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Tetrahedron 59 (2003) 6095–6102

TETRAHEDRON

# Enzymatic synthesis of optically active 1- and 2-aminoalkanephosphonates☆

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Received 22 January 2003; revised 20 May 2003; accepted 17 June 2003

**Abstract**—A number of 1- and 2-aminoalkanephosphonates were resolved with high enantioselectivity by *Candida antarctica* lipase B-catalyzed acetylation. By this method, optically pure aminoalkanephosphonates and amidoalkanephosphonates, the precursors of the corresponding aminoalkanephosphonic acids, were synthesized.


## 1. Introduction

Chiral aminoalkanephosphonates have received considerable attention due to their negligible mammalian toxicity and close chemical resemblance to amino acids, which makes them extremely important as antimetabolites.[1] They also serve as key substrates in the synthesis of phosphonopeptides.[1a] Surprisingly, however, there are only a few reports regarding the asymmetric synthesis of aminoalkanelphosphonic acids.[2]

Biocatalytic resolution of racemic molecules has attracted the interest of synthetic chemists for several decades.[3] Lipases, the most commonly used enzymes in organic synthesis, have been utilized in the resolution of racemic amines via aminolysis and transesterification.[4] To the best of our knowledge, however, there are still no reports concerning the lipase-catalyzed resolution of aminoalkanephosphonates.

Recently we have developed the *Candia antarctic* lipase B (CALB)- and *Candida rugosa* lipase (CRL)-catalyzed resolution of hydroxyalkanephosphonates.[5] Now we wish to report that CALB can serve as an effective catalyst in the enantioselective acetylation of aminoalkanephosphonates using ethyl acetate or ethyl 1-methoxyacetate as acylating reagent.

## 2. Results and discussion

In our previous study, vinyl acetate was chosen as the acylating reagent for the enzymatic resolution of hydroxyalkanephosphonates.[5] Because of their stronger nucleophilicity, aminoalkanephosphonates, however, reacted with vinyl acetate even in the absence of CALB to give the corresponding amides. Ethyl acetate was therefore used as both the acylating reagent and the solvent to resolve diethyl 2-aminopropylphosphonate (**1a**) (Scheme 1). To determine the enantiomeric value of the amine, diethyl 2-aminopropylphosphonate **2a** was converted to its benzyloxycarbamate derivative **4a**.[6]

As shown in Scheme 1, CALB-catalyzed acylation of **1a** using ethyl acetate as an acetylating reagent led to optically enriched **2a** and **3a** with ee values of 97 and 88% respectively. Under the same conditions, however, the enantioselectivity of the resolution of diisopropyl 2-aminopropylphosphonate was very low (Table 1). To improve the enantioselectivity, different solvents were examined[7] (Table 1). It was found that diisopropyl ether was the best reaction medium not only for **1c** but also for other 2-aminoalkanephosphonates' substrates (Scheme 2).

The configuration of the resulting 2-aminoalkanephosphonates (**2**) was assigned as *S* based on the optical rotation of (*S*)-2-aminopropanephosphonic acid derived from **2a**[2a] (Scheme 3).

The results in Table 2 indicated that vinyl-substituted **1g** was not a suitable substrate, and almost no conversion was observed. According to the general trends observed for CALB-catalyzed resolution,[9] in most cases, the medium group ($R^1$) should not be too large for good selectivity. Here, when ethyl is $R^1$ the enantioselectivity is moderate, but the

☆ Studies on organophosphorus compounds 127.

*Keywords*: aminoalkanephosphonate; *Candida antarctica* lipase B; acetylation; kinetic resolution.

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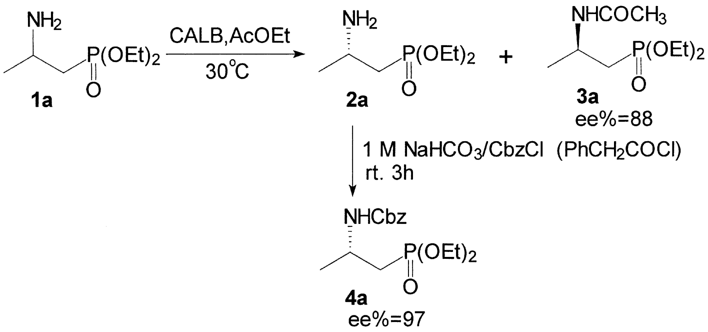
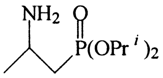
doi:10.1016/S0040-4020(03)00995-5

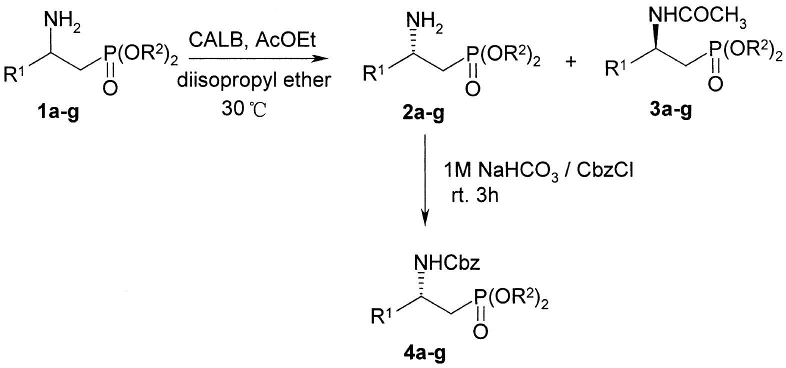



**Scheme 1.**

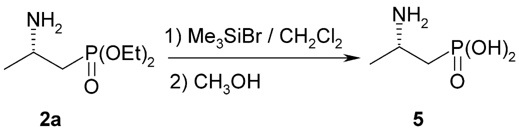
**Table 1**. Effect of solvent on catalytical acetylation by CALB

| Substrate | Time (days) | Acylating reagent | Solvent | Ratio[a] | ee% | | $E$[b] |
|---|---|---|---|---|---|---|---|
| | | | | | **2c**[c] | **3c**[d] | |
|  | 3 | Ethyl acetate | Diisopropyl ether | 1:4 | 70 | 100 | >200 |
| | | | 1,4-Dioxane | | 47 | 100 | >200 |
| | | | *n*-Hexane | | 58 | 100 | >200 |
| | | | Ethyl acetate | | 54 | 64 | 8 |

[a] Ratio of the acylating reagent to the solvent.
[b] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[8]
[c] The ee values were determined by the chiral HPLC of their derivatives **4c**.
[d] The ee values were determined by the chiral HPLC.




**Scheme 2.**




**Scheme 3.**

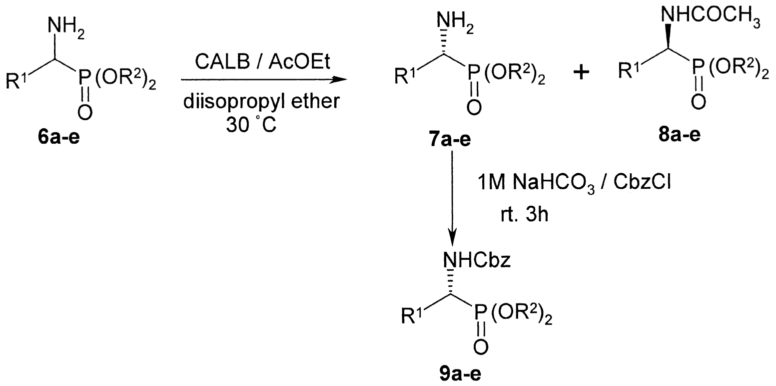
enantioselectivity dropped dramatically in the case of $R^1$ being the vinyl group. This selectivity is quite different from those of the corresponding 2-hydroxyalkanephosphonates.[5a]

We then turned to the resolution of 1-aminoalkanephosphonates that are the precursors of 1-aminoalkanephosphonic

**Table 2**. CALB catalyzed enantioselective acetylation of 2-aminoalkanephosphonates

| Entry | Substrate | $R^1$ | $R^2$ | Time (days) | **2** | | **3** | | $E$ |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Yield (%) | ee (%)[a] | Yield (%) | ee (%)[b] | |
| 1 | **1a** | Me | Et | 5 | 40 | 99.5 | 54 | 78 | 64 |
| 2 | **1b** | Me | *n*-Pr | 5 | 41 | 100 | 53 | 76 | >80 |
| 3 | **1c** | Me | *i*-Pr | 7 | 40 | 100 | 55 | 72 | >70 |
| 4 | **1d** | Et | Et | 7 | 44 | 64 | 42 | 79 | 16 |
| 5 | **1e** | Et | *n*-Pr | 10 | 41 | 56 | 40 | 74 | 12 |
| 6 | **1f** | Et | *i*-Pr | 10 | 43 | 26 | 41 | 41 | <5 |
| 7 | **1g** | Vinyl | Et | 1 | 0 | 0 | >90 | 0 | 0 |

[a] The ee values were determined by the chiral HPLC of their derivative **4**.
[b] The ee values were determined by the chiral HPLC.

