A New Synthetic Route to Diastereomerically Pure Cyclopropane-Phosphorus Derivatives Utilizing the Chiron 5-*L*-Menthyloxy-3-bromo-2(5*H*)-furanone and Racemic Dialkyl α-Hydroxyalkanephosphonate†

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A new chemical transformation for the construction of diversely functionalized cyclopropane-phosphorus derivatives utilizing chiron 4 and racemic diethyl α-hydroxylbenzylphosphonate as the key precursors is described. The diastereomeric pure phosphorus-containing derivatives 5a, 5′a, 5b and 5′b were obtained respectively, in good yields with *d. e.* ≥98% via asymmetric tandem double Michael addition/internal nucleophilic substitution of the corresponding compounds and further through the separation of the diastereomeric mixture by column chromatography. The diversely functionalized phosphorus derivatives are identified on the basis of their elemental analysis and spectroscopic data, such as IR, ^{1}H NMR, ^{13}C NMR and MS. The absolute configuration of the interesting cyclopropane-phosphorus compound 5a was established by X-ray crystallography. Thus, these results provide a valuable strategy for synthesizing some biologically active molecules.

Keywords diastereomerically pure cyclopropane-phosphorus derivatives, tandem asymmetric reaction, racemic diethyl α-hydroxylbenzylphosphonates, biological activity, absolute configuration, X-ray crystallography

Introduction

Cyclopropane-containing natural and nonnatural products have received considerable attention as synthetic targets as the incorporation of the rigidified cyclopropyl motif into bioactive analogues lead to conformably constrained molecules.[1,2] Such modifications are expected to have significant effects on bioactivities with concomitant medical implications. It is well known that phosphoric acid derivatives are very important in the chemistry of living systems and the organophosphorus compounds occupy an important position in the field of searching new drugs.[3-5] Despite the great advances in this two fields, the efficient synthesis of diastereomerically pure cyclopropane-phosphorus compounds still remains a considerable challenge. Particular notice is the deficiency in previous methods for the construction of multi-functionalized cyclopropanes.[6] We recently reported a valuable synthetic route to spiro-cyclopropane derivatives containing multiple stereogenic centers, that utilizes chiral synthon **4**, 5-*L*-menthyloxy-3-bromo-2(5*H*)-furanone, and different nucleophiles by tandem double Michael addition/internal nucleophilic substitution.[7-9] Given the high yields of functionalized spiro-cyclopropanes attainable, coupled with the obtained optically pure diastereomeric product and simplicity of the reaction, we were interested in the preparation of the chiral cyclopropane-phosphorus derivatives. On the basis of previous work, we have now accomplished the asymmetric tandem reaction of chiron 5-*L*-menthyloxy-3-bromo-2(5*H*)-furanone (**4**) with racemic diethyl α-hydroxylbenzylphosphonate (**3**) (Scheme 1) in acetonitrile at room temperature and the cyclopropane-

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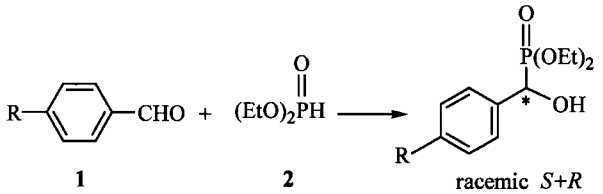
phosphorus derivatives with four stereogenic centers **5a**, **5'a**, **5b** and **5'b** were obtained in total 78%—84% yields with *d. e.* ≥ 98% after column chromatography (Scheme 2). Our results provide a valuable synthetic route to the potentially interesting diastereomerically pure spiro-cyclopropane phosphorus compounds. It would provide an important synthetic strategy for some complex chiral cyclic natural and nonnatural products.

Scheme 1



1a: R = H
1b: R = Cl

3a: R = H (*S*)
3b: R = Cl (*S*)
3'a: R = H (*R*)
3'b: R = Cl (*R*)

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-400 MHz spectrometer and the chemical shifts were expressed in δ-values using TMS as the internal standard. Mass spectra were determined with a Finnigan GC2000/TRACE TM/MS mass spectrometer. Microanalyses were performed on a Perkin-Elemer 240-C elemental analyser. Na-D line polarimetry was carried out at 20 ℃ on a Perkin-Elemer 241-C polarimeter. Melting points were determined on a Liuben 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 diethyl α-hydroxyl-4'-substituted-benzylphosphonate (**3a + 3'a**)

The preparation of racemic **3a + 3'a** in 66% yield has been reported as shown in Scheme 1.[10] M.p. 82—83.7 ℃ (Lit.[10] 83—83.2 ℃).

Synthesis of racemic diethyl α-hydroxyl-4'-substituted-benzylphosphonate (**3b + 3'b**)

The appropriate aldehyde (**1b**, 0.06 mol) was added dropwise to a stirred ice-cooled mixture of diethyl hydrogen phosphite (**2**, 0.05 mol) and triethylamine (0.025 mol), and the mixture heated at 75 ℃ for 30 min. The product was obtained in 74% yield after recrystallization.

