Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6721

www.rsc.org/obc

PAPER

Highly diastereoselective vinylogous Mukaiyama aldol reaction of α-keto phosphonates with 2-(trimethylsilyloxy)furan catalyzed by $Cu(OTf)_2$†

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Received 25th May 2011, Accepted 24th June 2011
DOI: 10.1039/c1ob05822c

The diastereospecific formation of δ-hydroxyalkylbutenolide phosphonate has been achieved *via* a vinylogous Mukaiyama aldol reaction. The reaction was performed using α-ketophosphonate **1** and 2-(trimethylsilyloxy)furan **2** mediated by $Cu(OTf)_2$ and 2,2,2-trifluoroethanol as additive in CH_2Cl_2. The reaction proceeds rapidly and affords the corresponding 5-(hydroxy(aryl)methyl) furan-2(5*H*)-one phosphonates **3** in high yields with good to excellent diastereoselectivities (d.r. up to >99 : 1). 5-(Hydroxy(alkyl)methyl)furan-2(5*H*)-one phosphonates could also be obtained with good diastereoselectivities.

Introduction

The catalytic coupling of trialkylsilyloxyfurans with aldehydes by means of aldol reaction has emerged as a pre-eminent strategy for butenolide synthesis.[1] In 1974, Mukaiyama and co-workers reported the Lewis acid-promoted condensation of trialkylsilyl enol-ethers with carbonyl compounds to produce cross-aldol products.[2] The vinylogous Mukaiyama aldol reaction rapidly provides 5-(hydroxy(aryl)methyl)furan-2(5*H*)-ones by addition of the γ-carbon of a dienolate on a carbonyl framework.[3] The corresponding vinylogous adducts were obtained as a mixture of racemic stereoisomer and the stereochemical behavior of the process began to be investigated over past years.[4] In recent years, the diastereoselective addition of variously substituted furan-based silyloxy diene synthons to a variety of achiral aldehydes and acetals using Lewis acids as catalysts has been reported. In 2005, Lera reported the simple diastereoselectivity of the $BF_3{\cdot}Et_2O$-catalyzed vinylogous Mukaiyama aldol reaction of 2-(trimethylsilyloxy)furans with aldehydes.[5] Ollevier and co-workers developed an efficient diastereoselective vinylogous Mukaiyama aldol reaction of 2-(trimethylsilyloxy)furans with various aromatic aldehydes mediated by bismuth triflate. The reaction proceeded rapidly and providing one major diastereoisomer with good diastereoselectivity.[4]

α-Functionalized phosphonic acid derivatives have attracted attention because of their widely used for pharmaceutical applications, such as anticancer[6] and antivirus activities.[7] They have been found to display inhibitory activity towards several important groups of enzymes, including renin,[8] HIV protease,[9] and various classes of protein tyrosine kinases and phosphatases.[10]

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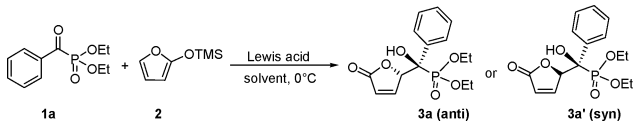
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob05822c

The pharmaceutical potential of these compounds has stimulated the development of methodology for their preparation, particularly in stereoselective enriched forms. Much effort has been directed toward the stereoselective synthesis of α-hydroxy phosphonates that can fix the stereochemistry of the α-hydroxy-substituted carbon.[11] Recently, Zhao and co-workers reported the organocatalytic enantioselective synthesis of both diastereomers of α-hydroxy phosphinates through the asymmetric aldol reaction of α-keto phosphinates.[12] Rawal developed diastereoselective and enantioselective synthesis of tertiary α-hydroxy phosphonates through hydrogen-bond catalysis.[13] However, the asymmetric vinylogous Mukaiyama aldol reaction of α-keto phosphonates has still not been decribed so far. Therefore, it is very desirable to develop an asymmetric synthesis of δ-hydroxyalkylbutenolide phosphonates. As a part of our ongoing interest in preparing chiral δ-butenolide derivatives,[14] we report herein a $Cu(OTf)_2$ catalyzed diastereoselective vinylogous Mukaiyama aldol reactions.

Results and discussion

The reaction has been first explored with diethyl benzoylphosphonate **1a** and 2-(trimethylsilyloxy)furan (TMSOF) **2** in Et_2O at 0 °C to examine the Lewis acid suitable for promoting the reaction. The results revealed that there was no product **3a** detected without the aid of a Lewis acid (Table 1, entry 1). With iodine (20 mol%) as catalyst only caused anomerization of α-ketophosphonate, and no product **3a** was observed (Table 1, entry 2). Other Lewis acids tested (*e.g.*, $BF_3{\cdot}OEt_2$, $FeCl_3$ and $AlCl_3$) were able to promote the addition (Table 1, entries 3–5). In the presence of $Zn(OTf)_2$ or $Cu(OTf)_2$ (0.2 equiv) at 0 °C, the aromatic α-ketophosphonate **1a** led to **3a** in good yield and excellent diastereoselectivity (Table 1, entries 6–7). In ^1H and ^{31}P NMR spectra, the diastereoisomer ratio was measured. The X-ray crystal structure of **3a** revealed the figuration *anti* between C5 and C6 (Fig. 1).[15] Since $Cu(OTf)_2$ gave

Table 1 Screening catalysts for the asymmetric vinylogous Makaiyama aldol reaction[a]