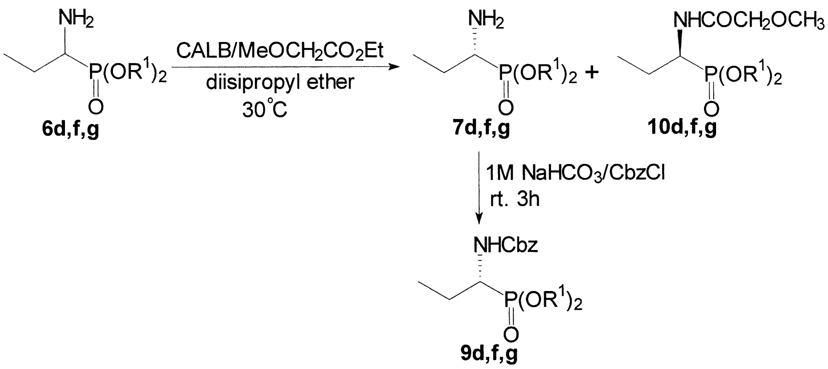



**Scheme 4.**

**Table 3**. CALB-catalyzed enantioselective acetylation of 1-aminoalkanephosphonates

| Entry | Substrate | $R^1$ | $R^2$ | Time (days) | **7** | | **8** | | *E* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Yield (%) | ee (%)[a] | Yield (%) | ee (%)[b] | |
| 1 | **6a** | Me | Et | 5 | 41 | 99.7 | 48 | 90 | >100 |
| 2 | **6b** | Me | *n*-Pr | 5 | 42 | 90 | 42 | 98 | >200 |
| 3 | **6c** | Me | *i*-Pr | 5 | 44 | 96 | 43 | 98 | >200 |
| 4 | **6d** | Et | Et | 5 | 73 | 18 | 10 | 100 | >200 |
| 5 | **6e** | $CF_3$ | Et | 5 | No reaction | | | | |

[a] The ee values were determined by the chiral HPLC of their derivatives **9**.
[b] The ee values were determind by the chiral HPLC of **8**.




**Scheme 5.**

acids, an important class of potentially bioactive compounds (Scheme 4). The results are listed in Table 3.

Because of the low reactivity of ethyl acetate toward substrate **6d**, we selected ethyl 1-methoxyacetate[10] as the acyl group to resolve these compounds (Scheme 5) with satisfactory results (Table 4).

**Table 4**. CALB catalyzed enantioselective acetylation of 1-aminopropylphosphonates

| Entry | Substrate | $R^1$ | Time (days) | **7** | | **10** | | *E* |
|---|---|---|---|---|---|---|---|---|
| | | | | Yield (%) | ee (%)[a] | Yield (%) | ee (%)[b] | |
| 1 | **6d** | Et | 5 | 40 | 98 | 54 | –[c] | – |
| 2 | **6f** | *n*-Pr | 5 | 41 | 91 | 53 | 70 | 17 |
| 3 | **6g** | *i*-Pr | 5 | 39 | 64 | 52 | 50 | 6 |

[a] The ee values were determined by the chiral HPLC of their derivative **9**.
[b] The ee values were determined by the chiral HPLC of **10**.
[c] **10d** can not be determined by chiral HPLC.

It should be pointed out that the preparation of optically active 1-amino-2,2,2-trifluoroethanephosphonates by this methodology was unsuccessful even with the prolonged of reaction time.

That (*S*)-1- and (*R*)-2-aminoalkanephosphonates were preferentially acetylated under catalysis by CALB is in accordance with the general rule[9] predicted for CALB catalyzed resolutions (Fig. 1).

## 3. Conclusion

In conclusion, a number of 1- and 2-aminoalkanephosphonates have been successfully resolved by a CALB-catalyzed acetylation process. The high enantioselectivities

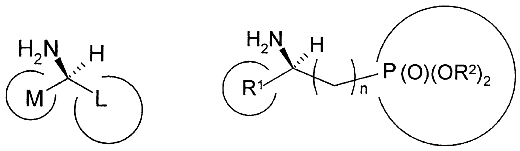



**Figure 1.** Configuration of the preferential enantiomer of aminoalkylphosphonate acetylation catalyzed by CALB.

achieved in these reactions as well as the simplicity of the procedure makes this strategy a useful alternative for the preparation of optically pure aminoalkanephosphonates.

## 4. Experimental

### 4.1. General methods

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A mass spectrometer. $^1$H NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard).

CALB (Novozym 435) is a gift from the Novo Norvodisk Co. Solvents used for enzymatic reactions were dried by standard methods and stored over 4 Å sieves before use.

### 4.2. General procedure for the preparation of 1- or 2-aminoalkylphosphonates[11]

A solution of $Ph_3P$ (3.14 g, 12 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise with stirring and external cooling to a solution of DEAD (2.09 g, 12 mmol) in $CH_2Cl_2$ (5 mL) at −5°C. The mixture was cooled to −10°C and a solution of $HN_3$ in $CHCl_3$ (10 mL)[12] was added dropwise. After stirring for 5 min at 0°C, the 1- or 2-hydroxyalkanephosphonate[5] (10 mmol) was added. The mixture was kept for 30 min at 0°C, and stirring was then continued for 24 h at rt. The white precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was extracted with *n*-hexane (3×50 mL). The combined extracts were evaporated in vacuum. The oily residue was dissolved in benzene (15 mL) and $Ph_3P$ (2.75 g, 10.5 mmol) was added in one portion to the solution. After stirring 2 h at rt, water (1.8 mL, 0.1 mol) was added, and the mixture was heated for 4.5 h at 50–55°C. The reaction mixture was cooled to rt and extracted with aq. HCl (3×5 mL). The combined acid extracts were washed with ethyl acetate (3×15 mL). The acid phase was neutralized to pH=8–9 with $Na_2CO_3$ and then extracted with ethyl acetate (3×15 mL).The combined organics were washed with brine (3×25 mL) then dried over $Na_2SO_4$ and evaporated in vacuum to furnish the product.

### 4.3. General procedure for CALB-catalyzed acetylation of aminoalkane phosphonates

To the aminoalkanephosphonate (100 mg) in diisopropyl ether (2.4 mL) and ethyl acetate (0.6 mL) was added CALB (35 mg). The reaction mixture was kept at 30°C. When the reaction proceeded to a certain conversion rate, the enzyme was filtered, and washed with ethyl acetate (10 mL). The volatiles were removed under reduced pressure and the residue was subjected to flash chromatography to furnish almost pure aminoalkanephosphonates and their acetamides.

The aminoalkylphosphonates **6d**, **6g**, **6h** (100 mg) were dissolved in diisopropyl ether (1.0 mL) and ethyl 1-methoxyacetate (0.2 mL).

**4.3.1. (*S*)-Diethyl 2-aminopropanephosphonate (2a).**[13] Colourless oil; $[\alpha]_D^{20}=+6.6$ (*c* 0.70, $CH_3OH$); $\nu_{max}$ (liquid film) 3436, 2984, 2911, 1226, 1053, 1026, 966 cm$^{-1}$;$\delta_H$ (300 MHz, $CDCl_3$) 4.92–4.05 (4H, m, OC$H_2$CH$_3$), 3.43–3.40 (1H, m, C*H*NH$_2$), 2.07–1.79 (2H, m, C$H_2$P(O)), 1.38–1.31 (6H, m, OCH$_2$C$H_3$), 1.23–1.19 (3H, m, NH$_2$CHC$H_3$); *m*/*z* (EI) 195 (9, M$^+$), 177 (5), 154 (5), 117 (6), 89 (20), 69 (27), 45 (29), 44 (100%).

