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Asymmetric synthesis of phosphonic acid analogues for acylcarnitine

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Abstract—Phosphonic acid analogues of acylcarnitine were prepared in an optically active form expecting CPT I inhibitory activities. The synthetic methodology was based on catalytic asymmetric dihydroxylation of β,γ-unsaturated phosphonates and subsequent regioselective amination via the cyclic sulfates.

1. Introduction

Hyperglycemia of type II diabetes is considered to be primarily due to excess long-chain fatty acid oxidation, which is crucial to drive gluconeogenesis at higher rates.[1] Carnitine palmitoyltransferase I (CPT I) located on the outer mitochondrial membrane plays an important role in β-oxidation of long-chain free fatty acids, which catalyzes a formation of acylcarnitine from carnitine and long-chain fatty acids, then a translocase transports the fatty acids carnitine esters across the inner mitochondrial membrane.[2] CPT I inhibitors indirectly reduce gluconeogenesis by inhibiting the β-oxidation and are hence helpful in the treatment of type II diabetes as hypoglycemic agents.[3] Recent studies demonstrated modification of the functional groups of acylcarnitine was one access to the development of potent CPT I inhibitors. In these studies, aminoacylcarnitine derivatives, in which the β-oxygen atom of acylcarnitine was replaced with nitrogen, were discovered as good inhibitors.[4] The absolute configuration of these molecules was found to influence their inhibitory activities; the (*R*)-isomer inhibited CPT I more strongly than the corresponding enantiomer.

Since phosphonic acids are known to function as a bioisosteric group of carboxylic acids,[5] modification of the carboxylic moiety of acylcarnitine has been also examined. To date, three kinds of phosphonic acid analogues of acylcarnitine were prepared as racemate and showed modest activities.[4a] However, the structure–activity relationship of phosphonic acid analogues for acylcarnitine including effects of the chirality on activities has never been investigated probably due to lack of a general method for asymmetric synthesis of γ-amino-β-acyloxyphosphonic acid derivatives. Then, we investigated a new method for asymmetric synthesis of γ-amino-β-acyloxyphosphonates and their transformation to phosphonic acid analogues of acylcarnitine (Fig. 1). In this paper, we now describe full details of our study.[6]

2. Result and discussion

For obtaining the targeted molecules, a protected form of chiral γ-amino-β-hydroxyphosphonates would be required as synthetic intermediates. Inspection of the literature revealed that the key reactions used in this synthesis involved optical resolution,[7a] enzymatic resolution of γ-chloro-β-hydroxyphosphonates,[7b] hydrolytic kinetic resolution of epoxyphosphonates with an asymmetric catalyst,[7c] ring-opening of epichlorohydrin with silylphosphites,[7d] and diastereoselective reduction of γ-amino-β-ketophosphonates.[7e] Although

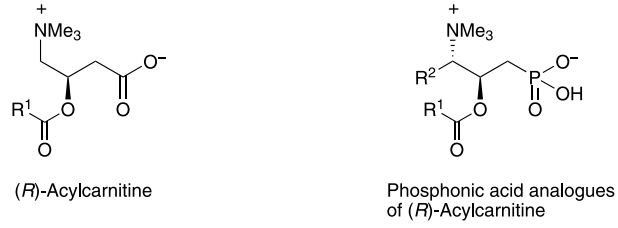

Figure 1.

Keywords: Acylcarnitine; Phosphonic acid; Asymmetric dihydroxylations; Regioselectivity.
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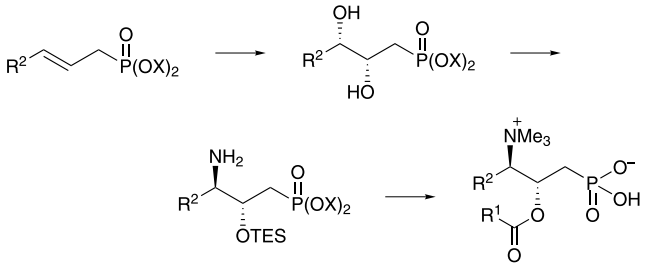
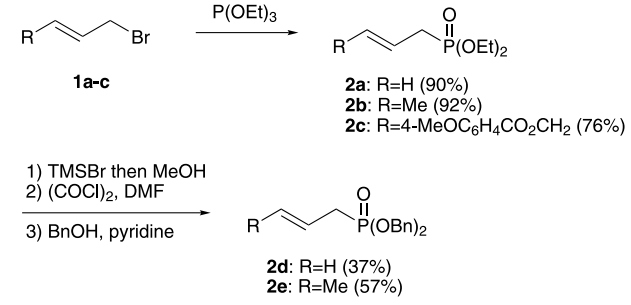
catalytic asymmetric aminohydroxylation of β,γ-unsaturated phosphonates developed by Sharpless et al. is an attractive method, the chemical yields were not satisfactory due to formation of the regioisomer of the desired amino alcohols and diols as byproducts.[7f] We examined asymmetric synthesis of γ-amino-β-acyloxyphosphonic acid derivatives by our own approach, which involved osmium-catalyzed asymmetric dihydroxylation (AD)[8] of β,γ-unsaturated phosphonates, followed by selective amination of the hydroxy group at the γ-position (Scheme 1).



Scheme 1.

2.1. AD reactions of β,γ-unsaturated phosphonates

The requisite starting materials **2a–c** were readily prepared by Arbuzov reactions of the corresponding allyl bromide derivatives **1a–c** with triethylphosphite (Scheme 2). The compounds having a dibenzylphosphonyl group, **2d** and **2e**, were prepared from **2a** and **2b**, respectively, through sequential deesterification, chlorination of the acid moiety, followed by treatment with benzyl alcohol and pyridine.



Scheme 2.

AD reaction of β,γ-unsaturated phosphonate having a phenyl group at the γ-position with AD-mix reagents was previously reported by us to provide diols in high ee (98% ee).[9] According to the reported protocol, AD reactions of **2a–e** were performed with AD-mix-α in the presence of $MeSO_2NH_2$ and additional $K_2OsO_4\cdot 2H_2O$ (0.8 mol%) in the *t*-BuOH–H_2O solvent system (1/1) at room temperature.[10] The results are summarized in Table 1.

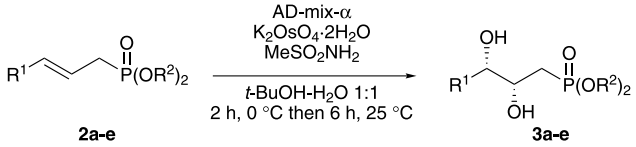
In the series of AD reactions of ethyl esters **2a–c** with AD-mix-α, very low enantioselectivity (10% ee) was observed when R^1 is a proton (entry 1). However, the enantioselectivity was slightly increased to 35% ee when R^1 is a methyl group (entry 2). Excellent selectivity (97% ee) was observed in the case of **2c** having a 4-methoxybenzoyloxymethylene group as R^1 substituent (entry 3). In the series of AD reactions of benzyl esters **2d**,**e**, the reaction with **2d** having a proton as R^1 substituent also proceeded in poor ee (10% ee) as in the case of the corresponding ethyl ester **2a** (entry 4).[11] However, **2e** having a methyl group as R^1 substituent reacted with AD-mix-α reagent to give **3e** in 61% ee (entry 5). It is worthy of note that the enantioselectivity for **2e** significantly improved in comparison to that for **2b** (35% ee) and crystalline **3e** could be obtained in an optically pure form (>99% ee) through one recrystallization from AcOEt (38% recovery).

Considering Corey's working model of the chemical architecture provided by the ligand of AD-mix-α, in which the ligand–osmium complex preferred the U-shaped conformation, the high ee of **3c** was accounted for by the 4-methoxybenzoyl group participating in π-stacking interactions with the methoxyquinoline ring of the catalyst.[12] An improved ee of **3e** may be ascribed to the enhanced hydrophobicity of substrate **2e** compared to **2b**, which facilitated substrates to be trapped into the lipophilic cavity of the ligand–osmium complex.[13]

Similar reaction of **2c** using AD-mix-β instead of AD-mix-α proceeded to give *ent*-**3c** in good selectivity (98% ee) (Scheme 3). The reaction of **2e** furnished product *ent*-**3e** in 68% ee, which could be increased to >99% ee by one recrystallization from AcOEt (59% recovery).

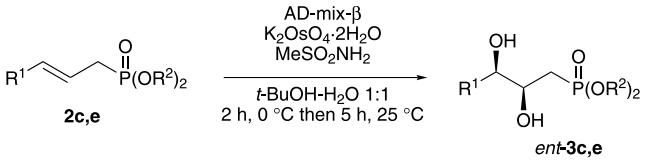
The absolute stereochemistry of **3a** was verified to be *R* by comparison of optical rotation with that reported.[14]

Table 1. AD reactions of β,γ-unsaturated phosphonates **2a–e** with AD-mix-α



Entry	**3**	R^1	R^2	Yield (%)	ee (%)[a]
1	**a**	H	Et	41	10
2	**b**	Me	Et	60	35
3	**c**	4-$MeOC_6H_4CO_2CH_2$	Et	58	97[b]
4	**d**	H	Bn	71	10
5	**e**	Me	Bn	69	61[c]

[a] Determined by ^{31}P NMR (121 MHz, $CDCl_3$) analysis of the corresponding bis-MTPA esters unless stated otherwise.
[b] Determined by HPLC analysis on a chiral phase (DAICEL CHIRALPAK AS column).
[c] Determined by HPLC analysis on a chiral phase (DAICEL CHIRALPAK OD column).



ent-**3**	R^1	R^2	yield (%)	ee (%)
c	4-$MeOC_6H_4CO_2CH_2$	Et	70	98
e	Me	Bn	64	68 (>99)[a]

[a] After one recrystallization from AcOEt

Scheme 3.

