European Journal of Medicinal Chemistry 45 (2010) 710–718

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and cytotoxic evaluation of β-alkyl or β-aryl-δ-methyl-α-methylene-δ-lactones. Comparison with the corresponding γ-lactones

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ARTICLE INFO

Article history:
Received 5 June 2009
Received in revised form
17 July 2009
Accepted 6 November 2009
Available online 14 November 2009

Keywords:
α-Methylene-γ-lactones
α-Methylene-δ-lactones
Horner–Wadsworth–Emmons reaction
Diastereoselective synthesis
Cytotoxic activity

ABSTRACT

We present a simple and general strategy for the synthesis of β,δ-disubstituted-α-methylene-δ-lactones starting from easily available *tert*-butyl 2-(diethoxyphosphoryl)alk-2-enoates. The elaborated synthetic protocol includes pyrrolidine-catalyzed Michael addition of acetone, diastereoselective reduction of the carbonyl group, lactonization and finally the Horner–Wadsworth–Emmons reaction with formaldehyde. All α-methylene-δ-lactones were evaluated *in vitro* against mouse leukemia cell line L-1210 and two human leukemia cell lines HL-60 and NALM-6. Comparison of cytotoxic activity with corresponding α-methylene-γ-lactones is also discussed.

1. Introduction

α-Alkylidene-γ-lactones **1** are found, as structural subunits, in a variety of natural and synthetic products possessing diverse biological activity [1]. Representative examples of natural α-alkylidene-γ-lactones such as: tulipaline A (**2**) and tulipaline B (**3**) [2,3], eupomatilone 2 (**4**) [4] or helenalin (**5**) [5] are shown in Fig. 1. The α-alkylidene-γ-lactone moiety **1** seems to play a crucial role in the diverse pharmacological properties of these products, such as cytotoxic, allergenic, anti-inflammatory, phytotoxic or antimicrobial activity. The ability of the unsaturated lactone functionality to act as a highly reactive Michael acceptor has brought forth the realization of its crucial role as a physiologically important building block. Indeed, these compounds have been shown to be active thiol alkylators and to react with bionucleophiles, especially cysteine mercapto groups what is crucial for their, usually strong and specific, cytotoxic activity [5,6]. Structure–activity relationships (SAR) in the α-alkylidene-γ-lactones series have been extensively studied, in particular in the context of leukemia as well as other cancer cell lines [7–14].

On the other hand, α-methylene-δ-lactones **6**, although much less abundant in nature [15–23], are well known. Representative examples of naturally occurring α-methylene-δ-lactones such as: vernolepin (**7**) [15], vernomenin (**8**) [15], teucriumlactone (**9**) [17], crassin (**10a**) and its acetate **10b** [21,22] or pentalenolactone E (**11**) [16] are depicted in Fig. 1. Many methods of their preparation have been reported in the literature [24–36]. α-Methylene-δ-lactones **2** also can act as Michael acceptors, therefore it is really surprising that the data about the cytotoxic activity of these compounds are scarce and no systematic SAR investigations have been undertaken so far. To the best of our knowledge, there are only two publications on this subject describing cytotoxicities of several estrogen derivatives containing α-methylene-δ-lactone moiety as a part of the A or D-ring (Fig. 1, compounds **12**, **13**) [37,38].

Recently, we have significantly developed the methodology for the synthesis of α-alkylidene-γ- and δ-lactones based on the Horner–Wadsworth–Emmons olefination reaction which can be efficiently used for the introduction of the alkylidene moiety into the γ-lactone [14,39,40] and δ-lactone [41–47] ring. In this communication we present further application of our methodology in the synthesis of

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doi:10.1016/j.ejmech.2009.11.018

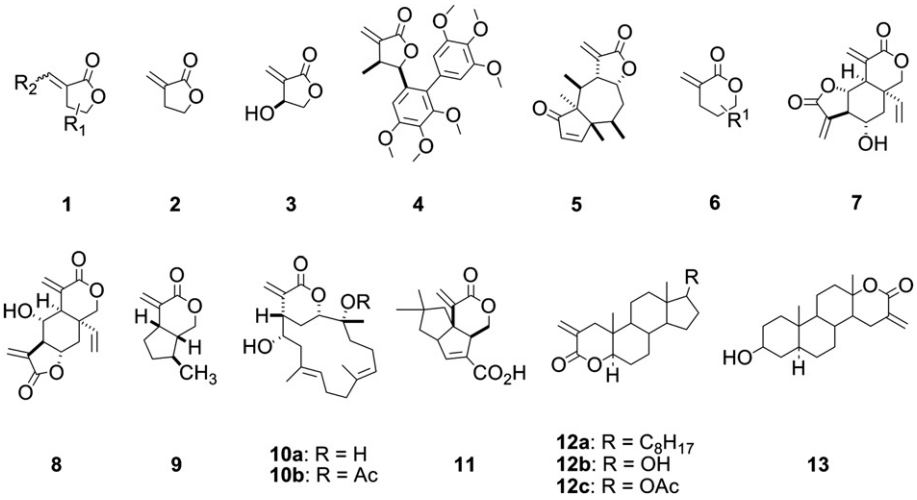


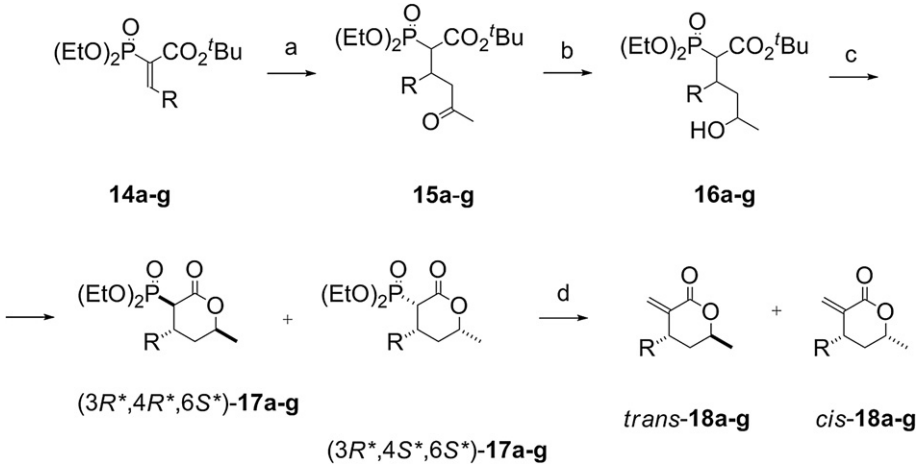
Fig. 1.

β-alkyl or β-aryl-δ-methyl-α-methylene-δ-lactones **18** and cytotoxic evaluation of these compounds against the mouse leukemia cell line L-1210 and two human leukemia cell lines NALM-6 and HL-60. Furthermore, we compare the activity of α-methylene-δ-lactones **18** with the activity of the corresponding β-aryl-γ-methyl-α-methylene-γ-lactones **19**, which were very recently synthesized in our laboratory using the same methodology [40].

2. Chemistry

β,δ-Disubstituted-α-methylene-δ-lactones **18** evaluated in this study were obtained from easily available *tert*-butyl 2-(diethoxyphosphoryl)alk-2-enoates **14a–g** [48,49] as outlined in Scheme 1. Our synthesis of these compounds begins with Michael addition of acetone to the alk-2-enoates **14a–g**. After preliminary experiments it was found that the use of acetone as the reagent and solvent, and pyrrolidine (0.2 equiv) as the catalyst gave the best results in terms of yield and purity of the products. The additions proceeded efficiently at room temperature and were terminated within 3–14 days. Data presented in Table 1 shows that a reasonable reaction rate is limited to the alk-2-enoates **14a**,**b** bearing electron-withdrawing substituents on the aromatic ring. All the phosphonates **15a–g** obtained were formed as inseparable mixtures of diastereoisomers.

In the next step, chemoselective reduction of the carbonyl group was performed. In our initial studies *tert*-butyl 2-(diethoxyphosphoryl)-3-(4-nitrophenyl)-5-oxohexanoate **15a** was chosen as a model substrate and various methods for its conversion into the α-diethoxyphosphoryl-δ-lactone **17a** were evaluated. The use of KBH_4 as a reducing agent provided 5-hydroxyhexanoate **16a** accompanied by the corresponding lactone **17a**. 5-Hydroxyhexanoate **16a** was completely converted into the lactone **17a** by treatment of the obtained mixture with CF_3CO_2H in DCM. ^{31}P NMR data of the lactone **17a** revealed the formation of two diastereoisomers in a ratio 0.67:1. In order to find an effective, alternative procedure for the highly diastereoselective synthesis of the lactone **17a** we examined the stereoselectivity of the reduction of the oxoester **15a** in the presence of selected metal salts. Model studies revealed that the treatment of the oxoester **15a** with $KBH_4/CaCl_2$, $KBH_4/CeCl_3$, $KBH_4/BaCl_2$ systems followed by lactonization under standard conditions gave the expected α-diethoxyphosphoryl-δ-lactone **17a**, however no improvement of diastereselectivity was observed. The problem of highly diastereoselective reduction of 5-oxohexanoate **15a** was eventually solved by employing DIBAL-H as a reducing agent. The reduction performed in THF at −78 °C for 3 h followed by CF_3CO_2H promoted cyclization of the resulting 5-hydroxyhexanoate **16a** provided the lactone **17a** as a mixture of two diastereoisomers in a 0.05:0.95 ratio.



Scheme 1. Reagents and conditions: (a) Acetone, pyrrolidine (0.2 equiv), rt. (b) DIBAL-H (2.2 equiv), THF, Ar atm., −70 °C, 3 h (c) CF_3CO_2H–CH_2Cl_2 (1:2), rt, overnight. (d) ^tBuOK (1.2 equiv), Et_2O, rt, 0.5 h.; then $(HCHO)_n$ (5 equiv), Et_2O, rt, 1 h.

Table 1
tert-Butyl 3-substituted-2-diethoxyphosphoryl-5-oxohexanoates prepared **15a–g**.

	R	Yield [%]	Reaction time[days]	dr[a]
a	4-NO_2–C_6H_4–	93	3	30:70
b	4-Br–C_6H_4–	87	3	31:69
c	4-CH_3O–C_6H_4–	88	7	30:70
d	3,4-(OCH_2O)–C_6H_3–	91	7	29:71
e	2-CH_3O–C_6H_4–	84	14	32:68
f	^{i}Pr	89	11	43:57
g	*c*-Hex-	91	5	43:57

[a] Determined by ^{31}P NMR.

This protocol was successfully extended to other 2-diethoxyphosphoryl-5-oxohexanoates **15b–g**. The α-diethoxyphosphoryl-δ-lactones **17b–g** were formed as mixtures of diastereoisomers. Their ratios were determined by ^{31}P NMR and are shown in Table 2. Analysis of these data revealed that electronic effect of the substituents on the aromatic ring had a profound impact on the diastereoselectivity of the reduction. α-Diethoxyphosphoryl-δ-lactones **17a**,**b**,**f**,**g** derived from 3-aryl-5-oxohexanoates **15a**,**b** bearing electron-withdrawing group on the aromatic ring and 3-alkyl-5-oxohexanoates **15f**,**g** exhibited high diastereoselectivity. In contrary, 3-aryl-5-oxohexanoates **15c–e** bearing electron-donating substituents on the phenyl ring gave the corresponding products **17c–e** with moderate diastereoselectivity.

