O*C*H$_2$CHO), 73.79 (Ph*C*H$_2$), 78.23 (*C*-5), 127.76, 128.03, 128.55 (arom *C*), 131.04 (*C*-4), 137.21 (*C*-3), 167.03 (*C*=OCH$_3$); IR (CHCl$_3$): ν = 3089, 3065, 2918, 1777, 1667, 1582, 1496, 1454, 1371, 1210, 1193, 1115, 1012, 755 cm^{-1}; MS (CI): m/z (%) = (263, M$^+$ + 1). No satisfactory elemental analysis was obtained.

(*R*)-(–)-3-Acetoxy-5-(2-methylpropyl)-2(5H)-furanone (1c): The hydrazone **7c** [3] was treated with ozone and Ac$_2$O as described above. Flash column chromatography (silica gel, petroleum ether/CH$_2$Cl$_2$ 1 : 2) yielded **1c** as a colourless solid (56%), m.p. 41.5-42 °C; ee = 90% (GC, chiral stationary phase); $[\alpha]_D^{22}$ = –15.7 (c 0.35, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.99 (d, J = 4.12, 3H, C*H*$_3$CH), 1.01 (d, J = 4.12, 3H, C*H*$_3$CH), 1.59 (m, 2H, C*H*$_2$CHO), 1.90 (m, 1H, C*H*(CH$_3$)$_2$), 2.31 (s, 3H, C*H*$_3$CO), 5.07 (m, 1H, *H*-4), 7.25 (d, J = 1.92, 1H, *H*-3); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 20.92 (*C*H$_3$CO), 22.20, 22.99 (CH(*C*H$_3$)$_2$), 25.12 (*C*H$_2$CHO), 42.78 (*C*H(CH$_3$)$_2$), 78.10 (*C*-5), 134.24 (*C*-4), 137.46 (*C*-3), 167.19 (*C*OCH$_3$), 216.20 (*C*-2); IR (KBr): ν = 2958, 2873, 1774, 1646, 1560, 1431, 1310, 1125, 1030 cm^{-1}; MS (70 eV, EI): m/z (%) = 198 (2.4, M$^+$), 156 (15), 128 (34), 111 (83), 55 (100); Anal. Calcd for $C_{10}H_{14}O_4$ (198.22): C 60.59, H 7.12; Found: C 60.64, H 7.01.

(*R*)-(–)-3-Acetoxy-5-butyl-2(5H)-furanone (1d): The hydrazone **7d** [3] was treated with ozone and Ac$_2$O as described above. Flash column chromatography (silica gel, petroleum ether/CH$_2$Cl$_2$ 1 : 1) yielded **1d** as a colourless oil (56%), ee = 89 % (GC, chiral stationary phase); $[\alpha]_D^{22}$ = –14 (c 0.25, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.92 (t, J = 6.72, 3H, C*H*$_3$CH$_2$), 1.32-1.48 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$), 1.67-1.82 (m, 2H, C*H*$_2$CHO), 2.31 (s, 3H, C*H*$_3$CO), 5.03 (dt, J = 1.68, J = 5.37, 1H, *H*-5), 7.25 (d, J = 2.01, 1H, *H*-4); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.83 (*C*H$_3$CH$_2$), 20.93 (*C*H$_3$CO), 22.39 (CH$_3$*C*H$_2$), 26.81 (CH$_3$CH$_2$*C*H$_2$), 33.33 (CH$_3$CH$_2$CH$_2$*C*H$_2$), 79.37 (*C*-5), 133.85 (*C*-4), 137.80 (*C*-3), 167.19 (CH$_3$*C*O); IR (film): ν = 3103, 2959, 1775, 1666, 1647, 1467, 1372, 1195, 1031, 879 cm^{-1}; MS (70 eV, EI): m/z (%) =199 (2.4, M$^+$ + 1), 128 (52), 111(66), 100(14), 55 (100); Anal. Calcd for $C_{10}H_{14}O_4$ (198.22): C 60.59, H 7.12; Found: C 60.47, H 7.36.

(*S*)-(–)-3-Acetoxy-5-phenyl-2(5H)-furanone (1e): The hydrazone **7e** [3] was treated with ozone and Ac$_2$O as described above. Flash column chromatography (silica gel, petroleum ether/CH$_2$Cl$_2$ 1 : 4) yielded **1e** as a colourless oil (12%), ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.34 (s, 3H, C*H*$_3$CO), 6.01 (d, J = 2.02, 1H, *H*-5), 7.30-7.42 (m, 5H, Ar*H*), 7.35 (d, J = 2.02, 1H, *H*-4); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 20.91 (*C*H$_3$CO), 80.36 (*C*-5), 126.80, 129.10, 129.60 (arom *C*), 133.34 (*C*-4), 134.17 (arom *C*), 137.40 (*C*-3), 167.10 (CH$_3$*C*O); IR (film): ν = 3106, 3035, 2938, 1778, 1665, 1647, 1602, 1497, 1456, 1371, 1194, 1046, 700 cm^{-1}; MS (70 eV, EI): m/z (%) = 218 (9, M$^+$), 176 (59), 147 (27), 131 (100), 103 (60); No satisfactory elemental analysis was obtained.