Entry	Lewis acid (equiv.)	Solvent	Time (h)	Yields (%)[b]	Dr (*anti*/*syn*)[c]
1	—	Et_2O	24	n.r.[d]	—
2	I_2 (0.2)	Et_2O	24	n.r.	—
3	$BF_3{\cdot}Et_2O$ (0.2)	Et_2O	3	36	84 : 16
4	$FeCl_3$ (0.2)	Et_2O	4	77	50 : 50
5	$AlCl_3$ (0.2)	Et_2O	6	79	86 : 14
6	$Zn(OTf)_2$ (0.2)	Et_2O	1	66	90 : 10
7	$Cu(OTf)_2$ (0.2)	Et_2O	1	69	94 : 6
8	$Cu(OTf)_2$ (0.2)	CH_2Cl_2	1	78	95 : 5
9	$Cu(OTf)_2$ (0.2)	toluene	1	94	84 : 16
10	$Cu(OTf)_2$ (0.2)	THF	1	77	80 : 20
11	$Cu(OTf)_2$ (0.2)	$CHCl_3$	1	81	92 : 8
12	$Cu(OTf)_2$ (0.2)[e]	CH_2Cl_2	0.1	86	95 : 5
13	$Cu(OTf)_2$ (0.05)[e]	CH_2Cl_2	0.1	88	95 : 5
14	$Cu(OTf)_2$ (0.01)[e]	CH_2Cl_2	1	n.r.	—

[a] Unless otherwise noted all the reactions were performed with 1 mmol of **1a**, 2.0 mmol TMSOF in 2 mL solvent at 0 °C. [b] After purification by chromatography. [c] Diastereomeric ratio (Dr) values were determined by ^1H and ^{31}P NMR of unpurified products. [d] No reaction. [e] 1.2 Equiv of 2,2,2-trifluoroethanol was added.

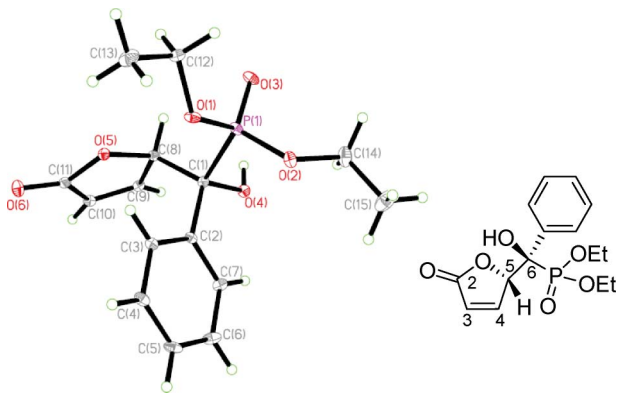


Fig. 1 The X-ray crystal structure of **3a**.

the higher diastereoselectivity (d. r. = 94 : 6) compared with other Lewis acids, it was used in further investigations.

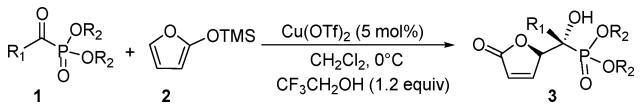
With the best Lewis acid $Cu(OTf)_2$ being identified, we next carried out the vinylogous Mukaiyama aldol reaction of **1a** with **2** in different solvents to determine the best solvent for this reaction. Among the various solvents tested, dichloromethane, toluene, tetrahydrofuran and trichloromethane afforded good yields of the expected product with moderate to good diastereoselectivities (Table 1, entries 8–11). The most suitable solvent was found to be dichloromethane. 5-(Hydroxy(phenyl)methyl)furan-2(5*H*)-one phosphonate **3a** was obtained in good yield and excellent diastereoselectivity. In order to improve the reactivity and diastereoselectivity, the effect of additive was investigated. It was reported that 2,2,2-trifluoroethanol (TFE) has the effect to improve the reactivity and diastereoselectivity of the vinylogous Mukaiyama aldol reaction.[16] In our investigation, after screening the Lewis acid, it was found that $Cu(OTf)_2$ combined with TFE gave superior results in terms of reactivity and diastereoselectivity (86% yield, 95 : 5 d.r., Table 1, entry 12).

With further optimization of the reaction conditions, we found that a lower catalyst loading (5 mol%) afforded the product with the same diastereoselectivity and higher yield (Table 1, entry 13). When decreasing the amount of catalyst to 1 mol%, the reaction did not proceed (Table 1, entry 14). Thus, the optimal reaction conditions for this transformation were determined to be 1.0 mmol of α-ketophosphonate **1**, 2 equivalents of 2-(trimethylsilyloxy)furan **2**, 5 mol% of $Cu(OTf)_2$ and 1.2 equivalent of TFE as additive in CH_2Cl_2 as solvent at 0 °C.

Based on the above optimization efforts, the substrate scope of this reaction was investigated (Table 2). A variety of aromatic α-ketophosphonates were found to be suitable coupling partners with TMSOF. Electron-donating and electron-withdrawing substrates underwent reaction in isolated yields ranging from 56% to 89% and with good to excellent diastereoselectivities. Moreover, variation in the electronic nature of the substituent position on the aromatic ring has apparently no influence on the efficiency and diastereoselectivity of the reaction. Particularly, this process was efficient for aliphatic α-ketophosphonates and afforded the desired products with good diastereoselectivities in 46–71% yields but with longer reaction time.