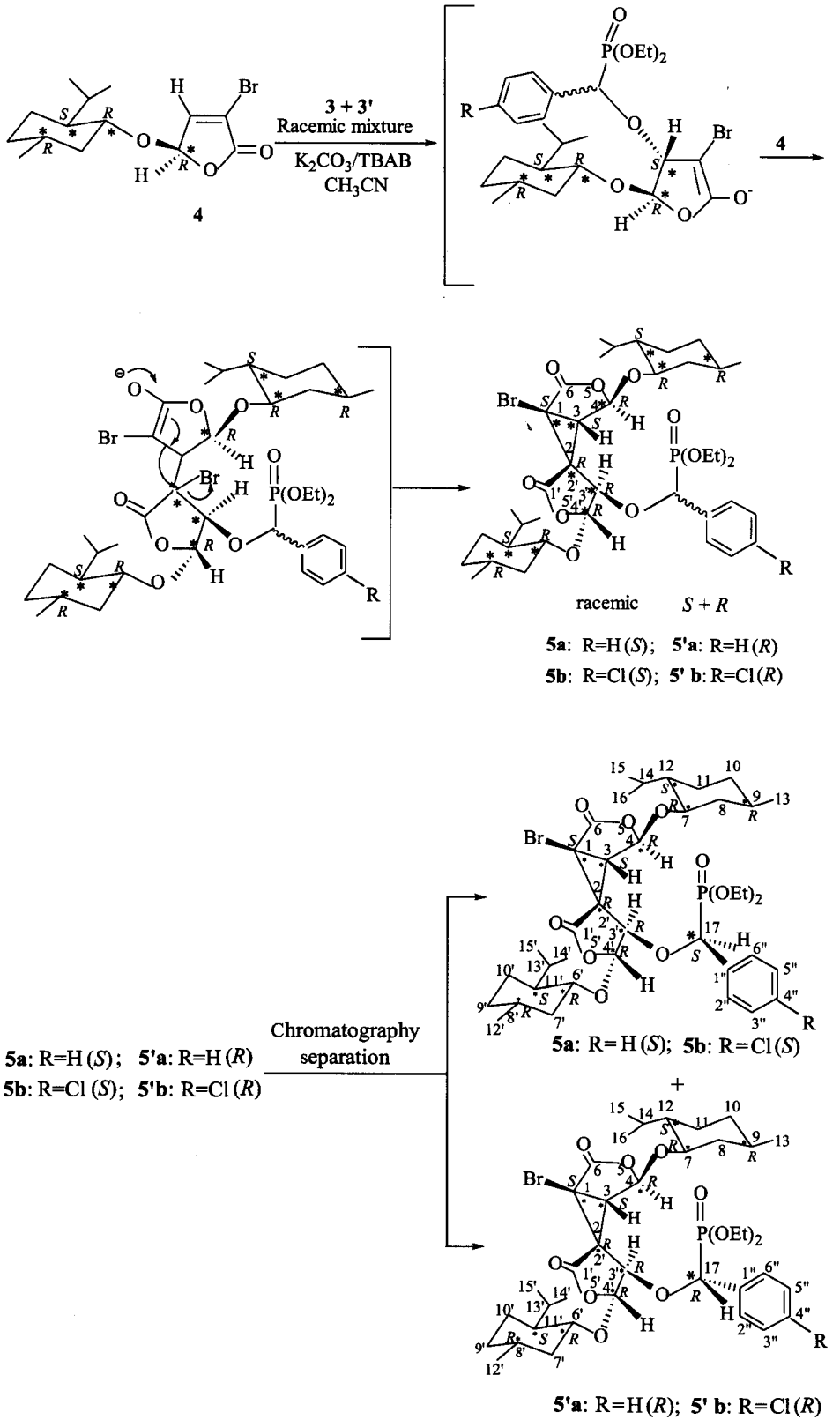
3b + 3'b M.p. 69.5—70.5 ℃; R_f = 0.1 [EtOAc-petroleum ether (30—60 ℃) = 4:1 (*V*:*V*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.26 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 4.02 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.05 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 5.01 (d, *J* = 11.2 Hz, 1H, CH-P), 5.26 (br, 1H, OH), 7.31 (d, *J* = 8.4 Hz, 2H, 2 × ArH), 7.42 (dd, *J* = 8.8, 2.0 Hz, 2H, 2 × ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3 ($^3J_{PC}$ = 4.3 Hz, 2 × OCH_2CH_3), 63.0 ($^2J_{PC}$ = 6.9 Hz, OCH_2CH_3), 63.5 ($^2J_{PC}$ = 6.5 Hz, OCH_2CH_3), 69.9 ($^1J_{PC}$ = 159.3 Hz, HC - P = O), 128.3 (C-2', 6'), 128.4 ($^2J_{PC}$ = 4.9 Hz, C-1'), 133.6 (C-3', 5'), 135.4 (C-4'); IR (KBr) ν: 3249 (br, OH), 2984, 1490, 1233, 1204, 981 cm^{-1}; EIMS *m/z* (%): 280 (M^+ + 2, 23), 279 (M^+ + 1, 33), 278 (M^+, 42), 261 (M^+ - OH, 35), 249 ($M^+ - C_2H_5$, 12), 233 ($M^+ - OC_2H_5$, 21), 141 ($C_7H_6OCl^+$, 43), 137 ($C_4H_{10}O_3P^+$, 67), 110 ($C_2H_7O_3P^+$, 100), 82 ($H_3O_3P^+$, 100). Anal. calcd for $C_{11}H_{16}O_4ClP$: C 47.41, H 5.79; found C 46.99, H 5.66.