**4.3.2. (*R*)-Diethyl 2-acetylaminopropanephosphonate (3a).** Colourless oil; $[\alpha]_D^{20}=+12.0$ (*c* 0.70, $CH_3OH$); $\nu_{max}$ (liquid film) 3437, 3280, 2984, 2936, 1656, 1553, 1232, 1053, 1027, 967 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.53 (1H, d, $J$=6.9 Hz, N*H*), 4.43–4.32 (1H, m, C*H*NH), 4.20–4.09 (4H, m, OC$H_2$CH$_3$), 2.08–2.01 (2H, m, C$H_2$P(O)), 2.00 (3H, s, COC$H_3$), 1.39–1.28 (9H, m, OCH$_2$C$H_3$, NH$_2$CHC$H_3$); *m*/*z* (EI) 238 (100, M$^+$+1), 194 (34), 180 (24), 179 (18), 152 (34), 125 (21), 123 (22), 43 (27%); HRMS (EI): M$^+$, found: 237.1115. $C_9H_{20}NO_4P$ requires 237.1130.

**4.3.3. (*S*)-Diethyl 2-benzyloxycarbonylaminopropanephosphonate (4a).** colorless oil; [Found: C, 54.66; H, 7.58; N, 4.14. $C_{15}H_{24}NO_5P$ requires C, 54.71; H, 7.35; N, 4.25%] $[\alpha]_D^{20}=+3.0$ (*c* 0.60, $CH_3OH$); $\nu_{max}$ (liquid film) 3271, 3065, 2982, 2910, 1719, 1537, 1255, 1055, 1028, 963 cm$^{-1}$;$\delta_H$(300 MHz, $CDCl_3$) 7.38–7.30 (5H, m, C$_6$*H*$_5$), 5.52 (1H, d, $J$=6.3 Hz, N*H*), 5.10 (2H, s, OC$H_2$Ph), 4.17–4.03 (5H, m, OC$H_2$CH$_3$, NHC*H*CH$_3$), 2.12–1.97 (2H, m, C$H_2$P(O)), 1.35–1.25 (9H, m, OCH$_2$C$H_3$, CHC$H_3$); *m*/*z* (EI) 329 (14, M$^+$), 270 (3), 222 (78), 194 (17), 152 (26), 125 (20), 91 (100), 65 (11), 57 (17%).

**4.3.4. (*S*)-Dipropyl 2-aminopropanephosphonate (2b).** Colourless oil; $[\alpha]_D^{20}$ +10.9 (*c* 1.60, $CH_3OH$); $\nu_{max}$ (liquid film) 3367, 2968, 2881, 1236, 1068, 994, 904 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.06–3.94 (4H, m, OC$H_2$CH$_2$CH$_3$), 3.42–3.37 (1H, m, C*H*NH$_2$), 1.96–1.81 (2H, m, C$H_2$P(O)), 1.79–1.64(4H, m, OCH$_2$C$H_2$CH$_3$), 1.20 (3H, dd, $J$=6.3, 2.1 Hz, NH$_2$CHC$H_3$), 0.97 (6H, m, OCH$_2$CH$_2$C$H_3$); *m*/*z* (EI) 223 (2, M$^+$), 208 (23), 167 (27), 139 (53), 125 (26), 124 (45), 97 (100), 57 (57), 44 (29%); HRMS (EI): M$^+$, found: 223.1360. $C_9H_{22}NO_3P$ requires 223.1337.

**4.3.5. (*R*)-Dipropyl 2-acetylaminopropanephosphonate (3b).** Colourless oil; [Found: C, 50.08; H, 9.16; N, 5.31. $C_{11}H_{24}NO_4P$ requires C, 49.80; H, 9.12; N, 5.28%]; $[\alpha]_D^{20}=+12.5$ (*c* 1.10, $CH_3OH$); $\nu_{max}$ (liquid film): 3284, 2972, 2939, 2882, 1674, 1550, 1236, 1067, 998 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.55 (1H, d, $J$=7.5 Hz, N*H*), 4.39–4.30 (1H, m, C*H*NH), 4.06–3.94 (4H, m, OC$H_2$CH$_2$CH$_3$), 2.06–1.98 (2H, dq, $J$=18.0, 5.4 Hz, C$H_2$P(O)), 1.96 (3H, s, COC$H_3$), 1.76–1.63 (4H, m, OCH$_2$C$H_2$CH$_3$), 1.32 (3H, d, $J$=6.6 Hz, NHCHC$H_3$), 0.99–0.93 (6H, dt, $J$=7.8, 3.3 Hz,

$OCH_2CH_2CH_3$); *m/z* (EI) 265 (8, $M^+$), 222 (62), 208 (51), 166 (29), 139 (88), 124 (28), 123 (54), 97 (100), 43 (52%).

**4.3.6. (*S*)-Dipropyl 2-benzyloxycarbonylaminopropanephosphonate (4b).** Colourless oil; [Found: C, 56.95; H, 8.01; N, 3.76. $C_{17}H_{28}NO_5P$ requires C, 57.13; H, 7.90; N, 3.92%] $[\alpha]_D^{20}=+3.0$ (*c* 1.40, $CH_3OH$); $\nu_{max}$ (liquid film) 3271, 3036, 2971, 2881, 1720, 1537, 1256, 1066, 1041, 998 $cm^{-1}$;$\delta_H$(300 MHz, $CDCl_3$) 7.37–7.29 (5H, m, $C_6H_5$), 5.46 (1H, d, *J*=4.3 Hz, N*H*), 5.08 (2H, s, $OCH_2Ph$), 4.13–3.92 (5H, m, $OCH_2CH_2CH_3$, NHC*H*$CH_3$), 2.10–1.97 (2H, m, $CH_2P(O)$), 1.71–1.60 (4H, m, $OCH_2CH_2CH_3$), 1.33 (3H, d, *J*=6.9 Hz, $NHCHCH_3$), 0.97–0.91 (6H, dt, *J*=7.5, 3.6 Hz, $OCH_2CH_2CH_3$); *m/z* (EI) 357 (100, $M^+$), 298 (4), 251 (5), 222 (7), 180 (7), 167 (5), 138 (7), 92 (8), 65 (9%).

**4.3.7. (*S*)-Diisopropyl 2-aminopropanephosphonate (2c).** Colourless oil; [Found: C, 48.66; H, 9.65; N, 6.35. $C_9H_{22}NO_3P$ requires C, 48.42; H, 9.93; N, 6.27%]; $[\alpha]_D^{20}=+6.6$ (*c* 1.25, $CH_3OH$); $\nu_{max}$ (liquid film) 3368, 2980, 2935, 1386, 1236, 1009, 983 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.90–4.83 (2H, m, $OCH(CH_3)_2$), 4.56–3.41 (1H, m, $CHNH_2$), 2.17–2.07 (2H, m, $CH_2P(O)$), 1.50 (12H, dd, *J*=6.0, 2.1 Hz, $OCH(CH_3)_2$), 1.32 (3H, dd, *J*=6.6, 1.5 Hz, $NH_2CHCH_3$); *m/z* (EI) 223 (9, $M^+$), 208 (11), 180 (29), 166 (37), 138 (62), 124 (83), 96 (100), 80 (27), 57 (37), 44 (54%).

**4.3.8. (*R*)-Diisopropyl 2-acetylaminopropanephosphonate (3c).** Colourless oil; $[\alpha]_D^{20}=+16.4$ (*c* 1.05, $CH_3OH$); $\nu_{max}$ (liquid film) 3419, 3282, 2980, 2936, 1657, 1553, 1367, 1230, 1011, 988 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.53 (1H, d, *J*=6.6 Hz, N*H*), 4.78–4.62 (2H, m, $OCH(CH_3)_2$), 4.40–4.26 (1H, m, $CHNH_2$), 1.99–1.91 (2H, m, $CH_2P(O)$), 1.97 (3H, s, $COCH_3$), 1.35–1.30 (15H, m, $OCH(CH_3)_2$, $NHCHCH_3$); *m/z* (EI) 265 (21, $M^+$), 250 (3), 222 (31), 180 (54), 164 (94), 138 (100), 124 (77), 97 (99), 58 (21), 43 (51%); HRMS (EI): $M^+$, found: 265.1451. $C_{11}H_{24}NO_4P$ requires 265.1443.