The possible mechanistic pathway of the vinylogous Mukaiyama aldol reaction of trimethylsilyloxyfuran and α-ketophosphonate catalyzed by $Cu(OTf)_2$ is illustrated in Fig. 2. The reaction was proposed to proceed *via* the staggered acyclic transition state.[17] The $Cu(OTf)_2$ occupied a coordination site on the two oxygen atoms of α-ketophosphonate (TS I). It is conceivable that interaction of a filled nonbonding orbital on oxygen of the phosphoryl group with the π-orbital of the carbon atom of the carbonyl group could occur. The molecular models imply, assuming sp^2-hybridization on oxygen of the phosphonyl group, that overlap of the type postulated is probable maximum when the P→O bond is perpendicular to the plane composed of the aryl ring, carbon, and phosphorus.[18] In fact, the *anti*-diastereoselectivity has to be attributed to the

Table 2 The vinylogous Mukaiyama aldol reaction with α-ketophosphonates



Product	R_1	R_2	Time [h]	Yield (%)[a]	Dr (*anti*/*syn*)[b]
3a	C_6H_5	Et	0.1	88	95 : 5
3b	C_6H_5	Me	0.2	74	89 : 11
3c	*p*-ClC_6H_4	Me	0.2	77	>99 : 1
3d	*p*-ClC_6H_4	Et	0.1	84	>99 : 1
3e	*o*-$CH_3C_6H_4$	Me	0.1	70	95 : 5
3f	*m*-$CH_3C_6H_4$	Et	0.1	64	>99 : 1
3g	*p*-$CH_3C_6H_4$	Me	0.1	77	88 : 12
3h	*p*-$CH_3C_6H_4$	Et	0.1	89	>99 : 1
3i	*p*-$CH_3OC_6H_4$	Me	0.2	89	>99 : 1
3j	*p*-$CH_3OC_6H_4$	Et	0.2	56	>99 : 1
3k	*p*-BrC_6H_4	Et	0.1	66	>99 : 1
3l	Me	Et	20	71	95 : 5
3m	Et	Me	24	46	83 : 17
3n	Et	Et	22	55	96 : 4

[a] After purification by chromatography. [b] Diastereomeric ratio determined from the crude product by ^{31}P NMR.

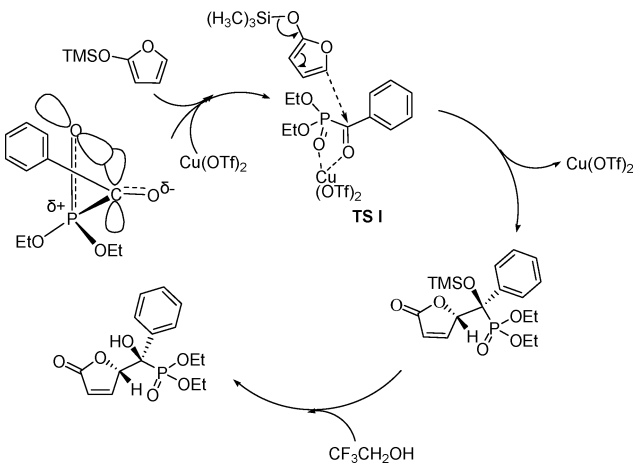


Fig. 2 The possible mechanistic pathway of the vinylogous Mukaiyama aldol reaction.

steric effect caused by the coordination of $Cu(OTf)_2$ and α-ketophosphonate. Therefore, transition state I (TS I) is more favorable by positioning the least steric hinder, leading preferably to the *anti*-diastereoselectivity. 2,2,2-Trifluoroethanol could help to remove the TMS group and increase the nucleophilic ability of 2-(trimethylsilyloxy)furan.

Conclusions

In conclusion, we have developed an efficient and highly diastereoselective synthesis of δ-hydroxyalkylbutenolide phosphonates from the vinylogous Mukaiyama aldol reaction of α-ketophosphonate and 2-(trimethylsilyloxy)furan catalyzed by $Cu(OTf)_2$ with TFE as additive. A wide range of stereoselective novel functionalized tertiary α-hydroxy phosphonates were obtained in high yields with good to excellent diastereoselectivities (up to 99 : 1 d.r.). A plausible transition state has been proposed to explain the origin of the activation and the asymmetric induction. Further investigations on the enantioselective vinylogous Mukaiyama aldol reaction are currently underway.

Experimental

General remarks

All reactions were carried out under an inert atmosphere and in heat-dried glassware. Anhydrous CH_2Cl_2 were obtained by standard method. Flash column chromatography was performed on silica gel (particle size 10–40 μm, Ocean Chemical Factory of Qingdao, China). ^1H and ^{13}C NMR spectra were recorded on Brucker-400 (400 MHz for ^1H, 100 MHz for ^{13}C, 121 MHz for ^{31}P). Chemical shifts were reported in ppm downfield from internal $Si(CH_3)_4$. The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Mass spectra were recorded on a LCQ advantage spectrometer with ESI resource. HR-MS were recorded on APEXII and ZAB-HS spectrometer. Melting points were determined on a T-4 melting point apparatus (uncorrected).

