Synthesis of Chiral γ-Amino-β-hydroxyphosphonate Derivatives from Unsaturated Phosphonates

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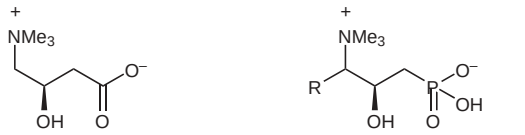
Abstract: γ-Amino-β-hydroxyphosphonates, useful intermediates for the synthesis of phosphonic acid analogues of carnitine, were prepared as their protected derivatives in an enantioselective manner from β,γ-unsaturated phosphonates through asymmetric dihydroxylation and subsequent regioselective amination via the cyclic sulfates.

Key words: phosphorus, asymmetric synthesis, dihydoxylations, sulfates, regioselectivity

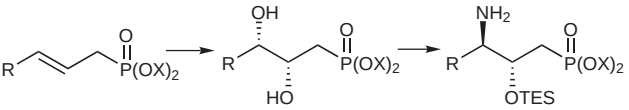
Hyperglycemia of type II diabetes is considered to be primarily due to excess long-chain fatty acid oxidation, which is crucial to drive gluconeogenesis at higher rates.[1] Carnitine palmitoyltransferase I (CPT I) located on the outer mitochondrial membrane plays an important role in β-oxidation of long-chain 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 that modification of the functional groups of carnitine was one way to access potent CPT I inhibitors. It was found that aminocarnitine derivatives (where the hydroxy group of carnitine was replaced with an amino group) were good inhibitors.[4] However, to the best of our knowledge, little investigation has been carried out on modifying the carboxylic moiety of carnitine.[4] The fact that phosphonic acids have been utilized as one of the bioisosteric groups of carboxylic acids prompted us to investigate a synthesis of a phosphonic acid analogue of carnitine (Figure 1). 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,[5a] enzymatic resolution of γ-chloro-β-hydroxyphosphonates,[5b] hydrolytic kinetic resolution of epoxyphosphonates with an asymmetric catalyst,[5c] ring-opening of epichlorohydrin with silylphosphites,[5d] and diastereoselective reduction of γ-amino-β-ketophosphonates.[5e] Although catalytic asymmetric aminohydroxylation of β,γ-unsaturated phosphonates is known for the synthesis of γ-amino-β-hydroxyphosphonates, the chemical yields are reported to be low.[5f] We investigated a new synthesis of γ-amino-β-hydroxyphosphonate derivatives by our own approach, which involved osmium-catalyzed asymmetric dihydroxylation (AD)[6] of β,γ-unsaturated phosphonates, followed by selective amination of the hydroxy group at the γ-position (Scheme 1). In this paper, we describe the preliminary results of this approach.



(*R*)-(–)-Carnitine

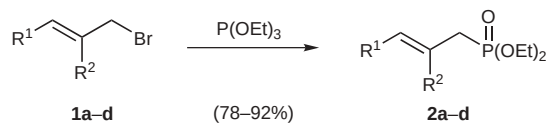
Phosphonic acid analogues of (*R*)-(–)-Carnitine

Figure 1



Scheme 1

We have previously reported AD reaction of α,β-unsaturated phosphonates with AD-mix reagents, which could provide a variety of chiral α,β-dihydroxyphosphonates.[7,8] Although β,γ-dihydroxyphosphonate having a phenyl group at the γ-position could be also prepared in high enantiomeric excess (98% ee) through AD reaction of β,γ-unsaturated phosphonate,[9] similar reactions using other substrates have not been investigated. For both expanding the scope of this protocol and obtaining various carnitine analogues, AD reactions of β,γ-unsaturated phosphonates were examined. The requisite starting materials **2a**–**d** were readily prepared by Arbuzov reactions of the corresponding allyl bromides **1a**–**d** with triethylphosphite (Scheme 2).



