A New Approach to the Asymmetric Reaction of the Chiron 5-*L*-Menthyloxy-2(5*H*)-furanones with Horner-Emmons Reagent†

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The asymmetric reaction of the chiron 2(5*H*)-furanones (4a—4c) with the Horner-Emmons reagents (5a—5b) has been investigated. The newly chiral organophosphorus derivatives 6 and 7 were obtained using the phosphoryl-stabilized carbanion as a building block in DMSO under mild conditions. Through the asymmetric introduction, the Horner-Emmons reagent could be transformed to a chiral building block to afford the novel functionalized phosphorus derivatives. The structures of the synthesized compounds 6 and 7 were identified on the basis of their elementary and spectroscopic data, such as IR, ^{1}H NMR, ^{13}C NMR, MS and X-ray crystallography. These results provided a valuable approach to the synthesis of potentially interesting chiral organophosphorus derivatives and probing their biological activities.

Keywords chiron 2(5*H*)-furanones, asymmetric reaction, Horner-Emmons reagent, building block, chiral organophosphorus derivative, biological activity, X-ray crystallography

Introduction

Recently, the asymmetric synthesis of various natural products, which contain organophosphorus group, has attracted much attention due to their special biological function and antibiological activities.[1-3] The successful synthesis of a wide variety of unsaturated moieties in the natural compounds by Wittig reagent with carbonyl compounds has stimulated the search for the asymmetric reactions that employ organophosphorus reagents.[4-7] One of the most fruitful results is the discovery that the Horner-Emmons reagents as the nucleophilic phosphoryl-stabilized carbanions have wide application in the organic synthesis and offer significant advantages over conventional procedures.[5-7]

The great advances of the reaction of Horner-Emmons reagents with α,β-unsaturated carbonyl compounds have found application in synthesis of some natural products, but the asymmetric reaction of chiral 2(5*H*)-furanones with the P(O)-stabilized carbanion reagents still remains unreported. On the basis of our previous research work,[8-14] we have explored the reactions of the chiral 5-*L*-menthyloxy-2(5*H*)-furanones (**4a—4c**) with Horner-Emmons reagents **5**. The synthesis of enantiopure **4a—4c** is conveniently achieved starting from 5-hydroxy-2(5*H*)-furanone (**2a**) via the improved photosynthetic procedure using 95% C_2H_5OH as a solvent at room temperature. The halogenation of furfural **1** in the aqueous medium is suitable for the preparation of **2b—2c**.[8-11] Epimeric mixture of 5-*L*-menthyloxy-2(5*H*)-furanones (**3a—3c**) is readily available through acetalization of the resulting 5-hydroxy-2(5*H*)-furanone with *L*-(−)-menthol under refluxing of benzene in the presence of a catalytic amount of concentrated sulfuric acid. The preparation of enantiopure **4a** (X = H), **4b** (X = Cl) and **4c** (X = Br) are based on the recrystallization of epimeric mixture of 5-menthyloxy-2(5*H*)-furanone (**4**) from petroleum ether (30—60 ℃) (Scheme 1). The absolute configuration at the acetal carbon of **4a** has been proved to be *R* by means of an X-ray structure analysis.[12-14] However, the absolute configurations at the acetal carbon of **4b** and **4c** with crystalline enantiomerical purity have been proved to be *S*.[8-11]

Now we describe the synthesis of the novel functionalized phosphorus derivatives **6** and **7** (Schemes 2 and 3) by the asymmetric reaction of the chiron 2(5*H*)-furanones **4a—4c** (Scheme 1) with the Horner-Emmons reagents **5a—5b** as the nucleophilic phosphoryl-stabilized carbanions. The structures of the newly synthesized compounds **6** and **7** were identified on the basis of their elementary and spectroscopic data, such as IR, ^{1}H NMR, ^{13}C NMR, MS and X-ray crystallography. These results provided a valuable approach to the synthesis of potentially interesting chiral organophosphorus derivatives and probing their biological activities.

Results and discussion

The synthesis and properties of γ-substituted butenolides have attracted much attention in the field of organic chemistry owing to their unique carbon skeleton of 2(5*H*)-