General procedure for the synthesis of dialkyl (2,5-dihydro-5-oxofuran-2-yl)(hydroxy)methylphosphonate 3. A solution of α-keto phosphonate **1** (1.0 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C, 2-(trimethylsilyloxy)furan **2** (0.32 g, 2.0 mmol) and $Cu(OTf)_2$ (0.018 g, 0.05 mmol) were added, subsequently added the TFE (0.12 g, 1.2 mmol). The mixture was stirred for corresponding time at 0 °C. The mixture was hydrolyzed with H_2O (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude products **3**, which were purified by flash column chromatography on silica gel [petroleum ether/ethyl acetate, 1 : 1 (v/v)] to provide pure products **3**.

Diethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(phenyl)methylphosphonate (3a). White solid; mp 104–106 °C; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 18.64, 18.80; ^1H-NMR (400 MHz, $CDCl_3$): δ 1.25 (td, $^3J_{H-H}$ = 7.0 Hz, $^3J_{P-H}$ = 5.0 Hz, 6H, $(POCH_2CH_3)_2$),

3.93–4.15 (m, 4H, P(OCH_2CH$_3$)$_2$), 5.60 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHCH), 6.07 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHCH), 7.31 (t, $^3J_{H-H}$ = 7.2 Hz, 1H, Ph), 7.36 (t, $^3J_{H-H}$ = 7.4 Hz, 2H, Ph), 7.62 (d, $^3J_{H-H}$ = 7.6 Hz, 2H, Ph), 7.66 (t, $^3J_{H-H}$ = 5.7 Hz, 1H, HC=CHCH); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 16.32 (t, $^3J_{C,P}$ = 5.0 Hz, P(OCH$_2$CH_3)$_2$), 64.23 (d, $^2J_{C,P}$ = 7.8 Hz, P(OCH_2CH$_3$)$_2$), 64.44 (d, $^2J_{C,P}$ = 7.5 Hz, P(OCH_2CH$_3$)$_2$), 76.45 (d, $^1J_{C,P}$ = 162.5 Hz, CP(OCH$_2$CH$_3$)$_2$), 85.00 (d, $^2J_{C,P}$ = 10.0 Hz, HC=CHCH), 123.00, 126.12 (d, $^3J_{C,P}$ = 4.2 Hz), 128.19 (d, $^4J_{C,P}$ = 1.7 Hz), 128.23 (d, $^2J_{C,P}$ = 9.2 Hz), 135.58, 153.65 (d, $^3J_{C,P}$ = 4.7 Hz), 172.60; ESI-MS: 349.0 ([M+Na]$^+$); HRMS calcd for $C_{15}H_{19}O_6P$: 349.0811 (M+Na)$^+$, found: 349.0819.

Dimethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(phenyl)methylphosphonate (3b). White solid; mp 131–134 °C; ^{31}P-NMR (121 MHz, CDCl$_3$): δ 20.15, 20.81; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 3.67 (d, $^3J_{P-H}$ = 10.5 Hz, 3H, P(OCH$_3$)$_2$), 3.77 (d, $^3J_{P-H}$ = 10.5 Hz, 3H, P(OCH$_3$)$_2$), 5.61 (d, $^3J_{H-H}$ = 6.0 Hz, 1H, HC=CHCH), 6.11 (dd, $^3J_{H-H}$ = 6.0 Hz, $^4J_{H-H}$ = 1.6 Hz, 1H, HC=CHCH), 7.32–7.41 (m, 3H, Ph), 7.62–7.69 (m, 3H, Ph, HC=CHCH); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 54.56 (d, $^2J_{C,P}$ = 7.8 Hz, P(OCH$_3$)$_2$), 54.83 (d, $^2J_{C,P}$ = 7.3 Hz, P(OCH$_3$)$_2$), 76.72 (d, $^1J_{C,P}$ = 162.2 Hz, CP(OCH$_3$)$_2$), 84.79 (d, $^2J_{C,P}$ = 9.6 Hz, HC=CHCH), 123.10, 126.02 (d, $^3J_{C,P}$ = 4.4 Hz), 128.35 (d, $^2J_{C,P}$ = 8.4 Hz), 128.45 (d, $^4J_{C,P}$ = 2.2 Hz), 135.20, 153.50 (d, $^3J_{C,P}$ = 4.9 Hz), 172.48; ESI-MS: 321.0 ([M+Na]$^+$); HRMS calcd for $C_{13}H_{15}O_6P$: 321.0498 (M+Na)$^+$, found: 321.0507.

Dimethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*p*-chlorophenyl)methylphosphonate (3c). White solid; mp 123–126 °C; ^{31}P-NMR (121 MHz, CDCl$_3$): δ 20.76; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 3.52 (d, $^3J_{P-H}$ = 10.6 Hz, 3H, P(OCH$_3$)$_2$), 3.94 (d, $^3J_{P-H}$ = 10.6 Hz, 3H, P(OCH$_3$)$_2$), 5.74 (t, $^3J_{H-H}$ = 2.0 Hz, 1H, HC=CHCH), 6.18 (d, $^3J_{H-H}$ = 5.8 Hz, 1H, HC=CHCH), 6.85 (d, $^3J_{H-H}$ = 5.8 Hz, 1H, HC=CHCH), 7.43 (d, $^3J_{H-H}$ = 8.5 Hz, 2H, Ph), 7.63 (dd, $^3J_{H-H}$ = 8.7 Hz, $^4J_{P-H}$ = 2.0 Hz, 2H, Ph); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 54.46 (d, $^2J_{C,P}$ = 7.5 Hz, P(OCH_3)$_2$), 54.69 (d, $^2J_{C,P}$ = 6.6 Hz, P(OCH_3)$_2$), 75.68 (d, $^1J_{C,P}$ = 159.8 Hz, CP(OCH$_3$)$_2$), 85.56 (d, $^2J_{C,P}$ = 3.9 Hz, HC=CHCH), 123.96, 126.77 (d, $^3J_{C,P}$ = 4.3 Hz), 129.14, 133.55, 134.82 (d, $^4J_{C,P}$ = 3.1 Hz), 151.86 (d, $^2J_{C,P}$ = 9.9 Hz), 172.15; ESI-MS: 354.9 ([M+Na]$^+$); HRMS calcd for $C_{13}H_{14}ClO_6P$: 355.0109 (M+Na)$^+$, found: 355.0116.

Diethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*p*-chlorophenyl)methylphosphonate (3d). White solid; mp 77–80 °C; ^{31}P-NMR (121 MHz, CDCl$_3$): δ 18.54; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.28 (q, $^3J_{H-H}$ = 7.5 Hz, 6H, P(OCH$_2$CH_3)$_2$), 3.98–4.19 (m, 4H, P(OCH_2CH$_3$)$_2$), 5.56 (d, $^3J_{H-H}$ = 5.5 Hz, 1H, HC=CHCH), 6.11 (dd, $^3J_{H-H}$ = 5.8 Hz, $^4J_{H-H}$ = 1.0 Hz, 1H, HC=CHCH), 7.34 (d, $^3J_{H-H}$ = 8.5 Hz, 2H, Ph), 7.57 (dd, $^3J_{H-H}$ = 8.7 Hz, $^4J_{P-H}$ = 1.8 Hz, 2H, Ph), 7.64 (d, $^3J_{H-H}$ = 5.8 Hz, 1H, HC=CHCH); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 16.31 (d, $^3J_{C,P}$ = 5.6 Hz, P(OCH$_2$CH_3)$_2$), 16.39 (d, $^3J_{C,P}$ = 5.6 Hz, P(OCH$_2$CH_3)$_2$), 64.41 (d, $^2J_{C,P}$ = 7.6 Hz, P(OCH_2CH$_3$)$_2$), 64.58 (d, $^2J_{C,P}$ = 7.6 Hz, P(OCH_2CH$_3$)$_2$), 76.80 (d, $^1J_{C,P}$ = 161.7 Hz, CP(OCH$_2$CH$_3$)$_2$), 84.60 (d, $^2J_{C,P}$ = 9.2 Hz, HC=CHCH), 123.29, 127.63 (d, $^3J_{C,P}$ = 3.9 Hz), 128.38 (d, $^4J_{C,P}$ = 1.1 Hz), 134.04, 134.36 (d, $^3J_{C,P}$ = 2.5 Hz), 153.28 (d, $^2J_{C,P}$ = 5.0 Hz), 172.32; ESI-MS: 383.0 ([M+Na]$^+$); HRMS calcd for $C_{15}H_{18}ClO_6P$: 383.0422 (M+Na)$^+$, found: 383.0415.

Dimethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*o*-tolyl)methylphosphonate (3e). White solid; mp 89–91 °C; ^{31}P-NMR (121 MHz, CDCl$_3$): δ 20.75, 22.24; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 2.63 (s, 3H, CH$_3$), 3.55 (d, $^3J_{P-H}$ = 10.5 Hz, 3H, P(OCH$_3$)$_2$), 3.78 (d, $^3J_{P-H}$ = 10.5 Hz, 3H, P(OCH$_3$)$_2$), 5.93 (s, 1H, HC=CHCH), 6.18 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHCH), 7.18–7.26 (m, 3H, Ph), 7.66 (d, $^3J_{H-H}$ = 5.9 Hz, 1H, Ph), 7.70 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHCH); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 23.11, 54.38 (d, $^2J_{C,P}$ = 7.7 Hz, P(OCH_3)$_2$), 54.63 (d, $^2J_{C,P}$ = 7.7 Hz, P(OCH_3)$_2$), 79.53 (d, $^1J_{C,P}$ = 161.1 Hz, HCP(OCH$_3$)$_2$), 85.50 (d, $^2J_{C,P}$ = 14.4 Hz, HC=CHCH), 122.68, 125.70, 128.10 (d, $^3J_{C,P}$ = 3.5 Hz), 128.44, 128.82, 130.94, 133.30, 154.16, 173.15; ESI-MS: 312.7 ([M+H]$^+$); HRMS calcd for $C_{14}H_{17}O_6P$: 335.0655 (M+Na)$^+$, found: 335.0660.

Diethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*m*-tolyl)methylphosphonate (3f). White solid; mp 48–51 °C; ^{31}P-NMR (121 MHz, CDCl$_3$): δ 18.67; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.22 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, P(OCH$_2$CH_3)$_2$), 1.28 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, P(OCH$_2$CH_3)$_2$), 2.37 (s, 3H, CH$_3$), 3.84–4.16 (m, 4H, P(OCH_2CH$_3$)$_2$), 5.62 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHCH), 6.12 (dd, $^3J_{H-H}$ = 5.6 Hz, $^3J_{H-H}$ = 1.8 Hz, 1H, HC=CHCH), 7.13 (d, $^3J_{H-H}$ = 7.4 Hz, 1H, Ph), 7.26 (d, $^3J_{H-H}$ = 15.2 Hz, 1H, Ph), 7.42 (d, $^3J_{H-H}$ = 11.1 Hz, 2H, Ph), 7.69 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHCH); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 16.30 (d, $^3J_{C,P}$ = 5.5 Hz, P(OCH$_2$CH_3)$_2$), 21.63, 64.25 (d, $^2J_{C,P}$ = 7.7 Hz, P(OCH_2CH$_3$)$_2$), 64.46 (d, $^2J_{C,P}$ = 7.3 Hz, P(OCH_2CH$_3$)$_2$), 76.46 (d, $^1J_{C,P}$ = 161.5 Hz, CP(OCH$_2$CH$_3$)$_2$), 85.12 (d, $^2J_{C,P}$ = 10.6 Hz, HC=CHCH), 122.96, 123.17(d, $^3J_{C,P}$ = 3.9 Hz), 126.66 (d, $^3J_{C,P}$ = 4.4 Hz), 128.08 (d, $^4J_{C,P}$ = 1.2 Hz), 129.02 (d, $^4J_{C,P}$ = 1.6 Hz), 135.48, 137.85, 153.66 (d, $^3J_{C,P}$ = 4.1 Hz), 172.63; ESI-MS: 340.7 ([M+H]$^+$); HRMS calcd for $C_{16}H_{21}O_6P$: 363.0968 (M+Na)$^+$, found: 363.0962.

Dimethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*p*-tolyl)methylphosphonate (3g). White solid; mp 127–130 °C; ^{31}P-NMR (121 MHz, CDCl$_3$): δ 20.99, 21.26; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 2.34 (s, 3H, CH$_3$), 3.67 (d, $^3J_{P-H}$ = 10.4 Hz, 3H, P(OCH$_3$)$_2$), 3.77 (d, 3H, $^3J_{P-H}$ = 10.5 Hz, P(OCH$_3$)$_2$), 5.58 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHCH), 6.11 (dd, $^3J_{H-H}$ = 5.7 Hz, 1H, HC=CHCH), 7.19 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, Ph), 7.50 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ph), 7.65 (d, $^3J_{H-H}$ = 5.7 Hz, 1H, HC=CHCH); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 21.06, 54.54 (d, $^2J_{C,P}$ = 7.7 Hz, P(OCH_3)$_2$), 54.81 (d, $^2J_{C,P}$ = 7.4 Hz, P(OCH_3)$_2$), 76.65 (d, $^1J_{C,P}$ = 162.5 Hz, CP(OCH$_3$)$_2$), 84.73 (d, $^2J_{C,P}$ = 9.4 Hz, HC=CHCH), 122.96, 125.93 (d, $^3J_{C,P}$ = 4.1 Hz), 129.05, 132.07, 138.24 (d, $^4J_{C,P}$ = 2.1 Hz), 153.65 (d, $^3J_{C,P}$ = 5.4 Hz), 172.56; ESI-MS: 312.7 ([M+H]$^+$); HRMS calcd for $C_{14}H_{17}O_6P$: 335.0655 (M+Na)$^+$, found: 335.0662.

Diethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*p*-tolyl)methylphosphonate (3h). White solid; mp 87–89 °C; ^{31}P-NMR (121 MHz, CDCl$_3$): δ 18.86; ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.26 (t, $^3J_{H-H}$ = 7.1 Hz, 6H, P(OCH$_2$CH_3)$_2$), 2.33 (s, 3H, CH$_3$), 3.92–4.16 (m, 4H, P(OCH_2CH$_3$)$_2$), 5.58 (t, $^3J_{H-H}$ = 6.2 Hz, 1H, HC=CHCH), 6.12 (dd, $^3J_{H-H}$ = 9.9 Hz, $^3J_{H-H}$ = 4.6 Hz, 1H, HC=CHCH), 7.18 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, Ph), 7.50 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, Ph), 7.66 (t, $^3J_{H-H}$ = 6.2 Hz, 1H, HC=CHCH); ^{13}C-NMR (100 MHz, CDCl$_3$): δ 16.31 (d, $^3J_{C,P}$ = 2.5 Hz, P(OCH$_2$CH_3)$_2$), 16.37 (d, $^3J_{C,P}$ = 2.5 Hz, P(OCH$_2$CH_3)$_2$), 21.07, 64.12 (d, $^2J_{C,P}$ = 7.6 Hz, P(OCH_2CH$_3$)$_2$), 64.38 (d, $^2J_{C,P}$ = 7.6 Hz, P(OCH_2CH$_3$)$_2$), 76.40 (d, $^1J_{C,P}$ = 161.2 Hz, CP(OCH$_2$CH$_3$)$_2$), 85.10 (d, $^2J_{C,P}$ = 10.4 Hz, HC=CHCH), 123.01, 125.94 (d, $^4J_{C,P}$ = 4.3 Hz), 128.97 (d, $^3J_{C,P}$ = 5.6 Hz), 132.42, 138.07 (d,

$^4J_{C,P}$ = 2.0 Hz), 153.55 (d, $^3J_{C,P}$ = 4.6 Hz), 172.51; ESI-MS: 340.7 ([M+H]$^+$); HRMS calcd for $C_{16}H_{21}O_6P$: 363.0968 (M+Na)$^+$, found: 363.0962.

Dimethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*p*-methoxyphenyl)methylphosphonate (3i). White solid; mp 82–84 °C; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 21.15, 21.26; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.71 (d, $^3J_{P-H}$ = 10.3 Hz, 3H, $P(OCH_3)_2$), 3.77 (d, $^3J_{P-H}$ = 10.4 Hz, 3H, $P(OCH_3)_2$), 3.80 (s, 3H, OCH_3), 5.54 (d, $^3J_{H-H}$ = 5.5 Hz, 1H, HC=CHC*H*), 6.07 (dd, $^3J_{H-H}$ = 5.4 Hz, 1H, *H*C=CHCH), 6.89 (d, $^3J_{H-H}$ = 7.9 Hz, 2H, Ph), 7.53 (d, $^3J_{H-H}$ = 8.3 Hz, 2H, Ph), 7.61 (d, $^3J_{H-H}$ = 5.5 Hz, 1H, HC=C*H*CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 54.51 (d, $^2J_{C,P}$ = 7.5 Hz, $P(OCH_3)_2$), 54.83 (d, $^2J_{C,P}$ = 7.3 Hz, $P(OCH_3)_2$), 72.15, 76.48 (d, $^1J_{C,P}$ = 162.7 Hz, *C*P$(OCH_3)_2$), 84.77 (d, $^2J_{C,P}$ = 9.9 Hz, HC=CH*C*H), 113.70, 123.02, 127.38 (d, $^3J_{C,P}$ = 3.8 Hz), 152.82, 153.62 (d, $^3J_{C,P}$ = 5.2 Hz), 159.57, 172.51; ESI-MS: 328.6 ([M+H]$^+$); HRMS calcd for $C_{14}H_{17}O_7P$: 351.0600 (M+Na)$^+$, found: 351.0604.

Diethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*p*-methoxyphenyl)methylphosphonate (3j). White solid; mp 72–75 °C; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 18.97; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23–1.30 (m, 6H, $P(OCH_2CH_3)_2$), 3.81 (s, 3H, OCH_3), 3.91–4.18 (m, 4H, $P(OCH_2CH_3)_2$), 5.57 (d, $^3J_{H-H}$ = 4.6 Hz, 1H, HC=CHC*H*), 6.10 (dd, $^3J_{H-H}$ = 4.6 Hz, 1H, *H*C=CHCH), 7.18 (d, $^3J_{H-H}$ = 5.6 Hz, 2H, Ph), 7.50 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, Ph), 7.66 (d, $^3J_{H-H}$ = 6.0 Hz, 1H, HC=C*H*CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.32, 55.17, 64.10 (d, $^2J_{C,P}$ = 7.6 Hz, $P(OCH_2CH_3)_2$), 64.36 (d, $^2J_{C,P}$ = 7.4 Hz, $P(OCH_2CH_3)_2$), 76.23 (d, $^1J_{C,P}$ = 162.1 Hz, *C*P$(OCH_2CH_3)_2$), 84.99 (d, $^2J_{C,P}$ = 10.1 Hz, HC=CH*C*H), 113.56, 122.94, 127.27, 127.44 (d, $^3J_{C,P}$ = 4.0 Hz), 153.62 (d, $^3J_{C,P}$ = 4.8 Hz), 159.47 (d, $^4J_{C,P}$ = 1.2 Hz), 172.49; ESI-MS: 356.7 ([M+H]$^+$); HRMS calcd for $C_{16}H_{21}O_6P$: 379.0917 (M+Na)$^+$, found: 379.0925.

Diethyl hydroxy(5-oxo-2,5-dihydrofuran-2-yl)(*p*-bromophenyl)-methylphosphonate (3k). White solid; mp 119–122 °C; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 18.18; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.25–1.33 (m, 6H, $P(OCH_2CH_3)_2$), 4.08–4.16 (m, 4H, $P(OCH_2CH_3)_2$), 5.56 (d, $^3J_{H-H}$ = 3.6 Hz, 1H, HC=CHC*H*), 6.05 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, *H*C=CHCH), 7.48 (m, 3H, Ph, HC=C*H*CH), 7.60 (d, $^3J_{H-H}$ = 6.0 Hz, 2H, Ph); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.32 (t, $^3J_{C,P}$ = 5.6 Hz, $P(OCH_2CH_3)_2$), 64.44 (d, $^2J_{C,P}$ = 7.7 Hz, $P(OCH_2CH_3)_2$), 64.58 (d, $^2J_{C,P}$ = 7.7 Hz, $P(OCH_2CH_3)_2$), 76.23 (d, $^1J_{C,P}$ = 161.7 Hz, *C*P$(OCH_2CH_3)_2$), 84.61 (d, $^2J_{C,P}$ = 9.8 Hz, HC=CH*C*H), 121.54, 123.27, 127.98 (d, $^3J_{C,P}$ = 4.1 Hz), 131.30 (d, $^3J_{C,P}$ = 1.8 Hz), 134.78, 152.91, 173.74; ESI-MS: 404.7 ([M+H]$^+$); HRMS calcd for $C_{15}H_{18}BrO_6P$: 426.9916 (M+Na)$^+$, found: 426.9919.