Spectroscopic studies were not sufficient in determining the stereochemistry of the α-diethoxyphosphoryl-δ-lactones **17a–g** obtained. X-Ray crystallographic analysis conducted on the major diastereoisomer **17a** revealed that in the crystal the δ-lactone ring adopts $^4H_5$ chair conformation [50]. The Cremer and Pople puckering parameters [51] for the endocyclic atom sequence O5/C2/C1/C6/C5/C3 are $Q = 0.481(1)$ Å, $\theta = 135.2(2)°$, $\varphi = 22.2(2)°$. The phosphoryl and aryl groups are placed axially and are in mutual *trans* relationship. The methyl group occupies equatorial position and is located *trans* in respect to the 4-nitrophenyl subsituent (Fig. 2). This allowed us to assign the (3*R**, 4*R**, 6*S**) relative stereochemistry to the all major diastereoisomers **17a–g**. In this context, it is also worth noting that the values of coupling constants $^3J_{H3H4} = 1.9–2.6$ Hz, $^3J_{PCipso} = 12.9–14.0$ Hz and $^4J_{H3H5} = 1.3–1.7$ Hz observed for major diasteroisomers **17a–g** confirm the conformation with *trans* diaxial C-3 and C-4 substituents arrangement. The relative configuration of all minor diastereoisomers was assigned to be (3*R**, 4*S**, 6*S**) on the basis of ^{1}H and ^{13}C NMR data. The values of coupling constants $^3J_{H3H4} = 4.5–5.4$ Hz and $^3J_{PCipso} = 4.5–5.1$ Hz clearly proved the *cis* arrangement of the phosphoryl and aryl groups.

The Horner–Wadsworth–Emmons reaction of α-diethoxyphosphoryl-δ-lactones **17a–g** with excess of paraformaldehyde performed in THF in the presence of potassium *tert*-butoxide afforded the α-methylene-δ-lactones **18a–g** in high yield as inseparable mixtures of diastereoisomers. It is also worth to note that the ratios of diastereomeric α-methylene-δ-lactones **18a–g** reflect the degree of diastereoselection which is attained in the reduction of oxoesters **15a–g**.

Table 2
α-Diethoxyphosphoryl-δ-lactones **17a–g** and α-methylene-δ-lactones **18a–g** prepared.

	R	**17**		**18**	
		Yield[%][a]	dr[b](3*R**,4*R**,6*S**):(3*R**,4*S**,6*S**)	Yield [%]	dr(*trans*:*cis*)[c]
a	4-NO_2–C_6H_4–	66	95:5	85	>95:5
b	4-Br–C_6H_4–	65	89:11	87	89:11
c	4-CH_3O–C_6H_4–	62	63:37	78	63:37
d	3,4-(OCH_2O)–C_6H_3-	60	76:24	72	76:24
e	2-CH_3O–C_6H_4–	48	63:37	68	63:37
f	^{i}Pr	73	95:5	84	95:5
g	*c*-Hex-	74	94:6	84	94:6

[a] Overall yield for 2 steps.
[b] Determined by ^{31}P NMR.
[c] Determined by ^{1}H NMR.

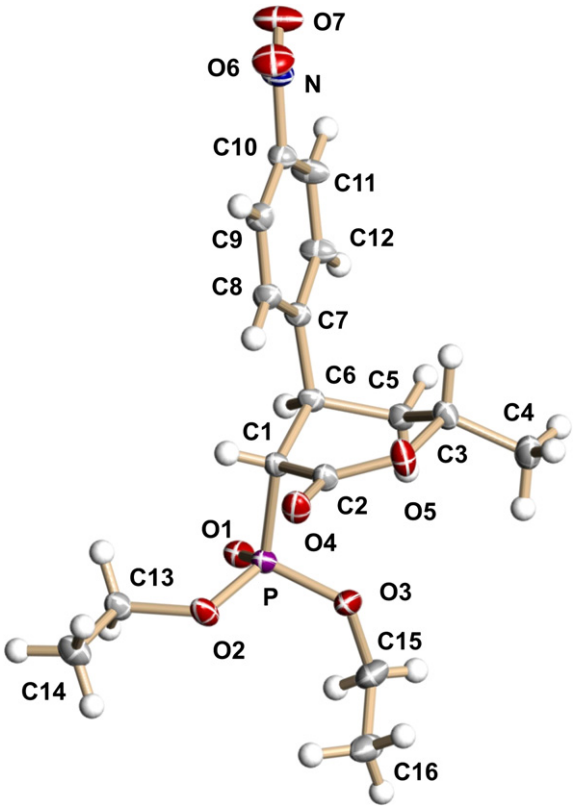


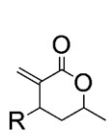
Fig. 2. The crystal structure of α-diethoxyphosphoryl-δ-lactone **17a**. The terminal C16 atom of the diethoxy substituent is disordered over two partially occupied positions. The picture shows site for which the occupation factor was 0.53(1). The slightly less occupied position has not been shown for clarity. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of an arbitrary radius.

3. Pharmacological results

All α-methylene-δ-lactones **18a–g** were evaluated *in vitro* against mouse leukemia cell line L-1210 and two human leukemia cell lines HL-60 and NALM-6. Cytotoxic activity of these compounds is expressed as the concentration (μM) required to inhibit tumor cells proliferation by 50% after 48 h exposure of the cells to a tested compound (IC_{50} values). Results are given in Table 3. We also evaluated the cytotoxicities of *trans*- and *cis*- β-aryl-γ-methyl-α-methylene-γ-lactones **19a–e** prepared recently in our laboratory [40] in order to compare the activity of γ- and δ-lactones. Carboplatin was used as a reference compound [52].

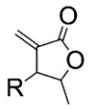
In general, the α-methylene-δ-lactones **18a–g** synthesized possess significant cytotoxic activity against all three cell lines. However, there is a pronounced difference in the cytotoxicities of β-aryl and β-alkyl substituted lactones. The first are much more active against all three cell lines (IC_{50} values in a range from 0.80 to 7.00 μM) and can be considered highly potent, according to the Kupchan's classification ($IC_{50} \leq 15$ μM) [53]. Moreover their activities against L-1210 cell line are generally higher than against HL-60 or NALM-6 cell lines. This observation confirms our earlier findings in the α-methylene-γ-lactones series, that the presence of the aryl substituent in the lactone ring increases cytotoxicity. β-Alkyl substituted lactones **18f**,**g** are less potent, with IC_{50} values between 13.0 and 61.2 μM.

Table 3
Cytotoxic Activity of α-methylene-δ-lactones, **18a–g** and α-methylene-γ-lactones **19a–e**.



18a-g

18a: R = 4-NO_2-C_6H_4-
18b: R = 4-Br-C_6H_4-
18c: R = 4-CH_3O-C_6H_4-
18d: R = 3,4-(OCH_2O)-C_6H_3-
18e: R = 2-CH_3O-C_6H_4-
18f: R = ^{i}Pr
18g: R = *c*-Hex



19a-e

19a: R = 4-NO_2-C_6H_4-
19b: R = 4-Br-C_6H_4-
19c: R = 4-CH_3O-C_6H_4-
19d: R = 3,4-(OCH_2O)-C_6H_3-
19e: R = 4-CH_3-C_6H_4-

Compound	Cytotoxicity IC_{50} (μM)[a]		
	L-1210	HL-60	NALM-6
18a	1.20 ± 0.20	6.12 ± 0.71	3.42 ± 0.41
18b	1.75 ± 0.35	4.77 ± 0.35	4.51 ± 0.63
18c	0.80 ± 0.09	5.95 ± 0.48	5.76 ± 0.41
18d	7.00 ± 1.20	5.52 ± 0.42	5.46 ± 0.21
18e	2.10 ± 0.72	6.44 ± 0.40	6.26 ± 0.28
18f	44.4 ± 3.47	61.2 ± 1.80	56.4 ± 2.80
18g	13.0 ± 1.90	40.6 ± 7.70	15.8 ± 2.50
cis-**19a**	1.90 ± 0.20	21.7 ± 6.65	3.77 ± 1.10
trans-**19b**	0.58 ± 0.08	6.66 ± 0.11	1.10 ± 0.14
cis-**19b**	7.80 ± 1.10	4.28 ± 0.54	4.25 ± 0.36
trans-**19c**	1.95 ± 0.05	5.56 ± 0.33	5.42 ± 0.26
cis-**19c**	4.40 ± 0.82	4.82 ± 0.61	5.59 ± 0.31
trans-**19d**	0.80 ± 0.06	5.35 ± 0.53	5.00 ± 0.74
cis-**19d**	1.40 ± 0.12	33.3 ± 3.6	4.70 ± 0.70
trans-**19e**	1.50 ± 0.19	5.01 ± 0.21	4.39 ± 0.37
cis-**19e**	5.50 ± 0.97	5.62 ± 0.21	5.97 ± 0.22
Carboplatin	9.7 ± 1.2	2.9 ± 0.1	0.7 ± 0.3

[a] IC_{50}, 50% inhibitory concentration determined by MTT assay after 48 h exposition of the cells to the drugs. IC_{50} values were calculated from concentration-survival curves using non-linear estimation (quasi-Newton algorithm) method. Each data represents the mean from dose response curves of at least three experiments.

Comparison of the cytotoxicities of β-aryl-δ-lactones **18a–e** with analogously substituted β-aryl-γ-lactones **19a–e** reveals no significant differences in their activities. Almost all cytotoxicities of **19a–e** are in the same range (between 0.5 and 7.8 μM) as the cytotoxicities of **18a–e** (between 0.8 and 7.0 μM). Only activities of *cis*-**19a** and *cis*-**19d** against HL-60 cell line are significantly lower. Such decrease in the activity for *cis* isomers was noticed by us previously in γ-aryl-β-methyl-α-methylene-γ-lactone serie [14]. Unfortunately, cytotoxicities of δ-lactones **18a–g** were determined for the mixtures of *trans* and *cis* diastereomers and no comparison in this respect can be made.

4. Conclusions

In conclusion, we have developed a simple and diastereoselective method for the synthesis of β,δ-disubstituted-α-methylene-δ-lactones from the corresponding *tert*-butyl 2-(diethoxyphosphoryl)alk-2-enoates. Our methodology benefits from easily available starting materials, experimental simplicity and high yields. Cytotoxicities of all β-aryl substituted δ-lactones **18a–e** against L-1210 and HL-60 and NALM-6 leukemia cell lines were very high and their activity was comparable with the activity of the previously prepared in our laboratory β-aryl substituted γ-lactones **19a–e** with the corresponding substitution pattern. Therefore, it seems that the size of the ring does not influences the cytotoxicity.

5. Experimental

5.1. Chemistry

5.1.1. General

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^{1}H and 62.9 MHz for ^{13}C and 101.3 MHz for ^{31}P NMR, respectively using tetramethylsilane as internal and 85% H_3PO_4 as external standard. The multiplicity of carbons were determined by DEPT experiments. IR spectra were measured on a Specord M80 (Zeiss) instrument. Elemental analyses were performed on a Perkin–Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. *tert*-Butyl 2-(diethoxyphosphoryl)alk-2-enoates **14a–g** [48,49] and α-methylene-γ-lactones **19a–e** [40] were prepared according to the literature procedures.