The absolute configuration of **3b** and **3c** was determined after conversion to 4-methoxybenzoate derivatives **5b** and **5c** (Scheme 4). The CD spectrum of **5b** showed a positive Cotton effect at 289 nm and a negative Cotton effect at 282 nm, which were analogous to that of methoxybenzoate **6** prepared from known β,γ-dihydroxyphosphonate **4**,[9] showing positive and negative Cotton effects at longer (286 nm) and shorter wavelengths (275 nm), respectively. The CD curve of **5c** (a positive Cotton effect at 284 nm and a negative Cotton effect at 276 nm) was also similar to that of **6**. Accordingly, **5b** and **5c** have the same absolute stereochemistry with **6**, indicating the stereochemistry of **3b** and **3c** was as shown in Scheme 4.

The absolute configuration of **3e** was verified after transformation to the corresponding phosphonic acid **7** through hydrogenolysis of the dibenzyl phosphonate moiety (Scheme 5). The sign of the optical rotation of **7** was identical with that of a sample derived from **3b**.

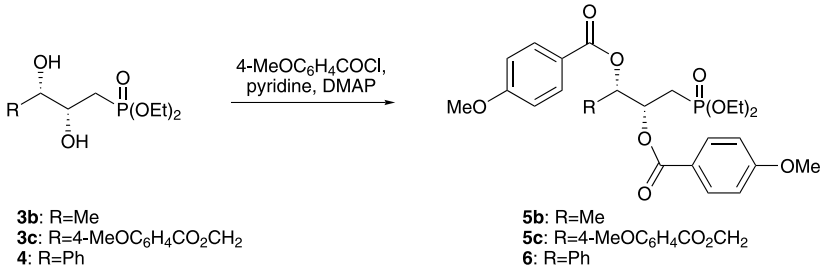
2.2. Synthesis of phosphonic acid analogues of acylcarnitine

With chiral β,γ-dihydroxyphosphonates in hand, we next directed our efforts toward the synthesis of phosphonic acid analogues of acylcarnitine. In these efforts, we first chose **3a** to tackle its transformation to phosphonic acid analogue **15** of acylcarnitine through the regioselective amination via a cyclic sulfate (Scheme 6).[15] Although the optical purity of **3a** is not sufficient, it will be valuable to obtain optically active **15** since the compound was previously prepared in racemic form.[4a]

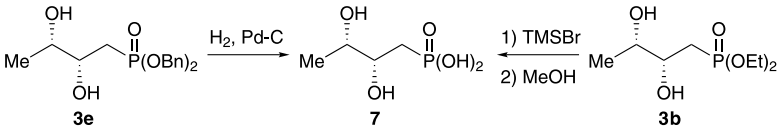
Treatment of **3a** with $SOCl_2$, followed by oxidation with $RuCl_3$–$NaIO_4$[16] afforded cyclic sulfate **8** in 80% yield. When **8** was treated with NaN_3 in acetone–H_2O at 50 °C, the starting material disappeared within 3 h on TLC. Subsequent treatment with 20% H_2SO_4 gave γ-azido-β-hydroxyphosphonate **9** with complete regioselectivity in 24% yield for two steps. Although an exact reason for the low chemical yield remained unclear, it might be associated with partial decomposition of the diethyl phosphonate moiety into the corresponding aqueous phosphonic acid or monoethyl ester in the reaction mixture. After transformation to TES ether **10**, catalytic hydrogenation was carried out to give γ-amino-β-silyloxyphosphonate **11**. Reductive dimethylation of **11** with formaldehyde and $NaBH_3CN$ provided **12** in 90% yield.[17] Deprotection of the silyl group, followed by treatment with myristoyl chloride in the presence of pyridine and DMAP afforded **13**, which underwent *N*-methylation with MeI to give **14**. Finally, **14** was deprotected with TMSBr and MeOH to give the desired **15** in 72% yield.

The methodology was next applied to the synthesis of γ-methyl-substituted phosphonic acid analogue **27** of acylcarnitine from diol **3e**. In this synthesis, γ-selective amination of the starting **3e** is a critical step because the corresponding cyclic sulfate **16** is prone to react with an azide anion at both β- and γ-positions. However, a molecular modeling of **16** reveals that the β-carbon is sterically more congested than the γ-carbon owing to the bulky dibenzyl phosphonate moiety in the most stable conformation and regioselective ring-opening reaction would be feasible due to the steric reason.[18] Then, we examined several representative conditions for ring-opening reaction of **16**, prepared from optically pure **3e** in an analogous manner to that for preparation of **8**, with metal azides (Table 2).

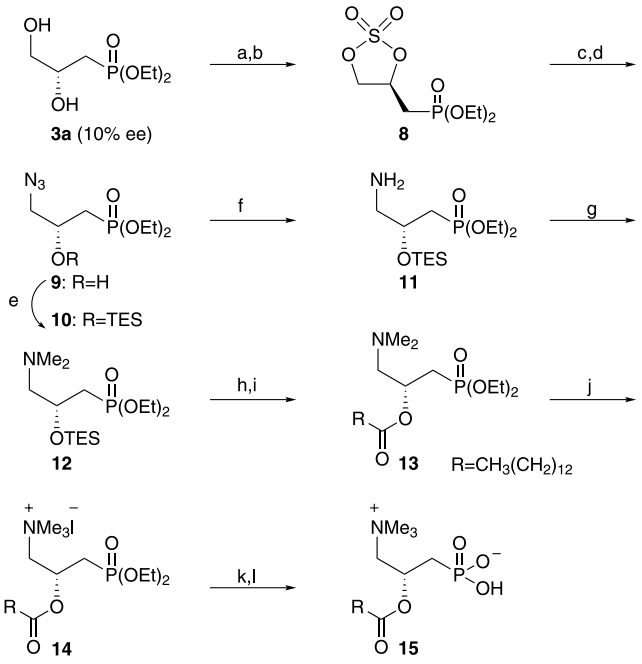
Upon treatment of **16** with LiN_3 in DMF at room temperature, the starting material disappeared within 12 h on TLC (entry 1). Quenching the reaction with 50% H_2SO_4



Scheme 4.



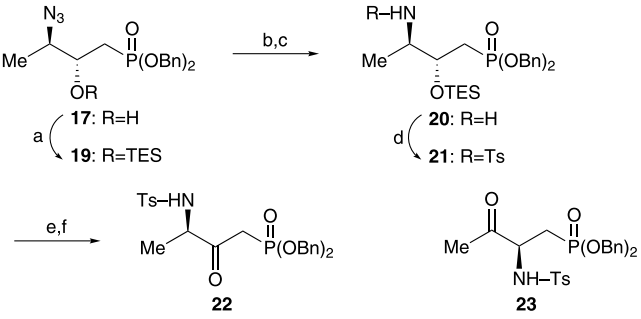
Scheme 5.



Scheme 6. Reagents and conditions: (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (b) $RuCl_3 \cdot nH_2O$, $NaIO_4$, CCl_4–CH_3CN–H_2O, 0 °C (80%, two steps); (c) NaN_3, acetone–H_2O, 50 °C; (d) 20% H_2SO_4, Et_2O, rt (24%, two steps); (e) TESCl, imidazole, DMF, rt (80%); (f) H_2, 10% Pd–C, MeOH, rt (97%); (g) 37% HCHO, $NaBH_3CN$, AcOH, CH_3CN, rt (90%); (h) TBAF, THF, 0 °C; (i) $CH_3(CH_2)_{12}COCl$, pyridine, DMAP, rt (52%, two steps); (j) MeI, acetone, rt (86%); (k) TMSBr, CH_2Cl_2, rt; (l) MeOH, rt (72%, two steps).

gave γ-azide **17** and β-azide **18** with a ratio of 5:1. Although the regioselectivity of the reaction was found to be the desired sense as expected, the chemical yield was poor (13%). Similar yield and ratio were observed when NaN_3 was used as an azide anion (entry 2). However, when the reaction was carried out in acetone–H_2O instead of DMF at 25 °C and subsequent treatment with 20% H_2SO_4, both yield (41%) and **17**/**18** ratio (10:1) were improved (entry 3). Increasing the reaction temperature up to 50 °C shortened the reaction time from 96 to 3 h (entry 4).

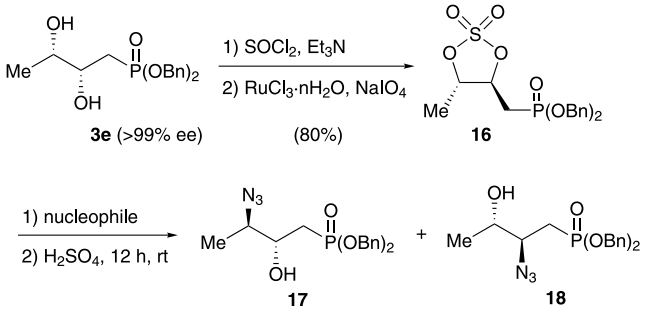
The structure of **17** was deduced after conversion into γ-amino-β-ketophosphonate **22** (Scheme 7). Staudinger reaction of TES ether **19** derived from **17** with PPh_3 and subsequent hydrolysis afforded γ-amino-β-siloxyphosphonate **20**. Tosylation of **20**, followed by desilylation, and oxidation with PDC gave **22**. In the ^1H NMR spectrum (400 MHz, $CDCl_3$) of **22**, a signal ascribed to the Me group at the γ-position was observed at 1.18 ppm as a doublet (J = 7.1 Hz) but not as a singlet corresponding to regioisomeric product **23**.



Scheme 7. Reagents and conditions: (a) TESCl, imidazole, DMF, rt (98%); (b) PPh_3, THF, rt; (c) H_2O, rt (97%, two steps); (d) TsCl, Et_3N, CH_2Cl_2, rt (13%); (e) TBAF, THF, 0 °C; (f) PDC, CH_2Cl_2, rt (47%, two steps).

Compound **20** was converted into **26** in the same manner to the case of **14** (Scheme 8). In this synthesis, deprotection of the benzyl ester moiety of **26** was attempted through hydrogenolysis in the presence of 10% Pd–C or 20% $Pd(OH)_2$–C. However, the hydrogenolysis did not work to give **27** in reproducible yield after several trials. Then, γ-methyl-substituted phosphonic acid analogue **27** of acylcarnitine was obtained through the TMSBr-mediated debenzylation of **26** in 48% yield (two steps).

