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Stereocontrolled synthesis of 5-(1′-hydroxyalkyl)-3-methylidenetetrahydro-2-furanones

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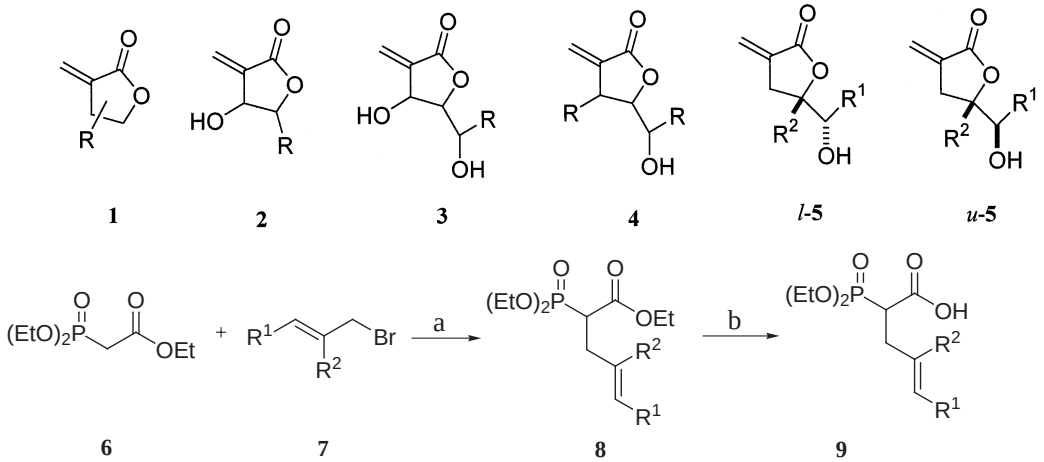
Abstract—Diastereo- and enantioselective synthesis of 5-(1′-hydroxyalkyl)-3-methylidenetetrahydro-2-furanones from 2-diethoxyphosphoryl-4-alkenoic acids or 2-diethoxyphosphoryl-4-alkenoates was readily accomplished using novel methodology involving *syn*- or *anti*-dihydroxylation procedures combined with Horner–Wadsworth–Emmons olefination techniques.

Due to the wide spectrum of biological activity exhibited by functionalised 3-methylidenetetrahydro-2-furanones **1**, this class of compound has been the subject of considerable synthetic effort.[1–3] It has been established that whereas the presence of a conjugated carbonyl system is essential for activity, there are also other factors which may enhance the biological properties of these compounds, e.g. the presence of stereochemically defined carbinol units at strategic positions.[4]

Synthesis of 4-hydroxy and/or 5-hydroxyalkyl substituted furanones of general structure **2**, **3**, and **4** has been so far accomplished chiefly by using carbohydrates as starting materials.[4–8] Although these methods give access to optically active products they are usually not general and have relatively low overall efficiency. Other strategies such as the palladium-catalysed carbonylation of vinyl halides,[9] the reaction of α-acetoxyaldehydes with ethyl 2-(phenylthio)propionate,[10] or the lactonisation of α-methylidene-γ-hydroxy-δ-alkoxyesters[11] have been shown to be of limited applicability and give racemic products. In this respect, continuing our investigations focused on the application of organophosphorus reagents in the synthesis of 3-methylidenetetrahydro-2-furanones,[12,13] we now describe our newly developed diastereo- and enantioselective techniques for the preparation of 5-(1′-hydroxyalkyl)-3-methylidenetetrahydro-2-furanones **5** from non-sugar precursors.



Scheme 1. *Conditions*: (a) NaH, THF, 0°C to rt, 20 h; (b) KOH (1.5 equiv.), $EtOH/H_2O = 7:1$, rt, 24 h.

Keywords: hydroxylation; Horner–Wadsworth–Emmons olefination; 2-furanones; diastereoselection; enantioselection.

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Table 1. Synthesis of alkenoates **8** and alkenoic acids **9**

Entry	Product	R^1	R^2	Yield[a] (%)	
				8	**9**
1	a	H	H	47	84
2	b	H	Me	64	89
3	c	Me	H	50	88
4	d	*n*-Pr	H	59	84
5	e	Ph	H	53	96

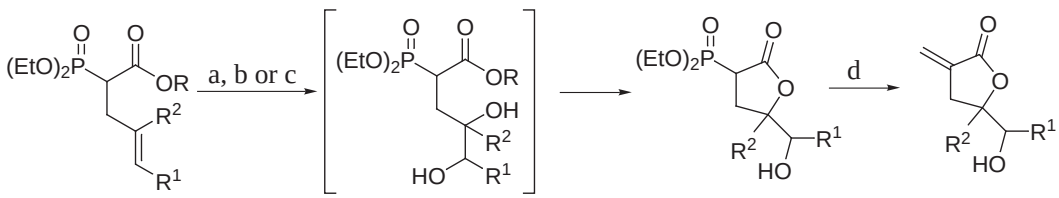
[a] All yields refer to pure, isolated products. All new compounds were fully characterised by IR, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and elemental analysis.