5.1.2. General procedure for the preparation of tert-butyl 3-substituted-2-diethoxyphosphoryl-5-oxohexanoates ***15a–g***

To a solution of the corresponding *tert*-butyl 2-(diethoxyphosphoryl)alk-2-enoate **14** (3 mmol) in acetone (12 mL) pyrrolidine (51 mg, 0.6 mmol) was added and the resulting mixture was stirred at room temperature for appropriate time shown in Table 1. After complete consumption of alk-2-enoate **14** (monitored by ^{31}P NMR spectroscopy) the solvent was evaporated under reduced pressure. The residue was dissolved in DCM (20 mL) and washed with 1 M HCl aq (10 mL). Water layer was extracted with DCM (2 × 10 mL). Combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane 2:1) to afford 3-substituted-2-diethoxyphosphoryl-5-oxohexanoates **15**.

*5.1.2.1. tert-Butyl 2-diethoxyphosphoryl-3-(4-nitrophenyl)-5-oxohexanoate (**15a**).* (93%); colorless oil. IR (film): 1712, 1592, 1468, 1388, 1256, 1148, 1020 cm^{-1} ^{31}P NMR ($CDCl_3$): δ = 20.55 (30%), 20.98 (70%); ^{1}H NMR ($CDCl_3$): δ = 1.14 (s, 9H, (CH_3)$_3$C, major and minor), 1.19–1.41 (m, 6H, (CH_3CH_2)$_2$OP, major and minor), 2.02 (s, 3H, CH_3, major), 2.04 (s, 3H, CH_3, minor), 2.89–3.46 (m, 2H, CH_2, major and minor), 3.95–3.99 (m, 2H, CHP, CHAr, major and minor), 4.01–4.24 (m, 4H, 2 × CH_2OP, major and minor), 7.47 (d, 2H, $^3J_{HH}$ = 8.7 Hz, CH_{Ar}, major and minor), 8.13 (d, 2H, $^3J_{HH}$ = 8.7 Hz, CH_{Ar}, major and minor); ^{13}C NMR ($CDCl_3$): δ = 15.93 (d, $^3J_{CP}$ = 8.7 Hz, CH_3CH_2OP, major and minor), 16.14 (d, $^3J_{CP}$ = 5.6 Hz, CH_3CH_2OP, major and minor), 27.16 ((CH_3)$_3$C, major), 27.58 ((CH_3)$_3$C, minor), 30.02 (CH_3, minor), 30.08 (CH_3, major), 38.94 (d, $^2J_{CP}$ = 2.7 Hz, CHAr, minor), 39.12 (d, $^2J_{CP}$ = 3.1 Hz, CHAr, major), 46.45 (d, $^3J_{CP}$ = 10.7 Hz, CH_2, minor),47.41 (CH_2, major), 51.07 (d, $^1J_{CP}$ = 128.3 Hz, PCH, major), 51.47 (d, $^1J_{CP}$ = 132.1 Hz, PCH, minor), 62.24 (d, $^2J_{CP}$ = 6.9 Hz, CH_3CH_2OP, minor), 62.48 (d, $^2J_{CP}$ = 6.9 Hz, CH_3CH_2OP, minor), 62.73 (d, $^2J_{CP}$ = 5.7 Hz, CH_3CH_2OP, major), 62.84 (d, $^2J_{CP}$ = 8.1 Hz, CH_3CH_2OP, major), 81.60 ((CH_3)$_3$C, major), 82.48 ((CH_3)$_3$C, minor), 123.05 (2 × CH_{Ar}, major), 123.12 (2 × CH_{Ar}, minor), 129.24 (2 × CH_{Ar}, minor), 129.30 (2 × CH_{Ar}, major), 146.52 (C_{Ar}, major), 146.62 (C_{Ar}, minor), 148.83 (d, $^3J_{CP}$ = 7.5 Hz, C_{Ar}, minor), 149.36 (d, $^3J_{CP}$ = 16.9 Hz, C_{Ar}, major), 166.09 (d, $^2J_{CP}$ = 4.4 Hz, COO, major), 166.68 (d, $^2J_{CP}$ = 5.6 Hz, COO, minor), 204.94 (C(O), minor), 205.03 (C(O), major). Anal. calcd for $C_{20}H_{30}NO_8P$: C, 54.17; H, 6.82. Found: C, 54.01; H, 6.62.

*5.1.2.2. tert-Butyl 3-(4-bromophenyl)-2-diethoxyphosphoryl-5-oxohexanoate (**15b**).* (87%); colorless oil. IR (film): 1720, 1592, 1488,

1388, 1260, 1148, 1024 cm^{-1} ^{31}P NMR ($CDCl_3$): $\delta = 21.10$ (31%), 21.62 (69%); ^{1}H NMR ($CDCl_3$): $\delta = 1.15$ (s, 9H, (CH_3)$_3$C, major and minor), 1.19–1.48 (m, 6H, (CH_3CH_2)$_2$OP, major and minor), 2.00 (s, 3H, CH_3, major), 2.04 (s, 3H, CH_3, minor), 2.87–3.36 (m, 2H, CH_2, major and minor), 3.76–4.01 (m, 2H, CHP, CHAr, major and minor), 4.14–4.25 (m, 4H, 2 × CH_2OP, major and minor), 7.12–7.18 (m, 2H, CH_{Ar}, major and minor), 7.35–7.41 (m, 2H, CH_{Ar}, major and minor); ^{13}C NMR ($CDCl_3$): $\delta = 15.81$ (d, $^{3}J_{CP} = 7.0$ Hz, CH_3CH_2OP, minor), 15.96 (d, $^{3}J_{CP} = 6.2$ Hz, CH_3CH_2OP, minor), 16.05 (d, $^{3}J_{CP} = 5.8$ Hz, (CH_3CH_2)$_2$OP, major), 27.07 ((CH_3)$_3$C, major), 27.51 ((CH_3)$_3$C, minor), 30.03 (CH_3, minor), 30.16 (CH_3, major), 38.64 (d, $^{2}J_{CP} = 3.3$ Hz, CHAr, minor), 38.92 (d, $^{2}J_{CP} = 3.3$ Hz, CHAr, major), 46.62 (d, $^{3}J_{CP} = 10.5$ Hz, CH_2, minor), 47.67 (CH_2, major), 51.48 (d, $^{1}J_{CP} = 128.5$ Hz, PCH, major), 51.85 (d, $^{1}J_{CP} = 131.8$ Hz, PCH, minor), 61.98 (d, $^{2}J_{CP} = 7.0$ Hz, CH_3CH_2OP, minor), 62.26 (d, $^{2}J_{CP} = 6.5$ Hz, CH_3CH_2OP, minor), 62.48 (d, $^{2}J_{CP} = 6.4$ Hz, CH_3CH_2OP, major), 62.66 (d, $^{2}J_{CP} = 7.2$ Hz, CH_3CH_2OP, major), 81.42 ((CH_3)$_3$C, major), 82.11 ((CH_3)$_3$C, minor), 120.38 (2 × CH_{Ar}, major), 120.51 (2 × CH_{Ar}, minor), 129.81 (2 × CH_{Ar}, minor), 129.90 (2 × CH_{Ar}, major), 130.90 (C_{Ar}, major), 131.00 (C_{Ar}, minor), 139.85 (d, $^{3}J_{CP} = 7.6$ Hz, C_{Ar}, minor), 140.32 (d, $^{3}J_{CP} = 17.1$ Hz, C_{Ar}, major), 166.18 (d, $^{2}J_{CP} = 5.3$ Hz, COO, major), 166.86 (d, $^{2}J_{CP} = 3.9$ Hz, COO, minor), 205.40 (C(O), minor), 205.41 (C(O), major). Anal. calcd for $C_{20}H_{30}BrO_6P$: C, 50.32; H, 6.33. Found: C, 50.63; H, 6.36.

*5.1.2.3. tert-Butyl 2-diethoxyphosphoryl-3-(4-methoxyphenyl)-5-oxohexanoate (**15c**).* (88%); colorless oil. IR (film): 1724, 1612, 1512, 1444, 1392, 1368, 1256, 1160, 1024 cm^{-1} ^{31}P NMR ($CDCl_3$): $\delta = 21.56$ (30%), 22.18 (70%); ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (s, 9H, (CH_3)$_3$C, major and minor), 1.17–1.48 (m, 6H, (CH_3CH_2)$_2$OP, major and minor), 1.96 (s, 3H, CH_3, major), 1.98 (s, 3H, CH_3, minor), 2.84–3.34 (m, 2H, CH_2, major and minor), 3.75 (CH_3, major), 3.77 (CH_3, minor), 3.78–3.99 (m, 2H, CHP, CHAr, major and minor), 4.12–4.24 (m, 4H, 2 × CH_2OP, major and minor), 6.77–6.88 (m, 2H, CH_{Ar}, major and minor), 7.17–7.20 (m, 2H, CH_{Ar}, major and minor); ^{13}C NMR ($CDCl_3$): $\delta = 15.90$ (d, $^{3}J_{CP} = 6.3$ Hz, CH_3CH_2OP, major and minor), 16.12 (d, $^{3}J_{CP} = 6.9$ Hz, CH_3CH_2OP, major and minor), 27.13 ((CH_3)$_3$C, major), 27.57 ((CH_3)$_3$C, minor), 30.07 (CH_3, minor), 30.27 (CH_3, major), 38.67 (d, $^{2}J_{CP} = 3.1$ Hz, CHAr, minor), 39.00 (d, $^{2}J_{CP} = 3.8$ Hz, CHAr, major), 47.13 (d, $^{3}J_{CP} = 11.3$ Hz, CH_2, minor), 48.22 (CH_2, major), 52.19 (d, $^{1}J_{CP} = 127.7$ Hz, PCH, major), 52.46 (d, $^{1}J_{CP} = 132.1$ Hz, PCH, minor), 54.85 (CH_3, minor), 54.88 (CH_3, major), 61.83 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, minor), 62.13 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, minor), 62.37 (d, $^{2}J_{CP} = 6.4$ Hz, CH_3CH_2OP, major), 62.56 (d, $^{2}J_{CP} = 7.5$ Hz, CH_3CH_2OP, major), 81.11 ((CH_3)$_3$C, major), 81.59 ((CH_3)$_3$C, minor), 113.29 (2 × CH_{Ar}, major), 113.39 (2 × CH_{Ar}, minor), 128.98 (2 × CH_{Ar}, minor), 129.08 (2 × CH_{Ar}, major), 132.65 (d, $^{3}J_{CP} = 16.9$ Hz, C_{Ar}, minor), 133.10 (d, $^{3}J_{CP} = 7.5$ Hz, C_{Ar}, major), 158.22 (C_{Ar}, major), 158.28 (C_{Ar}, minor), 166.44 (d, $^{2}J_{CP} = 6.6$ Hz, COO, major), 167.22 (d, $^{2}J_{CP} = 5.0$ Hz, COO, minor), 205.97 (C(O), major and minor); Anal. calcd for $C_{21}H_{33}O_7P$: C, 58.87; H, 7.76. Found: C, 58.41; H, 7.53.