**4.3.9. (*S*)-Diisopropyl 2-benzyloxycarbonylaminopropanephosphonate (4c).** Colourless oil; [Found: C, 56.89; H, 8.04; N, 3.69. $C_{17}H_{28}NO_5P$ requires C, 57.13; H, 7.90; N, 3.92%] $[\alpha]_D^{20}=+2.6$ (*c* 1.45, $CH_3OH$); $\nu_{max}$ (liquid film) 3270, 3036, 2980, 2935, 2878, 1717, 1538, 1253, 1107, 985 $cm^{-1}$;$\delta_H$(300 MHz, $CDCl_3$) 7.37–7.28 (5H, m, $C_6H_5$), 5.49 (1H, d, *J*=2.7 Hz, N*H*), 5.10 (2H, s, $OCH_2Ph$), 4.75–4.65 (2H, m, $OCH(CH_3)_2$), 4.17–4.05 (1H, m, NHC*H*), 2.10–1.91 (2H, m, $CH_2P(O)$), 1.35–1.25 (15H, m, $OCH(CH_3)_2$, $CHCH_3$); *m/z* (EI) 357 (16, $M^+$), 315 (6), 256 (13), 208 (17), 166 (100), 123 (21), 91 (92), 65 (8%).

**4.3.10. (*S*)-Diethyl 2-aminobutanephosphonate (2d).**[13] Colourless oil; $[\alpha]_D^{20}=+7.3$ (*c* 2.65, $CH_3OH$); $\nu_{max}$ (liquid film) 3502, 3370, 3300, 2981, 2910, 1240, 1057, 1029, 962 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.18–4.07 (4H, m, $OCH_2CH_3$), 3.14–3.12 (1H, m, $CHNH_2$), 2.05–1.93 (2H, m, $CH_2P(O)$), 1.80–1.44 (2H, m, $CHCH_2CH_3$), 1.37–1.32 (6H, m, $OCH_2CH_3$), 0.95 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m/z* (EI) 209 (1, $M^+$), 180 (100), 152 (43), 124 (60), 106 (44), 97 (22), 80 (21), 71 (33), 58 (34), 43 (22%).

**4.3.11. (*R*)-Diethyl 2-acetylaminobutanephosphonate (3d).** Colourless oil; [Found: C, 48.02; H, 8.90; N, 5.52. $C_{10}H_{22}NO_4$ P requires C, 47.80; H, 8.82; N, 5.57%]; $[\alpha]_D^{20}=+23.0$ (*c* 0.60, $CH_3OH$); $\nu_{max}$ (liquid film) 3284, 2976, 2912, 1653, 1327, 1229, 1028, 964 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.51 (1H, d, *J*=8.4 Hz, N*H*), 4.23–4.06 (5H, m, $OCH_2CH_3$, C*H*NH), 2.19–2.00 (2H, m, $CH_2P(O)$), 1.98 (3H, s, $COCH_3$), 1.70–1.64 (2H, m, $CHCH_2CH_3$), 1.37–1.27 (6H, m, $OCH_2CH_3$), 0.96–0.90 (3H, m, $CHCH_2CH_3$); *m/z* (EI) 222 (7, $M^+-29$), 180 (100), 152 (40), 137 (15), 125 (14), 124 (30), 106 (14), 97 (12), 55 (9), 43 (23%).

**4.3.12. (*S*)-Diethyl 2-benzyloxycarbonylaminobutanephosphonate (4d).** Colourless oil; [Found: C, 55.69; H, 7.85; N, 3.84. $C_{16}H_{26}NO_5P$ requires C, 55.97; H, 7.63; N, 4.08%]; $[\alpha]_D^{20}=-2.2$ (*c* 1.50, $CH_3OH$); $\nu_{max}$ (liquid film) 3271, 3036, 2987, 2935, 2879, 1720, 1539, 1244, 1056, 1029, 966 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 7.35–7.28 (5H, m, $C_6H_5$), 5.44 (1H, d, *J*=35.7 Hz, N*H*), 5.09 (2H, s, $OCH_2Ph$), 4.15–4.00 (4H, m, $OCH_2CH_3$), 3.97–3.80 (1H, m, C*H*NH), 2.08–1.98 (2H, m, $CH_2P(O)$), 1.32–1.23 (6H, m, $OCH_2CH_3$), 0.93 (3H, t, *J*=7.2 Hz, $CHCH_2CH_3$); *m/z* (EI) 343 (13, $M^+$), 314 (9), 270 (41), 236 (42), 208 (9), 180 (30), 152 (11), 137 (11), 91 (100), 65 (7%).

**4.3.13. (*S*)-Dipropyl 2-aminobutanephosphonate (2e).** Colourless oil; $[\alpha]_D^{20}=+6.4$ (*c* 0.50, $CH_3OH$); $\nu_{max}$ (liquid film): 3372, 2976, 2880, 1240, 1068, 995, 904, 848 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.06–3.96 (4H, m, $OCH_2CH_3$), 3.16–3.11 (1H, m, $CHNH_2$), 2.06–1.96 (2H, m, $CH_2P(O)$), 1.82–1.65 (4H, m, $OCH_2CH_2CH_3$), 1.55–1.43 (2H, m, $CHCH_2CH_3$), 1.00–0.93 (9H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$); m/z (EI) 238 (5, $M^++1$), 208 (83), 166 (44), 136 (17), 124 (100), 106 (31), 97 (37), 71 (31), 58 (30), 43 (39%); HRMS (EI): $M^+$, found: 237.1502. $C_{10}H_{24}NO_3P$ requires 237.1494.

**4.3.14. (*R*)-Dipropyl 2-acetylaminobutanephosphonate (3e).** Colourless oil; $[\alpha]_D^{20}=+10.0$ (*c* 0.75, $CH_3OH$); $\nu_{max}$ (liquid film) 3439, 3281, 2970, 2881, 1656, 1554, 1228, 1066, 1000, 952, 855 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.43 (1H, d, *J*=8.7 Hz, N*H*), 4.31–4.06 (1H, m, C*H*NH), 4.03–3.93 (4H, m, $OCH_2CH_2CH_3$), 2.07–2.00 (2H, m, $CH_2P(O)$), 1.99 (3H, s, $COCH_3$), 1.76–1.62 (6H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$), 0.96–0.90 (9H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$); *m/z* (EI) 281 (43, $M+2^+$), 251 (7), 208 (100), 178 (15), 166 (37), 137 (27), 124 (58), 106 (14), 97 (39), 43 (34%); HRMS (EI): $M^+$, found: 279.1627. $C_{12}H_{26}NO_4P$ requires 279.1600.

**4.3.15. (*S*)-Dipropyl 2-benzyloxycarbonylaminobutanephosphonate (4e).** Colourless oil; [Found: C, 58.41; H, 8.29; N, 3.59. $C_{18}H_{30}NO_5P$ requires C, 58.21; H, 8.14; N, 3.77%]; $[\alpha]_D^{20}=-1.5$ (*c* 0.65, $CH_3OH$); $\nu_{max}$ (liquid film) 3271, 3036, 2969, 2930, 2880, 1721, 1538, 1243, 1068, 998 $cm^{-1}$;$\delta_H$(300 MHz, $CDCl_3$) 7.36–7.26 (5H, m, $C_6H_5$), 5.41 (1H, d, *J*=8.1 Hz, N*H*), 5.09 (2H, s, $OCH_2Ph$), 4.00–3.90 (5H, m, C*H*NH, $OCH_2CH_2CH_3$), 2.09–2.00 (2H, m, $CH_2P(O)$), 1.74–1.60 (6H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$), 0.97–0.90 (9H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$); *m/z* (EI) 371 (12, $M^+$), 342 (7), 298 (29), 264 (20), 208 (22), 180 (10), 137 (13), 91 (100), 65 (6%).