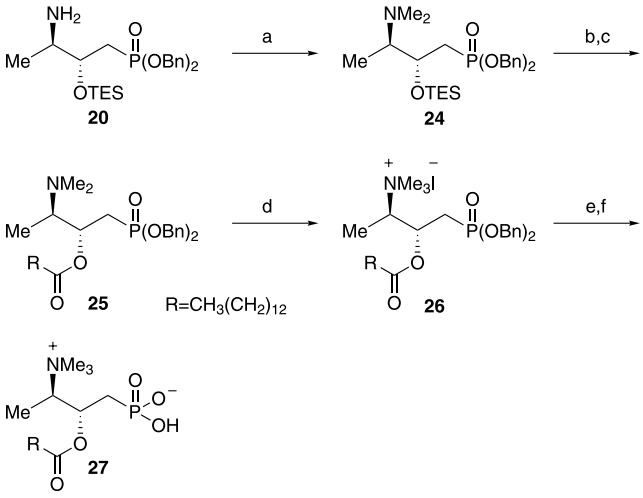
Table 2. Ring-opening reactions of **16** with metal azides



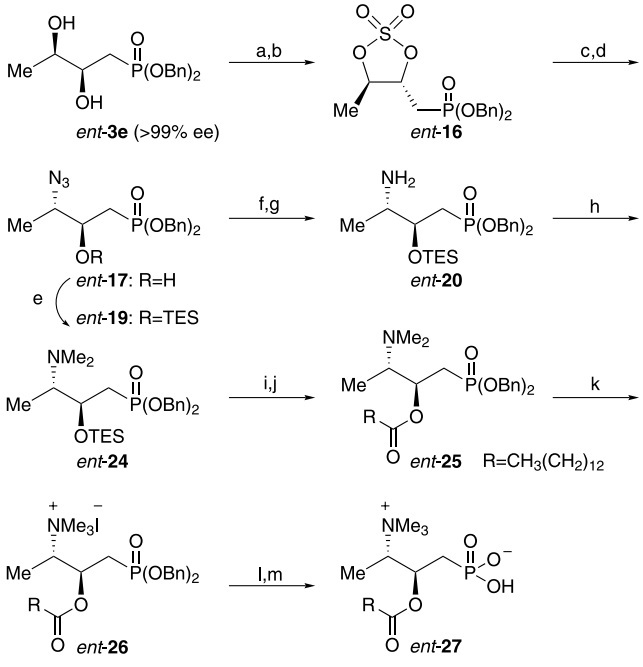
Entry	Nucleophile	Solvent	Temperature (°C)	Time (h)	H_2SO_4 (%)	Yield (%)[a]	**17**:**18**[b]
1	LiN_3	DMF	25	12	50	13	5:1
2	NaN_3	DMF	50	8	50	15	4:1
3	NaN_3	Acetone/H_2O 2:1	25	96	20	41	10:1
4	NaN_3	Acetone/H_2O 2:1	50	3	20	42	10:1

[a] Combined yield of **17** and **18**.
[b] Determined by ^{31}P NMR (121 MHz, $CDCl_3$) analysis of crude products.

The synthesis of enantiomer *ent*-**27** of **27** was also achieved starting from optically pure *ent*-**3e** through the same sequence (Scheme 9). Thus, we have obtained both enantiomers of γ-methyl substituted phosphonic acid analogues of acylcarnitine.



Scheme 8. Reagents and conditions: (a) 37% HCHO, $NaBH_3CN$, AcOH, CH_3CN, rt (85%); (b) TBAF, THF, 0 °C; (c) $CH_3(CH_2)_{12}COCl$, pyridine, DMAP, rt (23%, two steps); (d) MeI, acetone, rt (33%); (e) TMSBr, CH_2Cl_2, rt; (f) MeOH, rt (48%, two steps).



Scheme 9. Reagents and conditions: (a) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (b) $RuCl_3 \cdot nH_2O$, $NaIO_4$, CCl_4–CH_3CN–H_2O, 0 °C (76%, two steps); (c) NaN_3, acetone–H_2O, 50 °C; (d) 20% H_2SO_4 , Et_2O, rt (44%, two steps); (e) TESCl, imidazole, DMF, rt (97%); (f) PPh_3, THF, rt; (g) H_2O, rt (94%, two steps); (h) 37% HCHO, $NaBH_3CN$, AcOH, CH_3CN, rt (96%); (i) TBAF, THF, 0 °C; (j) $CH_3(CH_2)_{12}COCl$, pyridine, DMAP, rt (30%, two steps); (k) MeI, acetone, rt (30%); (l) TMSBr, CH_2Cl_2, rt; (m) MeOH, rt (34%, two steps).

3. Conclusion

In conclusion, we have developed a new method for preparing chiral γ-amino-β-acyloxyphosphonic acid derivatives through AD reactions of β,γ-unsaturated phosphonates and subsequent regioselective amination via cyclic sulfates. The method was applicable to the synthesis of optically active phosphonic acid analogues of acylcarnitine. A study on preparing a variety of derivatives and their CPT I inhibitory activities is underway.

4. Experimental

4.1. General

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 or P1030 digiital polarimeter. IR spectra were recorded on a JASCO FTIR-620. Mass spectra were measured on a Finnigan TSQ-700. Elemental analysis were recorded on an Elemental Vavio EL. NMR spectra were obtained on Bruker DPX400 NMR specrometer operating at 400 MHz for ^1H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P. The chemical shift data for each signal on ^1H NMR are given in units of δ relative to $CHCl_3$ ($\delta=7.26$) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are reported relative to the $CDCl_3$ resonance ($\delta=77.0$). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 ($\delta=0$) with broad-band ^1H decoupling.

4.1.1. Diethyl allylphosphonate (2a). To a stirred suspension of **1a** (12.3 g, 100 mmol) and KI (16.6 g, 100 mmol) in acetone–CH_3CN 10:8 (500 mL) was added triethyl phosphite (17.2 mL, 100 mmol). The mixture was stirred for 12 h at room temperature and then stirred for 5 h at 60 °C. After filtration of the mixture, the filtrate was concentrated to give a residue, which was distilled (73–75 °C, 5 mmHg) to give **2a** (16.0 g, 90%). A colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80–5.74 (1H, m), 5.23–5.16 (2H, m), 4.13–4.04 (4H, m), 2.59 (2H, dd, $J=21.9$, 7.4 Hz), 1.30 (6H, t, $J=7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.4 (d, $J_{CP}=11.2$ Hz), 119.7 (d, $J_{CP}=14.4$ Hz), 61.7 (d, $J_{CP}=6.6$ Hz), 31.6 (d, $J_{CP}=139.3$ Hz), 16.2 (d, $J_{CP}=5.9$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.46; IR (neat) 2983, 1255, 1027 cm^{-1}; ESIMS *m/z* 179 (MH^+); HRMS (ESI) calcd for $C_7H_{16}O_3P$: 179.0873 (MH^+). Found: 179.0840.

4.1.2. Diethyl (2*E*)-but-2-enylphosphonate (2b). Compound **2b** was prepared from **1b** (13.8 g, 100 mmol) in an analogous manner to that for preparation of **2a**. Purification of the residue by distillation (85–88 °C, 7 mmHg) gave **2b** (16.4 g, 92%). A colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64–5.58 (1H, m), 5.44–5.38 (1H, m), 4.14–4.05 (4H, m), 2.57–2.49 (2H, m), 1.71–1.64 (3H, m), 1.31 (6H, t, $J=$ 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.5 (d, $J_{CP}=$ 14.6 Hz), 119.5 (d, $J_{CP}=11.2$ Hz), 61.7 (d, $J_{CP}=6.6$ Hz), 30.3 (d, $J_{CP}=139.9$ Hz), 17.9 (d, $J_{CP}=2.2$ Hz), 16.3 (d, $J_{CP}=6.0$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.53; IR (neat) 2982, 1251, 1027 cm^{-1}; ESIMS *m/z* 193 (MH^+);

HRMS (ESI) calcd for $C_8H_{18}O_3P$: 193.0994 (MH^+). Found: 193.0993.

4.1.3. (2*E*)-4-(Diethoxyphosphoryl)but-2-enyl 4-methoxybenzoate (2c). A mixture of **1c** (9.36 g, 32.8 mmol) and triethyl phosphite (6.75 mL, 39.4 mmol) was stirred for 12 h at 160 °C. After being cooled, the mixture was chromatographed on silica gel (hexane/EtOAc=1:2) to give **2c** (10.2 g, 76%). A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (2H, d, J=8.9 Hz), 6.90 (2H, d, J=8.9 Hz), 5.94–5.84 (2H, m), 4.78–4.75 (2H, m), 4.19 (4H, q, J=7.1 Hz), 3.85 (3H, s), 2.63 (2H, dd, J=21.8, 5.8 Hz), 1.28 (6H, t, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.4, 131.6, 129.5 (d, J_{CP}=14.5 Hz), 124.1 (d, J_{CP}=11.1 Hz), 122.4, 113.5, 64.4, 62.0 (d, J_{CP}=6.7 Hz), 55.3, 30.3 (d, J_{CP}=139.9 Hz), 16.3 (d, J_{CP}=5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.72; IR (neat) 2983, 1715, 1257, 1167 cm^{-1}; ESIMS m/z 343 (MH^+); HRMS (ESI) calcd for $C_{16}H_{24}O_6P$: 343.1311 (MH^+). Found: 343.1289.