*5.1.2.4. tert-Butyl 3-(benzo[d][1,3]dioxol-5-yl)-2-diethoxyphosphoryl-5-oxohexanoate (**15d**).* (91%); colorless oil. IR (film): 1724, 1620, 1512, 1448, 1396, 1368, 1256, 1156, 1020 cm^{-1} ^{31}P NMR ($CDCl_3$): $\delta = 21.40$ (29%), 21.97 (71%); ^{1}H NMR ($CDCl_3$): $\delta = 1.19$ (s, 9H, (CH_3)$_3$C, major and minor), 1.23–1.53 (m, 6H, (CH_3CH_2)$_2$OP, major and minor), 2.00 (s, 3H, CH_3, major), 2.05 (s, 3H, CH_3, minor), 2.77–3.38 (m, 2H, CH_2, major and minor), 3.72–3.85 (m, 1H, CHAr, major and minor), 3.92–4.05 (m, 1H, CHP, major and minor), 4.11–4.23 (m, 4H, 2 × CH_2OP, major and minor), 5.89 (s, 2H, OCH_2O, major), 5.91 (s, 2H, OCH_2O, minor), 6.70–6.74 (m, 3H, CH_{Ar}, major and minor); ^{13}C NMR ($CDCl_3$): $\delta = 16.14$ (d, $^{3}J_{CP} = 6.1$ Hz, CH_3CH_2OP, minor), 16.24 (d, $^{3}J_{CP} = 6.3$ Hz, CH_3CH_2OP, major and minor), 16.33 (d, $^{3}J_{CP} = 6.2$ Hz, CH_3CH_2OP, major), 27.44 ((CH_3)$_3$C, major), 27.81 ((CH_3)$_3$C, minor), 30.34 (CH_3, minor), 30.52 (CH_3, major), 39.27 ((d, $^{2}J_{CP} = 3.3$ Hz, CHAr, minor), 39.66 (d, $^{2}J_{CP} = 3.5$ Hz, CHAr, major), 47.15 (d, $^{3}J_{CP} = 10.2$ Hz, CH_2, minor), 48.37 (CH_2, major), 52.46 (d, $^{1}J_{CP} = 127.8$ Hz, PCH, major), 52.60 (d, $^{1}J_{CP} = 131.5$ Hz, PCH, minor), 62.20 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, minor), 62.51 (d, $^{2}J_{CP} = 6.5$ Hz, CH_3CH_2OP, minor), 62.69 (d, $^{2}J_{CP} = 6.3$ Hz, CH_3CH_2OP, major), 62.87 (d, $^{2}J_{CP} = 7.1$ Hz, CH_3CH_2OP, major), 81.53 ((CH_3)$_3$C, major), 82.25 ((CH_3)$_3$C, minor), 100.81 (OCH_2O, major), 100.86 (OCH_2O, minor), 107.89 (CH_{Ar}, major), 108.01 (CH_{Ar}, minor), 108.49 (CH_{Ar}, minor),), 108.69 (CH_{Ar}, major), 121.44 (CH_{Ar}, major), 121.59 (CH_{Ar}, minor), 134.95 (C_{Ar}, minor), 135.22 (C_{Ar}, major), 146.31 (C_{Ar}, major), 146.43 (C_{Ar}, minor), 147.32 (C_{Ar}, major), 147.45 (C_{Ar}, minor), 166.55 (d, $^{2}J_{CP} = 5.2$ Hz, COO, major), 167.33 (d, $^{2}J_{CP} = 3.9$ Hz, COO, minor), 206.17 (C(O), major and minor). Anal. calcd for $C_{21}H_{31}O_8P$: C, 57.01; H, 7.06. Found: C, 57.22; H, 6.93.

*5.1.2.5. tert-Butyl 2-diethoxyphosphoryl-3-(2-methoxyphenyl)-5-oxohexanoate (**15e**).* (84%); colorless oil. IR (film): 1720, 1612, 1512, 1448, 1392, 1368, 1256, 1156, 1024 cm^{-1} ^{31}P NMR ($CDCl_3$): $\delta = 22.23$ (32%), 23.26 (68%); ^{1}H NMR ($CDCl_3$): $\delta = 1.15$ (s, 9H, (CH_3)$_3$C, major and minor), 1.17–1.48 (m, 6H, (CH_3CH_2)$_2$OP, major and minor), 2.00 (s, 3H, CH_3, major), 2.04 (s, 3H, CH_3, minor), 2.85–3.38 (m, 2H, CH_2, major and minor), 3.84 (CH_3, major), 3.85 (CH_3, minor), 3.74–3.96 (m, 2H, CHP, CHAr, major and minor), 4.15–4.24 (m, 4H, 2 × CH_2OP, major and minor), 6.79–6.86 (m, 2H, CH_{Ar}, major and minor), 7.15–7.22 (m, 2H, CH_{Ar}, major and minor); ^{13}C NMR ($CDCl_3$): $\delta = 15.99$ (d, $^{3}J_{CP} = 6.6$ Hz, CH_3CH_2OP, major and minor), 16.10 (d, $^{3}J_{CP} = 6.3$ Hz, CH_3CH_2OP, major and minor), 27.03 ((CH_3)$_3$C, major), 27.54 ((CH_3)$_3$C, minor), 29.77 (CH_3, minor), 29.92 (CH_3, major), 35.63 (CHAr, minor), 37.28 (CHAr, major), 44.96 (d, $^{3}J_{CP} = 11.1$ Hz, CH_2, minor), 45.86 (CH_2, major), 49.26 (d, $^{1}J_{CP} = 131.1$ Hz, PCH, minor), 49.75 (d, $^{1}J_{CP} = 129.1$ Hz, PCH, major), 54.96 (CH_3, major and minor), 61.61 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, minor), 62.09 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, minor), 62.19 (d, $^{2}J_{CP} = 6.6$ Hz, CH_3CH_2OP, major), 62.48 (d, $^{2}J_{CP} = 7.0$ Hz, CH_3CH_2OP, major), 80.73 ((CH_3)$_3$C, major), 81.58 ((CH_3)$_3$C, minor), 110.41 (CH_{Ar}, major), 110.65 (CH_{Ar}, minor), 119.97 (2 × CH_{Ar}, major and minor), 128.01 (CH_{Ar}, major), 128.26 (CH_{Ar}, minor), 129.94 (C_{Ar}, minor), 131.48 (C_{Ar}, major), 157.19 (C_{Ar}, minor), 157.20 (C_{Ar}, major), 166.71 (d, $^{2}J_{CP} = 5.0$ Hz, COO, major), 167.39 (d, $^{2}J_{CP} = 4.4$ Hz, COO, minor), 206.35 (C(O), minor), 206.57 (C(O), major). Anal. calcd for $C_{21}H_{33}O_7P$: C, 58.87; H, 7.76. Found: C, 58.41; H, 7.53.

*5.1.2.6. tert-Butyl 2-diethoxyphosphoryl-3-isopropyl-5-oxohexanoate (**15f**).* (89%); colorless oil. IR (film): 1724, 1592, 1488, 1388, 1256, 1148, 1020 cm^{-1} ^{31}P NMR ($CDCl_3$): $\delta = 23.55$ (43%), 23.82 (57%); ^{1}H NMR ($CDCl_3$): $\delta = 0.79$ (t, 3H, $^{3}J_{HH} = 7.2$ Hz, CH_3, minor), 0.85 (t, 3H, $^{3}J_{HH} = 6.7$ Hz, CH_3, minor), 0.86 (t, 3H, $^{3}J_{HH} = 6.7$ Hz, CH_3, major), 0.89 (t, 3H, $^{3}J_{HH} = 6.7$ Hz, CH_3, major), 1.29–1.35 (m, 6H, (CH_3CH_2)$_2$OP, major and minor), 1.47 (s, 9H, (CH_3)$_3$C, major and minor), 1.82–1.86 (m, 1H, (CH_3)$_2$CH), 2.16 (s, 3H, CH_3, major), 2.18 (s, 3H, CH_3, minor), 2.30–2.68 (m, 2H, CH_2, major and minor), 2.80–3.32 (m, 2H, CHP, CH, major and minor), 4.08–4.16 (m, 4H, 2 × CH_2OP, major and minor); ^{13}C NMR ($CDCl_3$): $\delta = 15.92$ (d, $^{3}J_{CP} = 5.6$ Hz, CH_3CH_2OP, minor), 15.98 (d, $^{3}J_{CP} = 6.3$ Hz, CH_3CH_2OP, major and minor), 16.11 (d, $^{3}J_{CP} = 5.6$ Hz, CH_3CH_2OP, major), 19.39 (CH_3, major), 19.48 (CH_3, minor), 27.43 ((CH_3)$_3$C, major), 27.48 ((CH_3)$_3$C, minor), 28.90 ((CH_3)$_2$CH, minor), 29.34 ((CH_3)$_2$CH, major), 29.52 (CH_3, minor), 29.69 (CH_3, major), 31.16 (CH_3, minor), 31.38 (CH_3, major), 36.37 (d, $^{2}J_{CP} = 3.8$ Hz, CH, minor), 36.85 (d, $^{2}J_{CP} = 3.8$ Hz, CH, major), 41.00 (d, $^{3}J_{CP} = 2.5$ Hz, CH_2, minor), 43.33 (d, $^{3}J_{CP} = 4.4$ Hz, CH_2, major), 46.30 (d, $^{1}J_{CP} = 132.7$ Hz, PCH, major), 49.81 (d, $^{1}J_{CP} = 130.8$ Hz, PCH, minor), 61.82 (d, $^{2}J_{CP} = 5.6$ Hz, CH_3CH_2OP, minor), 61.93 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, minor), 62.29 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, major), 62.34 (d, $^{2}J_{CP} = 6.9$ Hz, CH_3CH_2OP, major), 81.24 ((CH_3)$_3$C, major), 81.45 ((CH_3)$_3$C, minor), 167.47 (d, $^{2}J_{CP} = 3.1$ Hz, COO, major), 167.65

(d, $^2J_{CP}$ = 5.3 Hz, *C*OO, minor), 206.35 (*C*(O), minor), 206.80 (*C*(O), major). Anal. calcd for $C_{17}H_{33}O_6P$: C, 56.03; H, 9.13. Found: C, 56.24; H, 9.31.

*5.1.2.7. tert-Butyl 3-cyclohexyl-2-diethoxyphosphoryl-5-oxohexanoate (**15g**).* (91%); colorless oil. IR (film): 1724, 1596, 1468, 1388, 1256, 1188, 1024 cm^{-1} ^{31}P NMR ($CDCl_3$): δ = 23.80 (43%), 23.96 (57%); ^{1}H NMR ($CDCl_3$): δ = 0.82–1.00 (m, 2H, CH_2, major and minor), 1.12–1.24 (m, 3H, CH_2, *C*H, major and minor), 1.25–1.36 (m, 6H, (CH_3CH$_2$)$_2$OP, major and minor), 1.47 (s, 9H, (CH_3)$_3$C, major and minor), 1.58–1.82 (m, 6H, CH_2, major and minor), 2.10 (s, 3H, CH_3, major), 2.20 (s, 3H, CH_3, minor), 2.44–2.65 (m, 2H, CH_2, major and minor), 2.75–3.32 (m, 2H, C*H*P, *C*H, major and minor), 4.12–4.19 (m, 4H, 2 × CH_2OP, major and minor); ^{13}C NMR ($CDCl_3$): δ = 16.00 (d, $^3J_{CP}$ = 4.1 Hz, *C*H$_3$CH$_2$OP, minor), 16.03 (d, $^3J_{CP}$ = 5.0 Hz, *C*H$_3$CH$_2$OP, minor), 16.08 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$CH$_2$OP, major), 16.11 (d, $^3J_{CP}$ = 5.9 Hz, *C*H$_3$CH$_2$OP, major), 26.02 (*C*H$_2$, minor), 26.15 (2 × *C*H$_2$, major and minor), 26.34 (*C*H$_2$, minor), 26.89 (*C*H$_2$, major), 27.55 ((*C*H$_3$)$_3$C, major), 27.62 ((*C*H$_3$)$_3$C, minor), 29.57 (*C*H$_2$, major), 29.74 (*C*H$_2$, minor), 29.96 (*C*H$_2$, major), 30.02 (*C*H$_3$, major), 31.21 (*C*H$_3$, minor), 36.14 (d, $^2J_{CP}$ = 3.8 Hz, *C*H, major), 36.38 (d, $^2J_{CP}$ = 4.3 Hz, *C*H, minor), 40.30 (d, $^3J_{CP}$ = 12.9 Hz, *C*H, minor), 41.44 (d, $^3J_{CP}$ = 13.3 Hz, *C*H, major), 42.22 (d, $^3J_{CP}$ = 2.5 Hz, *C*H$_2$, minor), 43.69 (d, $^3J_{CP}$ = 3.9 Hz, *C*H, major), 46.16 (d, $^1J_{CP}$ = 133.6 Hz, PCH, major), 49.13 (d, $^1J_{CP}$ = 131.5 Hz, PCH, minor), 61.88 (d, $^2J_{CP}$ = 6.3 Hz, CH$_3$CH$_2$OP, minor), 62.02 (d, $^2J_{CP}$ = 6.9 Hz, CH$_3$CH$_2$OP, minor), 62.34 (d, $^2J_{CP}$ = 6.9 Hz, CH$_3$CH$_2$OP, major), 62.46 (d, $^2J_{CP}$ = 7.5 Hz, CH$_3$CH$_2$OP, major), 81.31 ((CH$_3$)$_3$*C*, major), 81.51 ((CH$_3$)$_3$*C*, minor), 167.54 (d, $^2J_{CP}$ = 2.5 Hz, *C*OO, major), 167.84 (d, $^2J_{CP}$ = 5.0 Hz, *C*OO, minor), 206.54 (*C*(O), minor), 206.94 (*C*(O), major). Anal. calcd for $C_{20}H_{37}O_6P$: C, 59.39; H, 9.22. Found: C, 59.42; H, 9.01.