**4.3.16. (*S*)-Diisopropyl 2-aminobutanephosphonate (2f).** Colourless oil; $[\alpha]_D^{20}=+3.3$ (*c* 0.70, $CH_3OH$); $\nu_{max}$ (liquid film) 3372, 2979, 2935, 2878, 1467, 1386, 1375, 1239, 1010, 984 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.76–4.68 (2H, m, OC*H*($CH_3$)$_2$), 3.19–3.00 (1H, m, C*H*$NH_2$), 1.96–1.83 (2H, m, C$H_2$P(O)), 1.74–1.43 (2H, m, CHC$H_2$$CH_3$), 1.33 (12H, dd, *J*=6.3, 1.8 Hz, OCH(C$H_3$)$_2$), 0.94 (3H, t, *J*=7.2 Hz, CH$CH_2$C$H_3$); *m/z* (EI) 238 (100, $M^+$+1), 208 (19), 196 (12), 166 (18), 124 (68), 106 (21), 96 (18), 58 (17%); HRMS (EI): $M^+$, found: 237.1486. $C_{10}H_{24}NO_3P$ requires 237.1494.

**4.3.17. (*R*)-Diisopropyl 2-acetylaminobutanephosphonate (3f).** Colourless oil; $[\alpha]_D^{20}$=+10.6 (*c* 0.70, $CH_3OH$); $\nu_{max}$ (liquid film) 3447, 3284, 2979, 2936, 2879, 1657, 1552, 1386, 1375, 1228, 988 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.50 (1H, d, *J*=8.1 Hz, N*H*), 4.80–4.61 (2H, m, OC*H*($CH_3$)$_2$), 4.22–4.10 (1H, m, C*H*NH) 2.09–1.91 (2H, m, C$H_2$P(O)), 1.98 (3H, s, COC$H_3$), 1.71–1.61 (2H, m, CHC$H_2$$CH_3$), 1.33 (12H, dd, *J*=5.1, 1.2 Hz, OCH(C$H_3$)$_2$), 0.92 (3H, t, *J*=7.5 Hz, CH$CH_2$C$H_3$); *m/z* (EI) 279 (7, $M^+$), 250 (16), 208 (60), 178 (42), 166 (61), 152 (20), 137 (30), 124 (100), 106 (25), 96 (28), 43 (69%); HRMS (EI): $M^+$, found: 279.1614. $C_{12}H_{26}NO_4P$ requires 279.1600.

**4.3.18. (*S*)-Diisopropyl 2-benzyloxycarbonylaminobutanephosphonate (4f).** Colourless oil; [Found: C, 58.01; H, 8.33; N, 3.55. $C_{18}H_{30}NO_5P$ requires C, 58.21; H, 8.14; N, 3.77%]; $[\alpha]_D^{20}$=−1.0 (*c* 1.05, $CH_3OH$); $\nu_{max}$ (liquid film) 3271, 3036, 2979, 2939, 2878, 1722, 1538, 1284, 1243, 983 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 7.38–7.26 (5H, m, $C_6$$H_5$), 5.45 (1H, d, *J*=7.8 Hz, N*H*), 5.10 (2H, s, OC$H_2$Ph), 4.78–4.61 (2H, m, OC*H*($CH_3$)$_2$), 3.97–3.81 (1H, m, C*H*NH), 2.05–1.81 (2H, m, C$H_2$P(O)), 1.76–1.61 (2H, m, CHC$H_2$$CH_3$), 1.32–1.24 (12H, m, OCH(C$H_3$)$_2$), 0.93 (3H, t, *J*=7.2 Hz, CH$CH_2$C$H_3$); *m/z* (EI) 371 (10, $M^+$), 342 (10), 298 (4), 270 (7), 256 (12), 214 (41), 180 (33), 137 (12), 91 (100), 65 (9%).

**4.3.19. Diethyl 2-amino-3-butenephosphonate (1g).** Colourless oil; $\nu_{max}$ (liquid film) 3476, 3369, 2984, 2908, 1393, 1249, 1052, 1027, 966 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 5.81–5.73 (2H, m, C$H_2$═CH), 5.60–5.54 (1H, m, $CH_2$═C*H*), 4.16–4.05 (4H, m, OC$H_2$$CH_3$), 3.33–3.29 (1H, m, C*H*$NH_2$), 2.63–2.54 (2H, m, C$H_2$P(O)), 1.35–1.30 (6H, m, O$CH_2$C$H_3$); *m/z* (EI) 207 (1, $M^+$), 178 (4), 133 (9), 109 (4), 97 (6), 81 (8), 69 (100), 54 (5), 43 (10%); HRMS (EI): $M^+$, found: 207.1030. $C_8H_{18}NO_3P$ requires 207.1024.

**4.3.20. Diethyl 2-acetylamino-3-butenephosphonate (3g).** Colourless oil; $\nu_{max}$ (liquid film) 3427, 3300, 2988, 2936, 1655, 1557, 1234, 1026, 972 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.15 (1H, s, N*H*), 5.67–5.57 (3H, m, C*H*═C$H_2$), 4.15–4.05 (4H, m, OC$H_2$$CH_3$), 3.88–3.83 (1H, m, C*H*NH), 2.63–2.53 (2H, dd, *J*=21.3, 6.0 Hz, C$H_2$P(O)), 1.99 (3H, s, COC$H_3$), 1.32 (6H, t, *J*=6.9 Hz, O$CH_2$C$H_3$); *m/z* (EI) 249 (6, $M^+$), 234 (43), 206 (34), 191 (37), 152 (37), 140 (37), 125 (61), 97 (63), 70 (49), 56 (58), 43 (100%); HRMS (EI): $M^+$, found: 249.1129. $C_{12}H_{26}NO_4P$ requires 249.1130.

**4.3.21. (*S*)-2-Aminopropanephosphonic acid (5).**[2a] Colourless oil; $[\alpha]_D^{20}$=+3.7 (*c* 0.75, 1 M NaOH); $\nu_{max}$ (liquid film) 3388, 2988, 1617, 1500, 1181, 1071, 998 $cm^{-1}$; $\delta_H$(300 MHz, $D_2O$): 3.50–3.42 (1H, m, C*H*$CH_3$), 1.92–1.81 (2H, m, C$H_2$P(O)), 1.24 (3H, d, *J*=6.9 Hz, CHC$H_3$).

**4.3.22. (*R*)-Diethyl 1-aminoethanephosphonate (7a).**[14] Colourless oil; $[\alpha]_D^{20}$=−8.0 (*c* 1.10, $CH_3OH$); $\nu_{max}$ (liquid film) 3374, 3296, 2982, 2909, 1238, 1058, 1029, 962 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.18–4.13 (4H, m, OC$H_2$$CH_3$), 3.20–3.08 (1H, m, C*H*$NH_2$), 1.38–1.30 (9H, m, O$CH_2$C$H_3$, CHC$H_3$); *m/z* (EI) 181 (1, $M^+$), 138 (2), 111 (8), 93 (2), 83 (9), 82 (12), 65 (5), 44 (100%).

**4.3.23. (*S*)-Diethyl 1-acetylaminoethanephosphonate (8a).**[15] Colourless oil; $[\alpha]_D^{20}$=+57.2 (*c* 1.00, $CH_3OH$); $\nu_{max}$ (liquid film) 3450, 3265, 2985, 2938, 1662, 1547, 1230, 1055, 1025, 970 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.37 (1H, d, *J*=8.4 Hz, N*H*), 4.57–4.46 (1H, m, C*H*$CH_3$), 4.19–4.07 (4H, m, OC$H_2$$CH_3$), 2.02 (3H, s, COC$H_3$), 1.40–1.25 (9H, m, O$CH_2$C$H_3$, CHC$H_3$); *m/z* (EI): 223(1, $M^+$), 180 (6), 138 (10), 111(15), 86 (39), 69 (11), 44 (100%).