The key intermediate components in our syntheses of *l*- and *u*-hydroxyalkylfuranones **5**[14] were the readily accessible 2-diethoxyphosphoryl-4-alkenoates **8** and the corresponding 4-alkenoic acids **9**. As shown in Scheme 1 and Table 1, alkenoates **8** were obtained by alkylation of ethyl diethoxyphosphorylacetate (**6**) with various allyl bromides **7** using a known literature procedure.[15] In turn, chemoselective hydrolysis of **8** gave acids **9**.†

In due course, *syn*-dihydroxylation of the carboxylic acids **9** was performed using the excellent OsO_4/NMO protocol in aqueous acetone.[16] Indeed, the diols **11** obtained lactonised spontaneously to the desired furanones **12** (Scheme 2, Table 2). Furthermore we were pleased to observe that the dihydroxylation is completely diastereoselective and gives access to lactones **12** with the *l* configuration at the newly formed vicinal stereogenic centres. Due to the additional stereogenic centre at C-3, all furanones **12** were obtained as mixtures of diastereoisomers with close to a 1:1 ratio.

anti-Dihydroxylation of alkenoates **8** was achieved by a standard reaction sequence involving oxidation with MCPBA, followed by cleavage of the epoxides with perchloric acid to deliver diols **10**.[17] Pleasingly, these diols underwent spontaneous transesterification to yield furanones **12** with the *u* configuration at the newly generated stereogenic centres.

Having accessed a range of phosphorylated furanones **12** possessing complementary stereochemistry, Horner–Wadsworth–Emmons techniques were then applied. More specifically, olefination of formaldehyde[13] yielded a series of the target *l*- or *u*-3-methylidene-2-furanones **5**‡ as defined diastereoisomers (Scheme 2, Table 2).§



8 (R=Et)
9 (R=H)
10 (R=Et)
11 (R=H)
12
5

Scheme 2. *Conditions*: (a) OsO_4 cat., NMO, H_2O/acetone, rt, 24 h; (b) MCPBA, CH_2Cl_2, rt, 24 h then 30% $HClO_4$, rt, 24 h; (c) AD-mix-α or AD-mix-β, 50% aqueous *tert*-BuOH, 0°C to rt, 48 h; (d) 36% formalin, K_2CO_3, 0–5°C, 15 min.

Table 2. Diastereoselective synthesis of 3-diethoxyphosphoryltetrahydrofuranones **12** and 3-methylidenetetrahydrofuranones **5**

Entry	Product	R^1	R^2	Mode of dihydroxylation	Yield[a] (%)	
					12	**5**
1	a	H	H	*syn*	73	70
2	b	H	Me	*syn*	74	63
3	c	Me	H	*syn*	82	44
4	c	Me	H	*anti*	78	59
5	d	*n*-Pr	H	*syn*	81	62
6	d	*n*-Pr	H	*anti*	72	68
7	e	Ph	H	*syn*	85	63
8	e	Ph	H	*anti*	90	41

[a] All yields refer to pure, isolated products. All new compounds were fully characterised by IR, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and elemental analysis.

† The procedure for chemoselective hydrolysis is described in Ref. 12.

‡ Compound *l*-**5e**: oil; IR ν_{max} (cm^{-1}) (film) 3432, 3095, 3064, 3032, 1764, 1664, 1496, 1452, 1439, 1128, 1040, 1020; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.62 (bs, 1H, OH), 2.65–2.86 (m, 2H, C-4H$_2$), 4.63–4.73 (m, 2H, C-5H, C1′H), 5.59 (t, ^4J=2.50 Hz, 1H, =CH), 6.21 (t, ^4J=2.5 Hz, 1H, =CH), 7.34–7.42 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.56 (C-4), 75.13 (C-5), 79.11 (C-1′), 121.35 (=CH$_2$), 126.14, 127.59, 127.65 and 137.28 (Ph), 132.91 (C-3), 169.16 (C-2). Anal. calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.71; H, 5.80.
Compound *u*-**5e**: oil; IR ν_{max} (cm^{-1}) (film) 3425, 3090, 3065, 3030, 1665, 1766, 1496, 1440, 1128, 1050, 1022; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.47 (bs, 1H, OH), 2.63 (ddt, ^2J=17.50 Hz, ^3J=8.25 Hz, ^4J=2.50 Hz, 1H, C-4H), 3.02 (ddt, ^2J=17.50 Hz, ^3J=5.75 Hz, ^4J=2.50 Hz, 1H, C-4H), 4.73 (ddd, ^3J=8.25 Hz, ^3J=5.75 Hz, ^3J=3.25 Hz, 1H, C-5H), 5.14 (d, ^3J=3.25 Hz, 1H, C-1′H), 5.60 (t, ^4J=2.50 Hz, 1H, =CH), 6.21 (t, ^4J=2.50 Hz, 1H, =CH), 7.30–7.40 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 26.52 (C-4), 72.91 (C-5), 80.11 (C-1′), 121.94 (=CH$_2$), 125.96, 128.03, 128.56 and 138.21 (Ph), 134.46 (C-3), 170.58 (C-2). Anal. calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.57; H, 5.98.