*5.1.3. General procedure for the preparation of 4-substituted-3-diethoxyphosphoryl-6-methyltetrahydro-2H-piran-2-ones **17a–g***

To a solution of the corresponding *tert*-butyl 2-diethoxyphosphoryl-5-oxohexanoate **15** (2 mmol) in THF (20 mL) at −70 °C 1.5 M solution of DIBAL-H (2.93 mL, 4.4 mmol) was added dropwise. The resulting mixture was stirred at this temperature for 3 h, quenched with 3 M HCl aq. (10 mL) and allowed to warm to room temperature. Solvent was evaported off under reduced pressure and the residue extracted with DCM (3 × 15 mL). Combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was dissolved in DCM (5 mL), CF_3CO_2H (2.5 mL) was added and the resulting solution left without stirring at room temperature overnight. The solvent was evaporated under reduced pressure, the residue dissolved in CH_2Cl_2 (20 mL), washed with sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane 4:1) to afford α-diethoxyphosphoryl-δ-lactone **17**.

*5.1.3.1. 3-Diethoxyphosphoryl-6-methyl-4-(4-nitrophenyl)tetrahydro-2H-piran-2-one (**17a**).* (66%); white crystals, mp 136–138 °C. IR (film): 1720, 1592, 1488, 1388, 1260, 1148, 1024 cm^{-1} ^{31}P NMR ($CDCl_3$): δ = 20.47 (95%), 21.23 (5%). (3*R**,4*R**,6*S**)-**17a**: ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 3H, $^3J_{HH}$ = 6.5 Hz, CH_3CH$_2$OP), 1.36 (t, 3H, $^3J_{HH}$ = 6.4 Hz, CH_3CH$_2$OP), 1.41 (d, 3H, $^3J_{HH}$ = 6.3 Hz, CH_3), 1.90–1.98 (m, 1H, CH_2), 2.36–2.48 (m, 1H, CH_2), 3.41 (ddd, 1H, $^2J_{HP}$ = 28.6 Hz, $^3J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 1.4 Hz, C*H*P), 3.98–4.04 (m, 1H, C*H*Ar), 4.08–4.27(m, 4H, 2 × CH_2OP), 4.33–4.4.40 (m, 1H, C*H*O), 7.36 (d, 2H, $^3J_{HH}$ = 8.6 Hz, CH_{Ar}), 8.22 (d, 2H, $^3J_{HH}$ = 8.6 Hz, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ = 15.92 (d, $^3J_{CP}$ = 7.0 Hz, *C*H$_3$CH$_2$OP), 16.05 (d, $^3J_{CP}$ = 6.9 Hz, *C*H$_3$CH$_2$OP), 20.78 (*C*H$_3$), 34.79 (d, $^3J_{CP}$ = 3.4 Hz, *C*H$_2$), 37.05 (d, $^2J_{CP}$ = 2.0 Hz, *C*HAr), 44.02 (d, $^1J_{CP}$ = 131.0 Hz, PCH), 62.72 (d, $^2J_{CP}$ = 4.8 Hz, CH$_3$CH$_2$OP), 63.70 (d, $^2J_{CP}$ = 7.0 Hz, CH$_3$CH$_2$OP), 73.82 (*C*HO), 123.83 (2 × *C*H$_{Ar}$), 127.80 (2 × CH$_{Ar}$), 146.79 (*C*$_{Ar}$), 149.93 (d, $^3J_{CP}$ = 12.9 Hz, *C*$_{Ar}$), 165.62 (d, $^2J_{CP}$ = 5.4 Hz, *C*OO). Anal. calcd for $C_{16}H_{22}NO_7P$: C, 51.75; H, 5.97. Found: C, 51.98; H, 5.61.

*5.1.3.2. 4-(4-Bromophenyl)-3-diethoxyphosphoryl-6-methyltetrahydro-2H-piran-2-one (**17b**).* (65%); colorless oil. IR (film): 1728, 1592, 1488, 1388, 1260, 1152, 1028 cm^{-1} ^{31}P NMR ($CDCl_3$): δ = 21.00 (89%), 21.67 (11%). (3*R**,4*R**,6*S**)-**17b**: ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3CH$_2$OP), 1.35 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3CH$_2$OP), 1.38 (d, 3H, $^3J_{HH}$ = 6.3 Hz, CH_3), 1.81–1.90 (m, 1H, CH_2), 2.31–2.43 (m, 1H, CH_2), 3.36 (ddd, 1H, $^2J_{HP}$ = 28.6 Hz, $^3J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 1.3 Hz, C*H*P), 3.82–3.94 (m, 1H, C*H*Ar), 4.12–4.27(m, 4H, 2 × CH_2OP), 4.31–4.4.41 (m, 1H, C*H*O), 7.05 (d, 2H, $^3J_{HH}$ = 7.5 Hz, CH_{Ar}), 7.47 (d, 2H, $^3J_{HH}$ = 7.5 Hz, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ = 15.97 (d, $^3J_{CP}$ = 7.1 Hz, *C*H$_3$CH$_2$OP), 16.08 (d, $^3J_{CP}$ = 6.8 Hz, *C*H$_3$CH$_2$OP), 20.92 (*C*H$_3$), 34.80 (d, $^3J_{CP}$ = 2.0 Hz, *C*H$_2$), 36.61 (d, $^2J_{CP}$ = 2.0 Hz, *C*HAr), 44.12 (d, $^1J_{CP}$ = 129.7 Hz, PCH), 62.75 (d, $^2J_{CP}$ = 6.8 Hz, CH$_3$CH$_2$OP), 63.56 (d, $^2J_{CP}$ = 7.1 Hz, CH$_3$CH$_2$OP), 73.84 (*C*HO), 120.84 (*C*$_{Ar}$), 128.41 (2 × *C*H$_{Ar}$), 131.74 (2 × CH$_{Ar}$), 141.12 (d, $^3J_{CP}$ = 13.2 Hz, *C*$_{Ar}$), 166.00 (d, $^2J_{CP}$ = 5.4 Hz, *C*OO). Anal. calcd for $C_{16}H_{22}BrO_5P$: C, 47.42; H, 5.47. Found: C, 47.21; H, 5.87.

*5.1.3.3. 3-Diethoxyphosphoryl-4-(4-methoxyphenyl)-6-methyltetrahydro-2H-piran-2-one (**17c**).* (62%); colorless oil. IR (film): 1716, 1592, 1486, 1388, 1256, 1152, 1012 cm^{-1} ^{31}P NMR ($CDCl_3$): δ = 21.49 (63%), 22.05 (37%); ^{1}H NMR ($CDCl_3$): δ = 1.23–1.40 (m, 9H, (CH_3CH$_2$)$_2$OP, CH_3, major and minor), 1.59–1.69 (m, 1H, CH_2, major), 1.80–1.89 (m, 1H, CH_2, minor), 2.14–2.22 (m, 1H, CH_2, minor), 2.31–2.42 (m, 1H, CH_2, major), 3.30 (dd, 1H, $^2J_{HP}$ = 28.6 Hz, $^3J_{HH}$ = 5.5 Hz, C*H*P, minor), 3.39 (ddd, 1H, $^2J_{HP}$ = 28.7 Hz, $^3J_{HH}$ = 2.2 Hz, $^4J_{HH}$ = 1.6 Hz, C*H*P, major), 3.71 (s, 3H, CH_3, major and minor), 3.83–4.05 (m, 1H, C*H*Ar, major and minor), 4.13–4.28 (m, 4H, 2 × CH_2OP, major and minor), 4.31–4.43 (m, 1H, C*H*O, major), 4.79–4.91 (m, 1H, C*H*O, minor), 6.84–6.88 (m, 2H, CH_{Ar}, major and minor), 7.06–7.16 (m, 2H, CH_{Ar}, major and minor); ^{13}C NMR ($CDCl_3$): δ = 15.86 (d, $^3J_{CP}$ = 4.9 Hz, *C*H$_3$CH$_2$OP, major and minor), 16.05 (d, $^3J_{CP}$ = 6.5 Hz, *C*H$_3$CH$_2$OP, major and minor), 20.74 (*C*H$_3$, minor), 20.97 (*C*H$_3$, major), 34.95 (d, $^3J_{CP}$ = 1.5 Hz, *C*H$_2$, major), 36.19 (d, $^3J_{CP}$ = 2.5 Hz, *C*H$_2$, minor), 38.53 (d, $^2J_{CP}$ = 3.4 Hz, *C*HAr, minor), 39.49 (d, $^2J_{CP}$ = 3.4 Hz, *C*HAr, major), 44.37 (d, $^1J_{CP}$ = 128.6 Hz, PCH, major), 47.86 (d, $^1J_{CP}$ = 125.5 Hz, PCH, minor), 55.00 (*C*H$_3$, major and minor), 62.55 (d, $^2J_{CP}$ = 6.9 Hz, CH$_3$CH$_2$OP, minor), 62.56 (d, $^2J_{CP}$ = 6.8 Hz, CH$_3$CH$_2$OP, major), 63.38 (d, $^2J_{CP}$ = 7.1 Hz, CH$_3$CH$_2$OP, major), 63.71 (d, $^2J_{CP}$ = 6.9 Hz, CH$_3$CH$_2$OP, minor), 73.92 (*C*HO, major), 75.02 (*C*HO, minor), 113.96 (2 × *C*H$_{Ar}$, major and minor), 127.59 (2 × *C*H$_{Ar}$, major), 127.74 (2 × *C*H$_{Ar}$, minor), 133.96 (d, $^3J_{CP}$ = 14.0 Hz, *C*$_{Ar}$, major), 135.81 (d, $^3J_{CP}$ = 4.5 Hz, *C*$_{Ar}$, minor), 158.38 (*C*$_{Ar}$, major and minor), 166.38 (d, $^2J_{CP}$ = 5.4 Hz, *C*OO, major), 167.00 (d, $^2J_{CP}$ = 5.0 Hz, *C*OO, minor). Anal. calcd for $C_{17}H_{25}O_6P$: C, 57.30; H, 7.07. Found: C, 57.14; H, 7.25.