General procedure for preparation of spiro-cyclopropane-phosphorus derivatives **5a**, **5'a**, **5b** and **5'b**

Racemic diethyl α-hydroxyl-4'-substituted-benzylphosphonate (1 mmol) under N_2 atmosphere was added to the mixture of powdered K_2CO_3 (1.11 g, 8 mmol), tetrabutyl ammonium bromide (0.32 g, 1 mmol) and acetonitrile (6 mL). The mixture was stirred for 20 min. Then, chiral synthon **4** (0.63 g, 2 mmol) was added and the mixture was stirred at room temperature for 1—2 d, by which time the chiral synthon **4** had been consumed as monitored by TLC. After the addition of acetonitrile (50 mL), the mixture was filtered and the salts were washed with acetonitrile. The organic layer was dried and evaporated under reduced pressure, and the residue was puri-

fied by column chromatography to give **5a—5'b**.

Scheme 2



Spiro [1-*bromo* (*S*)-4-*L*-(1*R*,2*S*,5*R*)-*menthyloxy*-5-*oxa*-6-*oxo*-*bicyclo* [3.1.0] *hexane*-2,2′-(3′-*diethyl*-α-(*S*)-*benzyloxyphosphonyl*-4′-(1*R*,2*S*,5*R*)-*menthyloxybutyrolactone*)] (**5a**) Yield 0.34 g (42%), R_f = 0.25 [EtOAc-petroleum ether (30—60 ℃) = 1:4 (*V*:*V*)]; m.p. 50—52 ℃; $[\alpha]_D^{20}$ − 116.4 (*c* 1.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.64 (d, *J* = 6.8 Hz, 3H, CH_3), 0.71 (d, *J* = 7.2 Hz, 3H, CH_3), 0.82 (d, *J* = 6.0 Hz, 3H, CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 0.94 (d, *J* = 6.0 Hz, 3H, CH_3), 0.95 (d, *J* = 6.4 Hz, 3H, CH_3), 1.03—1.18 (m, 6H, 2 × H-10′, 2 × H-11, H-9′e, H-10e), 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.25 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.28—1.58 (m, 6H, 2 × H-7′, 2 × H-8, H-9′a, 10a), 1.67—1.70 (m, 2H, H-13′, H-14), 2.08—2.26 (m, 4H, H-8′,9,11′,12), 3.13 (s, 1H, H-3), 3.25 (bt, *J* = 7.6, 2.8 Hz, 1H, H-6′), 3.65 (bt, *J* = 7.2, 3.2 Hz, 1H, H-7), 3.79 (s, 1H, H-3′), 3.98 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.99 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.54 (d, J_{PH} = 16.0 Hz, 1H, CH-P), 5.18 (s, 1H, H-4′), 6.27 (s, 1H, H-4), 7.41—7.46 (m, 5H, 5 × ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.4 (C-15′), 15.7 (C-16), 16.4 (2 × OCH_2CH_3), 20.7 (C-14′,15), 22.0 (C-12′), 22.1 (C-13), 22.6 (C-10′), 23.2 (C-11), 24.7 (C-13′), 25.5 (C-14), 31.2 (C-8′), 31.4 (C-9), 34.0 (C-9′), 34.1 (C-10), 34.6 (C-2), 38.5 (C-3), 39.0 (C-1), 40.2 (C-7′,8), 47.1 (C-11′), 47.4 (C-12), 63.1 ($^2J_{PC}$ = 7.1 Hz, $POCH_2$), 63.5 ($^2J_{PC}$ = 6.4 Hz, $POCH_2$), 76.6 (C-6′), 78.8 (C-7), 80.6 (C-3′), 84.1 ($^1J_{PC}$ = 143 Hz, C-17), 97.7 (C-4), 99.8 (C-4′), 128.3 ($^2J_{PC}$ = 5.9 Hz, C-1″), 129.0 (C-2″,6″), 129.5 (C-3″,5″), 134.1 (C-4″), 167.9 (C-1′), 168.8 (C-6); IR (KBr) ν: 3068, 2956, 1791, 1259, 1128, 1024, 929, 561 cm^{-1}; EIMS *m*/*z* (%): 799 (M^+ + 2, 5), 797 (M^+, 6), 661 (M^+ + 2 − $C_{10}H_{18}$, 6), 659 (M^+ − $C_{10}H_{18}$, 7), 523 (M^+ + 2 − $2C_{10}H_{18}$, 5), 521 (M^+ − $2C_{10}H_{18}$, 8), 476 (M^+ + 2 − $2C_{10}H_{19}$ − C_2H_5O, 12), 474 (M^+ − $2C_{10}H_{19}$ − C_2H_5O, 12), 441 (M^+ − $2C_{10}H_{18}$ − C_2H_5O − CH_5O, 28), 245 ($C_{11}H_{18}PO_4^+$, 40), 227 ($C_{11}H_{16}O_3P^+$, 89), 198 ($C_9H_{13}O_3P^+$, 51), 140 ($C_{10}H_{20}^+$, 21), 138 ($C_{10}H_{18}^+$, 78), 80 ($C_6H_8^+$, 100). Anal. calcd for $C_{39}H_{58}O_{10}BrP$: C 58.72, H 7.33; found C 58.24, H 7.20.