1a–d (78–92%) **2a–d**

a: $R^1 = R^2 = H$; **b**: R^1 = Me, R^2 = H; **c**: R^1 = 4-$MeOC_6H_4CO_2CH_2$, R^2 = H
d: R^1 = H, R^2 = Ph

Scheme 2

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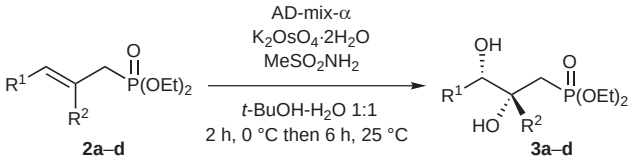
Reactions of **2a**–**d** were performed with AD-mix-α in the presence of $MeSO_2NH_2$ and additional $K_2OsO_4{\cdot}2H_2O$ (0.8 mol%) in the *t*-BuOH–H_2O solvent system (1:1) at room temperature according to our previous protocol.[7,10] The results are summarized in Table 1.

Table 1 AD of β,γ-Unsaturated Phosphonates **2a**–**d** with AD-mix-α

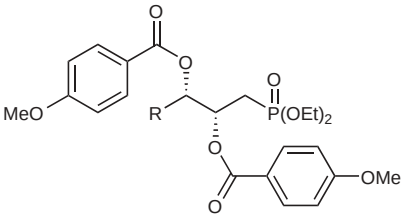


Entry	3	R^1	R^2	Yield (%)	ee (%)[a]
1	**a**	H	H	40	10
2	**b**	Me	H	60	35
3	**c**	4-$MeOC_6H_4CO_2CH_2$	H	58	97[b]
4	**d**	H	Ph	29	81[b]

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

AD reactions of **2a**–**c** proceeded to give diols **3a**–**c** in 40–60% yield (entries 1–3), albeit with decrease in the chemical yield of **3d** possessing a phenyl group at the β-position (entry 4). Low enantioselectivity was observed in reactions of **2a** and **2b** having a proton and a methyl group in the R^1 moiety, respectively (entries 1 and 2). AD reaction of **2c** having a 4-methoxybenzoyloxy group at the δ-position proceeded with excellent enantioselectivity (97% ee) to give **3c** (entry 3).[11] It is worthy of note that β,γ-dihydroxyphosphonate **3d** with a quarternary chiral center could be obtained in good enantiomeric excess (81% ee) by AD of **2d** (entry 4). 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 enantiomeric excess of **3c** may be accounted for by the 4-methoxybenzoyl group participating in π-stacking interactions with the methoxyquinoline ring of the catalyst.[12]

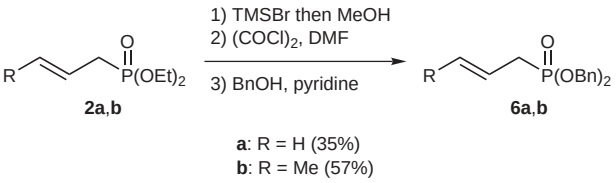
The absolute configuration of **3b** and **3c** was determined after conversion to 4-methoxybenzoate derivatives **4b** and **4c** (Figure 2). The CD spectrum of **4b** showed a positive Cotton effect at 289 nm and a negative Cotton effect at 282 nm, which were analogous to that of methoxybenzoate **5** prepared from known β,γ-dihydroxyphosphonates,[9] showing positive and negative Cotton effects at longer (286 nm) and shorter wavelengths (275 nm), respectively. The CD curve of **4c** was also similar to that of **5**. Accordingly, **4b** and **4c** have the same absolute stereochemistry with **5**, indicating the stereochemistry of **3b** and **3c** to be 2*S*,3*S*-configuration. The stereochemistry of **3d** was estimated as depicted on the basis of the empirical rule for AD with AD-mix-α.[6]



4b: R = Me; **4c**: R = 4-$MeOC_6H_4CO_2CH_2$; **5**: R = Ph

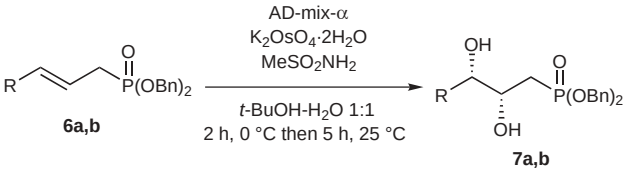
Figure 2

In general, AD reaction of hydrophobic compounds is prone to afford good enantioselectivity due to those being easily trapped into the lipophilic cavity of the ligand–osmium complex.[6] We envisioned that enhancing the hydrophobicity of **2a**,**b** by tuning the phosphonate moiety would lead to improvement of the enantioselectivity. In this context, β,γ-unsaturated dibenzyl phosphonates were next chosen as substrates for the AD reaction.[13] The required starting materials **6a**,**b** were prepared from **2a**,**b** through sequential deesterification, chlorination of the acid moiety, followed by treatment with benzyl alcohol and pyridine (Scheme 3).