*5.1.3.4. 4-(Benzo[d][1,3]dioxol-5-yl)-3-diethoxyphosphoryl-6-methyltetrahydro-2H-piran-2-one (**17d**).* (60%); colorless oil. IR (film): 1716, 1504, 1440, 1388, 1324, 1244, 1136, 1016 cm^{-1} ^{31}P NMR ($CDCl_3$): δ = 21.31 (76%), 21.92 (24%); ^{1}H NMR ($CDCl_3$): δ = 1.25–1.40 (m, 9H, (CH_3CH$_2$)$_2$OP, CH_3, major and minor), 1.60–1.91 (m, 1H, CH_2, major and minor), 2.29–2.41 (m, 1H, C*H*, major and minor), 3.28 (dd, 1H, $^2J_{HP}$ = 28.6 Hz, $^3J_{HH}$ = 5.4 Hz, C*H*P, minor), 3.36 (ddd, 1H, $^2J_{HP}$ = 28.8 Hz, $^3J_{HH}$ = 2.3 Hz, $^4J_{HH}$ = 1.6 Hz, C*H*P, major), 3.78–3.89 (m, 1H,C*H*Ar, major and minor), 4.06–4.28 (m, 4H, 2 × CH_2OP, major and minor), 4.32–4.46 (m, 1H, C*H*O, major), 4.80–4.87 (m, 1H, C*H*O, minor), 5.94 (s, 2H, OCH_2O, minor), 5.95 (s, 2H, OCH_2O, minor), 6.59–6.78 (m, 3H, CH_{Ar}, major and minor); ^{13}C NMR ($CDCl_3$): δ = 15.89 (d, $^3J_{CP}$ = 6.6 Hz, *C*H$_3$CH$_2$OP, major and minor), 16.00

(d, $^3J_{CP}$ = 6.4 Hz, *C*H$_3$CH$_2$OP, major and minor), 20.67 (*C*H$_3$, minor), 20.89 (*C*H$_3$, major), 34.94 (d, $^3J_{CP}$ = 1.7 Hz, *C*H$_2$, major), 36.66 (d, $^2J_{CP}$ = 2.4 Hz, *C*HAr, minor), 39.01 (d, $^3J_{CP}$ = 3.4 Hz, *C*H$_2$, minor), 39.37 (d, $^2J_{CP}$ = 5.5 Hz, *C*HAr, major), 44.38 (d, $^1J_{CP}$ = 128.8 Hz, P*C*H, major), 47.73 (d, $^1J_{CP}$ = 125.5 Hz, P*C*H, minor), 62.53 (d, $^2J_{CP}$ = 6.2 Hz, CH$_3$*C*H$_2$OP, minor), 62.64 (d, $^2J_{CP}$ = 6.6 Hz, CH$_3$*C*H$_2$OP, major), 63.37 (d, $^2J_{CP}$ = 7.1 Hz, CH$_3$*C*H$_2$OP, major), 63.69 (d, $^2J_{CP}$ = 6.9 Hz, CH$_3$*C*H$_2$OP, minor), 73.85 (*C*HO, major), 74.87 (*C*HO, minor), 100.86 (O*C*H$_2$O, minor), 100.94 (O*C*H$_2$O, major), 106.95 (*C*H$_{Ar}$, minor), 107.18 (*C*H$_{Ar}$, major), 108.01 (*C*H$_{Ar}$, major), 108.10 (*C*H$_{Ar}$, minor), 119.33 (*C*H$_{Ar}$, major), 119.87 (*C*H$_{Ar}$, minor), 135.78 (d, $^3J_{CP}$ = 13.9 Hz, *C*$_{Ar}$, major), 137.53 (d, $^3J_{CP}$ = 4.7 Hz, *C*$_{Ar}$, minor), 146.36 (*C*$_{Ar}$, major and minor), 147.75 (*C*$_{Ar}$, minor), 147.85 (*C*$_{Ar}$, major), 166.16 (d, $^2J_{CP}$ = 5.4 Hz, *C*OO, major), 166.79 (d, $^2J_{CP}$ = 5.0 Hz, *C*OO, minor). Anal. calcd for $C_{17}H_{23}O_7P$: C, 55.13; H, 6.26. Found: C, 55.23; H, 6.15.

*5.1.3.5. 3-Diethoxyphosphoryl-4-(2-methoxyphenyl)-6-methyltetrahydro-2H-piran-2-one (**17e**).* (48%); colorless oil. IR (film): 1720, 1592, 1486, 1388, 1256, 1154, 1016 cm^{-1} ^{31}P NMR (CDCl$_3$): δ = 22.29 (63%), 23.24 (37%); ^{1}H NMR (CDCl$_3$): δ = 1.22–1.38 (m, 9H, (C*H*$_3$CH$_2$)$_2$OP, C*H*$_3$, major and minor), 1.84–2.08 (m, 1H, C*H*$_2$, major and minor), 2.17–2.34 (m, 1H, C*H*$_2$, major and minor), 3.38 (dd, 1H, $^2J_{HP}$ = 28.1 Hz, $^3J_{HH}$ = 4.4 Hz, C*H*P, minor), 3.44 (ddd, 1H, $^2J_{HP}$ = 28.3 Hz, $^3J_{HH}$ = 2.4 Hz, $^4J_{HH}$ = 1.4 Hz, C*H*P, major), 3.81 (s, 3H, C*H*$_3$, minor), 3.83 (s, 3H, C*H*$_3$, major), 3.87–4.03 (m, 1H, C*H*Ar, major and minor), 4.03–4.27 (m, 4H, 2 × C*H*$_2$OP, major and minor), 4.31–4.44 (m, 1H, C*H*O, major), 4.86–4.99 (m, 1H, C*H*O, minor), 6.86–6.96 (m, 2H, C*H*$_{Ar}$, major and minor), 7.03 (dd, 1H, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.6 Hz, C*H*$_{Ar}$, major), 7.13 (dd, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.6 Hz, C*H*$_{Ar}$, minor), 7.21–7.30 (m, 1H, C*H*$_{Ar}$, major and minor); ^{13}C NMR (CDCl$_3$): δ = 15.82 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$CH$_2$OP, major and minor), 15.97 (d, $^3J_{CP}$ = 6.0 Hz, *C*H$_3$CH$_2$OP, major and minor), 20.54 (*C*H$_3$, minor), 20.90 (*C*H$_3$, major), 32.89 (*C*H$_2$, major and minor), 35.64 (d, $^2J_{CP}$ = 2.7 Hz, *C*HAr, minor), 36.79 (d, $^2J_{CP}$ = 2.9 Hz, *C*HAr, major), 43.49 (d, $^1J_{CP}$ = 129.8 Hz, P*C*H, major), 45.97 (d, $^1J_{CP}$ = 125.2 Hz, P*C*H, minor), 54.58 (*C*H$_3$, minor), 54.74 (*C*H$_3$, major), 62.35 (d, $^2J_{CP}$ = 6.6 Hz, CH$_3$*C*H$_2$OP, major and minor), 63.16 (d, $^2J_{CP}$ = 6.9 Hz, CH$_3$*C*H$_2$OP, major), 63.50 (d, $^2J_{CP}$ = 6.8 Hz, CH$_3$*C*H$_2$OP, minor), 74.34 (*C*HO, major), 74.47 (*C*HO, minor), 110.54 (*C*H$_{Ar}$, major), 110.86 (*C*H$_{Ar}$, minor), 120.25 (*C*H$_{Ar}$, minor), 120.31 (*C*H$_{Ar}$, major), 127.64 (*C*H$_{Ar}$, major), 128.12 (*C*H$_{Ar}$, major), 128.35 (*C*H$_{Ar}$, minor), 129.00 (*C*H$_{Ar}$, minor), 129.88 (d, $^3J_{CP}$ = 12.9 Hz, *C*$_{Ar}$, major), 130.86 (d, $^3J_{CP}$ = 5.1 Hz, *C*$_{Ar}$, minor), 156.29 (*C*$_{Ar}$, major and minor), 166.87 (d, $^2J_{CP}$ = 4.6 Hz, *C*OO, major), 167.53 (d, $^2J_{CP}$ = 3.3 Hz, *C*OO, minor). Anal. calcd for $C_{17}H_{25}O_6P$: C, 57.30; H, 7.07. Found: C, 57.01; H, 7.32.

*5.1.3.6. 3-Diethoxyphosphoryl-4-isopropyl-6-methyltetrahydro-2H-piran-2-one (**17f**).* (73%); colorless oil. IR (film): 1720, 1464, 1392, 1252, 1160, 1032 cm^{-1} ^{31}P NMR (CDCl$_3$): δ = 20.11 (5%), 22.13 (95%). (3*R**,4*R**,6*S**)-**17f**: ^{1}H NMR (CDCl$_3$): δ = 0.95 (d, 3H, $^3J_{HH}$ = 6.6 Hz, C*H*$_3$), 0.99 (d, 3H, $^3J_{HH}$ = 6.5 Hz, C*H*$_3$), 1.25–1.47 (m, 9H, (C*H*$_3$CH$_2$)$_2$OP, C*H*$_3$), 1.58–1.61 (m, 1H, C*H*), 1.75–1.88 (m, 1H, C*H*^{i}Pr), 2.02–2.21 (m, 2H, C*H*$_2$), 3.16 (ddd, 1H, $^2J_{HP}$ = 28.8 Hz, $^3J_{HH}$ = 2.1 Hz, $^4J_{HH}$ = 1.6 Hz, C*H*P), 4.13–4.26 (m, 4H, 2 × C*H*$_2$OP), 4.51–4.65 (m, 1H, C*H*O). ^{13}C NMR (CDCl$_3$): δ = 15.52 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$CH$_2$OP), 15.57 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$CH$_2$OP), 18.67 (*C*H$_3$), 20.19 (*C*H$_3$), 21.03 (*C*H$_3$), 28.54 (d, $^3J_{CP}$ = 2.2 Hz, *C*H$_2$), 28.98 (d, $^3J_{CP}$ = 13.2 Hz, (CH$_3$)$_2$*C*H), 37.52 (d, $^2J_{CP}$ = 3.7 Hz, *C*H), 43.09 (d, $^1J_{CP}$ = 129.2 Hz, P*C*H), 61.89 (d, $^2J_{CP}$ = 6.9 Hz, CH$_3$*C*H$_2$OP), 62.65 (d, $^2J_{CP}$ = 7.0 Hz, CH$_3$*C*H$_2$OP), 73.73 (*C*HO), 165.43 (d, $^2J_{CP}$ = 5.2 Hz, *C*OO). Anal. calcd for $C_{13}H_{25}O_5P$: C, 53.42; H, 8.62. Found: C, 53.61; H, 8.19.