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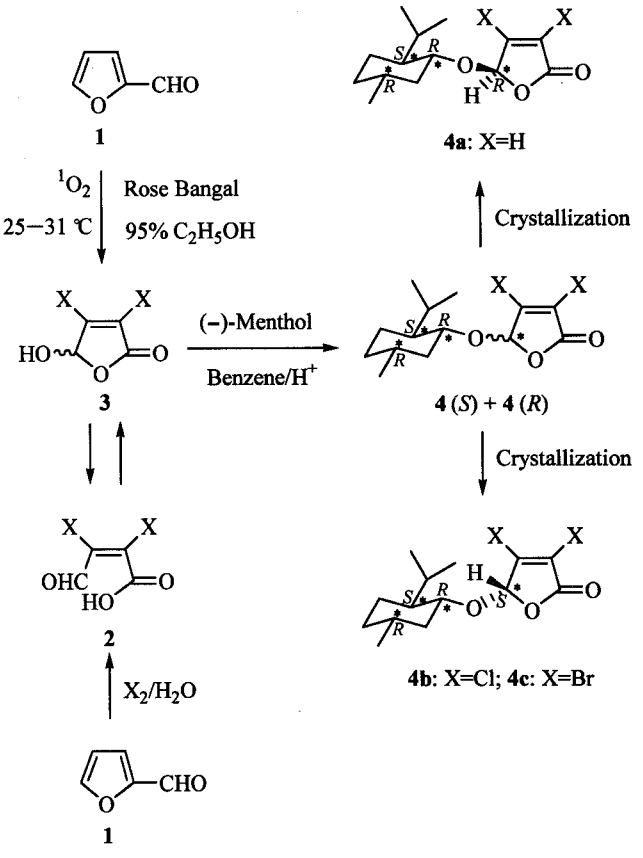
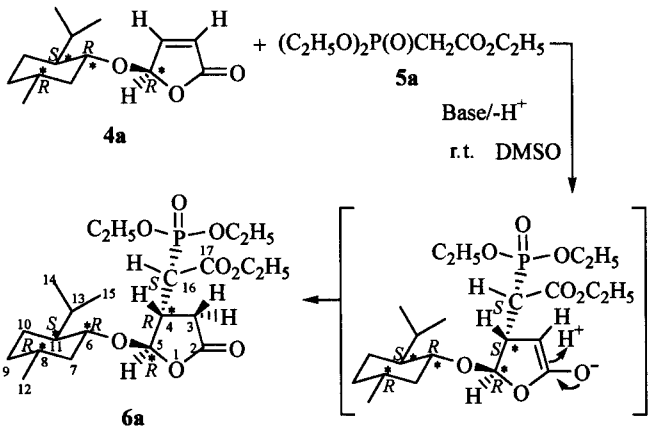
Scheme 1



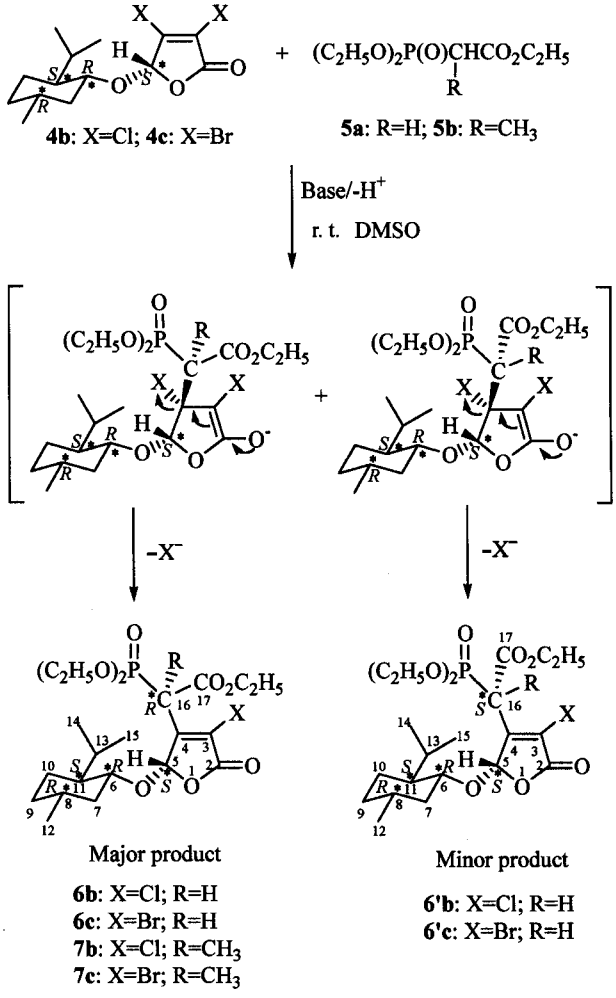
furanone, which is widely present in many natural products and shows interesting antibiotic activities as well as their important acting as synthetic intermediate.[15,16] The chiral 5-(*R*)-menthyloxy-2(5*H*)-furanone behaves as a Michael acceptor towards carbon, oxygen, sulphur and nitrogen nucleophiles to afford chiral 5-(*R*)-menthyloxy-4-substituted-2(5*H*)-furanone via a simple Michael addition. 5-(*S*)-Menthyloxy-3,4-dihalo(chloro, bromo)-2(5*H*)-furanone reacts with corresponding nucleophiles to form chiral 5-(*S*)-menthyloxy-4-substituted- 3-halo-2(5*H*)-furanone compounds by a tandem asymmetric Michael addition/elimination reaction.[8-11] The famous Wittig-Horner phosphorus reagents[4-7] can be used to introduce a carbon functional group under stronger base condition. In order to avoid the *t*-BuOK or RONa decomposing the chiral 2(5*H*)-furanones during the reaction process and complicating the products, we used metal sodium to replace *t*-BuOK or RONa in DMSO as the reaction solvent.