(*R*)-(–)-3-Acetoxy-4,5-dimethyl-2(5H)-furanone (1f): The hydrazone **7f** was treated with ozone and Ac$_2$O as described above. Flash column chromatography (silica gel, petroleum ether/diethyl ether 1 : 1) yielded

1f as a colourless oil (61%), ee = 94% (GC, chiral stationary phase); $[\alpha]_D^{22}$ = –10 °C (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, J = 7.05, 3H, CH_3CHO), 1.92 (d, J = 0.68), 3H, $CH_3C{=}C$), 2.30 (s, 3H, CH_3CO), 4.94 (dq, J = 1.01, J = 7.05, 1H, *H*-5); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.26 (CH_3CHO), 20.29 (CH_3CO), 29.90 ($CH_3C{=}C$), 80.80 (*C*-5), 134.3 (*C*-4), 150.30 (*C*-3), 167.11 (CH_3CO), 216.51 (*C*-2); IR (film): ν =2985, 1762, 1698, 1440, 1373, 1330, 1108, 1064, 931, 597 cm^{-1}; MS (70 eV, EI): m/z (%) = 170 (16, M^+), 128 (80), 83 (100), 74 (42); Anal. Calcd for $C_8H_{10}O_4$ (170.16): C 56.47, H 5.92; Found: C 56.31, H 5.84.

(*R*)-(–)-3-Acetoxy-4-benzyl-5-methyl-2(5H)-furanone (1g): The hydrazone **7g** was treated with ozone and Ac_2O as described above. Flash column chromatography (silica gel, petroleum ether/diethyl ether 1 : 1) yielded **1g** as a colourless oil (62%), $[\alpha]_D^{22}$ = –107.8 (c 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, J = 6.59, 3H, CH_3CHO), 2.18 (s, 3H, CH_3CO), 3.48 (d, J = 16.1, 1H, $PhCH_2$), 3.79 (d, J = 16.1, 1H, $PhCH_2$); 4.88 (q, J = 6.59, 1H, *H*-5), 7.19-7.38 (m, 5H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.47 (CH_3CHO), 20.20 (CH_3CO), 31.56 ($CH_2C{=}C$), 127.43, 128.86, 129.05 (arom *C*), 134.89 (*C*-4), 152.10 (*C*-3), 167.10 (CH_3CO); IR (film): ν = 3087, 3063, 1768, 1693, 1603, 1585, 1455, 1327, 1192, 1058, 707 cm^{-1}; MS (70 eV, EI): m/z (%) = 246 (48, M^+), 204 (64), 159 (75), 131(100), 91 (82); Anal. Calcd for $C_{14}H_{14}O_4$(246.26): C 68.28, H 5.73; Found: C 67.90, H 5.83.

General procedure for catalytic hydrogenation of butenolides 1a-g: The butenolides **1a-g** (0.4 mmol) and Pd on carbon (10%, 18 mg) or Pd on $CaCO_3$ (5%, 26 mg) in EtOH (5 mL) were hydrogenated at 1 atm for 24 h and filtered through Celite, and the catalyst was leached with more EtOH. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, petroleum ether/diethyl ether) to give butyrolactones **2a-d, f, h**.

(*3S,5R*)-(+)-3-Acetoxy-5-methyl-tetrahedrofuran-2-one (2a): The butenolide **1a** was hydrogenated over Pd on $CaCO_3$ as described above. Flash column chromatography (petroleum ether/diethyl ether 2 : 1) afforded **2a** as a colourless oil (75%), $[\alpha]_D^{22}$ = 79.8 (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, J = 6.05, 3H, CH_3CHO), 1.89 (ddd, J =12.42, J = 10.74, J = 10.08, 1H, *H*-4), 2.17 (s, 3H, CH_3CO), 2.82 (ddd, J = 12.42, J = 8.39, J = 5.37, 1H, *H*-4), 4.57 (m, 1H, *H*-5), 5.51 (dd, J = 10.74, J = 8.39, 1H, *H*-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.62 (CH_3CO), 21.03 (CH_3CHO), 36.77 (*C*-4), 69.03 (*C*-5), 73.48 (*C*-3), 169.86 (CH_3CO), 172.43 (C-2); IR (film): ν =2983, 1787, 1747, 1660, 1451, 1378, 1290,, 1022, 906 cm^{-1}; MS (70 eV, EI): m/z (%) = 159 (4.3, M^+ + 1), 86 (20), 72 (100); Anal. Calcd for $C_7H_{10}O_4$ (158.15): C 53.16, H 6.37; Found: C 53.44, H 6.38.