*5.1.3.7. 4-Cyclohexyl-3-diethoxyphosphoryl-6-methyltetrahydro-2H-piran-2-one (**17g**).* (74%); colorless oil. IR (film): 1724, 1448, 1392, 1248, 1176, 1128, 1032 cm^{-1} ^{31}P NMR (CDCl$_3$): δ = 20.24 (6%), 22.28 (94%). (3*R**,4*R**,6*S**)-**17g**: ^{1}H NMR (CDCl$_3$): δ = 0.91–1.00 (m, 2H, C*H*$_2$), 1.11–1.25 (m, 3H, C*H*$_2$, C*H*), 1.31–1.42 (m, 9H, (C*H*$_3$CH$_2$)$_2$OP, C*H*$_3$), 1.62–1.70 (m, 7H, 3xC*H*$_2$, C*H*), 1.75–1.86 (m, 1H, C*H*), 1.90–2.08 (m, 2H, C*H*$_2$), 3.20 (ddd, 1H, $^2J_{HP}$ = 28.9 Hz, $^3J_{HH}$ = 1.9 Hz, $^4J_{HH}$ = 1.7 Hz, C*H*P), 4.12–4.25 (m, 4H, 2 × C*H*$_2$OP), 4.48–4.60 (m, 1H, C*H*O). ^{13}C NMR (CDCl$_3$): δ = 15.92 (d, $^3J_{CP}$ = 6.2 Hz, *C*H$_3$CH$_2$OP), 15.95 (d, $^3J_{CP}$ = 6.2 Hz, *C*H$_3$CH$_2$OP), 21.49 (*C*H$_3$), 25.66 (2 × *C*H$_2$), 25.75 (*C*H$_2$), 28.44 (d, $^3J_{CP}$ = 1.9 Hz, *C*H$_2$), 29.28 (*C*H$_2$), 30.78 (*C*H$_2$), 36.55 (d, $^2J_{CP}$ = 3.7 Hz, *C*H*c*-Hex), 38.48 (d, $^3J_{CP}$ = 13.2 Hz, *C*H), 42.92 (d, $^1J_{CP}$ = 128.9 Hz, P*C*H), 62.32 (d, $^2J_{CP}$ = 6.8 Hz, CH$_3$*C*H$_2$OP), 63.03 (d, $^2J_{CP}$ = 7.0 Hz, CH$_3$*C*H$_2$OP), 74.31 (*C*HO), 166.05 (d, $^2J_{CP}$ = 5.2 Hz, *C*OO). Anal. calcd for $C_{16}H_{29}O_5P$: C, 57.82; H, 8.79. Found: C, 57.94; H, 8.52.

*5.1.4. General procedure for the preparation of 4-substituted-6-methyl-3-methylenetetrahydro-2H-piran-2-ones **18a-g***

To a solution of the corresponding α-diethoxyphosphoryl-δ-lactone **17** (1.0 mmol) in Et$_2$O (10 mL) potassium *tert*-butoxide (134 mg, 1.2 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. Then paraformaldehyde (150 mg, 5 mmol) was added in one portion. After 1 h the reaction mixture was quenched with brine (10 ml), layers separated and the water layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (eluent: ethyl acetate/hexane 1:4).

5.1.4.1. (4R,6S*)-6-methyl-3-methylene-4-(4-nitrophenyl)tetrahydro-2H-piran-2-one (**18a**).* (85%); colorless oil (dr >95:5). IR (film): 1712, 1512, 1352, 1196, 1132, 1056 cm^{-1} ^{1}H NMR (CDCl$_3$): δ = 1.39 (d, 3H, $^3J_{HH}$ = 6.4 Hz, C*H*$_3$), 2.16 (t, 2H, $^3J_{HH}$ = 5.4 Hz, C*H*$_2$), 4.21–4.26 (m, 1H, C*H*Ar), 4.39–4.47 (m, 1H, C*H*O), 5.56 (d, 1H, $^2J_{HH}$ = 1.1 Hz, C*H*), 6.75 (d, 1H, $^2J_{HH}$ = 1.1 Hz, C*H*), 7.37 (d, 2H, $^3J_{HH}$ = 8.4 Hz, C*H*$_{Ar}$), 8.22 (d, 2H, $^3J_{HH}$ = 8.4 Hz, C*H*$_{Ar}$); ^{13}C NMR (CDCl$_3$): δ = 20.92 (*C*H$_3$), 36.77 (*C*H$_2$), 41.52 (*C*HAr), 72.55 (*C*HO), 123.20 (2 × *C*H$_{Ar}$), 128.55 (2 × *C*H$_{Ar}$), 131.64 (*C*H$_2$), 135.01 (*C*), 146.57 (*C*$_{Ar}$), 149.78 (*C*$_{Ar}$), 164.63 (*C*OO). Anal. calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30. Found: C, 63.30; H, 5.62.

*5.1.4.2. 4-(4-Bromophenyl)-6-methyl-3-methylenetetrahydro-2H-piran-2-one (**18b**).* (87%); colorless oil (dr 89:11). IR (film): 1720, 1488, 1384, 1304, 1204, 1072 cm^{-1} (4*R**,6*S**)-**18b**: ^{1}H NMR (CDCl$_3$): δ = 1.37 (d, 3H, $^3J_{HH}$ = 6.4 Hz, C*H*$_3$), 2.04–2.12 (m, 2H, C*H*$_2$), 4.06–4.09 (m, 1H, C*H*Ar), 4.38–4.51 (m, 1H, C*H*O), 5.55 (t, 1H, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, C*H*), 6.69 (t, 1H, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, C*H*), 7.06 (d, 2H, $^3J_{HH}$ = 8.6 Hz, C*H*$_{Ar}$), 7.47 (d, 2H, $^3J_{HH}$ = 8.6 Hz, C*H*$_{Ar}$); ^{13}C NMR (CDCl$_3$): δ = 21.11 (*C*H$_3$), 37.18 (*C*H$_2$), 41.24 (*C*HAr), 72.65 (*C*HO), 120.80 (*C*$_{Ar}$), 129.29 (2 × *C*H$_{Ar}$), 131.18 (*C*H$_2$), 131.76 (2 × *C*H$_{Ar}$), 135.72 (*C*), 141.32 (*C*$_{Ar}$), 165.20 (*C*OO). (4*R**,6*R**)-**18b** (representative signals): 1.44 (d, 3H, $^3J_{HH}$ = 6.3 Hz, C*H*$_3$), 3.77–3.84 (m, 1H, C*H*Ar), 5.24 (dd, 1H, $^4J_{HH}$ = 2.7 Hz, $^2J_{HH}$ = 1.2 Hz, C*H*). Anal. calcd for $C_{13}H_{13}BrO_2$: C, 55.54; H, 4.66. Found: C, 55.28; H, 4.31.

*5.1.4.3. 4-(4-Methoxyphenyl)-6-methyl-3-methylenetetrahydro-2H-piran-2-one (**18c**).* (78%); colorless oil (dr 63:37). IR (film): 1712, 1468, 1364, 1312, 1224, 1068 cm^{-1} ^{1}H NMR (CDCl$_3$): δ = 1.36 (d, 3H, $^3J_{HH}$ = 6.4 Hz, C*H*$_3$, major), 1.44 (d, 3H, $^3J_{HH}$ = 6.3 Hz, C*H*$_3$, minor), 1.85–2.17 (m, 2H, C*H*$_2$, major and minor), 3.71–3.76 (m, 1H, C*H*Ar, minor), 3.80 (m, 3H, C*H*$_3$O, major), 3.81 (m, 3H, C*H*$_3$O, minor), 4.06 (t, 1H, $^3J_{HH}$ = 4.7 Hz, C*H*Ar, major), 4.43–4.50 (m, 1H, C*H*O, major), 4.51–4.65 (m, 1H, C*H*O, minor), 5.25 (dd, 1H, $^4J_{HH}$ = 2.6 Hz, $^2J_{HH}$ = 1.3 Hz, C*H*, minor), 5.55 (t, 1H, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, C*H*, major), 6.57 (ddd, 1H, $^4J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 0.7 Hz, $^2J_{HH}$ = 1.3 Hz, C*H*, minor), 6.66 (t, 1H, $^4J_{HH}$ = $^2J_{HH}$ = 1.4 Hz, C*H*, major), 6.85–6.90 (m, 2H, C*H*$_{Ar}$, major and minor), 7.07–7.12 (m, 2H, C*H*$_{Ar}$, major and minor); ^{13}C NMR (CDCl$_3$): δ = 21.03 (*C*H$_3$, major), 21.45 (*C*H$_3$, minor), 37.36 (*C*H$_2$, major), 38.60 (*C*H$_2$, minor), 40.82 (*C*HAr, major),

43.64 (*C*HAr, minor), 55.01 (*C*H_3O, major and minor), 72.66 (*C*HO, major), 75.50 (*C*HO, minor), 113.89 (2 × *C*H_{Ar}, major), 113.99 (2 × *C*H_{Ar}, minor), 128.39 (2 × *C*H_{Ar}, major), 128.72 (2 × *C*H_{Ar}, minor), 129.70 (*C*H_2, minor), 130.37 (*C*H_2, major), 133.95 (*C*, minor), 134.11 (*C*, major), 136.50 (*C*$_{Ar}$, major), 138.93 (*C*$_{Ar}$, minor), 158.26 (*C*$_{Ar}$, major), 158.42 (*C*$_{Ar}$, minor), 165.50 (*C*OO, major and minor). Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.31; H, 6.88.

*5.1.4.4. 4-(Benzo[d][1,3]dioxol-5-yl)-6-methyl-3-methylenetetrahydro-2H-piran-2-one (**18d**).* (72%); colorless oil (dr 76:24). IR (film): 1720, 1468, 1368, 1312, 1224, 1024 cm^{-1} ^{1}H NMR ($CDCl_3$): $\delta = 1.37$ (d, 3H, $^3J_{HH} = 6.4$ Hz, C*H*$_3$, major), 1.43 (d, 3H, $^3J_{HH} = 6.3$ Hz, C*H*$_3$, minor), 1.83–2.17 (m, 2H, C*H*$_2$, major and minor), 3.69–3.78 (m, 1H, C*H*Ar, minor), 4.03 (t, 1H, $^3J_{HH} = 4.8$ Hz, C*H*Ar, major), 4.41–4.64 (m, 1H, C*H*O, major and minor), 5.31 (dd, 1H, $^4J_{HH} = 2.6$ Hz, $^2J_{HH} = 1.3$ Hz, C*H*, minor), 5.56 (t, 1H, $^4J_{HH} = {}^2J_{HH} = 1.4$ Hz, C*H*, major), 5.95 (s, 2H, OC*H*$_2$O, major), 5.96 (s, 2H, OC*H*$_2$O, minor), 6.58–6.80 (m, 4H, C*H*, C*H*$_{Ar}$, major and minor); ^{13}C NMR ($CDCl_3$): $\delta = 20.93$ (*C*H_3, major), 21.34 (*C*H_3, minor), 37.27 (*C*H_2, major), 38.52 (*C*H_2, minor), 41.19 (*C*HAr, major), 44.05 (*C*HAr, minor), 72.59 (*C*HO, major), 75.32 (*C*HO, minor), 100.80 (O*C*H_2O, minor), 100.86 (O*C*H_2O, major), 107.65 (*C*H_{Ar}, major and minor), 107.97 (*C*H_{Ar}, major), 108.07 (*C*H_{Ar}, minor), 120.48 (*C*H_2, major), 121.02 (*C*H_2, minor), 129.76 (*C*H_{Ar}, minor), 130.52 (*C*H_{Ar}, major), 135.63 (*C*H_{Ar}, minor), 135.88 (*C*H_{Ar}, major), 136.27 (*C*, major), 138.58 (*C*, minor), 146.21 (*C*$_{Ar}$, major), 146.35 (*C*$_{Ar}$, minor), 147.75 (*C*$_{Ar}$, major and minor), 165.23 (*C*OO, major), 165.37 (*C*OO, minor). Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 67.97; H, 5.62.