The reaction of chiral **4a** with Horner-Emmons reagent **5a** was undergone an asymmetric Michael addition to afford the chiral 4-substituted-phosphorus group-2(5*H*)-furanone (**6a**) in 75% yield with ≥98% *ee* (Schemes 2 and 3). The acetal proton in **6a** was proofed from the ^1H NMR spectrum, which showed the signals at δ 5.57 (s, 1H, **6a**-H-5). Most remarkable is the high stereoselectivity of the reaction process. This is easily explained when a bulky protecting group of *L*-menthyloxy is present as in substrate **4a**. On the basis of literature precedent[8-14] most probably the phosphorylated anion as a nucleophile attacks stereoselectively the 4-position of **4a** from the side opposite to the menthyloxy group, namely the less hindered as shown in A form (Scheme 4). In the transition state model, the favored configuration of intermediate

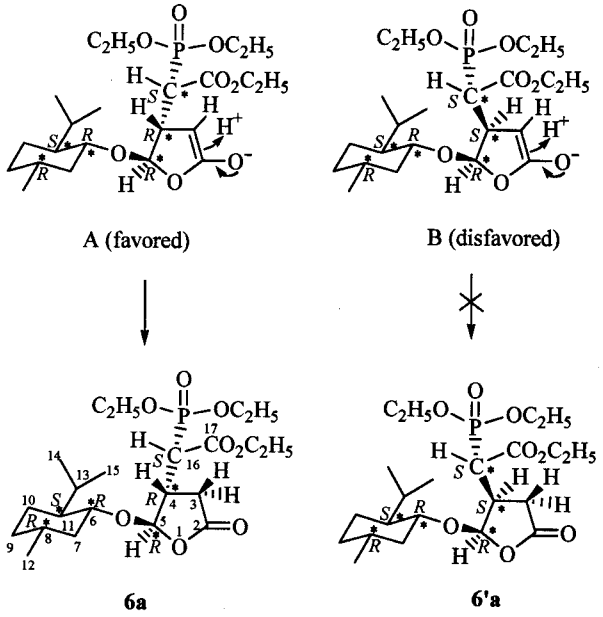
Scheme 2



Scheme 3



Scheme 4



anion in which the largest group $(C_2H_5O)_2P(O)$ is far away from the menthyloxy group to offer the novel enantiopure C—C adduct **6a** was identified on the basis of their spectroscopic data.

5-(*S*)-Menthyloxy-3,4-dihalo (chloro, bromo)-2(5*H*)-furanones (**4b**, **4c**) react with the Horner-Emmons reagent **5** at room temperature in DMSO with metal sodium as a base undergoing the tandem asymmetric Michael addition/elimination reaction. The nucleophile, phosphorylated anion enters stereoselectively the 4-position of **4** from the side opposite to the menthyloxy, after that, a mole of hydrogen halide has been eliminated to offer the 4-sunstituted phosphorylated group butenolide compounds **6** and **7**. In the favored transition state model as shown in Scheme 3, the largest group $(C_2H_5O)_2P(O)$ is far away from the chiral auxiliary menthyloxy (favored model), but the other form is disfavored where the $(C_2H_5O)_2P(O)$ group is near to the menthyloxy. After the elimination of HX the chiral 4-phosphorylated group-2(5*H*)-furanone derivatives (**6b**, **6'b**, **6c**, **6'c**) were obtained in molar ratio of 7.3:1.0 and 2.6:1.0, respectively. The presence of 5-menthyloxy-2(5*H*)-furanone moieties in **6b** and **6'b**, **6c** and **6'c** was deduced from the ^{1}H NMR spectrum, which showed the signals at δ 6.18 (d, J = 2.88 Hz, 0.88H, **6b**-H-5) and at δ 6.03 (d, J = 2.94 Hz, 0.12H, **6'b**-H-5) assignable to the acetal protons. It was also proved that **6c** and **6'c** are a pair of enantiomer which showed the signals at δ 6.19 (d, J = 2.79 Hz, 0.72H, **6c**-H-5) and at δ 6.04 (d, J = 2.55 Hz, 0.28H, **6'c**-H-5). Along with the bulk of the Horner-Emmons reagent **5b** becoming bigger, the high stereocontrolled products **7b** and **7c** were formed in enantiopure with $\geqslant$98% *ee* via the asymmetric reaction of the chiral synthon **4b** and **4c**. The acetal proton C-5-H of the chiral center in **7b** and **7c** was shown the signals at δ 6.11 (s, 1H, **7b**-C-5-H) and at δ 6.14 (s, 1H, **7c**-C-5-H), respectively. The chemical structures of the interesting chiral phosphorus derivatives **6** and **7** were established on the basis of their spectroscopic data, such as UV, IR, ^{1}H NMR, ^{13}C NMR, MS and elementary analysis. The stereochemistry and absolute configuration of this novel chiral compound **7c** are readily confirmed by X-ray crystallography.