(*3S,5S*)-(+)-3-Acetoxy-5-hydroxymethyl-tetrahedrofuran-2-one (2b) and (3S,5S)-(+)-3-Acetoxy-5-benzyloxymethyl-tetrahedrofuran-2-one (2h): The butenolide **1b** was hydrogenated over Pd on carbon as described above. Flash column chromatography (petroleum ether/diethyl ether 1 : 4) afforded **2b** (62%) and **2h** (10%) as colourless oils. **2b**: $[\alpha]_D^{22}$ = 33.5 (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3H, CH_3CO), 2.25 (ddd, J = 12.76, J = 10.74, J = 10.41, 1H, *H*-4), 2.32 (br, 1H, O*H*), 2.69 (ddd, J = 12.76, J = 8.72, J = 6.04, 1H, *H*-4), 3.68 (dd, J = 12.75, J = 4.36, 1H, $OHCH_2$), 3.98 (dd, J =12.75, J = 2.69, 1H, $OHCH_2$), 4.58 (m, 1H, *H*-5), 5.53 (dd, J = 10.74, J = 8.72, 1H, *H*-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.60 (CH_3CO), 29.59 (*C*-4), 63.02 ($OHCH_2$), 68.66 (*C*-5), 77.21 (*C*-3), 169.88 (CH_3CO), 172.28 (*C*-2); IR ($CHCl_3$): ν = 3409, 2941, 1785, 1747, 1643, 1449, 1379, 1340, 1234, 1103, 1021, 611 cm^{-1}; HRMS calcd for $C_7H_{11}O_5$ (M^+ + 1): 175.0606; Found: 175.0608. **2h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3H, CH_3CO), 2.23 (m, 1H, *H*-4), 2.72 (ddd, J = 12.76, J = 8.73, J = 6.04, 1H, *H*-4), 3.63 (dd, J = 5.04, J = 11.42, 1H, OCH_2CHO), 3.73 (dd, J = 3.70, J = 11.42, 1H, OCH_2CHO), 4.60 (br, 2H, $PhCH_2$), 4.63 (m, 1H, *H*-5), 5.50 (dd, J = 10.74, J = 8.73, 1H, *H*-3), 7.31- 7.36 (m, 5H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.60 (CH_3CO), 30.74 (CH_3CO), 68.34 (OCH_2CHO), 70.30 (*C*-5), 73.65 ($PhCH_2$), 75.80 (*C*-3), 127.75, 127.95, 128.53 (arom *C*), 169.85 (CH_3CO), 172.25 (*C*-2); IR ($CHCl_3$): ν = 3064, 2931, 1790, 1748, 1605, 1497, 1454, 1376, 1052, 701 cm^{-1}; MS (70 eV, EI): m/z (%) = 264 (2.5, M^+), 158 (13), 98(49), 91 (100).

(*3S,5R*)-(+)-3-Acetoxy-5-(2-methylpropyl)-tetrahedrofuran-2-one (2c): The butenolide **1c** was hydrogenated over Pd on $CaCO_3$ as described above. Flash column chromatography (petroleum ether/diethyl ether 2 : 1) afforded **2c** as a colourless oil (77%), $[\alpha]_D^{22}$ = 42.7 (c 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.59, 6H, CH(C*H*$_3$)$_2$), 1.1.48-1.76 (m, 3H, $(CH_3)_2$C*H*C*H*$_2$), 1.87-1.94 (m, 1H, *H*-4), 2.17 (s, 3H, C*H*$_3$CO), 2.80 (ddd, J = 12.64, J = 8.51, J = 5.22, 1H, *H*-4), 4.52 (m, 1H, *H*-5), 5.49 (dd, J = 10.99, J = 8.51, 1H, *H*-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.62 (*C*H$_3$CO), 22.19, 22.84 (CH(*C*H$_3$)$_2$), 24.84 (*C*H(CH$_3$)$_2$), 35.64 (*C*H$_2$CHO), 44.66 (*C*-4), 68.70 (*C*-5), 75.66 (*C*-3), 169.84 (CH$_3$*C*O), 172.37 (*C*-2); IR ($CHCl_3$): ν = 2959, 1790, 1749, 1469, 1376, 1231, 1109, 1001 cm^{-1}; MS (70 eV, EI): m/z (%) = 201 (1.6, M$^+$ + 1), 114 (37), 100 (43), 96 (100); Anal. Calcd for $C_{10}H_{16}O_4$ (200.23): C 59.98, H 8.05; Found: C 59.48, H 8.00.