4.1.4. Dibenzyl allylphosphonate (2d). To a stirred solution of **2a** (1.60 g, 10 mmol) in CH_2Cl_2 (20 mL) was added TMSBr (5.3 mL, 40 mmol) at room temperature. The mixture was stirred for 9 h at the same temperature and then concentrated to give a residue. To an ice-cooled, stirred solution of this residue in CH_2Cl_2 (20 mL) was slowly added oxalyl chloride (3.0 mL, 35 mmol) and DMF (a few drops). After being stirred for 6 h at room temperature, the mixture was concentrated to give a residue. To a stirred solution of this residue in THF (30 mL) was added benzyl alcohol (2.3 mL, 22 mmol) and pyridine (1.8 mL, 22 mmol) at −21 °C. After the mixture was stirred for 30 min at the same temperature, stirring was continued for 6 h at room temperature. The mixture was poured into saturated aqueous $KHSO_4$ and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane/EtOAc=10:1–1:1) to give **2d** (1.10 g, 37%). A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (10H, m), 5.83–5.71 (1H, m), 5.19–5.13 (2H, m), 5.06 (2H, dd, J=11.9, 8.8 Hz), 4.99 (2H, dd, J=11.9, 8.2 Hz), 2.65 (1H, ddd, J=7.4, 1.1, 1.1 Hz), 2.60 (1H, ddd, J=7.4, 1.1, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (d, J_{CP}=5.7 Hz), 128.4, 128.2, 127.8, 126.9 (d, J_{CP}=11.5 Hz), 120.1 (d, J_{CP}=14.5 Hz), 67.3 (d, J_{CP}=6.6 Hz), 31.9 (d, J_{CP}=139.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.22; IR (neat) 1255 cm^{-1}; ESIMS m/z 325 (MNa^+); HRMS (ESI) calcd for $C_{17}H_{19}O_3NaP$: 325.0970 (MNa^+). Found: 325.0976.

4.1.5. Dibenzyl (2*E*)-but-2-enylphosphonate (2e). Compound **2e** (46.1 g, 57%) was prepared from **2b** (50.0 g, 260 mmol) in an analogous manner to that for preparation of **2a** after purification by column chromatography on silica gel (hexane/EtOAc=10:1–1:1). A pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.30 (10H, m), 5.58–5.51 (1H, m), 5.41–5.34 (1H, m), 5.06 (2H, dd, J=11.9, 8.7 Hz), 4.99 (2H, dd, J=11.9, 8.1 Hz), 2.59–2.52 (2H, m), 1.67–1.63 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3 (d, J_{CP}=5.9 Hz), 131.0 (d, J_{CP}=15.0 Hz), 128.4, 128.2, 127.8, 119.0 (d, J_{CP}=11.5 Hz), 67.3 (d, J_{CP}=6.5 Hz), 30.6 (d, J_{CP}=139.7 Hz), 17.9 (d, J_{CP}=2.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.37; IR 2960, 1253 cm^{-1}; ESIMS m/z 317 (MH^+); HRMS (ESI) calcd for $C_8H_{22}O_3P$: 317.1307 (MH^+). Found: 317.1331.

4.2. General procedure for AD reactions of 2a–e

To a stirred suspension of AD-mix-α (5.60 g) in H_2O/*t*-BuOH 1:1 (32 mL) was added $K_2OsO_4\cdot 2H_2O$ (12 mg, 0.8 mol%) at room temperature. After the mixture was stirred until two clear phases were observed, $MeSO_2NH_2$ (380 mg, 4.0 mmol) was added at the same temperature. After the mixture was chilled with an ice-water bath, **2a–e** (4.0 mmol) was added slowly and this mixture was stirred for 2 h at the same temperature and then stirring was continued for 6 h at room temperature. Sodium sulfite (12.0 g) was added to quench the reaction and the mixture was stirred for 1 h at room temperature. The mixture was extracted with EtOAc and the combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (EtOAc to $CHCl_3$/MeOH=20:1) to give **3a–e**.

4.2.1. (2*R*)-Diethyl 2,3-dihydroxypropylphosphonate (3a). Compound **3a** (330 mg, 41%) was prepared from **2a** (712 mg, 4.0 mmol) with AD-mix-α. A colorless oil; $[\alpha]_D^{30}$ −0.67 (*c* 0.55, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17–4.06 (5H, m), 3.69 (1H, ddd, J=11.4, 3.6, 1.3 Hz), 3.53 (1H, dd, J=11.4, 5.6 Hz), 2.09–1.90 (2H, m), 1.34 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.1 (d, J_{CP}=4.0 Hz), 66.7 (d, J_{CP}=16.1 Hz), 62.0 (d, J_{CP}=9.4 Hz), 61.9 (d, J_{CP}=9.4 Hz), 29.8 (d, J_{CP}=140.3 Hz), 16.3 (d, J_{CP}=5.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.44; IR (neat) 3346, 1221 cm^{-1}; ESIMS m/z 213 (MH^+); HRMS (ESI) calcd for $C_7H_8O_5P$: 213.0892 (MH^+). Found: 213.0883.

4.2.2. (2*R*,3*S*)-Diethyl 2,3-dihydroxybutylphosphonate (3b). Compound **3b** (540 mg, 60%) was prepared from **2b** (768 mg, 4.0 mmol) with AD-mix-α. A colorless oil; $[\alpha]_D^{26}$ −3.22 (*c* 1.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21–4.07 (4H, m), 3.88–3.85 (1H, m), 3.66 (1H, dt, J=11.3, 5.4 Hz), 2.04–1.93 (2H, m), 1.34 (6H, t, J=7.1 Hz), 1.20 (3H, d, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.6 (d, J_{CP}=16.7 Hz), 70.4 (d, J_{CP}=5.5 Hz), 62.0 (d, J_{CP}=9.3 Hz), 30.0 (d, J_{CP}=140.1 Hz), 18.9, 16.3 (d, J_{CP}=5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.87; IR (neat) 3356, 1220 cm^{-1}; ESIMS m/z 249 (MNa^+); HRMS (ESI) calcd for $C_8H_{19}O_5NaP$: 249.0868 (MNa^+). Found: 249.0864.

4.2.3. (2*S*,3*R*)-4-(Diethoxyphosphoryl)-2,3-dihydroxybutyl 4-methoxybenzoate (3c). Compound **3c** (840 mg, 58%) was prepared from **2c** (1.37 g, 4.0 mmol) with AD-mix-α. A colorless oil; $[\alpha]_D^{26}$ −2.14 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 4.38 (2H, d, J=5.8 Hz), 4.09 (4H, q, J=6.9 Hz), 4.05–4.00 (1H, m), 3.87–3.85 (1H, m), 3.82 (3H, s), 2.22–1.96 (2H, m), 1.29 (6H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 163.5, 131.7, 122.2, 113.6, 72.4 (d, J_{CP}=14.9 Hz), 66.8 (d, J_{CP}=4.5 Hz), 65.5, 62.1 (d, J_{CP}=3.2 Hz), 55.4, 30.1 (d, J_{CP}=140.0 Hz), 16.3 (d, J_{CP}=5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.36; IR (neat) 3356, 1713, 1258, 1168 cm^{-1}; ESIMS m/z 399 (MNa^+);

HRMS (ESI) calcd for $C_{16}H_{25}O_8NaP$: 399.1185 (MNa^+). Found: 399.1185.

4.2.4. (2*R*)-Dibenzyl 2,3-dihydroxypropylphosphonate (3d). Compound **3d** (850 mg, 71%) was prepared from **2d** (1.10 g, 3.6 mmol) with AD-mix-α. White needles; mp 55–58 °C; $[\alpha]_D^{25}$ −0.64 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (10H, m), 5.06 (2H, ddd, *J*=11.8, 9.0, 4.4 Hz), 4.97 (2H, ddd, *J*=11.8, 8.1, 3.7 Hz), 4.10–4.03 (1H, m), 3.85 (1H, b), 3.63 (1H, dd, *J*=11.2, 1.7 Hz), 3.48 (1H, dd, *J*=11.2, 5.7 Hz), 2.95 (1H, b), 2.07 (1H, ddd, *J*=15.4, 16.8, 8.8 Hz), 1.97 (1H, ddd, *J*=15.4, 19.3, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (d, J_{CP}=5.7 Hz), 128.6–127.0 (aromatic), 67.6 (d, J_{CP}=6.9 Hz), 67.5 (d, J_{CP}=6.9 Hz), 67.0 (d, J_{CP}=4.0 Hz), 66.7 (d, J_{CP}=17.3 Hz), 30.2 (d, J_{CP}=139.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.43; IR (KBr) 3374, 1216 cm^{-1}; ESIMS *m*/*z* 359 (MNa^+); HRMS (ESI) calcd for $C_{17}H_{21}O_5NaP$: 359.1024 (MNa^+). Found: 359.1035.

4.2.5. (2*R*,3*S*)-Dibenzyl 2,3-dihydroxybutylphosphonate (3e). Compound **3e** (2.30 g, 69%) was prepared from **2e** (3.00 g, 9.6 mmol) with AD-mix-α. One recrystallization from EtOAc gave an optically pure **3e** (870 mg, 38%). White needles; mp 93–95 °C; $[\alpha]_D^{22}$ −7.92 (*c* 1.0, MeOH) for a sample of >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (10H, m), 5.12–4.96 (4H, m), 3.70 (1H, dq, *J*=14.9, 4.2 Hz), 3.59 (1H, dt, *J*=11.3, 5.6 Hz), 2.04–1.96 (2H, m), 1.13 (3H, d, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0 (d, J_{CP}=5.3 Hz), 135.9 (d, J_{CP}=5.3 Hz), 128.7, 128.6, 128.5, 128.1, 128.0, 70.7 (d, J_{CP}=17.4 Hz), 70.4 (d, J_{CP}=5.6 Hz), 67.6 (d, J_{CP}=6.4 Hz), 30.5 (d, J_{CP}=139.6 Hz), 18.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.91; IR (KBr) 3359, 2968, 1214 cm^{-1}; ESIMS *m*/*z* 351 (MH^+); HRMS (ESI) calcd for $C_{18}H_{24}O_5P$: 351.1361 (MH^+). Found: 351.1352.

4.2.6. (2*R*,3*S*)-4-(Diethoxyphosphoryl)-2,3-dihydroxybutyl 4-methoxybenzoate (*ent*-3c). Compound *ent*-**3c** (670 mg, 70%) was prepared from **2c** (1.37 g, 4.0 mmol) with AD-mix-β. A colorless oil; $[\alpha]_D^{25}$ +6.01 (*c* 1.0, MeOH). The ^{1}H NMR spectrum was identical with that of *ent*-**3c**.