Description of crystal structure of **7c**

The orientation temperature plot (ORTEP) drawing of **7c** is shown in Fig. 1. The packing diagram of **7c** is shown in Fig. 2. The absolute configuration of (1*R*,2*S*,5*R*)-(−)-menthyloxy keeps unchanged during the asymmetric reaction process. The whole chiral molecule **7c** has five chiral centers including original four chiral centers C(13) (*S*), C(14) (*R*), C(16) (*R*), C(20) (*S*) and a new stereogenic centers C(6) (*R*). The chiral diethyl(ethoxycarbonyl)-α-methyl-methylphosphonyl group and the menthyloxy group are located on both sides of the lactone ring respectively. The chiral center C(6) maintains *R*-configuration of diethyl(ethoxycarbonyl)-α-methyl-methylphosphonyl building block.

Experimental

Instruments and materials

Infrared spectra were recorded on a Fourier 170-sx spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DMX-300 MHz spectrometer and the chemical shifts were expressed in δ values using TMS as the internal standard. Mass spectra were determined with a Zabspec mass spectrometer. Microanalyses were performed on a Perkin-Elemer 240-C Elemental Analyser. Na-D line polarimetry was carried out at 20 ℃ in a Perkin-Elemer 241-C polarimeter. Melting points were determined on a Yanaco/mp-506 microthermopan and were uncorrected.

All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried in a routine way and redistilled.

Synthesis of racemic hydroxyl-3,4-dichloro-2(5H)-furanone (**3b**) The preparation of **3b** was obtained in 64% yield. m.p. 126—127 ℃, Lit.[8-11] 127 ℃.

Synthesis of racemic hydroxyl-3,4-dibromo-2(5H)-furanone (**3c**) The preparation of **3c** was obtained in 72% yield. m.p. 124—125 ℃, Lit.[8-11] 123—124 ℃.

Synthesis of 5-(R)-menthyloxy-2(5H)-furanone (**4a**) The preparation of enantiopure **4a** in 61% yield has been reported as shown in Scheme 1.[12-14] $[\alpha]_D^{22}$ −141.5, m.p. 76—77 ℃.

Synthesis of 5-(S)-menthyloxy-3,4-dichloro-2(5H)-furanone (**4b**) The preparation of **4b** in 64% yield has been reported as shown in Scheme 1. m.p. 112—113 ℃, Lit.[8-11] 110—111 ℃.

Synthesis of 5-(S)-menthyloxy-3,4-dibromo-2(5H)-furanone (**4c**) The preparation of **4c** in 58%

yield has been reported as shown in Scheme 1. m.p. 141—142 ℃, Lit.[8-11] 146—147 ℃.

General procedure for the asymmetric reaction of the chiron 5-L-menthyloxy-2(5H)-furanones (**4**) *with Horner-Emmons reagents* (**5a—5b**)

A mixture of 20 mL of dried DMSO and 0.092 g of metal sodium (4 mmol) in a 50-mL of flask was stirred at room temperature for 10—20 min. Horner-Emmons reagent **5** (0.8 mL, 4 mmol) was added and continuously stirred for 30 min until the sodium solid disappeared. Then the chiron **4** (2 mmol) was added and the mixture was stirred for 5—10 h, in which the chiron **4** had been consumed as monitored by TLC. Then 20 mL of ice water was added to the reaction mixture, which was already cooled by ice bath. The mixture was extracted with three 50 mL portions of ether. The combined extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated. The crude products were purified by column chromatography and crystallization to give the products.

Menthyloxy-4-diethyl(ethoxycarbonyl)methylphosphonyl-2(5H)-furanone (**6a**) Yield 0.69 g (65%), m.p. 96—97 ℃. $[\alpha]_D^{20}$ 100.5 (*c* 66, $CHCl_3$); *ee* ≥ 98%; UV (95% C_2H_5OH) λ_{max}: 215.5 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.80 (d, J = 6.9 Hz, 3H, CH_3), 0.85 (d, J = 7.6 Hz, 3H, CH_3), 0.90 (d, J = 7.2 Hz, 3H, CH_3), 0.95—0.97 (m, 2H, 2 × H-10), 1.20—1.30 (m, 2H, 2 × H-9), 1.35 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.37 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.39 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.68—1.70 (m, 2H, H-8, 13), 2.08—2.10 (m, 1H, H-11), 2.82 (m, 2H, 2 × H-3), 2.98 (m, 1H, H-4), 3.00 (dd, $^1J_{P-H}$ = 35.0 Hz, 1H, CH-P), 3.52 (bt, J = 10.6, 4.8, 4.4 Hz, 1H, H-6), 4.19 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.23 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.26 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 5.57 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.9 (OCH_2CH_3), 16.5 (C-15), 17.2 ($^3J_{P-C}$ = 5.1 Hz, OCH_2CH_3), 17.3 ($^3J_{P-C}$ = 5.7 Hz, OCH_2CH_3), 21.7 (C-14), 23.1 (C-13), 23.9 (C-9), 26.3 (C-10), 32.2 (C-8), 33.3 (C-3), 35.1 (C-13), 40.5 (C-7), 41.6 ($^2J_{P-C}$ = 4.3 Hz, C-4), 47.0 (C-16), 48.6 ($^1J_{P-C}$ = 12.8 Hz, C-16), 62.9 (OCH_2CH_3), 64.0 ($^2J_{P-C}$ = 7.1 Hz, OCH_2CH_3), 64.3 ($^2J_{P-C}$ = 6.3 Hz, OCH_2CH_3), 78.4 (C-6), 103.9 (C-5), 168.2 ($^2J_{P-C}$ = 5.1 Hz, C-17), 175.6 (C-2); IR (KBr) ν: 2950, 1780, 1730, 1460, 1380, 1310, 1240, 1160, 1030, 960 cm^{-1}; MS (FAB) *m/z* (%): 463 (M^+ + 1, 51), 435 ($M^+ - C_{10}H_{17}$, 100), 309 ($M^+ - C_{10}H_{17}O$, 41), 137 [$P(O)O_2C_4H_{10}^+$, 10], 133 ($C_{10}H_{13}^+$, 83), 83 ($C_6H_{11}^+$, 38). Anal. calcd for $C_{22}H_{39}O_8P$: C 57.13, H 8.50; found C 56.64, H 8.73.