Spiro [1-*bromo* (*S*)-4-*L*-(1*R*,2*S*,5*R*)-*menthyloxy*-5-*oxa*-6-*oxo*-*bicyclo* [3.1.0] *hexane*-2,2′-(3′-*diethyl*-α-(*R*)-*benzyloxyphosphonyl*-4′-(1*R*,2*S*,5*R*)-*menthyloxybutyrolactone*)] (**5′a**) Yield 0.29 g (36%), R_f = 0.17 [EtOAc-petroleum ether (30—60 ℃) = 1:4 (*V*:*V*)]; m.p. 43—45 ℃; $[\alpha]_{20}^{D}$ − 81.9 (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.64 (d, *J* = 6.8 Hz, 3H, CH_3), 0.82 (d, *J* = 7.2 Hz, 3H, CH_3), 0.84 (d, *J* = 6.0 Hz, 3H, CH_3), 0.86 (d, *J* = 7.2 Hz, 3H, CH_3), 0.92 (d, *J* = 7.2 Hz, 3H, CH_3), 0.95 (d, *J* = 6.4 Hz, 3H, CH_3), 1.03—1.18 (m, 6H, 2 × H-10′, 2 × H-11, H-9′e, H-10e), 1.23 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.25 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.28—1.58 (m, 6H, 2 × H-7′, 2 × H-8, H-9′a, H-10a), 1.67—1.69 (m, 2H, H-13′, H-14), 2.02—2.28 (m, 4H, H-8′, 9, 11′, 12), 3.12 (s, 1H, H-3), 3.25 (bt, *J* = 7.6, 2.8 Hz, 1H, H-6′), 3.65 (bt, *J* = 7.2, 3.2 Hz, 1H, H-7), 3.79 (s, 1H, H-3′), 3.98 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.99 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.53 (d, $^2J_{PH}$ = 16.0 Hz, 1H, CH-P), 5.18 (s, 1H, H-4′), 6.27 (s, 1H, H-4), 7.40—7.47 (m, 5H, 5 × ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.4 (C-15′), 15.6 (C-16), 16.4 ($^3J_{PC}$ = 4.4 Hz, 2 × OCH_2CH_3), 20.6 (C-14′), 20.8 (C-15), 22.0 (C-12′), 22.2 (C-13), 22.8 (C-10′), 23.1 (C-11), 24.7 (C-13′), 25.4 (C-14), 31.1 (C-8′), 31.4 (C-9), 34.0 (C-9′), 34.1 (C-10), 34.6 (C-2), 38.5 (C-3), 39.0 (C-1), 39.2 (C-7′), 40.1 (C-8), 47.1 (C-11′), 47.4 (C-12), 63.2 ($^2J_{PC}$ = 7.2 Hz, $POCH_2$), 63.6 ($^2J_{PC}$ = 7.6 Hz, $POCH_2$), 76.9 (C-6′), 78.7 (C-7), 80.5 (C-3′), 84.1 ($^1J_{PC}$ = 140 Hz, C-17), 97.4 (C-4), 100.2 (C-4′), 128.3 ($^2J_{PC}$ = 6.1 Hz, C-1″), 128.9 (C-2″,6″), 129.5 (C-3″, 5″), 134.1 (C-4″), 167.8 (C-1′), 168.8 (C-6); IR (KBr) ν: 3066, 2956, 1791, 1257, 1127, 1025, 926, 561 cm^{-1}; EIMS *m*/*z* (%): 799 (M^+ + 2, 6), 797 (M^+, 6), 661 (M^+ + 2 − $C_{10}H_{18}$, 6), 659 (M^+ − $C_{10}H_{18}$, 5), 523 (M^+ + 2 − $2C_{10}H_{18}$, 10), 521 (M^+ − $2C_{10}H_{18}$, 12), 476 (M^+ + 2 − $2C_{10}H_{19}$ − C_2H_5O, 18), 474 (M^+ − $2C_{10}H_{19}$ − C_2H_5O, 18), 441 (M^+ − $2C_{10}H_{19}$ − C_2H_5O − CH_5O, 17), 245 ($C_{11}H_{18}PO_4^+$, 40), 227 ($C_{11}H_{16}O_3P^+$, 88), 198 ($C_9H_{13}O_3P^+$, 49), 138 ($C_{10}H_{18}^+$, 70), 82 ($C_6H_{10}^+$, 100). Anal. calcd for $C_{39}H_{58}O_{10}BrP$: C 58.72, H 7.33; found C 59.18, H 7.49.