4.2.7. (2*S*,3*R*)-Dibenzyl 2,3-dihydroxybutylphosphonate (*ent*-3e). Compound *ent*-**3e** (24.6 g, 64%) was prepared from **2e** (34.8 g, 110 mmol) with AD-mix-β. One recrystallization from EtOAc gave an optically pure *ent*-**3e** (14.6 g, 59%). White needles; $[\alpha]_D^{24}$ +7.76 (*c* 1.2, MeOH) for a sample of >99% ee. The ^{1}H NMR spectrum was identical with that of *ent*-**3e**.

4.2.8. (1*S*,2*R*)-3-(Diethoxyphosphoryl)-2-[(4-methoxybenzoyl)oxy]-1-methylpropyl 4-methoxybenoate (5b). To a stirred solution of 4-methoxybenzoyl chloride (1.40 g, 8.0 mmol) in CH_2Cl_2 (1 mL) was sequentially added a solution of **3b** (720 mg, 3.2 mmol) in CH_2Cl_2 (5 mL), pyridine (0.65 mL, 8.0 mmol) and DMAP (39 mg, 0.32 mmol). After stirring for 24 h at room temperature, the mixture was poured into saturated aqueous $KHSO_4$ and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane/EtOAc=1:1) to provide **5b** (600 mg, 38%). A colorless oil; $[\alpha]_D^{26}$ −5.01 (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.99 (4H, m), 6.93–6.91 (4H, m), 5.65–5.61 (1H, m), 5.39 (1H, td, *J*=3.4, 3.1 Hz), 4.06–4.03 (4H, m), 3.86 (6H, s), 2.33–2.29 (2H, m), 1.38 (3H, t, *J*=6.4 Hz), 1.34 (6H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 165.1, 163.5, 163.4, 131.8–113.6 (aromatic), 71.2 (d, J_{CP}=18.7 Hz), 71.0 (d, J_{CP}=10.4 Hz), 63.4 (d, J_{CP}=5.5 Hz), 55.4, 27.9 (d, J_{CP}=142.9 Hz), 16.2, 16.1 (d, J_{CP}=10.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.87; IR (neat) 1715, 1258 cm^{-1}; ESIMS *m*/*z* 495 (MH^+); HRMS (ESI) calcd for $C_{24}H_{32}O_9P$: 495.1784 (MH^+). Found: 495.1786.

4.2.9. (2*S*,3*R*)-4-(Diethoxyphosphoryl)-2,3-bis[(4-methoxybenzoyl)oxy]butyl 4-methoxybenzoate (5c). Compound **5c** (910 mg, 70%) was prepared from **3c** (730 mg, 2.0 mmol) in an analogous manner to that for preparation of **5b** after purification by column chromatography on silica gel (hexane/EtOAc=1:1). A colorless oil; $[\alpha]_D^{26}$ −7.25 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (4H, d, *J*=8.6 Hz), 7.91 (2H, d, *J*=8.8 Hz), 6.91–6.89 (4H, m), 6.85 (2H, d, *J*=8.8 Hz), 5.89–5.81 (1H, m), 5.76 (1H, td, *J*=4.7, 4.5 Hz), 4.56 (2H, d, *J*=2.2 Hz), 4.07–4.04 (4H, m), 3.86 (3H, s), 3.85 (3H, s), 3.83 (3H, m), 2.40–2.35 (2H, m), 1.23 (6H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.1, 164.9, 163.7, 163.6, 163.4, 131.9–113.6 (aromatic), 71.8 (d, J_{CP}=10.0 Hz), 67.3, 62.5, 62.0, 55.4, 55.3, 28.0 (d, J_{CP}=143.3 Hz), 16.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.84; IR (neat) 1719. 1257 cm^{-1}; ESIMS *m*/*z* 645 (MH^+); HRMS (ESI) calcd for $C_{32}H_{38}O_{12}P$: 645.2101 (MH^+). Found: 645.2098.

4.2.10. (1*S*,2*R*)-3-(Diethoxyphosphoryl)-2-[(4-methoxybenzoyl)oxy]-1-phenylpropyl 4-methoxybenzoate (6). Compound **6** (553 mg, 50%) was prepared from **4** (576 mg, 2.0 mmol) in an analogous manner to that for preparation of **5b** after purification by column chromatography on silica gel (hexane/EtOAc=1:1). A colorless oil; $[\alpha]_D^{26}$ −9.24 (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J*=9.1 Hz), 7.28–7.20 (5H, m), 6.80 (4H, d, *J*=8.7 Hz), 6.13 (1H, d, *J*=6.7 Hz), 5.84 (1H, ddt, *J*=12.9, 6.5, 6.4 Hz), 3.98–3.90 (4H, m), 3.74 (6H, s), 2.15 (1H, d, *J*=6.4 Hz), 2.10 (1H, d, *J*=6.5 Hz), 1.13 (3H, t, *J*=7.1 Hz), 1.07 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 163.3, 163.2, 136.3–113.4 (aromatic), 76.6 (d, J_{CP}=14.1 Hz), 69.7 (d, J_{CP}=4.6 Hz), 61.6 (d, J_{CP}=6.3 Hz), 55.1, 27.4 (d, J_{CP}=143.3 Hz), 16.0 (d, J_{CP}=6.7 Hz), 15.9 (d, J_{CP}=6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.18; IR (neat) 1719, 1258 cm^{-1}; ESIMS *m*/*z* 557 (MH^+); HRMS (ESI) calcd for $C_{29}H_{33}O_9P$: 557.1940 (MH^+). Found: 557.1927.

4.2.11. (2*R*,3*S*)-2,3-Dihydroxybutylphosphonic acid (7). To a solution of **3e** (350 mg, 1.0 mmol) in MeOH (20 mL) was added 10% Pd–C (40 mg) and the mixture was stirred for 12 h at room temperature under hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite, the filtrate was concentrated to give **7** (160 mg, 94%). Amorphous; $[\alpha]_D^{26}$ −0.23 (*c* 0.7, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90–3.81 (1H, m), 3.79–3.27 (1H, m), 2.21–1.86 (2H, m), 1.21 (3H, d, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.4 (d, J_{CP}=4.4 Hz), 71.1

(d, J_{CP}=14.2 Hz), 31.5 (d, J_{CP}=137.9 Hz), 18.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.35; IR (neat) 3336, 997 cm^{-1}; ESIMS *m/z* 171 (MH^+); HRMS (ESI) calcd for $C_4H_{12}O_5P$: 171.0422 (MH^+). Found: 171.0410.

4.2.12. (2*R*,3*S*)-2,3-Dihydroxybutylphosphonic acid (7). To a stirred solution of **3b** (226 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added TMSBr (0.53 mL, 4.0 mmol) and the mixture was stirred for 12 h at room temperature. Concentration of the mixture gave a residue, which was dissolved in MeOH (0.1 mL). After stirring for 2 h at room temperature, the solution was concentrated to provide **7** (158 mg, 93%). Amorphous; $[\alpha]_D^{26}$ −1.55 (*c* 0.9, MeOH). The ^{1}H NMR spectrum was identical to that of **7** prepared from **3e**.

4.2.13. (4*R*)-Diethyl (2,2-dioxido-1,3,2-dioxathiolan-4-yl)methylphosphonate (8). To a stirred solution of **3a** (990 mg, 5.0 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (2.8 mL, 20 mmol) and a solution of $SOCl_2$ (0.50 mL, 15 mmol) in CH_2Cl_2 (3 mL) at 0 °C and the mixture was stirred for 1 h at the same temperature. The mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue. To a stirred solution of this residue in CCl_4–CH_3CN–H_2O 1:1:1.5 (50 mL) was added $NaIO_4$ (2.00 g, 10 mmol) and $RuCl_3\cdot nH_2O$ (52 mg) at 0 °C and the mixture was stirred for 2 h at the same temperature. The mixture was poured into H_2O and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (EtOAc) to give **8** (1.09 g, 80%). A pale yellow oil; $[\alpha]_D^{25}$ −0.72 (*c* 0.8, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27–5.18 (1H, m), 4.85 (1H, dd, *J*=9.2, 6.0 Hz), 4.59 (1H, dd, *J*=9.2, 7.5 Hz), 4.15–4.07 (4H, m), 2.54 (1H, ddd, *J*=20.2, 15.0, 4.9 Hz), 2.33 (1H, ddd, *J*=18.4, 15.0, 9.9 Hz), 1.36 (6H, t, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.6 (d, J_{CP}=3.5 Hz), 73.1 (d, J_{CP}=4.6 Hz), 63.6 (d, J_{CP}=5.8 Hz), 29.9 (d, J_{CP}=139.6 Hz), 16.3 (d, J_{CP}=6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.55; IR (neat) 1386, 1212, 1163 cm^{-1}; ESIMS *m/z* 275 (MH^+); HRMS (ESI) calcd for $C_7H_{16}O_7PS$: 275.0354 (MH^+). Found: 275.0381.

4.2.14. (2*R*)-Diethyl 3-azido-2-hydroxypropylphosphonate (9). To a stirred solution of **8** (9.73 g, 35.5 mmol) in acetone (532 mL) was added NaN_3 (6.98 g, 106.5 mmol), followed by addition of H_2O (266 mL). The mixture was stirred for 3 h at 50 °C and concentrated to give a residue, which was dissolved in Et_2O (1.78 L). To the solution was added 20% aqueous H_2SO_4 (887 mL) and the mixture was stirred for 12 h at room temperature. The mixture was extracted with Et_2O and to the combined extracts was added K_2CO_3 (1.78 g). After stirring for 30 min at room temperature, this mixture was dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane/EtOAc=3:1–1:1) to give **9** (2.02 g, 24%). A colorless oil; $[\alpha]_D^{25}$ −0.18 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22–4.07 (5H, m), 3.38 (1H, dd, *J*=12.4, 4.4 Hz), 3.34 (1H, dd, *J*=12.4, 5.7 Hz), 2.11–1.93 (2H, m), 1.35 (6H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.9 (d, J_{CP}=4.1 Hz), 62.5 (d, J_{CP}=6.5 Hz), 62.3 (d, J_{CP}=6.5 Hz), 30.7 (d, J_{CP}=140.6 Hz), 16.3 (d, J_{CP}=5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.28; IR (neat) 3361, 2104, 1220 cm^{-1}; ESIMS *m/z* 238 (MH^+); HRMS (ESI) calcd for $C_7H_{17}N_3O_4P$: 238.0957 (MH^+). Found: 238.0977.