Menthyloxy-4-diethyl(ethoxycarbonyl)methylphosphonyl-3-chloro-2(5H)-furunone (**6b**:**6'b** = 7.3:1) Yield 0.63 g (64%), m.p. 51—52 ℃. $[\alpha]_D^{20}$ +33.6 (*c* 2.28, $CHCl_3$); *ee* = 76%; UV (95% C_2H_5OH) λ_{max}: 223.1, 352.2 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.75 (d, J = 6.8 Hz, 3H, CH_3), 0.81 (d, J = 4.7 Hz, 3H, CH_3), 0.85 (d, J = 4.8 Hz, 3H, CH_3), 0.88—0.90 (m, 2H, 2 × H-10), 0.91—1.01 (m, 2H, 2 × H-9), 1.23 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.28 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.32 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.62 (d, $^1J_{P-H}$ = 11.9 Hz, 1H, CH-P), 2.07—2.29 (m, 3H, H-8, 11, 13), 3.55 (bt, J = 10.6, 4.8, 4.4 Hz, 0.12H, **6'b**-H-6), 3.66 (bt, J = 10.6, 4.8, 4.4 Hz, 0.88H, **6b**-H-6), 4.12 (q, J = 7.2 Hz, 0.24H, **6'b**-OCH_2CH_3), 4.15 (q, J = 7.2 Hz, 1.76H, **6b**-OCH_2CH_3), 4.20 (q, J = 7.2 Hz, 0.24H, **6'b**-OCH_2CH_3), 4.23 (q, J = 7.2 Hz, 1.76H, **6b**-OCH_2CH_3), 4.25 (q, J = 7.2 Hz, 0.24H, **6'b**-OCH_2CH_3), 4.25 (q, J = 7.2 Hz, 1.76H, **6b**-OCH_2CH_3), 6.03 (d, J = 2.9 Hz, 0.12H, **6'b**-H-5), 6.19 (d, J = 2.9 Hz, 0.88H, **6b**-H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.7 (**6b**, **6'b**-OCH_2CH_3), 15.5 (**6b**, **6'b**-15), 20.8 ($^3J_{P-C}$ = 7.5 Hz, **6b**, **6'b**-$2OCH_2CH_3$), 21.9 (**6b**, **6'b**-14), 22.5 (**6'b**-C-12), 22.6 (**6b**-C-12), 24.2 (**6b**, **6'b**-C-9), 25.1 (**6b**, **6'b**-C-10), 31.4 (**6'b**-C-13), 33.7 (**6b**-C-13), 41.9 (**6b**, **6'b**-C-7), 43.5 (**6b**, **6'b**-C-8), 43.7 (**6b**, **6'b**-C-11), 47.6 ($^1J_{P-C}$ = 30 Hz, **6'b**-C-16), 48.0 ($^1J_{P-C}$ = 30 Hz, **6b**-C-16), 62.1 (**6'b**-C-18), 62.4 (**6b**-C-18), 63.3 ($^2J_{P-C}$ = 7.2 Hz, **6'b**-OCH_2CH_3), 64.0 ($^2J_{P-C}$ = 7.6 Hz, **6b**-OCH_2CH_3), 81.8 (**6'b**-C-6), 83.4 (**6b**-C-6), 101.6 (**6'b**-C-5), 102.8 (**6b**-C-5), 127.4 ($^3J_{P-C}$ = 7.5 Hz, **6'b**-C-3), 127.6 ($^3J_{P-C}$ = 7.5 Hz, **6b**-C-3), 146.8 ($^2J_{P-C}$ = 7.5 Hz, **6'b**-C-4), 147.2 ($^2J_{P-C}$ = 7.5 Hz, **6b**-C-4), 163.5 (**6'b**-C-17), 163.8 (**6b**-C-17), 164.8 (**6'b**-C-2), 165.1 (**6b**-C-2); IR (KBr) ν: 2950, 1780, 1740, 1640, 1460, 1260, 1160, 1140, 1040, 980 cm^{-1}; MS (FAB) *m/z* (%): 495 (M^+ + 1, 15), 359 ($M^+ - C_{10}H_{15}$, 35), 357 ($M^+ - C_{10}H_{17}$, 100), 339 ($M^+ - C_{10}H_{19}O$, 40), 157 ($C_{10}H_{19}O^+$, 4), 133 ($C_{10}H_{13}^+$, 7), 83 ($C_6H_{11}^+$, 21). Anal. calcd for $C_{22}H_{36}O_8PCl$: C 53.38, H 7.49; found C 53.67, H 7.56.