Spiro [1-*bromo* (*S*)-4-*L*-(1*R*,2*S*,5*R*)-*menthyloxy*-5-*oxa*-6-*oxo*-*bicyclo* [3.1.0] *hexane*-2,2′-(3′-*diethyl*-α-

(*S*)-4″-*Cl*-*benzyloxyphosphonyl*-4′-(1*R*, 2*S*, 5*R*)-*menthyloxybutyrolactone*)] (**5b**) Yield 0.33 g (39%), R_f = 0.47 [EtOAc-petroleum ether (30—60 ℃) = 1:4 (*V*:*V*)]; m.p. 73—74 ℃; $[\alpha]_D^{20}$ − 129.8 (*c* 1.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.64 (d, *J* = 6.8 Hz, 3H, CH_3), 0.81 (d, *J* = 6.8 Hz, 3H, CH_3), 0.83 (d, *J* = 6.8 Hz, 3H, CH_3), 0.86(d, *J* = 6.4 Hz, 3H, CH_3), 0.92 (d, *J* = 6.8 Hz, 3H, CH_3), 0.95 (d, *J* = 6.8 Hz, 3H, CH_3), 1.00—1.29 (m, 6H, 2 × H-10′, 2 × H-11, H-9′e, H-10e), 1.24 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.28 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.30—1.63 (m, 6H, 2 × H-7′, 2 × H-8, H-9′a, 10a), 1.64—1.73 (m, 2H, H-13′, H-14), 2.05—2.23 (m, 4H, H-8′, 9, 11′, 12), 3.13 (s, 1H, H-3), 3.30 (bt, *J* = 10.4, 4.0 Hz, 1H, H-6′), 3.65 (bt, *J* = 10.4, 4.0 Hz, 1H, H-7), 3.77 (s, 1H, H-3′), 3.96 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.07 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.51 (d, $^2J_{PH}$ = 16.4 Hz, 1H, CH-P), 5.15 (s, 1H, H-4′), 6.24 (s, 1H, H-4), 7.38—7.41 (m, 4H, 4 × ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.4 (C-15′), 15.7 (C-16), 16.4 (2 × OCH_2CH_3), 20.8 (C-14′, 15), 22.1 (C-12′), 22.2 (C-13), 22.7 (C-10′), 23.2 (C-11), 24.7 (C-13′), 25.5 (C-14), 31.1 (C-8′), 31.5 (C-9), 34.0 (C-9′), 34.2 (C-10), 34.6 (C-2), 38.6 (C-3), 38.7 (C-1), 40.0 (C-7′), 40.2 (C-8), 47.2 (C-11′), 47.5 (C-12), 63.3 ($^2J_{PC}$ = 6.3 Hz, $POCH_2$), 63.6 ($^2J_{PC}$ = 6.2 Hz, $POCH_2$), 78.1 (C-6′), 78.7 (C-7), 79.8 (C-3′), 84.1 ($^1J_{PC}$ = 136 Hz, C-17), 97.7 (C-4), 99.8 (C-4′), 129.2 (C-3″, 5″), 129.6 ($^2J_{PC}$ = 4.8 Hz, C-1″), 132.7 (C-2″, 6″), 135.5 (C-4″), 167.9 (C-1′), 168.7 (C-6); IR (KBr) ν: 3072, 2956, 2360, 1791, 1259, 1128, 1024, 929 cm^{-1}; EIMS *m*/*z* (%): 834 (M^+ + 2, 2), 833 (M^+ + 1, 2), 832 (M^+, 2), 695 (M^+ + 2 − $C_{10}H_{19}$, 6), 693 (M^+ − $C_{10}H_{19}$, 5), 557 (M^+ + 2 − $C_{10}H_{18}$ − $C_{10}H_{19}$, 6), 555 (M^+ − $C_{10}H_{18}$ − $C_{10}H_{19}$, 6), 512 (M^+ + 2 − $C_{10}H_{18}$ − $C_{10}H_{19}$ − OC_2H_5, 2), 510 (M^+ − $C_{10}H_{18}$ − $C_{10}H_{19}$ − OC_2H_5, 10), 477 (M^+ − 2 − $C_{11}H_{17}O_4PCl$ − C_6H_6, 12), 475 (M^+ − $C_{11}H_{17}O_4PCl$ − C_6H_6, 32), 279 ($C_{11}H_{17}O_4PCl^+$, 40), 263 (M^+ + 2 − $C_8H_6O_5Br$, 26), 261 (M^+ − $C_8H_6O_5Br$, 71), 233 ($C_9H_{11}O_3PCl^+$, 52), 138 ($C_{10}H_{18}^+$, 100), 83 ($C_4H_3O_2^+$, 53), 81 ($C_6H_9^+$, 54), 67 ($C_5H_7^+$, 45); Anal. calcd for $C_{39}H_{57}O_{10}BrClP$: C 56.29, H 6.90; found C 56.68, H 6.97.