4.2.15. (2*R*)-Diethyl 3-azido-2-[(triethylsilyl)oxy]propylphosphonate (10). To a stirred solution of **9** (2.09 g, 8.82 mmol) in DMF (30 mL) was added imidazole (1.44 g, 21.2 mmol) at 0 °C and the mixture was stirred for 15 min at the same temperature. To the solution was added TESCl (1.8 mL, 10.6 mmol) and the mixture was stirred for 5 h at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane/EtOAc=3:1) to provide **10** (2.48 g, 80%). A colorless oil; $[\alpha]_D^{26}$ +1.79 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23–4.17 (1H, m), 4.14–4.02 (4H, m), 3.49 (1H, dd, *J*=12.6, 3.1 Hz), 3.29 (1H, dd, *J*=12.6, 5.4 Hz), 2.19 (1H, ddd, *J*=16.8, 15.6, 9.3 Hz), 1.98 (1H, ddd, *J*=20.0, 15.6, 3.9 Hz), 1.33 (6H, t, *J*=7.1 Hz), 0.98 (9H, t, *J*=7.9 Hz), 0.65 (6H, q, *J*=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.5, 61.7, (d, J_{CP}=4.6 Hz), 56.6 (d, J_{CP}=3.1 Hz), 32.0 (d, J_{CP}=135.9 Hz), 16.3 (d, J_{CP}=6.1 Hz), 6.7, 4.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.87; IR (neat) 2157, 1228 cm^{-1}; ESIMS *m/z* 352 (MH^+); HRMS (ESI) calcd for $C_{13}H_{31}N_3O_4SiP$: 352.1821 (MH^+). Found: 352.1808.

4.2.16. (2*R*)-Diethyl 3-amino-2-[(triethylsilyl)oxy]propylphosphonate (11). A solution of **10** (100 mg, 0.28 mmol) in MeOH (5.7 mL) was stirred over 10% Pd–C (11 mg) for 12 h at room temperature under hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite, the filtrate was concentrated to give a residue, which was chromatographed on silica gel (EtOAc) to provide **11** (93.2 mg, 97%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16–4.00 (5H, m), 2.92 (1H, dd, *J*=13.3, 3.6 Hz), 2.76 (1H, dd, *J*=13.3, 5.0 Hz), 2.13 (1H, ddd, *J*=17.3, 15.4, 9.1 Hz), 1.95 (1H, ddd, *J*=19.9, 15.4, 4.2 Hz), 1.32 (6H, t, *J*=7.1 Hz), 0.96 (9H, t, *J*=7.9 Hz), 0.62 (6H, q, *J*=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.8, 61.5 (d, J_{CP}=4.9 Hz), 47.8 (d, J_{CP}=3.4 Hz), 31.7 (d, J_{CP}=135.7 Hz), 16.3 (d, J_{CP}=6.0 Hz), 6.7, 4.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.10; IR (neat) 3416, 1237 cm^{-1}; ESIMS *m/z* 326 (MH^+); HRMS (ESI) calcd for $C_{13}H_{33}NO_4SiP$: 326.1917 (MH^+). Found: 326.1895.

4.2.17. (2*R*)-Diethyl 3-(dimethylamino)-2-[(triethylsilyl)oxy]propylphosphonate (12). To a stirred solution of **11** (91 mg, 0.28 mmol) in CH_3CN (1.4 mL) was added 37% aqueous formaldehyde (112 mg, 1.4 mmol) and $NaBH_3CN$ (31 mg, 0.45 mmol) and the mixture was stirred for 2 h at room temperature. To the solution was added acetic acid to be pH=3.0 and stirring was continued for 45 min. After pH was adjusted to be 9.0 with 1 M KOH, the mixture was extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane/EtOAc=2:1 to $CHCl_3$/MeOH=20:1) to provide **12** (88 mg, 90%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16–4.04 (5H, m), 2.38–2.28 (3H, m), 2.23 (6H, s), 1.89 (1H, ddd, *J*=18.3, 15.4, 6.1 Hz), 1.32 (6H, t,

J=7.1 Hz), 0.97 (9H, t, J=7.9 Hz), 0.63 (6H, q, J=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.6, 66.0 (d, J_{CP}=9.6 Hz), 61.3 (d, J_{CP}=3.2 Hz), 61.2 (d, J_{CP}=3.2 Hz), 46.4, 32.2 (d, J_{CP}=138.5 Hz), 16.4 (d, J_{CP}=6.1 Hz), 16.3 (d, J_{CP}=6.1 Hz), 6.8, 4.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.83; IR (neat) 1238 cm^{-1}; ESIMS m/z 354 (MH^+); HRMS (ESI) calcd for $C_{15}H_{37}NO_4SiP$: 354.2230 (MH^+). Found: 354.2238.

4.2.18. (1*R*)-2-(Diethoxyphosphoryl)-1-[(dimethylamino)methyl]ethyl myristate (13). To a stirred solution of **12** (402 mg, 1.14 mmol) in THF (6 mL) was added a 1 M THF solution of TBAF (2.3 mL, 2.3 mmol) at 0 °C and the mixture was stirred for 2 h at the same temperature. The mixture was concentrated to give a residue, which was dissolved in CH_2Cl_2 (2.5 mL). To this solution was added a solution of myristoyl chloride (0.63 mL, 2.3 mmol) in CH_2Cl_2 (2.5 mL), pyridine (0.16 mL, 2.1 mmol) and DMAP (14 mg, 0.11 mmol) at 0 °C and the mixture was stirred for 3.5 h at room temperature. The mixture was poured into H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel ($CHCl_3$/MeOH=1:0–20:1) to provide **13** (207 mg, 52%). A colorless oil; $[\alpha]_D^{26}$ +5.19 (c 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, dddd, J=12.5, 12.5, 6.2, 6.2 Hz), 4.16–4.06 (4H, m), 2.54 (1H, dd, J=12.8, 6.0 Hz), 2.46 (1H, dd, J=12.8, 5.5 Hz), 2.32–2.22 (9H, m), 2.07 (1H, ddd, J=18.2, 15.5, 7.0 Hz), 1.34–1.25 (28H, m), 0.88 (3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 66.9, 62.6 (d, J_{CP}=9.8 Hz), 61.7 (d, J_{CP}=7.2 Hz), 61.6 (d, J_{CP}=7.2 Hz), 46.0, 34.4, 31.9, 29.6, 29.5, 29.3, 29.2, 29.1, 28.3, 24.8, 22.7, 16.4 (d, J_{CP}=7.1 Hz), 14.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.42; IR (neat) 1738, 1257 cm^{-1}; ESIMS m/z 450 (MH^+); HRMS (ESI) calcd for $C_{23}H_{49}NO_5P$: 450.3348 (MH^+). Found: 450.3344.

4.2.19. (2*R*)-3-(Diethoxyphosphoryl)-*N*,*N*,*N*-trimethyl-2-(tetradecanoyloxy)propan-1-aminium iodide (14). To a stirred solution of **13** (200 mg, 0.45 mmol) in acetone (1.9 mL) was added iodomethane (0.03 mL, 0.37 mmol) and the mixture was stirred for 10 h at room temperature. The solution was concentrated to give a residue, which was chromatographed on silica gel ($CHCl_3$/MeOH=1:0–10:1) to provide **14** (249 mg, 86%). A colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (1H, dddd, J=13.8, 13.8, 7.0, 7.0 Hz), 4.38–4.34 (1H, m), 4.18–4.09 (5H, m), 3.49 (9H, s), 2.43–2.24 (4H, m), 1.34–1.23 (28H, m), 0.86 (3H, t, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 68.1 (d, J_{CP}=9.9 Hz), 62.6 (d, J_{CP}=6.4 Hz), 62.5 (d, J_{CP}=6.4 Hz), 54.5, 34.1, 31.7, 29.6, 29.4, 29.2, 29.1, 29.0, 28.9, 28.2, 24.2, 22.4, 16.2 (d, J_{CP}=5.8 Hz), 13.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.81; IR (neat) 1741, 1241 cm^{-1}; ESIMS m/z 464 (M^+-I); HRMS (ESI) calcd for $C_{24}H_{51}NO_5P$: 464.3505 (M^+-I). Found: 464.3471.

4.2.20. (2*R*)-*N*,*N*,*N*-Trimethyl-3-phosphono-2-(tetradecanoyloxy)propan-1-aminium (15). To a stirred solution of **14** (178 mg, 0.3 mmol) in CH_2Cl_2 (0.6 mL) was added TMSBr (0.06 mL, 0.48 mmol) and the mixture was stirred for 20 h at room temperature. Concentration of the mixture gave a residue, which was dissolved in MeOH (0.06 mL). After stirring for 12 h at room temperature, the solution was concentrated to provide **15** (88 mg, 72%). Amorphous; $[\alpha]_D^{26}$ +2.25 (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64–5.55 (1H, m), 3.95 (1H, dd, J=14.4, 8.7 Hz), 3.84 (1H, d, J=14.4 Hz), 3.23 (9H, s), 2.41 (2H, t, J=7.5 Hz), 2.24–2.17 (2H, m), 1.31–1.28 (22H, m), 0.89 (3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 71.4, 69.7, 65.7, 54.8, 35.1, 33.0, 31.2, 30.7, 30.6, 30.4, 30.2, 26.0, 25.5, 23.7, 14.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.01; IR (neat) 970 cm^{-1}; ESIMS m/z 408 (MH^+); HRMS (ESI) calcd for $C_{20}H_{43}NO_5P$: 408.2879 (MH^+). Found: 408.2913.