Menthyloxy-4-diethyl(ethoxycarbonyl)methylphosphonyl-3-bromo-2(5H)-furanone (**6c**:**6'c** = 2.61:1) Yield 0.40 g (37%), m.p. 65—66 ℃, $[\alpha]_D^{20}$ +5.3 (*c* 4.13, $CHCl_3$); *ee* = 46%; UV (95% C_2H_5OH) λ_{max}: 231.8, 353.9 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.75 (d, J = 7.0 Hz, 3H, CH_3), 0.82 (d, J = 7.0 Hz, 3H, CH_3), 0.87 (d, J = 7.0 Hz, 3H, CH_3), 0.88—0.89 (m, 2H, 2 × H-10), 1.00—1.20 (m, 2H, 2 × H-9), 1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.30 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.33 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.60 (d, $^1J_{P-H}$ = 10.6 Hz, 1H, CH-P), 2.05—2.29 (m, 3H, H-8, 11, 13), 3.57 (bt, J = 10.6, 4.8, 4.4 Hz, 0.28H, **6'c**-H-6), 3.61 (bt, J = 10.6, 4.8, 4.4 Hz, 0.72H, **6c**-H-6), 4.13 (q, J = 7.2 Hz, 0.56H, **6'c**-OCH_2CH_3), 4.16 (q, J = 7.2 Hz, 1.44H, **6c**-OCH_2CH_3), 4.18 (q, J = 7.2 Hz, 0.56H,

6′c-OC**H**$_2$CH$_3$), 4.21 (q, J = 7.2 Hz, 1.44H, **6c**-OC**H**$_2$CH$_3$), 4.23 (q, J = 7.2 Hz, 0.56H, **6′c**-OC**H**$_2$CH$_3$), 4.25 (q, J = 7.2 Hz, 1.44H, **6c**-OC**H**$_2$CH$_3$), 6.04 (d, J = 2.9 Hz, 0.28H, **6′c**-H-5), 6.19 (d, J = 2.7 Hz, 0.72H, **6c**-H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.8 (**6c**, **6′c**-OCH$_2$CH$_3$), 15.5 (**6c**, **6′c**-15), 16.3 ($^3J_{P\text{-}C}$ = 7.5 Hz, **6c**, **6′c**-2OCH$_2$CH$_3$), 20.9 ($^3J_{P\text{-}C}$ = 7.5 Hz, **6c**, **6′c**-2OCH$_2$CH$_3$), 21.9 (**6′c**-14), 22.0 (**6c**-14), 22.5 (**6′c**-C-12), 22.6 (**6c**-C-12), 24.2 (**6c**, **6′c**-C-9), 25.1 (**6c**, **6′c**-C-10), 31.5 (**6′c**-C-13), 33.8 (**6c**-C-13), 41.8 (**6′c**-C-7), 41.9 (**6c**-C-7), 46.5 (**6c**, **6′c**-C-8), 47.1 (**6c**, **6′c**-C-11), 47.9 ($^1J_{P\text{-}C}$ = 30 Hz, **6c**, **6′c**-C-16), 62.1 (**6c**, **6′c**-OCH$_2$CH$_3$), 63.5 ($^2J_{P\text{-}C}$ = 7.2 Hz, **6c**, **6′c**-OCH$_2$CH$_3$), 63.8 ($^2J_{P\text{-}C}$ = 7.6 Hz, **6c**, **6′c**-OCH$_2$CH$_3$), 81.8 (**6′c**-C-6), 83.4 (**6c**-C-6), 102.2 (**6′c**-C-5), 103.9 (**6c**-C-5), 116.0 ($^3J_{P\text{-}C}$ = 7.5 Hz, **6′c**-C-3), 118.4 ($^3J_{P\text{-}C}$ = 7.5 Hz, **6c**-C-3), 151.1 ($^2J_{P\text{-}C}$ = 7.5 Hz, **6′c**-C-4), 151.6 ($^2J_{P\text{-}C}$ = 7.5 Hz, **6c**-C-4), 163.4 (**6′c**-C-17), 163.8 (**6c**-C-17), 165.4 (**6′c**-C-2), 165.7 (**6c**-C-2); IR (KBr) ν: 2950, 1792, 1742, 1642, 1456, 1260, 1160, 1136, 1022, 970 cm^{-1}; MS (FAB) m/z (%): 540 (M^+ + 1, 20), 539 (M^+, 20), 402 (M^+ + 1 − $C_{10}H_{18}$, 100), 401 (M^+ − $C_{10}H_{18}$, 100), 323 (M^+ − $C_{10}H_{17}$ − C_6H_6, 47), 133 ($C_{10}H_{13}^+$, 6), 83 ($C_6H_{11}^+$, 29). Anal. calcd for $C_{22}H_{36}O_8PBr$: C 48.99, H 6.73; found C 59.25, H 6.94.