Spiro[1-*bromo* (*S*)-4-*L*-(1*R*, 2*S*, 5*R*)-*menthyloxy*-5-*oxa*-6-*oxo*-*bicyclo*[3.1.0]*hexane*-2, 2′-(3′-*diethyl*-*α*-(*R*)-4″-*Cl*-*benzyloxyphosphonyl*-4′-(1*R*, 2*S*, 5*R*)-*menthyloxybutyrolactone*)] (**5′b**) Yield 0.38 g (45%), R_f = 0.34 [EtOAc-petroleum ether (30—60 ℃) = 1:4(*V*:*V*)]; m.p. 42—43 ℃; $[\alpha]_D^{20}$ − 54.0 (*c* 1.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.68 (d, *J* = 6.8 Hz, 3H, CH_3), 0.73 (d, *J* = 6.8 Hz, 3H, CH_3), 0.85 (d, *J* = 7.2 Hz, 3H, CH_3), 0.87 (d, *J* = 7.2 Hz, 3H, CH_3), 0.90 (d, *J* = 7.2 Hz, 3H, CH_3), 0.98 (d, *J* = 6.4 Hz, 3H, CH_3), 1.01—1.50 (m, 8H, 2 × H-9′, 2 × H-10, 2 × H-10′, 2 × H-11), 1.20 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.32 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.52—1.75 (m, 6H, 2 × H-7′, 2 × H-8, H-13′, 14), 1.86—2.20 (m, 4H, H-8′, H-9, H-11′, H-12), 2.98 (s, 1H, H-3), 3.08 (bt, *J* = 10.8, 4.0 Hz, 1H, H-6′), 3.62 (bt, *J* = 10.8, 4.0 Hz, 1H, H-7), 3.70 (s, 1H, H-3′), 3.92 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.13 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.47 (d, $^2J_{PH}$ = 14.0 Hz, 1H, CH-P), 5.19 (s, 1H, H-4′), 6.07 (s, 1H, H-4), 7.39—7.41 (m, 4H, 4 × ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.4 (C-15′), 15.5 (C-16), 16.4 (2 × OCH_2CH_3), 20.7 (C-14′), 20.9 (C-15), 22.2 (C-12′), 22.3 (C-13), 22.8 (C-10′), 23.0 (C-11), 24.7 (C-13′), 25.3 (C-14), 31.4 (C-8′, C-9), 34.0 (C-9′, C-10), 34.1 (C-2), 37.9 (C-3), 38.8 (C-1), 39.2 (C-7′), 40.3 (C-8), 47.2 (C-11′), 47.4 (C-12), 63.4 ($^2J_{PC}$ = 6.4 Hz, $POCH_2$), 63.7 ($^2J_{PC}$ = 6.0 Hz, $POCH_2$), 76.9 (C-6′), 79.1 (C-7), 79.5 (C-3′), 82.3 ($^1J_{PC}$ = 181 Hz, C-17), 97.2 (C-4), 100.4 (C-4′), 129.1 (C-3″, 5″), 129.9 ($^2J_{PC}$ = 6.0 Hz, C-1″), 131.8 (C-2″, 6″), 135.7 (C-4″), 167.5 (C-1′), 168.7 (C-6); IR (KBr) ν: 3070, 2957, 2358, 1790, 1257, 1128, 1088, 1024, 925 cm^{-1}; EIMS *m*/*z* (%): 834 (M^+ + 2, 2), 833 (M^+ + 1, 3), 832 (M^+, 2), 695 (M^+ + 2 − $C_{10}H_{19}$, 5), 693 (M^+ − $C_{10}H_{19}$, 5), 557 (M^+ + 2 − $C_{10}H_{18}$ − $C_{10}H_{19}$, 10), 555 (M^+ − $C_{10}H_{18}$ − $C_{10}H_{19}$, 10), 512 (M^+ + 2 − $C_{10}H_{18}$ − $C_{10}H_{19}$ − OC_2H_5, 5), 510 (M^+ − $C_{10}H_{18}$ − $C_{10}H_{19}$ − OC_2H_5, 12), 477 (M^+ + 2 − $C_{11}H_{17}O_4PCl$ − C_6H_6, 6), 475 (M^+ − $C_{11}H_{17}O_4PCl$ − C_6H_6, 9), 279 ($C_{11}H_{17}O_4PCl^+$, 43), 263 (M^+ + 2 − $C_8H_6O_5Br$, 66), 261 (M^+ − $C_8H_6O_5Br$, 100), 233 ($C_9H_{11}O_3PCl^+$, 70), 139 ($C_{10}H_{19}^+$, 88), 138 ($C_{10}H_{18}^+$, 73), 95 ($C_7H_{11}^+$,

77), 83 ($C_4H_3O_2^+$, 81), 81 ($C_6H_9^+$, 84), 55 ($C_4H_8^+$, 79), 41 ($C_3H_5^+$, 71). Anal. calcd for $C_{39}H_{57}O_{10}BrClP$: C 56.29, H 6.90; found C 56.74, H 7.02.