**4.3.24. (*R*)-Diethyl 1-benzyloxycarbonylaminoethanephosphonate (9a).** Colorless oil; [Found: C, 53.35; H, 7.03; N, 4.44. $C_{14}H_{22}NO_5P$ requires C, 53.33; H, 7.03; N, 4.44%]; $[\alpha]_D^{20}$=−22.4 (*c* 1.80, $CH_3OH$); $\nu_{max}$ (liquid film) 3239, 3037, 2983, 2937, 2910, 1721, 1541, 1301, 1230, 1044, 1027, 969 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 7.36–7.33 (5H, m, $C_6$$H_5$), 5.16–5.07 (3H, m, N*H*, OC$H_2$Ph), 4.17–4.08 (5H, m, OC$H_2$$CH_3$, C*H*$CH_3$), 1.43–1.23 (9H, m, O$CH_2$C$H_3$, CHC$H_3$); *m/z* (EI): 315(11, $M^+$), 262 (1), 228 (5), 178 (10), 134 (22), 109 (7), 91 (100), 65 (8%).

**4.3.25. (*R*)-Dipropyl 1-aminoethanephosphonate (7b).** Colorless oil; $[\alpha]_D^{20}$=−1.2 (*c* 1.00, $CH_3OH$); $\nu_{max}$ (liquid film) 3467, 3377, 2971, 2939, 2881, 1232, 1068, 997 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.07–4.00 (4H, m, OC$H_2$$CH_2$$CH_3$), 3.19–3.11 (1H, m, C*H*$NH_2$), 1.73–1.65 (4H, m, O$CH_2$-C$H_2$$CH_3$), 1.34 (3H, q, *J*=17.7, 7.2 Hz, CHC$H_3$), 0.97 (6H, t, *J*=7.5 Hz, O$CH_2$$CH_2$C$H_3$); *m/z* (EI) 209 (4, $M^+$), 194 (1), 168 (5), 153 (5), 138 (3), 125 (8), 111 (7), 96 (7), 83 (24), 82 (18), 44 (100%); HRMS (EI): $M^+$, found: 209.1158. $C_8H_{20}NO_3P$ requires 209.1181.

**4.3.26. (*S*)-Dipropyl 1-acetylaminoethanephosphonate (8b).** Colorless oil; [Found: C, 48.05; H, 8.79; N, 5.37. $C_{10}H_{22}NO_4P$ requires C, 47.80; H, 8.83; N, 5.57]; $[\alpha]_D^{20}$=+56.4 (*c* 0.50, $CH_3OH$); $\nu_{max}$ (liquid film) 3467, 3265, 2973, 2940, 1882, 1663, 1548, 1230, 1066, 1005 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.34 (1H, d, *J*=9.3 Hz, N*H*), 4.56–4.50 (1H, m, C*H*$CH_3$), 4.07–3.97 (4H, m, OC$H_2$$CH_2$$CH_3$), 2.02 (3H, s, COC$H_3$), 1.74–1.64 (4H, m, O$CH_2$C$H_2$$CH_3$), 1.37 (3H, q, *J*=16.8, 7.5 Hz, CHC$H_3$), 0.99–0.92 (6H, m, O$CH_2$$CH_2$C$H_3$); *m/z* (EI) 251 (1, $M^+$), 210 (14), 208 (10), 192 (5), 166 (6), 150 (13), 125 (36), 86 (84), 83 (45), 69 (27), 44 (100%).

**4.3.27. (*R*)-Dipropyl 1-benzyloxycarbonylaminoethanephosphonate (9b).** Colourless oil; [Found: C, 55.87; H, 7.90; N, 3.82. $C_{16}H_{26}NO_5P$ requires C, 55.97; H, 7.63; N, 4.08%]; $[\alpha]_D^{20}$=−15.5 (*c* 1.20, $CH_3OH$); $\nu_{max}$ (liquid film) 3239, 3037, 2971, 2939, 2881, 1721, 1542, 1253, 1230, 1056, 1002 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 7.35–7.27 (5H, m, $C_6$$H_5$), 5.20–5.11 (3H, m, N*H*, OC$H_2$Ph), 4.20–4.09 (1H, m, C*H*$CH_3$), 4.13–3.95 (4H, m, OC$H_2$$CH_2$$CH_3$), 1.75–1.60

(4H, m, $OCH_2CH_2CH_3$), 1.39 (3H, q, $J$=16.2, 7.2 Hz, $CHCH_3$), 0.96–0.88 (6H, m, $OCH_2CH_2CH_3$); $m/z$ (EI) 343 (11 $M^+$), 256 (5), 208 (7), 178 (10), 172 (4), 134 (27), 123 (6), 91 (100), 83 (7), 65 (7%).

**4.3.28. (*R*)-Diisopropyl 1-aminoethanephosphonate (7c).**[16] Colourless oil; $[\alpha]_D^{20}$=−1.5 ($c$ 0.85, $CH_3OH$); $\nu_{max}$ (liquid film) 3375, 3296, 2980, 2935, 2876, 1386, 1375, 1238, 1110, 983 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.76–4.70 (2H, m, $OCH(CH_3)_2$), 3.07–3.02 (1H, m, $CHNH_2$), 1.36–1.30 (15H, m, $OCH(CH_3)_2$, $CHCH_3$); $m/z$ (EI) 209 (1 $M^+$), 194 (5), 152 (8), 124 (11), 110 (19), 96 (35), 82 (16), 70 (43), 44 (100%).

**4.3.29. (*S*)-Diisopropyl 1-acetylaminoethanephosphonate (8c).** Colourless oil; [Found: C, 47.53; H, 8.49; N, 5.38. $C_{10}H_{22}NO_4P$ requires C, 47.80; H, 8.83; N, 5.57]; $[\alpha]_D^{20}$=+55.3 ($c$ 0.55, $CH_3OH$); $\nu_{max}$ (liquid film) 3264, 2983, 293.8, 2876, 2820, 1681, 1551, 1388, 1375, 1228, 985 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.30 (1H, d, $J$=6.9 Hz, NH), 4.74–4.68 (2H, m, $OCH(CH_3)_2$), 4.05–4.40 (1H, m, $CHCH_3$), 2.03 (3H, s, $COCH_3$), 1.39–1.30 (15H, m, $OCH(CH_3)_2$, $CHCH_3$); $m/z$ (EI) 251 (1, $M^+$), 210 (3), 192 (2), 166 (8), 150 (26), 124 (52), 109 (11), 86 (36), 82 (20), 69 (18), 44 (100), 43 (64%).

**4.3.30. (*R*)-Diisopropyl 1-benzyloxycarbonylaminoethanephosphonate (9c).** Colourless oil; [Found: C, 55.74; H, 7.49; N, 3.93. $C_{16}H_{26}NO_5P$ requires C, 55.97; H, 7.63; N, 4.08%]; $[\alpha]_D^{20}$=−18.9 ($c$ 0.55, $CH_3OH$); $\nu_{max}$ (liquid film) 3236, 3037, 2981, 2938, 2876, 1721, 1541, 1269, 1251, 1228, 1047, 990 cm$^{-1}$;$\delta_H$(300 MHz, $CDCl_3$) 7.36–7.26 (5H, m, $C_6H_5$), 5.11 (2H, s, $OCH_2Ph$), 5.03 (1H, d, $J$=9.3 Hz, NH), 4.78–4.61 (2H, m, $OCH(CH_3)_2$), 4.13–4.08 (1H, m, $CHCH_3$), 1.36–1.24 (15H, m, $OCH(CH_3)_2$, $CHCH_3$); $m/z$ (EI) 343 (7, $M^+$), 301 (4), 256 (5), 242 (3), 208 (7), 178 (10), 166 (7), 134 (24), 124 (23), 91 (100), 82 (5), 65 (7%).

**4.3.31. (*R*)-Diethyl 1-aminopropanephosphonate (7d).**[17] Colourless oil; $[\alpha]_D^{20}$=−2.7 ($c$ 1.10, $CH_3OH$); $\nu_{max}$ (liquid film) 3468, 3382, 2982, 2910, 1393, 1231, 1056, 1027, 963 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.22–4.12 (4H, m, $OCH_2CH_3$), 2.95–2.86 (1H, m, $CHNH_2$), 1.95–1.85 (1H, m, $CHCH_2CH_3$), 1.60–1.51 (1H, m, $CHCH_2CH_3$), 1.36 (6H, t, $J$=7.2 Hz, $OCH_2CH_3$), 1.90 (3H, t, $J$=7.5 Hz, $CHCH_2CH_3$); $m/z$ (EI) 195 (1, $M^+$), 166 (2), 138 (4), 110 (7), 82 (8), 65 (6), 58 (100), 41 (6%).