4.2.21. Dibenzyl [(4*R*,5*S*)-5-methyl-2,2-dioxido-1,3,2-dioxathiolan-4-yl]methylphosphonate (16). Compound **16** (850 mg, 80%) was prepared from **3e** (850 mg, 2.5 mmol) in an analogous manner to that for preparation of **8** after purification by column chromatography on silica gel (EtOAc). A pale yellow oil; $[\alpha]_D^{26}$ −12.95 (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.33 (10H, m), 5.10–4.95 (4H, m), 4.80 (1H, dt, J=12.9, 6.4 Hz), 4.68 (1H, qd, J=7.2, 7.1 Hz), 2.42–2.17 (2H, m), 1.47 (3H, d, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4 (d, J_{CP}=5.1 Hz), 135.3 (d, J_{CP}=5.1 Hz), 128.9, 128.8, 128.3, 128.2, 83.8 (d, J_{CP}=9.4 Hz), 82.6, 68.2 (d, J_{CP}=3.1 Hz), 68.1 (d, J_{CP}=3.1 Hz), 29.9 (d, J_{CP}=141.8 Hz), 17.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.12; IR (neat) 1383, 1260, 1211 cm^{-1}; ESIMS m/z 413 (MH^+); HRMS (ESI) calcd for $C_{18}H_{22}O_7PS$: 413.0840 (MH^+). Found: 413.0824.

4.2.22. (2*R*,3*R*)-Dibenzyl 3-azido-2-hydroxybutylphosphonate (17). Compound **17** (473 mg, 42%) was prepared from **16** (1.20 g, 3.0 mmol) in an analogous manner to that for preparation of **9** after purification by column chromatography on silica gel (hexane/EtOAc=3:1–1:1). A colorless oil; $[\alpha]_D^{30}$ −17.56 (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (10H, m), 5.11–5.05 (2H, m), 5.02–4.96 (2H, m), 3.84–3.77 (1H, m), 3.66 (3H, s), 3.48 (1H, dt, J=12.6, 6.3 Hz), 2.07–1.88 (2H, m), 1.18 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (d, J_{CP}=5.7 Hz), 135.8 (d, J_{CP}=5.7 Hz), 128.7, 128.6, 128.0, 69.5 (d, J_{CP}=4.9 Hz), 67.7 (d, J_{CP}=6.3 Hz), 67.6 (d, J_{CP}=6.7 Hz), 61.4 (d, J_{CP}=17.3 Hz), 29.5 (d, J_{CP}=140.4 Hz), 14.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.56; IR (neat) 3347, 2098, 1220 cm^{-1}; ESIMS m/z 398 (MNa^+); HRMS (ESI) calcd for $C_{18}H_{22}N_3O_4NaP$: 398.1246 (MNa^+). Found: 398.1241.

4.2.23. (2*R*,3*R*)-Dibenzyl 3-azido-2-[(triethylsilyl)oxy]-butylphosphonate (19). Compound **19** (8.83 g, 98%) was prepared from **17** (6.90 g, 18.4 mmol) in an analogous manner to that for preparation of **10** after purification by column chromatography on silica gel (hexane/EtOAc=2:1). A colorless oil; $[\alpha]_D^{27}$ −1.20 (c 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (10H, m), 5.04 (2H, dd, J=11.5, 9.7 Hz), 4.95 (1H, dd, J=8.5, 3.0 Hz), 4.92 (1H, dd, J=8.6, 3.1 Hz), 4.12–4.05 (1H, m), 3.63 (1H, qd, J=6.7, 2.7 Hz), 2.07–1.95 (2H, m), 1.13 (3H, d, J=6.7 Hz), 0.98–0.90 (9H, m), 0.60 (6H, t, J=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (d, J_{CP}=5.5 Hz), 128.6–128.1 (aromatic), 70.2, 67.4 (d, J_{CP}=5.7 Hz), 67.3 (d, J_{CP}=5.6 Hz), 60.7 (d, J_{CP}=5.7 Hz), 31.5 (d, J_{CP}=137.3 Hz), 12.5, 6.8, 4.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.91; IR (neat) 2955, 2105, 1249 cm^{-1}; ESIMS m/z 490 (MH^+); HRMS (ESI) calcd for $C_{24}H_{37}N_3O_4SiP$: 490.2291 (MH^+). Found: 490.2283.

4.2.24. (2*R*,3*R*)-Dibenzyl 3-amino-2-[(triethylsilyl)oxy]-butylphosphonate (20). To a stirred solution of **19** (9.00 g, 18.4 mmol) in THF (180 mL) was added triphenylphosphine (5.30 g, 20 mmol) and the mixture was stirred for 2 h at room temperature. To the solution was added H_2O (50 mL) and the mixture was stirred for 12 h at room temperature. The mixture was extracted with $CHCl_3$ and then the combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (EtOAc to $CHCl_3$/MeOH=10:1) to provide **20** (7.84 g, 97%). A colorless oil; $[\alpha]_D^{24}$ −1.13 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (10H, m), 5.03 (2H, dd, *J*=11.8, 9.1 Hz), 4.95 (2H, dd, *J*=11.8, 8.2 Hz), 4.02–3.87 (1H, m), 3.15–3.11 (1H, m), 2.06–1.97 (2H, m), 1.00 (3H, d, *J*=6.6 Hz), 0.91 (9H, t, *J*=7.9 Hz), 0.58 (6H, q, *J*=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (d, J_{CP}=5.4 Hz), 128.5–127.7 (aromatic), 71.6, 67.2 (d, J_{CP}=6.6 Hz), 67.1 (d, J_{CP}=6.6 Hz), 51.3 (d, J_{CP}=7.6 Hz), 30.1 (d, J_{CP}=138.0 Hz), 17.0, 6.8, 4.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.81; IR (neat) 3457, 1608, 1240 cm^{-1}; ESIMS *m*/*z* 464 (MH^+); HRMS (ESI) calcd for $C_{24}H_{39}NO_4SiP$: 464.2386 (MH^+). Found: 464.2382.

4.2.25. (2*R*,3*R*)-Dibenzyl 3-{[(4-methylphenyl)sulfonyl]amino}-2-[(triethylsilyl)oxy]butylphosphonate (21). To a stirred solution of **20** (370 mg, 0.8 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (0.14 mL, 0.97 mmol) and a solution of tosyl chloride (0.18 g, 0.97 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the mixture was stirred for 12 h at room temperature. The mixture was poured into saturated aqueous $KHSO_4$ and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane/EtOAc=10:1) to provide **21** (60 mg, 13%). A colorless oil; $[\alpha]_D^{25}$ +29.28 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J*=8.3 Hz), 7.38–7.31 (10H, m), 7.22 (2H, d, *J*=8.2 Hz), 5.04 (1H, dd, *J*=9.4, 5.6 Hz), 5.01 (1H, dd, *J*=9.4, 5.6 Hz), 4.95 (1H, dd, *J*=8.2, 3.5 Hz), 4.92 (1H, dd, *J*=8.2, 3.5 Hz), 4.79 (1H, d, *J*=8.3 Hz), 4.08–4.06 (1H, m), 3.64–3.62 (1H, m), 2.37 (3H, s), 1.97–1.90 (2H, m), 0.92 (3H, d, *J*=6.6 Hz), 0.87 (9H, t, *J*=7.9 Hz), 0.50 (6H, q, *J*=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 138.3, 136.1 (d, J_{CP}=5.5 Hz), 129.6–127.0 (aromatic), 70.2 (d, J_{CP}=1.8 Hz), 67.5 (d, J_{CP}=6.5 Hz), 67.4 (d, J_{CP}=6.5 Hz), 53.2 (d, J_{CP}=2.7 Hz), 32.1 (d, J_{CP}=135.3 Hz), 21.4, 14.6, 6.8, 4.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.40; IR (neat) 3159, 1323, 1261, 1146 cm^{-1}; ESIMS *m*/*z* 618 (MH^+); HRMS (ESI) calcd for $C_{31}H_{45}NO_6SiPS$: 618.2475 (MH^+). Found: 618.2507.

4.2.26. (3*R*)-Dibenzyl 3-{[(4-methylphenyl)sulfonyl]-amino}-2-oxobutylphosphonate (22). To a stirred solution of **21** (60 mg, 0.1 mmol) in THF (0.5 mL) was added a 1 M THF solution of TBAF (0.22 mL, 0.22 mmol) at 0°C and the mixture was stirred for 2 h at the same temperature. The mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was dissolved in CH_2Cl_2 (1 mL). To the solution was added PDC (41 mg, 0.11 mmol) and the mixture was stirred for 12 h at room temperature. After filtration of the mixture through a pad of Celite, the filtrate was concentrated to give a residue, which was chromatographed on silica gel (hexane/EtOAc=10:1–3:1) to give **22** (27 mg, 47%). A colorless oil; $[\alpha]_D^{25}$ +11.52 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (2H, d, *J*=8.2 Hz), 7.38–7.29 (10H, m), 7.24 (2H, d, *J*=8.2 Hz), 5.92 (1H, d, *J*=8.2 Hz), 5.08–4.91 (4H, m), 4.02 (1H, dt, *J*=15.2, 7.4 Hz), 3.45 (1H, dd, *J*=23.3, 13.7 Hz), 3.03 (1H, dd, *J*=22.5, 13.7 Hz), 2.36 (3H, s), 1.18 (3H, d, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8 (d, J_{CP}=6.0 Hz), 143.6, 137.4, 135.5, 129.8–127.0 (aromatic), 68.4 (d, J_{CP}=6.0 Hz), 68.3 (d, J_{CP}=6.0 Hz), 58.2, 39.2 (d, J_{CP}=128.0 Hz), 21.5, 18.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.48; IR (neat) 3277, 1724, 1243 cm^{-1}; ESIMS *m*/*z* 502 (MH^+); HRMS (ESI) calcd for $C_{25}H_{29}NO_6PS$: 502.1453 (MH^+). Found: 502.1422.