Scheme 3

A reaction of **6a** with AD-mix-α furnished diol **7a** in 71% yield, however, the enantioselectivity was not improved (Scheme 4). On the other hand, employing **6b** improved the selectivity giving **7b** in 48% ee in comparison to **3b** (35% ee). The product **7b** was isolated as a crystal, therefore, optically pure **7b** could be obtained through one recrystallization from EtOAc (38% recovery).[14]

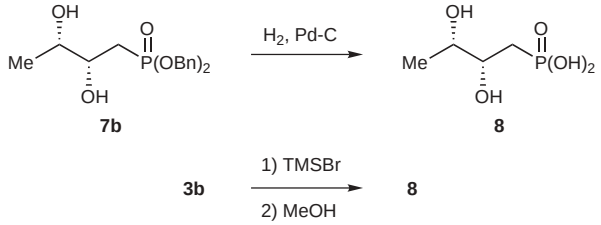


7	R	yield (%)	ee (%)
a	H	71	10
b	Me	69	48 (100)[a]

[a] After one recrystallization from EtOAc

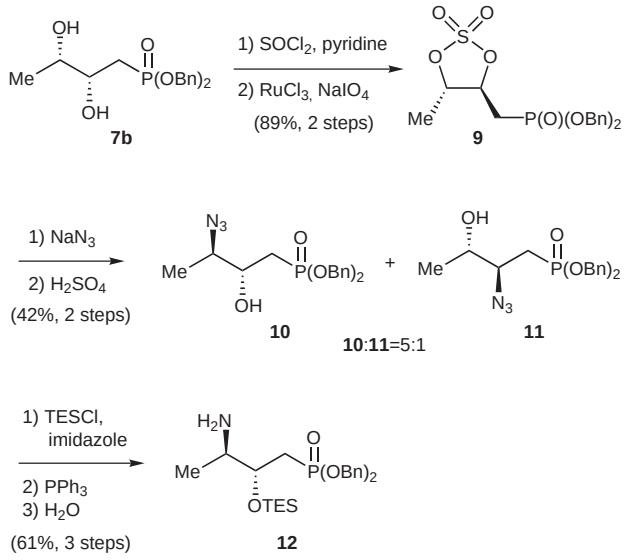
Scheme 4

The absolute configuration of **7b** was verified after conversion to the corresponding phosphonic acid **8** through hydrogenolysis of the dibenzyl phosphonate moiety (Scheme 5). The sign of the optical rotation of **8** was identical with that of a sample derived from **3b**.



Scheme 5

Having achieved the preparation of chiral β,γ-dihydroxyphosphonates, we next focused on their transformation into γ-amino-β-hydroxyphosphonate derivatives via cyclic sulfates (Scheme 6).[15] Treatment of **7b** with $SOCl_2$, followed by oxidation with $RuCl_3$–$NaIO_4$[16] afforded cyclic sulfate **9** in 89% yield. Ring-opening of **9** with NaN_3 in acetone–H_2O and subsequent treatment with 20% H_2SO_4 gave a mixture of γ-azide **10** and β-azide **11** in a ratio of 5:1 (42% yield). Although the exact reason for the γ-selectivity has remained unclear, it might be associated with the steric congestion at the β-position by the bulky dibenzyl phosphonate moiety. After the mixture of **10** and **11** was converted into the TES ether, Staudinger reaction with PPh_3 and subsequent hydrolysis were performed. At this stage, γ-amino-β-siloxyphosphonate **12** in pure form was provided in 61% yield after column chromatography on silica gel.[17,18] Compound **12** would be a useful intermediate for transforming phosphonic acid analogues of carnitine.



Scheme 6

In conclusion, we have developed a new method for preparing a protected form of chiral γ-amino-β-hydroxyphosphonates through AD reactions of β,γ-unsaturated phosphonates. A study on transforming optically active γ-amino-β-siloxyphosphonates into phosphonic acid analogues of carnitine is under progress and will be the subject of future reports.