**4.3.32. (*S*)-Diethyl 1-acetylaminopropanephosphonate (8d).** Colourless oil; $[\alpha]_D^{20}$=+14.4 ($c$ 0.50, $CH_3OH$); $\nu_{max}$ (liquid film) 3437, 3265, 2980, 2936, 2879, 1661, 1549, 1234, 1052, 1025, 971 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.22 (1H, d, $J$=9.9 Hz, NH), 4.43–4.43 (1H, m, CHNH), 4.18–4.05 (4H, m, $OCH_2CH_3$), 2.05 (3H, s, $COCH_3$), 1.98–1.81 (1H, m, $CHCH_2CH_3$), 1.67–1.50 (1H, m, $CHCH_2CH_3$), 1.35–1.25 (6H, m, $OCH_2CH_3$), 0.99 (3H, t, $J$=7.2 Hz, $CHCH_2CH_3$); $m/z$ (EI) 237 (1, $M^+$), 194 (2), 166 (3), 138 (8), 111 (10), 100 (45), 83 (9), 58 (100), 43 (16%); HRMS (EI): $M^+$, found: 237.1126. $C_8H_{20}NO_3P$ requires 237.1130.

**4.3.33. (*S*)-Diethyl 1-benzyloxycarbonylaminopropanephosphonate (9d).** Colourless oil; [Found: C, 54.64; H, 7.35; N, 4.28. $C_{10}H_{22}NO_5P$ requires C, 54.71; H, 7.35; N, 4.25]; $[\alpha]_D^{20}$=−24.7 ($c$ 0.70, $CH_3OH$); $\nu_{max}$ (liquid film) 3238, 3037, 2979, 2910, 1720, 1541, 1282, 1028, 970 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 7.36–7.27 (5H, m, $C_6H_5$), 5.17–5.07 (3H, m, NH, $OCH_2Ph$), 4.16–3.96 (5H, m, $OCH_2CH_3$, CHNH), 1.94–1.87 (1H, m, $CHCH_2CH_3$), 1.68–1.57 (1H, m, $CHCH_2CH_3$), 1.63–1.23 (6H, m, $OCH_2CH_3$), 1.01 (3H, t, $J$=7.5 Hz, $CHCH_2CH_3$); $m/z$ (EI) 329 (8, $M^+$), 228 (7), 192 (7), 166 (2), 148 (37), 109 (5), 91 (100), 65 (7%).

**4.3.34. (*R*)-Diethyl 1-(1-methoxy)acetylaminopropanephosphonate (10d).** Colourless oil; [Found: C, 44.99; H, 8.12; N, 5.24. $C_{10}H_{22}NO_5P$ requires C, 44.94; H, 8.30; N, 5.24]; $[\alpha]_D^{20}$=+25.1 ($c$ 0.90, $CH_3OH$); $\nu_{max}$ (liquid film) 3414, 3271, 2980, 2937, 1679, 1525, 1235, 1116, 1050, 1024, 971 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.62 (1H, d, $J$=10.2 Hz, NH), 4.41–4.34 (1H, m, CHNH), 4.19–4.08 (4H, m, $OCH_2CH_3$), 3.96–3.93 (2H, m, $COCH_2OCH_3$), 3.46 (3H, s, $OCH_3$), 2.01–1.93 (1H, m, $CHCH_2CH_3$), 1.68–1.61 (1H, m, $CHCH_2CH_3$), 1.39–1.26 (6H, m, $OCH_2CH_3$), 1.00 (3H, t, $J$=7.5 Hz, $CHCH_2CH_3$); $m/z$ (EI) 267 (1, $M^+$), 222 (4), 194 (5), 166 (9), 130 (100), 122 (7), 105 (17), 70 (45), 58 (13), 45 (70%).

**4.3.35. Diethyl 1-amino-2,2,2-trifluoroethanephosphonate (7e).**[18] Colourless oil; $\nu_{max}$ (liquid film) 3407, 3328, 2989, 2937, 1322, 1262, 1183, 1117, 1054, 1026, 977 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.30–4.20 (4H, m, $OCH_2CH_3$), 3.59 (1H, dq, $J$=19.5, 8.4 Hz, $CHNH_2$), 1.37 (6H, dt, $J$=7.2, 0.6 Hz, $OCH_2CH_3$); $m/z$ (EI) 235 (1, $M^+$), 138 (22), 120 (11), 111 (20), 106 (100), 82 (20), 79 (38), 59 (18), 44 (18%).

**4.3.36. (*R*)-Dipropyl 1-aminopropanephosphonate (7f).** Colourless oil; [Found: C, 48.28; H, 9.63; N, 6.40. $C_9H_{22}NO_3P$ requires C, 48.42; H, 9.93; N, 6.27]; $[\alpha]_D^{20}$=−1.9 ($c$ 0.65, $CH_3OH$); $\nu_{max}$ (liquid film) 3484, 3379, 3303, 1968, 1939, 2896, 1465, 1236, 1068, 995 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.08–4.00 (4H, m, $OCH_2CH_2CH_3$), 2.93–2.91 (1H, m, $CHNH_2$), 1.97–1.82 (1H, m, $CHCH_2CH_3$), 1.75–1.65 (4H, m, $OCH_2CH_2CH_3$), 1.60–1.53 (2H, m, $CHCH_2CH_3$), 1.08 (3H, t, $J$=7.2 Hz, $CHCH_2CH_3$), 0.99–0.94 (6H, m, $OCH_2CH_2CH_3$); $m/z$ (EI) 223 (1, $M^+$), 152 (1), 110 (4), 83 (16), 82 (7), 65 (3), 58 (100), 43 (10%).

**4.3.37. (*R*)-Dipropyl 1-benzyloxycarbonylaminopropanephosphonate (9f).** Colourless oil; [Found: C, 57.07; H, 7.80; N, 3.67. $C_{17}H_{28}NO_5P$ requires C, 57.13; H, 7.90; N, 3.92]; $[\alpha]_D^{20}$=−22.9 ($c$ 0.80, $CH_3OH$); $\nu_{max}$ (liquid film) 3237, 2970, 2938, 2880, 1721, 1540, 1456, 1282, 1230, 1064, 990 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 7.37–7.28 (5H, m, $C_6H_5$), 5.18–5.02 (3H, m, NH, $OCH_2Ph$), 4.04–3.94 (5H, m, $OCH_2CH_3$, CHNH), 1.98–1.83 (1H, m, $CHCH_2CH_3$), 1.71–1.60 (6H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$), 1.05–0.88 (9H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$); $m/z$ (EI) 357 (8, $M^+$), 256 (7), 222 (8), 192 (17), 166 (4), 148 (46), 123 (5), 91 (100), 83 (7), 65 (6%).

**4.3.38. (*S*)-Dipropyl 1-(1-methoxy)acetylaminopropanephosphonate (10f).** Colourless oil; $[\alpha]_D^{20}$=+32.2 ($c$ 1.30, $CH_3OH$); $\nu_{max}$ (liquid film) 3416, 3268, 2971, 2939, 2881, 1687, 1521, 1239, 1065, 1001 cm$^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.62 (1H, d, $J$=9.9 Hz, NH), 4.45–4.32 (1H, m, CHNH), 4.06–3.43 (6H, m, $OCH_2CH_2CH_3$, $COCH_2OCH_3$), 3.42 (3H, s, $OCH_3$), 2.03–1.92 (1H, m, $CHCH_2CH_3$), 1.74–1.60 (5H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$), 1.02–0.92 (9H, m, $OCH_2CH_2CH_3$, $CHCH_2CH_3$); *m/z* (EI) 296 (2, $M+1^+$), 254 (4), 194 (4), 166 (15), 148 (7), 130 (100), 83 (11), 70 (37), 45 (58%); HRMS (EI): $M^+$, found: 295.1560. $C_{12}H_{26}NO_5P$ requires 295.1549.