Table 3. Enantioselective synthesis of 3-diethoxyphosphoryltetrahydrofuranones **12** and 3-methylidenetetrahydrofuranones **5**

Entry	Product	R^1	R^2	AD-mix	**12**	**5**			
					Yield[a] (%)	$[\alpha]_D^{21}$	ee%	Configuration	Yield[a] (%)
1	a	H	H	α	73	–	<5	–	72
2	a	H	H	β	75	–	<5	–	59
3	d	*n*-Pr	H	α	64	+19.1	30	5*S*,1′*S*	58
4	d	*n*-Pr	H	β	68	−26.5	40	5*R*,1′*R*	69
5	e	Ph	H	α	61	+32.6	70	5*S*,1′*S*	65
6	e	Ph	H	β	60	−42.7	90	5*R*,1′*R*	71

[a] All yields refer to pure, isolated products. All new compounds were fully characterised by IR, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and elemental analysis.

Following the establishment of the described protocols for preparation of *l*- and *u*-furanones **5**, we attempted to formulate methods for the enantioselective synthesis of the same class of compounds. In this respect, the commercially available Sharpless reagents[18] (AD-mix-α and AD-mix-β) were employed in *syn*-dihydroxylation reactions of the phosphorylated alkenoic acids **9**.¶ The results obtained are shown in Table 3. Surprisingly, no enantioselection was observed with the terminal olefin ($R^1=R^2=H$, entries 1 and 2). On the other hand, the alkyl ($R^1=n$-Pr, entries 3 and 4) and aryl ($R^1=$Ph, entries 5 and 6) substituted olefins gave moderate to high levels of enantioselection, respectively. The observed enhancement in selectivity induced by aryl substitution of the double bond is a well known phenomenon and has been reported for the asymmetric dihydroxylations of 1-alkenylphosphonates[19] as well as other olefins.[18]

The enantiomeric excesses and absolute configurations of optically active furanones **5** were determined by their transformation into Mosher's esters,[20] followed by the analysis of the resulting diastereoisomers by ^{1}H NMR. In configurational assignments the shielding effects of phenyl groups were diagnostic, e.g. the chemical shifts of the methoxy groups in appropriate Mosher esters derived from (+)- and (−)-**5e** (entries 5 and 6) were 3.61 and 3.47 ppm, respectively.

In summary, we have developed an efficient and stereocontrolled route to a variety of 5-(1′-hydroxyalkyl)-3-methylidene-2-furanones **5** by a unique combination of *syn*- or *anti*-dihydroxylation of 4-alkenoic acids **9** or alkenoates **8** and Horner–Wadsworth–Emmons olefination techniques. Importantly, this new methodology is completely diastereoselective and gives access to *l*- or *u*-2-furanones **5**. Furthermore, the initial results from our asymmetric dihydroxylation studies indicate that *l*-2-furanones **5** of high enantiomeric purity can be obtained from readily available 5-aryl substituted 4-alkenoic acids **9**. Work to enhance the overall efficacy of these and other organophosphorus-based techniques for the preparation of functionalised furanones is currently continuing in our laboratory.

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§ Compounds **5c** were obtained as a mixtures of diastereoisomers (entry 3 *l*/*u*=80/20, entry 4 *l*/*u*=20/80). This is a consequence of using commercially available *E*/*Z* mixture of crotyl bromide **7c** (*E*/*Z*∼85/15) in the alkylation of **6**. For that reason alkenoate **8c** and alkenoic acid **9c** were prepared as a mixtures of diastereoisomers (*E*/*Z*=80/20) and also furanones **12c** were mixtures of four diastereoisomers.

¶ General procedure for asymmetric dihydroxylation of 4-alkenoic acids **9**: A mixture of AD-mix-α or AD-mix-β (2.08 g) and potassium osmate dihydrate (6.0 mg, 0.8 mol%) in 50% aqueous *tert*-BuOH (20 mL) was stirred at rt until two clear phases were formed. Then $CH_3SO_2NH_2$ (0.19 g, 2.0 mmol) was added. The resultant mixture was cooled to 0°C and a solution of alkenoic acid **9** (2 mmol) in 50% aqueous *tert*-BuOH (4 mL) was added in one portion. After stirring for 2 h the mixture was allowed to warm to rt and was stirred for an additional 48 h. The reaction was quenched with Na_2SO_3 (6.0 g), stirred for 1 h and acidified to pH∼2 with 3N HCl. Then solvents were evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (5×20 mL). Combined chloroform extracts were dried over $MgSO_4$ and evaporated to give a crude product which was purified by column chromatography (silica gel, AcOEt/MeOH, 95:5, as eluent).

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