Menthyloxy-4-diethyl(ethoxycarbonyl)-α-methylmethylphosphonyl-3-chloro-2(5H)-furanone (**7b**) Yield 0.31 g (31%), m.p. 124—125 ℃, $[\alpha]_D^{20}$ +15.8 (c 0.95, $CHCl_3$); *ee* ≥ 98%; UV (95% C_2H_5OH) λ_{max}: 205, 227.7 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.76 (d, J = 6.9 Hz, 3H, CH_3), 0.90 (d, J = 7.5 Hz, 3H, CH_3), 0.92 (d, J = 7.0 Hz, 3H, CH_3), 1.17—1.19 (m, 2H, 2 × H-10), 1.25—1.26 (m, 2H, 2 × H-9), 1.27 (t, J = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.29 (t, J = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.34 (t, J = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.63—1.67 (m, 2H, 2 × H-7), 1.79 (s, 3H, CH_3), 2.12—2.18 (m, 3H, H-8, 11, 13), 3.65 (bt, J = 10.6, 4.8, 4.4 Hz, 1H, H-6), 4.16 (q, J = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 4.24 (q, J = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 4.29 (q, J = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 6.11 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.8 (OCH$_2$**C**H$_3$), 16.6 (C-15), 17.3 ($^3J_{P\text{-}C}$ = 22.8 Hz, OCH$_2$**C**H$_3$), 17.4 ($^3J_{P\text{-}C}$ = 21.0 Hz, OCH$_2$**C**H$_3$), 19.5 (C-14), 22.1 (C-12), 23.1 (C-9), 23.6 (C-10), 26.0 (C-8), 32.6 ($^2J_{P\text{-}C}$ = 3.2 Hz, P-CH$_3$), 34.8 (C-13), 42.8 (C-7), 49.2 (C-11), 51.8 ($^1J_{P\text{-}C}$ = 142.1 Hz, C-16), 63.4 (O**C**H$_2$CH$_3$, C-18), 64.1 ($^2J_{P\text{-}C}$ = 6.8 Hz, O**C**H$_2$CH$_3$), 65.4 ($^2J_{P\text{-}C}$ = 6.8 Hz, O**C**H$_2$CH$_3$), 82.2 (C-6), 102.7 (C-5), 127.2 ($^3J_{P\text{-}C}$ = 7.5 Hz, C-3), 151.2 ($^2J_{P\text{-}C}$ = 8.3 Hz, C-4), 166.5 ($^2J_{P\text{-}C}$ = 1.9 Hz, C-17), 169.4 (C-2); IR (KBr) ν: 2950, 1780, 1740, 1640, 1460, 1440, 1260, 1120, 1050, 980 cm^{-1}; MS (FAB) m/z (%): 509 (M^+ + 1, 10), 508 (M^+, 30), 372 (M^+ − $C_{10}H_{17}$, 34), 371 (M^+ − $C_{10}H_{18}$, 100), 354 (M^+ − $C_{10}H_{19}O$, 32), 83 ($C_6H_{11}^+$, 21). Anal. calcd for $C_{23}H_{38}O_8PCl$: C 54.27, H 7.52; found C 54.47, H 7.70.

Menthyloxy-4-diethyl(ethoxycarbonyl)-α-methylmethylphosphonyl-3-bromo-2(5H)-furanone (**7c**) Yield 0.23 g (22%), m.p. 122—125 ℃, $[\alpha]_D^{20}$ +8.8 (c 0.72, $CHCl_3$); *ee* ≥ 98%; UV (95% C_2H_5OH) λ_{max}: 205, 236 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.78 (d, J = 6.9 Hz, 3H, CH_3), 0.91 (d, J = 7.5 Hz, 3H, CH_3), 0.94 (d, J = 7.0 Hz, 3H, CH_3), 1.17—1.29 (m, 2H, 2 × H-10), 1.27—1.29 (m, 2H, 2 × H-9), 1.31 (t, J = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.34 (t, J = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.36 (t, J = 7.2 Hz, 3H, OCH$_2$C**H**$_3$), 1.65—1.70 (m, 2H, 2 × H-7), 1.83 (s, 3H, CH_3), 2.14—2.22 (m, 3H, H-8, 11, 13), 3.66 (bt, J = 10.7, 4.8, 4.4 Hz, 1H, H-6), 4.20 (q, J = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 4.25 (q, J = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 4.30 (q, J = 7.2 Hz, 2H, OC**H**$_2$CH$_3$), 6.14 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.8 (OCH$_2$**C**H$_3$), 16.6 (C-15), 17.3 ($^3J_{P\text{-}C}$ = 22.2 Hz, OCH$_2$**C**H$_3$), 17.5 ($^3J_{P\text{-}C}$ = 21.8 Hz, OCH$_2$**C**H$_3$), 19.7 (C-14), 22.1 (C-12), 23.1 (C-9), 23.7 (C-10), 26.1 (C-8), 32.6 ($^2J_{P\text{-}C}$ = 3.2 Hz, P-CH$_3$), 34.8 (C-13), 42.8 (C-7), 49.2 (C-11), 52.1 ($^1J_{P\text{-}C}$ = 142.0 Hz, C-16), 63.5 (O**C**H$_2$CH$_3$, C-18), 64.1 ($^2J_{P\text{-}C}$ = 7.0 Hz, O**C**H$_2$CH$_3$), 65.4 ($^2J_{P\text{-}C}$ = 7.0 Hz, O**C**H$_2$CH$_3$), 82.2 (C-6), 103.7 (C-5), 117.8 ($^3J_{P\text{-}C}$ = 10.8 Hz, C-3), 155.1 ($^2J_{P\text{-}C}$ = 8.3 Hz, C-4), 167.2 ($^2J_{P\text{-}C}$ = 2.9 Hz, C-17), 169.4 (C-2); IR (KBr) ν: 2950, 1780, 1740, 1630, 1460, 1440, 1260, 1120, 1050, 1020, 980, 920 cm^{-1}; MS (FAB) m/z (%): 555 (M^+ + 2, 35), 554 (M^+ + 1, 20), 553 (M^+, 20), 475 (M^+ − C_6H_6, 15), 415 (M^+ − $C_{10}H_{18}$, 100), 398 (M^+ − $C_{10}H_{19}O$, 33), 337 (M^+ − $C_{12}H_{24}O_3$, 50), 83($C_6H_{11}^+$, 31). Anal. calcd for $C_{23}H_{38}O_8PBr$: C 49.91, H 6.92; found C 50.04, H 7.18.