*5.1.4.5. 4-(2-Methoxyphenyl)-6-methyl-3-methylenetetrahydro-2H-piran-2-one (**18e**).* (68%); colorless oil (dr 63:37). IR (film): 1720, 1488, 1384, 1308, 1212, 1068 cm^{-1} ^{1}H NMR ($CDCl_3$): $\delta = 1.33$ (d, 3H, $^3J_{HH} = 6.4$ Hz, C*H*$_3$, major), 1.42 (d, 3H, $^3J_{HH} = 6.3$ Hz, C*H*$_3$, minor), 1.90–2.20 (m, 2H, C*H*$_2$, major and minor), 3.80 (m, 3H, C*H*$_3$O, major), 3.85 (m, 3H, C*H*$_3$O, minor), 4.12–4.21 (m, 1H, C*H*Ar, minor), 4.36 (t, 1H, $^3J_{HH} = 4.7$ Hz, C*H*Ar, major and minor), 4.40–4.57 (m, 1H, C*H*O, major and minor), 5.26 (dd, 1H, $^4J_{HH} = 2.5$ Hz, $^2J_{HH} = 1.3$ Hz, C*H*, minor), 5.53 (t, 1H, $^4J_{HH} = {}^2J_{HH} = 1.4$ Hz, C*H*, major), 6.41 (dd, 1H, $^4J_{HH} = 2.7$ Hz, $^2J_{HH} = 1.3$ Hz, C*H*, minor), 6.61 (t, 1H, $^4J_{HH} = {}^2J_{HH} = 1.4$ Hz, C*H*, major), 6.88–6.96 (m, 2H, C*H*$_{Ar}$, major and minor), 6.99–7.29 (m, 2H, C*H*$_{Ar}$, major and minor); ^{13}C NMR ($CDCl_3$): $\delta = 21.07$ (*C*H_3, major), 21.28 (*C*H_3, minor), 35.41 (*C*H_2, major), 36.56 (*C*H_2, minor), 37.17 (*C*HAr, major), 38.97 (*C*HAr, minor), 55.01 (*C*H_3O, major and minor), 73.18 (*C*HO, major), 75.38 (*C*HO, minor), 110.64 (*C*$_{Ar}$, major), 110.94 (*C*$_{Ar}$, minor), 120.36 (*C*H_{Ar}, major), 120.69 (*C*H_{Ar}, minor), 127.75 (*C*H_{Ar}, minor), 128.03 (*C*H_{Ar}, major), 128.16 (*C*H_{Ar}, minor), 128.52 (*C*H_2, minor), 128.67 (*C*H_{Ar}, major), 129.55 (*C*H_2, major), 131.00 (*C*H_{Ar}, major and minor), 136.64 (*C*, major), 138.47 (*C*, minor), 156.39 (*C*$_{Ar}$, major), 156.56 (*C*$_{Ar}$, minor), 166.00 (*C*OO, major), 166.64 (*C*OO, minor). Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.51; H, 6.82.

*5.1.4.6. 4-Isopropyl-6-methyl-3-methylenetetrahydro-2H-piran-2-one (**18f**).* (84%); colorless oil (dr 95:5). IR (film): 1724, 1464, 1384, 1296, 1184, 1136, 1048 cm^{-1} (4*R**,6*S**)-**18f**: ^{1}H NMR ($CDCl_3$): $\delta = 0.94$ (d, 3H, $^3J_{HH} = 6.5$ Hz, C*H*$_3$), 0.96 (d, 3H, $^3J_{HH} = 6.5$ Hz, C*H*$_3$), 1.38 (d, 3H, $^3J_{HH} = 6.3$ Hz, C*H*$_3$), 1.67–1.85 (m, 2H, C*H*$_2$, C*H*), 2.09 (ddd, 1H, $^2J_{HH} = 14.3$ Hz, $^3J_{HH} = 3.6$ Hz, $^3J_{HH} = 4.1$ Hz, C*H*$_2$), 2.28–2.35 (m, 1H, (CH$_3$)$_2$C*H*), 4.62–4.69 (m, 1H, C*H*O), 5.47 (dd, 1H, $^4J_{HH} = 1.6$ Hz, $^2J_{HH} = 1.1$ Hz, C*H*), 6.41 (dd, 1H, $^4J_{HH} = 1.6$ Hz, $^2J_{HH} = 1.1$ Hz, C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 16.77$ (*C*H_3), 19.11 (*C*H_3), 20.64 (*C*H_3), 28.53 (*C*H), 32.04 (*C*H_2), 43.79 (*C*H), 73.24 (*C*HO), 127.56 (*C*H_2), 137.49 (*C*), 165.75 (*C*OO). (4*R**,6*R**)-**18f** (representative signals): 1.39 (d, 3H, $^3J_{HH} = 6.3$ Hz, C*H*$_3$), 4.20–4.32 (m, 1H, C*H*O), 5.55 (dd, 1H, $^4J_{HH} = 2.0$ Hz, $^2J_{HH} = 1.2$ Hz, C*H*), 6.35 (dd, 1H, $^4J_{HH} = 1.6$ Hz, $^2J_{HH} = 1.2$ Hz, C*H*). Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.65; H, 9.64.

*5.1.4.7. 4-Cyclohexyl-6-methyl-3-methylenetetrahydro-2H-piran-2-one (**18g**).* (84%); colorless oil (dr 96:4). IR (film): 1720, 1468, 1384, 1312, 1224, 1136, 1012 cm^{-1} (4*R**,6*S**)-**18g**: ^{1}H NMR ($CDCl_3$): $\delta = 0.83$–0.95 (m, 2H, C*H*$_2$), 1.14–1.27 (m, 3H, C*H*$_2$), 1.37 (d, 3H, $^3J_{HH} = 6.3$ Hz, C*H*$_3$), 1.63–1.83 (m, 7H, C*H*$_2$, C*H*), 2.13 (ddd, 1H, $^2J_{HH} = 14.4$ Hz, $^3J_{HH} = 3.6$ Hz, C*H*$_2$), 2.30–2.35 (m, 1H, C*H*), 4.57–4.71 (m, 1H, C*H*O), 5.42 (dd, 1H, $^4J_{HH} = 1.6$ Hz, $^2J_{HH} = 1.0$ Hz, C*H*), 6.39 (dd, 1H, $^4J_{HH} = 1.6$ Hz, $^2J_{HH} = 1.0$ Hz, C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 21.45$ (*C*H_3), 25.81 (3x*C*H_2), 29.23 (*C*H_2), 30.41 (*C*H), 37.17 (*C*H_2), 42.48 (*C*H), 72.87 (*C*HO), 128.88 (*C*H_2), 136.77 (*C*), 165.06 (*C*OO). (4*R**,6*R**)-**18g** (representative signals): 4.19–4.29 (m, 1H, C*H*O), 5.51 (dd, 1H, $^4J_{HH} = 1.9$ Hz, $^2J_{HH} = 1.3$ Hz, C*H*), 6.30 (dd, 1H, $^4J_{HH} = 1.6$ Hz, $^2J_{HH} = 1.3$ Hz, C*H*). Anal. calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.12; H, 9.98.

5.2. Pharmacology

5.2.1. Cells and cytotoxicity assays

Mouse leukemia L-1210 cells were cultured in RPMI 1640 medium (Sigma, St. Louis, MO) supplemented with 10% foetal calf serum (Gibco, Berlin, Germany), gentamycin (50 μg/mL) and 0.02 M HEPES buffer (Gibco). Cytostatic effects were assayed by measuring inhibitory effects on L-1210 cell proliferation. In this assay, cells were seeded in 2 mL aliquots onto a 24-well plate (NUNC, Denmark) at a concentration 1.5×10^3 cells/mL. After 24 h drug solution were added and incubation was carried out for an additional 48 h. The cell number relative to control was determined by a tetrazolium dye method [54].

Human leukemia promyelocytic HL-60 and lymphoblastic NALM-6 cell lines were used. Leukemia cells were cultured in RPMI 1640 medium supplemented with 10% heat–inactivated foetal bovine serum (Invitrogen, Paisley, UK) and antibiotics (100 μg/ml streptomycin and 100 U/ml penicillin). Cells were grown in 37 °C in a humidified atmosphere of 5% CO_2 in air. Cytotoxic activity was determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenylterazolium bromide, Sigma, St. Louis, USA] assay [55]. Exponentially growing leukemia cells were seeded at 8×10^3/well on 96-well plate (Nunc, Roskilde, Denmark). Stock solutions of the analyzed compounds were freshly prepared in DMSO and diluted with complete culture medium to obtain the concentration range from 10^{-7} to 10^{-3} M. Cells were exposed to the test compounds for 46 h, then MTT reagent was added and incubation was continued for 2 h. After incubation, MTT–formazan crystals were dissolved in 20% SDS and 50% DMF at pH 4.7 and absorbance was read at 562 and 630 nm on an ELISA–plate reader (ELX 800, Bio-Tek, USA). As a control, cultured cells were grown in the absence of drugs. The values of IC_{50} (the concentration of the tested compound required to reduce the cells survival fraction to 50% of the control) were calculated from concentration-response curves and used as a measure of cellular sensitivity to a given treatment. Data points represent means of at least three experiments each made in 6 repeats ± SD.

5.3. X-ray single crystal analysis for **17a**

Crystal and X-ray data. Formula: $C_{16}H_{22}NO_7P$, $M_w = 371.32$, colourless crystal $0.50 \times 0.20 \times 0.15$ mm, $a = 14.0936(8)$, $b = 17.4422(10)$, $c = 8.0163(5)$ Å, $\beta = 120.6630(10)°$, $V = 1695.07(17)$ Å^3, $\rho_{calcd} = 1.455$ g cm^{-3}, $\lambda = 0.71073$ Å, $\mu = 2.00$ cm^{-1}, semi-empirical absorption correction based on multiple scanned equivalent reflections $0{,}8686 < T < 0.9704$, $Z = 4$, crystal system: monoclinic, space group: *Cc*, $T = 90$ K, ω scans, 17749 reflections collected, ($\pm h$, $\pm k$, $\pm l$), $2\theta_{max} = 60.0°$, 2468 unique reflections ($R_{int} = 0.019$) and 2454 observed reflections [$I \geq 2\sigma(I)$], 344 refined parameters, refinement on F^2, $R_{obs} = 0.0225$, $R_{all} = 0.0224$, $wR(F^2) = 0.0621$, max (min) residual electron density $\Delta\rho_{max} = 0.34$ ($\Delta\rho_{min} = -0.17$) eÅ^{-3},

X-ray data collected with Bruker SMART APEX2 CCD area detector diffractometer. Computer programs used: data collection *APEX2* [56], data reduction *SAINT-PLUS* [57], absorption correction *SADABS* [58], structure solution, refinement, and molecular graphics *SHELXTL* [59]. All hydrogen atoms were located on difference Fourier map and their positional and isotropic displacement parameters were allowed to refine without constraints. Disorder of methyl in one of the ethoxyl groups were satisfactory refined using a two site model with both site occupancies representing each of the disordered atoms tied to sum to unity. Crystallographic data (excluding structure factors) for the structure reported herein, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 721865. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Any request should be accompanied by a full literature citation.

Acknowledgments

Financial support from the Ministry of Education and Science (Project No. 3 T09A 075 28), augmented in part by Medical University of Lodz (503-30-15-2 to M. R.) and Institute of General and Ecological Chemistry (JW, WMW) is gratefully acknowledged.

Appendix. Supporting information

Supplementary data associated with this article can be found in online version at doi:10.1016/j.ejmech.2009.11.018.

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