**4.3.39. (*R*)-Diisopropyl 1-aminopropanephosphonate (7g).**[19] Colourless oil; $[\alpha]_D^{20}=+1.4$ (*c* 0.85, $CH_3OH$); $\nu_{max}$ (liquid film) 3472, 3306, 2979, 2877, 1375, 1236, 1109, 982 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 4.76–4.70 (2H, m, $OCH(CH_3)_2$), 2.85–2.77 (1H, m, $CHNH_2$), 1.93–1.81 (1H, m, $CHCH_2CH_3$), 1.57–1.43 (1H, m, $CHCH_2CH_3$), 1.33 (12H, d, *J*=6.0 Hz, $OCH(CH_3)_2$), 1.07 (3H, t, *J*=7.2 Hz, $CHCH_2CH_3$); *m/z* (EI) 223 (1, $M^+$), 180 (1), 166 (2), 138 (4), 124 (6), 110 (7), 82 (11), 58 (100), 43 (10), 41 (12%).

**4.3.40. (*R*)-Diisopropyl 1-benzyloxycarbonylaminopropanephosphonate (9g).** Colourless oil; [Found: C, 56.98; H, 7.83; N, 3.69. $C_{17}H_{28}NO_5P$ requires C, 57.13; H, 7.90; N, 3.92]; $[\alpha]_D^{20}=-15.6$ (*c* 0.75, $CH_3OH$); $\nu_{max}$ (liquid film) 3235, 3037, 2979, 2936, 2877, 1721, 1540, 1280, 1246, 1228, 1010, 990 $cm^{-1}$; δH(300 MHz, $CDCl_3$) 7.37–7.28 (5H, m, $C_6H_5$), 5.14 (2H, s, $OCH_2Ph$), 4.99 (1H, d, *J*=10.2 Hz, N*H*), 4.74–4.64 (2H, m, $OCH(CH_3)_2$), 3.98–3.91 (1H, m, C*H*NH), 1.96–1.87 (1H, m, $CHCH_2CH_3$), 1.60–1.50 (1H, m, $CHCH_2CH_3$), 1.33–1.22 (12H, m, $OCH(CH_3)_2$), 1.01 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m/z* (EI) 357 (6, $M^+$), 315 (2), 273 (2), 256 (9), 222 (9), 192 (15), 166 (6), 148 (39), 124 (13), 91 (100), 65 (6), 43 (9%).

**4.3.41. (*S*)-Diisopropyl 1-(1-methoxy)acetylaminopropanephosphonate (10g).** Colourless oil; $[\alpha]_D^{20}=+22.8$ (*c* 2.35, $CH_3OH$); $\nu_{max}$ (liquid film) 3416, 3276, 2980, 2937, 2879, 1682, 1522, 1231, 1109, 989 $cm^{-1}$; $\delta_H$(300 MHz, $CDCl_3$) 6.61 (1H, d, *J*=10.2 Hz, N*H*), 4.76–4.67 (2H, m, $OCH(CH_3)_2$), 4.38–4.24 (1H, m, C*H*NH), 4.02–3.87 (2H, m, $COCH_2OCH_3$), 3.44 (3H, s, $OCH_3$), 2.05–1.90 (1H, m, $CHCH_2CH_3$), 1.67–1.54 (1H, m, $CHCH_2CH_3$), 1.35–0.99 (12H, m, $OCH(CH_3)_2$), 0.98 (3H, t, *J*=7.2 Hz, $CHCH_2CH_3$); *m/z* (EI) 296 (7, $M^++1$), 254 (5), 194 (18), 166 (20), 130 (100), 124 (21), 102 (7), 82 (11), 70 (43), 45 (65%); HRMS (EI): $M^+$, found: 295.1552. $C_{12}H_{26}NO_5P$ requires 295.1549.

## Acknowledgements

This project was supported by the National Natural Science Foundation of China (Grant No. 20272075 and 20072052).

## References

1. (a) Kafarski, P.; Lejczak, B. *Beitr. Wirkstofforschung* **1985**, *25*, 1–5. (b) Yuan, C. Y.; Qi, Y. M. *Acta Chimi. Sinica* **1986**, *44*, 280–287. (c) Yuan, C. Y.; Qi, Y. M. *Synthesis* **1986**, 821–825. (d) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur SiliconRelat. Elem.* **1991**, *63*, 193–215.
2. (a) Oshikawa, T.; Yamashita, M. *Bull. Chem. Soc.* **1990**, *63*, 2728–2730. (b) Yuan, C. Y.; Cui, S. H. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *55*, 159–164. (c) Yuan, C. Y.; Li, S. S.; Wang, G. Q. *Chin. Chem. Lett.* **1993**, *4*, 753–756. (d) Mikolajcyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.; Blaszczyk, J. *J. Chem. Soc. Chem. Commum.* **1996**, *13*, 1503–1504.
3. (a) Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*. *Tetrahedron Organic Series*; Pergamon: London, 1994; Chapter 2; pp 41–113. (b) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; VCH: Weinhein, 1995; Vol. II. Chapter 11; pp 335–697. (c) Faber, K. *Biotransformations in Organic Chemistry*; 3rd ed. Springer: Beijing, 1997; Chapter 2, pp 23–245.
4. (a) Adamczyk, M.; Grote, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2099–2100. (b) García, M. J.; Rebolledom, R.; Gotor, V. *Tetrahedron Lett.* **1993**, *34*, 6141–6142. (c) Puertas, S.; Rebolledo, R.; Gotor, V. *J. Org. Chem.* **1996**, *61*, 6024–6027. (d) Zoete, M. C.; Kock-van Dalen, A. C.; van Rantwijk, F.; Sheldon, R. A. *J. Mol. Catal. B: Enzyme* **1996**, *2*, 19–25.
5. (a) Zhang, Y. H.; Yuan, C. Y.; Li, Z. Y. *Tetrahedron* **2002**, *58*, 2973–2978. (b) Zhang, Y. H.; Li, Z. Y.; Yuan, C. Y. *Tetrahedron Lett.* **2002**, *43*, 3247–3249.
6. (a) Sanchez, M. V.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 37–40. (b) Iglesias, E. L.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **2000**, *11*, 1047–1050.
7. Wescott, C. R.; Klibanov, A. M. *Biochim. Biophys. Acta Protein Struct. Mol. Enzymol.* **1994**, *1206*, 1–9.
8. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Shi, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
9. (a) Orrenius, C.; Oehrner, N.; Rottiui, D.; Mattson, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1217–1220. (b) Rotticu, D.; Halffner, F.; Orrenius, C.; Norin, T.; Hult, K. *J. Mol. Catal. B* **1998**, *5*, 267–272.
10. Balkenhohl, F.; Ditrich, K.; Hauer, B.; Ladner, W. *J. Prakt. Chem./Chem.-Ztg, GE* **1997**, *4*, 381–384.
11. Gajda, T.; Matusiak, M. *Synth. Commun.* **1992**, *22*, 2193–2203.
12. Wolef, H. *Organic Reactions*; Wiley: New York, 1947; Vol. 3. Chapter 8, pp 327–329.
13. Varlet, J. M. *Synth. Commun.* **1978**, *8*, 335–343.
14. Kametani, T.; Suzuki, Y.; Kigasawa, K.; Hiiragi, M. *Heterocycles* **1982**, *18*, 295–319.
15. Kudzin, Z. H.; Luczak, J. *Synthesis* **1995**, 509–511.
16. Chakraborty, S. K.; Engel, R. *Synth. Commun.* **1991**, *21*(8), 1039–1046.
17. Chalmers, M. E.; Kosolapoff, G. M. *J. Am. Chem. Soc.* **1953**, *75*, 5278–5280.
18. Flynn, G. A.; Beight, D. W.; Bohme, E. H. W.; Metcalf, B. W. *Tetrahedron Lett.* **1985**, *26*, 285–288.
19. Green, D.; Patel, G.; Elgendy, S.; Baban, J. A.; Skordalakes, E. *Phosphorus Sulfur Silicon Relat. Elem.* **1996**, *109*, 533–536.