Single crystal preparation of **7b** *and its* X*-ray crystallography*

A colorless single crystal of **7b** was separated out from the solution of petroleum ether (30—60 ℃)/acetone (30:1, V:V) after standing for several days. X-Ray crystallography of **7b**: 0.60 mm × 0.60 mm × 0.20 mm colorless monocrystal, $C_{23}H_{38}O_8ClP$, M_r 508.95, orthorhobic system and $P2_12_12_1$ space group. The crystal lattice parameters are a = 0.9729(2) nm, b = 1.0521(2) nm, c = 2.6528(4) nm, V = 2.7155(8) nm^3, Z = 4, D_c = 1.245 g/cm^3, μ = 0.241 mm^{-1}, F(000) = 1088. The deflection factor [$F^2 > 2\sigma(F^2)$]: R = 0.0543, R_w = 0.1058. The absolute structure parameter is 0.18(13) and the maximum residual peak in the D-value Fourier scheme is 0.286 × 102 e·nm^{-3}. All were calculated and rectified on Siemens SHELXL-93 program.

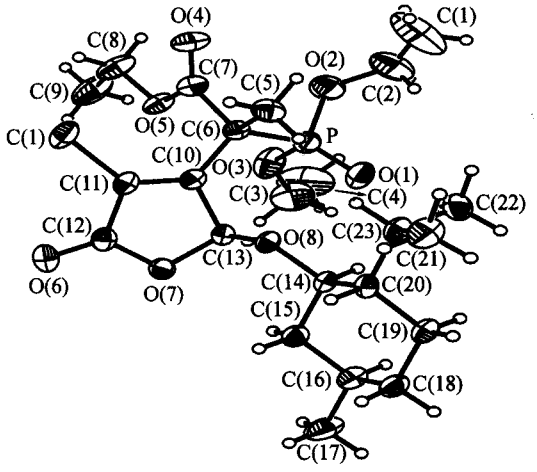


Fig. 1 Molecular structure of **7b**.

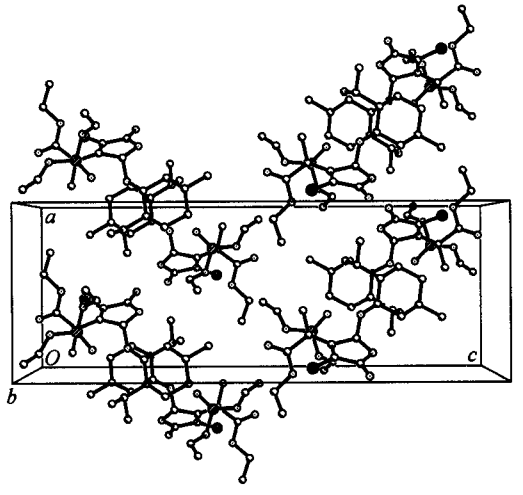


Fig. 2 Packing diagram of **7b**.

Conclusion

These results provided a valuable synthetic approach to potentially interesting chiral organophosphorus derivatives **6** and **7** by the asymmetric reaction of the chiral synthon **4** with the Horner-Emmons reagent **5**. Through the asymmetric introduction, the Horner-Emmons reagent could be transformed to a chiral building block to afford the novel functionalized phosphorus derivatives. It is particularly significant that the approach would be valuable as a groundwork for future applications of the organophosphorus reagents in synthesis of chiral building block to provide new strategy and thread of ideas in synthesis of more complex molecules containing active functional groups and study of their biological activities.

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