4.2.27. (2*R*,3*R*)-Dibenyl 3-(dimethylamino)-2-[(triethylsilyl)oxy]butylphosphonate (24). Compound **24** (830 mg, 85%) was prepared from **20** (920 mg, 2.0 mmol) in an analogous manner to that for preparation of **12** after purification by column chromatography on silica gel (hexane/EtOAc=2:1–$CHCl_3$/MeOH=20:1). A colorless oil; $[\alpha]_D^{25}$ +5.26 (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (10H, m), 5.05–4.91 (4H, m), 4.08 (1H, dq, *J*=16.3, 5.5 Hz), 2.64 (1H, dt, *J*=12.2, 6.7 Hz), 2.31–2.21 (2H, m), 2.17 (6H, s), 0.93 (3H, d, *J*=2.5 Hz), 0.92 (9H, t, *J*=7.9 Hz), 0.59 (6H, q, *J*=7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5 (d, J_{CP}=5.9 Hz), 128.5–127.8 (aromatic), 69.7, 66.9 (d, J_{CP}=6.3 Hz), 63.3 (d, J_{CP}=6.2 Hz), 41.6, 32.6 (d, J_{CP}=137.2 Hz), 8.5, 6.9, 5.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.88; IR (neat) 2956, 1240, 1120 cm^{-1}; ESIMS *m*/*z* 492 (MH^+); HRMS (ESI) calcd for $C_{26}H_{43}NO_4SiP$: 492.2699 (MH^+). Found: 492.2701.

4.2.28. (1*R*,2*R*)-1-{[Bis(benzyloxy)phosphoryl]methyl}-2-(dimethylamino)propyl myristate (25). Compound **25** (487 mg, 23%) was prepared from **24** (1.76 g, 3.6 mmol) in an analogous manner to that for preparation of **13** after purification by column chromatography on silica gel ($CHCl_3$/MeOH=1:0–30:1). A colorless oil; $[\alpha]_D^{25}$ −0.97 (*c* 0.7, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (10H, m), 5.31–5.23 (1H, m), 5.06–4.91 (4H, m), 4.12 (1H, q, *J*=7.0 Hz), 2.32 (2H, t, *J*=3.8 Hz), 2.22–2.08 (8H, m), 1.32–1.25 (25H, m), 0.88 (3H, t, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 172.9, 136.2, 128.7, 128.6, 128.4, 128.1, 128.0, 68.1, 67.5 (d, J_{CP}=6.5 Hz), 67.4 (d, J_{CP}=6.5 Hz), 61.6 (d, J_{CP}=10.7 Hz), 60.4, 40.5, 34.4, 34.3, 31.9, 29.6, 29.5, 29.3, 29.2, 28.3, 25.0, 24.6, 22.7, 21.0, 14.1, 8.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.33; IR (neat) 1736, 1249, 1115 cm^{-1}; ESIMS *m*/*z* 588 (MH^+); HRMS (ESI) calcd for $C_{34}H_{55}NO_5P$: 588.3818 (MH^+). Found: 588.3826.

4.2.29. (2*R*,3*R*)-4-[Bis(benzyloxy)phosphoryl]-*N*,*N*,*N*-trimethyl-3-(tetradecanoyloxy)butan-2-aminium iodide (26). Compound **26** (70 mg, 33%) was prepared from **25** (170 mg, 0.29 mmol) in an analogous manner to that for preparation of **14** after purification by column chromatography on silica gel ($CHCl_3$/MeOH=1:0–10:1). A colorless oil; $[\alpha]_D^{25}$ −5.65 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (10H, m), 5.68 (1H, dt, *J*=7.5, 7.5 Hz), 5.08–4.91 (4H, m), 3.96 (1H, q, *J*=6.8 Hz), 3.08 (9H, s), 2.26 (2H, td, *J*=7.6, 2.1 Hz), 2.14 (2H, dd, *J*=19.4, 6.8 Hz), 1.45 (3H, d, *J*=6.8 Hz), 1.27–1.23 (22H, m), 0.88

(3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.7, 128.8, 128.7, 128.3, 128.2, 72.0 (d, J_{CP}=11.2 Hz), 68.1 (d, J_{CP}=6.5 Hz), 67.9 (d, J_{CP}=6.5 Hz), 64.5, 63.2, 51.6, 34.1, 31.9, 31.0, 30.9, 29.6, 29.4, 29.3, 29.2, 29.0, 24.4, 22.6, 15.2, 14.1, 8.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.34; IR (neat) 1739, 1224 cm^{-1}; ESIMS *m/z* 602 (M^+-I); HRMS (ESI) calcd for $C_{35}H_{57}NO_5P$: 602.3974 (M^+-I). Found: 602.4066.

4.2.30. (2*R*,3*R*)-*N*,*N*,*N*-Trimethyl-4-phosphono-3-(tetradecanoyloxy)butan-2-aminium (27). Compound **27** (38 mg, 48%) was prepared from **26** (139 mg, 0.19 mmol) in an analogous manner to that for preparation of **15**. Amorphous; $[\alpha]_D^{25}$ −4.03 (*c* 0.7, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, dt, J=7.4, 7.4 Hz), 4.01–3.96 (1H, m), 3.67 (9H, s), 2.41 (2H, t, J=7.5 Hz), 2.22–2.14 (2H, m), 1.58 (3H, t, J=6.7 Hz), 1.30–1.22 (22H, m), 0.88 (3H, t, J=4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 73.7 (d, J_{CP}=7.3 Hz), 53.6, 35.0, 32.9 (d, J_{CP}=6.5 Hz), 31.5, 30.7, 30.5, 30.4, 30.1, 25.5, 23.6, 14.4, 8.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.88; IR (neat) 1000 cm^{-1}; ESIMS *m/z* 422 (MH^+); HRMS (ESI) calcd for $C_{21}H_{45}NO_5P$: 422.3035 (MH^+). Found: 422.3040.

4.2.31. Dibenzyl [(4*S*,5*R*)-5-methyl-2,2-dioxido-1,3,2-dioxathiolan-4-yl]methylphosphonate (*ent*-16). Compound *ent*-**16** (13.0 g, 76%) was prepared from *ent*-**3e** (14.6 g, 41.6 mmol) in an analogous manner to that for preparation of **8** after purification by column chromatography on silica gel (hexane/EtOAc=10:1–1:1). A pale yellow oil; $[\alpha]_D^{20}$ +18.90 (*c* 1.1, MeOH). The ^{1}H NMR spectrum was identical with that of **16**.

4.2.32. (2*S*,3*S*)-Dibenzyl 3-azido-2-hydroxybutylphosphonate (*ent*-17). Compound *ent*-**17** (330 mg, 44%) was prepared from *ent*-**16** (824 mg, 2.0 mmol) in an analogous manner to that for preparation of **9** after purification by column chromatography on silica gel (hexane/EtOAc=3:1–1:1). A colorless oil; $[\alpha]_D^{24}$ +14.48 (*c* 1.1, MeOH). The ^{1}H NMR spectrum was identical with that of **17**.

4.2.33. (2*S*,3*S*)-Dibenzyl 3-azido-2-[(triethylsilyl)oxy]butylphosphonate (*ent*-19). Compound *ent*-**19** (6.27 g, 97%) was prepared from *ent*-**17** (4.96 g, 13.2 mmol) in an analogous manner to that for preparation of **10** after purification by column chromatography on silica gel (hexane/EtOAc=2:1). A colorless oil; $[\alpha]_D^{24}$ +3.06 (*c* 0.7, MeOH). The ^{1}H NMR spectrum was identical with that of **19**.

4.2.34. (2*S*,3*S*)-Dibenzyl 3-amino-2-[(triethylsilyl)oxy]-butylphosphonate (*ent*-20). Compound *ent*-**20** (5.80 g, 94%) was prepared from *ent*-**19** (6.46 g, 13.2 mmol) in an analogous manner to that for preparation of **11** after purification by column chromatography on silica gel (EtOAc to $CHCl_3$/MeOH=10:1). A colorless oil; $[\alpha]_D^{24}$ +2.38 (*c* 1.0, MeOH). The ^{1}H NMR spectrum was identical with that of **20**.

4.2.35. (2*S*,3*S*)-Dibenyl 3-(dimethylamino)-2-[(triethylsilyl)oxy]butylphosphonate (*ent*-24). Compound *ent*-**24** (830 mg, 96%) was prepared from *ent*-**20** (1.50 g, 3.4 mmol) in an analogous manner to that for preparation of **12** after purification by column chromatography on silica gel (hexane/EtOAc=2:1–$CHCl_3$/MeOH=20:1). A colorless oil; $[\alpha]_D^{24}$ −10.46 (*c* 1.1, MeOH). The ^{1}H NMR spectrum was identical with that of **24**.

4.2.36. (1*S*,2*S*)-1-{[Bis(benzyloxy)phosphoryl]methyl}-2-(dimethylamino)propyl myristate (*ent*-25). Compound *ent*-**25** (1.50 g, 30%) was prepared from *ent*-**24** (4.12 g, 8.38 mmol) in an analogous manner to that for preparation of **13** after purification by column chromatography on silica gel ($CHCl_3$/MeOH=1:0–30:1). A colorless oil; $[\alpha]_D^{25}$ +0.30 (*c* 0.6, MeOH). The ^{1}H NMR spectrum was identical with that of **25**.

4.2.37. (2*S*,3*S*)-4-[Bis(benzyloxy)phosphoryl]-*N*,*N*,*N*-trimethyl-3-(tetradecanoyloxy)butan-2-aminium iodide (*ent*-26). Compound *ent*-**26** (500 mg, 30%) was prepared from *ent*-**25** (1.50 g, 2.55 mmol) in an analogous manner to that for preparation of **14** after purification by column chromatography on silica gel ($CHCl_3$/MeOH=1:0–10:1). A colorless oil; $[\alpha]_D^{25}$ +7.58 (*c* 1.0, MeOH). The ^{1}H NMR spectrum was identical with that of **26**.

4.2.38. (2*S*,3*S*)-*N*,*N*,*N*-Trimethyl-4-phosphono-3-(tetradecanoyloxy)butan-2-aminium (*ent*-27). Compound *ent*-**27** (276 mg, 34%) was prepared from *ent*-**26** (487 mg, 1.15 mmol) in an analogous manner to that for preparation of **15**. Amorphous; $[\alpha]_D^{26}$ +3.34 (*c* 0.5, MeOH). The ^{1}H NMR spectrum was identical with that of **27**.

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