Single crystal preparation of **5a** *and its X-ray crystallography*

5a was dissolved in ethyl acetate-petroleum ether (30—60 ℃). A colorless single crystal was separated out from the solution at room temperature after standing for several days.

X-Ray crystallography 0.30 nm × 0.30 nm × 0.20 nm colorless monocrystal of chiral compound **5a**, $C_{39}H_{58}O_{10}BrP$, M_r 797.74, The crystal **5a** is attributed to monoclinic system and $P2_1$ space group. The crystal lattice parameters are $a = 1.2858(3)$ nm, $b = 2.5130(5)$ nm, $c = 1.4125(3)$ nm, $V = 4.4053(15)$ nm^3, $Z = 2$, $D_c = 1.203$ g/cm^3, $\mu = 1.019$ mm^{-1}, $F(000) = 1688$. It was selected to be determined on a R-axis-IV X-ray diffractometer with the incident radiation of Mo Kα ray ($\lambda = 0.071073$ nm), which was monochromalized by graphite. 11247 diffraction points of diffraction intensity ($2\theta_{max} = 50°$) were collected at r.t. [(21 ± 1) ℃] with ω-θ scanning pattern, in which there were 5758 perceivable points of $I \geqslant 2\sigma(I)$. The rectified results of nonhydrogen atom coordinates and their thermoparameters of aeolotropism by minimum-binary-multiplication were: the deflection factor [$F^2 > 2\sigma(F^2)$], $R = 0.0788$, $R_w = 0.1241$, the absolute structure parameter is 0.00 (0) and the maximum residual peak in the D-value Fourier scheme is 0.272×10^2 e/nm^3. All were calculated and rectified on Siemens SHELXTL-97 program.

Results and discussion

As it is well known that the phosphoric acid derivatives are so extremely important in life science. Many practical uses for organophosphorus compounds and cyclopropane derivatives in addition to those in medicine and agriculture have been developed in the last few decades. The cyclopropane-phosphorus derivatives would be accepted as valuable chemotherapeutic and antibacterial agents as well as insecticides. As the chiral building blocks, the racemic diethyl α-hydroxybenzylphosphonate (**3**), which are useful reagents for the synthesis of organophosphorus compounds, can be easily prepared by the acid- or base-catalyzed addition of aldehydes (**1**) to dialkyl hydrogen phosphates (**2**). The m.p. of racemic **3a** + **3′a** was confirmed by those reported in the literature.[10] The racemic mixture of enantiomers, **3b** + **3′b** was identified on the basis of its analytical and spectroscopic data, such as IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.

In general, the tandem asymmetric double-Michael addition/internal nucleophilic substitution reaction of **4** with nucleophilic reagents afforded the corresponding optically pure spiro-cyclopropane products.[7-9] The synthesis of diastereomerical mixture of cyclopropane-phosphorus derivatives **5a** + **5′a** and **5b** + **5′b** was accomplished by the asymmetric reaction of the readily available **4** with the racemic diethyl α-hydroxy-4-substituted-benzylphosphonates (**3** + **3′**) under mild conditions. After the separation by column chromatography on a silica gel and using ethyl acetate/petroleum ether mixture as the eluent, the diastereomerically pure cyclopropane-phosphorus derivatives **5a**, **5′a**, **5b** and **5′b** were easily obtained in fair yields with *d.e.* ≥98%. The R_f value of TLC using EtOAc-petroleum ether (30—60 ℃) = 1:4 (*V*:*V*) as the eluent for each pair of diastereomers has shown the corresponding datum: **5a** $R_f = 0.25$, **5′a** $R_f = 0.17$, **5b** $R_f = 0.47$ and **5′b** $R_f = 0.34$. The chemical structure and stereochemistry of this novel chiral compounds **5** were readily confirmed by analytical data and spectroscopic data, such as IR, ^{1}H NMR, ^{13}C NMR, MS, $[\alpha]_D^{20}$ and elemental analysis. On the basis of the data, the proposed structure of spiro-[1-bromo (*S*)-4-*L*-(1*R*, 2*S*, 5*R*)-menthyloxy-5-oxa-6-oxo-bicyclo [3. 1. 0] hexane-2, 2′-(3′-diethyl-α-(*S*)-benzyloxyphosphonyl-4′-(1*R*, 2*S*, 5*R*)-menthyloxybutyrolactone)] (**5a**) was consistent with the stereochemistry and absolute configuration of its molecule, and this was further confirmed by its X-ray crystallography as shown in Fig. 1. The examination of the X-ray structure of the diastereomer **5a** led to the important conclusion that the absolute configuration at the α-benzyl carbon in the diastereomer **5′a** should be *R*. In addition, the absolute configurations at the α-benzyl carbon of the diastereomers **5b** and **5′b** are comparable and relative though the one of the single crystal structures is not yet established by X-ray crystallography.