Diethyl 1-(2,5-dihydro-5-oxofuran-2-yl)-1-hydroxyethylphosphonate (3l). Colorless oil; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 21.87, 22.50; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.26–1.31 (m, 6H, $P(OCH_2CH_3)_2$), 1.39 (d, $^3J_{P-H}$ = 15.1 Hz, CCH_3), 4.12–4.18 (m, 4H, $P(OCH_2CH_3)_2$), 4.65 (s, 1H, O*H*), 5.16 (d, $^3J_{H-H}$ = 5.6 Hz, 1H, HC=CHC*H*), 6.13 (d, $^3J_{H-H}$ = 4.5 Hz, 1H, *H*C=CHCH), 7.64 (d, $^3J_{H-H}$ = 5.0 Hz, 1H, HC=C*H*CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 15.43 (d, $^3J_{C,P}$ = 5.2 Hz, $P(OCH_2CH_3)_2$), 18.15 (d, $^2J_{C,P}$ = 1.8 Hz, C*C*H$_3$), 62.61 (d, $^2J_{C,P}$ = 7.5 Hz, $P(OCH_2CH_3)_2$), 62.89 (d, $^2J_{C,P}$ = 7.3 Hz, $P(OCH_2CH_3)_2$), 71.48 (d, $^1J_{C,P}$ = 166.3 Hz, *C*P$(OCH_2CH_3)_2$), 83.78 (d, $^2J_{C,P}$ = 11.0 Hz, HC=CH*C*H), 121.65, 153.10 (d, $^3J_{C,P}$ = 4.3 Hz), 171.86; ESI-MS: 286.8 ([M+Na]$^+$); HRMS calcd for $C_{10}H_{17}O_6P$: 287.0655 (M+Na)$^+$, found: 287.0649.

Dimethyl 1-(2,5-dihydro-5-oxofuran-2-yl)-1-hydroxypropylphosphonate (3m). Colorless oil; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 24.53, 24.59; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.08 (t, 3H, $^3J_{H-H}$ = 7.4 Hz, CH_2CH_3), 1.86–2.02 (m, 2H, CH_2CH_3), 3.85 (t, 6H, $^3J_{P-H}$ = 10.5 Hz, $P(OCH_2CH_3)_2$), 5.28 (td, $^3J_{H-H}$ = 7.4 Hz, $^3J_{H-H}$ = 1.8 Hz, 1H, HC=CHC*H*), 6.20 (dd, $^3J_{H-H}$ = 5.8 Hz, $^3J_{H-H}$ = 1.9 Hz, 1H, *H*C=CHCH), 7.65 (dd, $^3J_{H-H}$ = 5.8 Hz, $^3J_{H-H}$ = 1.2 Hz, 1H, HC=C*H*CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 7.14 (d, $^3J_{C,P}$ = 3.1 Hz, CCH_2CH_3), 26.26 (d, $^2J_{C,P}$ = 2.0 Hz, C*C*H$_2$CH$_3$), 52.70 (d, $^2J_{C,P}$ = 7.6 Hz, $P(OCH_3)_2$), 53.35 (d, $^2J_{C,P}$ = 7.4 Hz, $P(OCH_3)_2$), 75.00 (d, $^1J_{C,P}$ = 162.1 Hz, *C*P$(OCH_2CH_3)_2$), 82.60 (d, $^2J_{C,P}$ = 11.8 Hz, HC=CH*C*H), 121.62, 152.77 (d, $^3J_{C,P}$ = 3.2 Hz), 171.70; ESI-MS: 272.6 ([M+Na]$^+$); HRMS calcd for $C_9H_{15}O_6P$: 273.0498 (M+Na)$^+$, found: 274.0506.

Diethyl 1-(2,5-dihydro-5-oxofuran-2-yl)-1-hydroxypropylphosphonate (3n). Colorless oil; ^{31}P-NMR (121 MHz, $CDCl_3$): δ 20.80, 22.26; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.03 (t, 3H, $^3J_{H-H}$ = 7.5 Hz, CH_2CH_3), 1.29 (t, 6H, $^3J_{H-H}$ = 7.0 Hz, $P(OCH_2CH_3)_2$), 1.81–1.95 (m, 2H, CH_2CH_3), 4.11–4.20 (m, 4H, $P(OCH_2CH_3)_2$), 5.23 (d, $^3J_{H-H}$ = 6.5 Hz, 1H, HC=CHC*H*), 6.11 (d, $^3J_{H-H}$ = 5.0 Hz, 1H, *H*C=CHCH), 7.63 (d, $^3J_{H-H}$ = 5.8 Hz, 1H, HC=C*H*CH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 7.26 (d, $^3J_{C,P}$ = 2.6 Hz, CCH_2CH_3), 15.40 (d, $^3J_{C,P}$ = 2.7 Hz, $P(OCH_2CH_3)_2$), 15.45 (d, $^3J_{C,P}$ = 2.9 Hz, $P(OCH_2CH_3)_2$), 26.40 (d, $^2J_{C,P}$ = 1.1 Hz, C*C*H$_2$CH$_3$), 62.37 (d, $^2J_{C,P}$ = 7.6 Hz, $P(OCH_2CH_3)_2$), 62.84 (d, $^2J_{C,P}$ = 7.3 Hz, $P(OCH_2CH_3)_2$), 74.53 (d, $^1J_{C,P}$ = 162.0 Hz, *C*P$(OCH_2CH_3)_2$), 82.71 (d, $^2J_{C,P}$ = 12.6 Hz, HC=CH*C*H), 121.48, 153.02 (d, $^3J_{C,P}$ = 2.2 Hz), 171.83; ESI-MS: 300.6 ([M+Na]$^+$); HRMS calcd for $C_{11}H_{19}O_6P$: 301.0811 (M+Na)$^+$, found: 301.0818.

Acknowledgements

We thank the National Natural Science Foundation of China (21072102), the Committee of Science and Technology of Tianjin (11JCYBJC04200) and State Key Laboratory of Elemento-Organic Chemistry in Nankai University for financial support.

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