(*3S,5R*)-(+)-3-Acetoxy-5-butyl-tetrahedrofuran-2-one (2d): The butenolide **1d** was hydrogenated over Pd on $CaCO_3$ as described above. Flash column chromatography (petroleum ether/diethyl ether 3 : 1) afforded **2d** as a colourless oil (88%), $[\alpha]_D^{22}$ = 38.3 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 6.71, 3H, C*H*$_3$CH$_2$), 1.39-1.44(m, 4H, CH$_3$C*H*$_2$C*H*$_2$), 1.67-1.80 (m, 2H, C*H*$_2$CHO),1.91 (m, 1H, *H*-4), 2.17 (s, 3H, COC*H*$_3$), 2.79 (ddd, J = 12.43, J = 8.73, J = 5.38, 1H, *H*-4), 4.43 (m, 1H, *H*-5), 5.50 (dd, J = 11.08, J = 8.73, 1H, *H*-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.87 (*C*H$_3$CH$_2$), 20.62 (*C*H$_3$CO), 22.35 (CH$_3$*C*H$_2$), 27.01 (CH$_3$CH$_2$*C*H$_2$), 35.12 (2*C*H$_2$CHO), 68.78 (*C*-5), 77.15 (*C*-3), 169.83 (CH$_3$*C*O), 172.37 (*C*-2); IR (film): ν = 2958, 1790, 1749, 1649, 1434, 1377, 1232, 1015cm^{-1}; MS (70 eV, EI): m/z (%) = 201 (5.3, M$^+$ + 1), 114 (75), 96(77), 57(100); Anal. Calcd for $C_{10}H_{16}O_4$ (200.23): C 59.98, H 8.05; Found: C 59.84, H 7.84.

(*3S,4S,5R*)-(+)-3-Acetoxy-4,5-dimethyltetrahedrofuran-2-one (2f): The butenolide **1f** was hydrogenated over Pd on carbon as described above. Flash column chromatography (petroleum ether/diethyl ether 1 : 1) afforded **2f** as a colourless oil (57%), $[\alpha]_D^{22}$ = 67.1 (c 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, J = 7.05, 3H, C*H*$_3$CHCHO), 1.38 (d, J = 6.38, 3H, C*H*$_3$CHO), 2.21 (s, 3H, C*H*$_3$CO), 2.82 (ddt, J = 7.39, J = 7.05, J = 4.7, 1H, *H*-4), 4.63 (dt, J = 6.38, J = 4.7, 1H, *H*-5), 5.57 (d, J = 7.39, 1H, *H*-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.20 (*C*H$_3$CHCHO), 15.58 (*C*H$_3$CHO), 20.50 (*C*H$_3$CO), 37.70 (*C*-4), 72.01 (*C*-5), 75.93 (*C*-3),169.98 (CH$_3$*C*O); IR ($CHCl_3$): ν = 2982, 1790, 1751, 1446, 1375, 1238, 1113, 1002, 893 cm^{-1}; HRMS calcd for $C_8H_{13}O_4$(M$^+$ + 1): 173.0814; Found: 173.0813.

Synthesis of (*3S,5S*)-(+)-3-hydroxy-5-hydroxymethyl-tetrahedrofuran-2-one (3): A mixture of **2b** (20 mg, 0.12 mmol), 10% NaOH solution (0.5 mL) and MeOH (0.5 mL) was stirred overnight at room temperature. The mixture was acidified with a diluted HCl solution, and then the solvent was removed in high vacuo. The residue was subject to column chromatography (silica gel, EtOAc) to give **3** (13 mg, 87%) as a colourless oil, $[\alpha]_D^{27}$= 10.0 (c 0.4, $CHCl_3$) (lit. [2a], $[\alpha]_D^{28}$ = 23.5, c 3.61, MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 1.98 (ddd, $J_{4,4'}$ = 12.42, $J_{3,4'}$ = $J_{4',5}$ = 10.74, 1H, *H*-4'), 2.54 (ddd, $J_{4,4'}$ =12.43, $J_{3,4}$ = 8.39, $J_{4,5}$ = 5.71, 1H, *H*-4), 3.59 (dd, J = 12.76, J = 5.04, 1H, OHC*H*$_2$), 3.80 (dd, J = 12.76, J =3.0, 1H, OHC*H*$_2$), 4.42-4.50 (m, 1H, *H*-5), 4.56 (dd, $J_{3,4}$ = 8.39, $J_{3,4'}$ = 10.74, 1H, *H*-3); ^{13}C NMR (75 MHz, CD_3OD): δ = 33.61 (*C*-4), 63.84 (OH*C*H$_2$), 69.32 (*C*-5), 78.62 (*C*-3); IR (film): ν = 3372, 2947, 2835, 1775, 11651, 1450, 1385, 1205, 1116, 1027, 901, 877, 651 cm^{-1}; HRMS calcd for $C_5H_9O_4$ (M$^+$ + 1): 133.0501; Found: 133.0500.

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