Crystal structure description of **5a**

The orientation temperature plot (ORTEP) drawing of **5a** is shown in Fig. 1. The packing diagram of **5a** is shown in Fig. 2. The absolute configuration of (1*R*,2*S*,

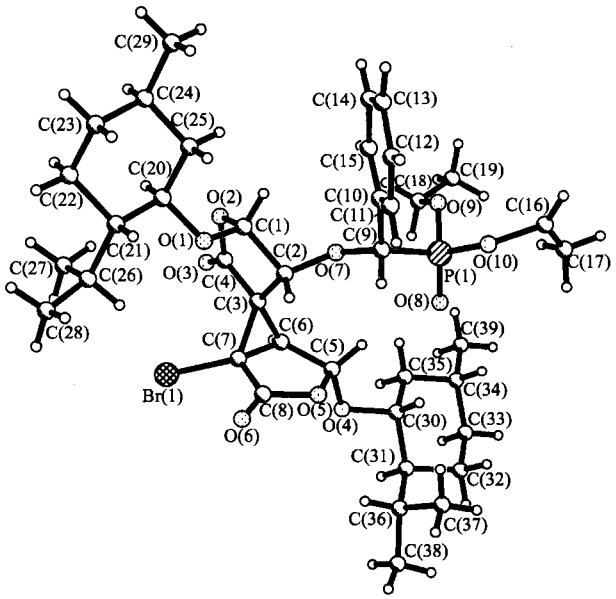


Fig. 1 The molecular structure of **5a**.

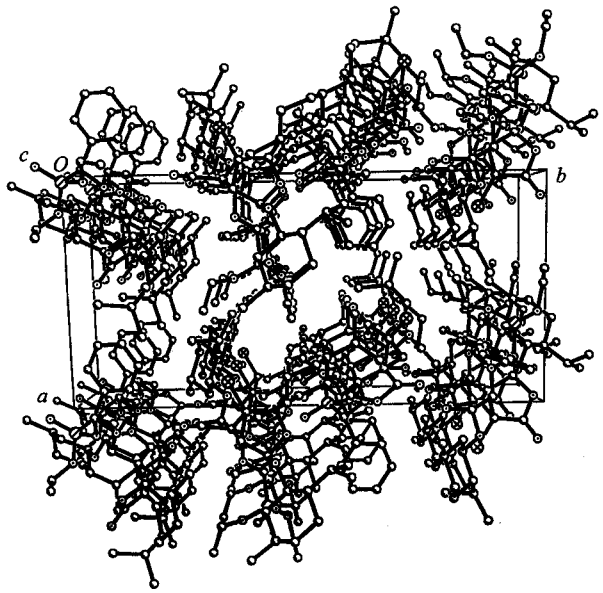


Fig. 2 The packing diagram of **5a**.

5*R*)-(－)-menthyloxy keeps unchanged during the asymmetric reaction process. The whole chiral molecule **5a** has 13 chiral centers including original nine chiral centers C(1)(*R*), C(20)(*R*), C(21)(*S*), C(24)(*R*), C(5)(*R*), C(30)(*R*), C(31)(*S*), C(34)(*R*), C(9)(*S*) and four new stereogenic centers C(6)(*S*), C(7)(*S*), C(3)(*R*), C(2)(*R*). From the viewpoint of the structure of cyclopropane-phosphorus derivative **5a**, the bond angles of the cyclopropane component of the whole molecule are: C(6)-C(3)-C(7) 58.9(6)°, C(7)-C(6)-C(3) 61.6(6)°, C(6)-C(7)-C(3) 59.6(6)°, which are approximate to 60° and in agreement with the theoretical value. Two lactone rings fuse with cyclopropane respectively to form the compound with [4.2] and [3.1.0] bicyclic skeleton. The chiral diethyl-α-(*S*)-benzyloxyphousphonyl and a menthyloxy group are located on both sides of the lactone ring respectively. The chiral center C(9) maintains original *S*-configuration of diethyl-α-(*S*)-benzyloxyphosphonyl building block.

Conclusion

Our results provided a valuable synthetic route to the interesting diastereomerically pure cyclopropane-phosphorus derivatives **5a**, **5′a**, **5b** and **5′b** in good yields with *d*. *e*. ≥ 98% from the readily available chiron, 5-*L*-menthyloxy-3-bromo-2(5*H*)-furanone (**4**) with the racemic diethyl α-hydroxybenzylphosphonates **3a** + **3′a** and **3b** + **3′b**. It is particularly significant that the approach proposed would be the groundwork for future applications of the interesting racemic diethyl α-hydroxybenzylphosphonates as chiral building block to provide a new strategy and thread of ideas in the synthesis of more complex molecules containing active phosphorus functional groups and study of their biological activity.

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