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(10) The 1.4 g of AD-mix-α, purchased from Aldrich, was used for conversion of 1.0 mmol of the olefin, which contained 0.2 mol% of $K_2OsO_4 \cdot 2H_2O$ and 1.0 mol% of chiral ligand $(DHQ)_2PHAL$. However, an additional $K_2OsO_4 \cdot 2H_2O$ (0.8 mol%) was critical for AD reactions of β,γ-unsaturated phosphonates since the AD reaction of **2b** in the absence of the osmium salt resulted in slow reaction rates (20 h at 25 °C) and slight decrease in enantioselectivity (54% yield, 30% ee).
(11) Compound **3c**: oil; $[\alpha]_D^{26}$ –2.14 (*c* 1.03, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (2 H, d, *J* = 8.8 Hz), 6.87 (2 H, d, *J* = 8.8 Hz), 4.38 (2 H, d, *J* = 5.8 Hz), 4.09 (4 H, q, *J* = 6.9 Hz), 4.05–4.00 (1 H, m), 3.87–3.85 (1 H, m), 3.82 (3 H, s), 2.22–1.96 (2 H, m), 1.29 (6 H, 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_{PC} = 14.9 Hz), 66.8 (d, J_{PC} = 4.5 Hz), 65.5, 62.1 (d, J_{PC} = 3.2 Hz), 55.4, 30.1 (d, J_{PC} = 140.0 Hz), 16.3 (d, J_{PC} = 5.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.36. IR (neat): 3356, 1713, 1258, 1168 cm^{-1}. ESI-MS: *m/z* = 399 [MNa^+]. HRMS: *m/z* calcd for $C_{16}H_{25}O_8NaP$ [MNa^+]: 399.1185. Found: 399.1185.
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(14) Compound **7b** (for a sample of 100% ee): mp 93–95 °C; $[\alpha]_D^{22}$ –7.92 (*c* 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.32 (10 H, m), 5.12–4.96 (4 H, m), 3.70 (1 H, qd, *J* = 4.2, 14.9 Hz), 3.59 (1 H, td, *J* = 5.6, 11.3 Hz), 2.04–1.96 (2 H, m), 1.13 (3 H, d, *J* = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0 (d, J_{PC} = 5.5 Hz), 135.9 (d, J_{PC} = 5.0 Hz), 128.7, 128.6, 128.6, 128.1, 128.0, 70.7 (d, J_{PC} = 17.4 Hz), 70.4 (d, J_{PC} = 5.6 Hz), 67.6 (d, J_{PC} = 6.4 Hz), 30.5 (d, J_{PC} = 139.6 Hz), 18.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.91. IR (KBr): 3359, 2968, 1214 cm^{-1}. ESI-MS: *m/z* = 351 [MH^+]. HRMS: *m/z* calcd for $C_{18}H_{24}O_5P$ [MH^+]: 351.1361. Found: 351.1352.

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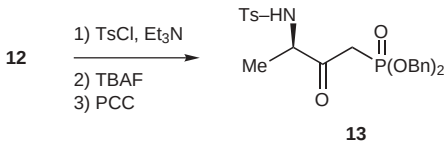
(17) Compound **12**: oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (10 H, m), 5.03 (2 H, dd, *J* = 9.1, 11.8 Hz), 4.95 (2 H, dd, *J* = 8.2, 11.8 Hz), 4.02–3.87 (1 H, m), 3.15–3.11 (1 H, m), 2.06–1.97 (2 H, m), 1.00 (3 H, d, *J* = 6.6 Hz), 0.91 (9 H, t, *J* = 7.9 Hz), 0.58 (6 H, q, *J* = 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.2 (d, J_{PC} = 5.4 Hz), 128.5–127.7 (aromatic), 71.6, 67.2 (d, J_{PC} = 6.6 Hz), 67.1 (d, J_{PC} = 6.5 Hz), 51.3 (d, J_{PC} = 7.6 Hz), 30.1 (d, J_{PC} = 138.0 Hz), 17.0, 6.8, 4.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.81. ESI-MS: *m/z* = 464 [MH^+]. HRMS: *m/z* calcd for $C_{24}H_{39}NO_4SiP$ [MH^+]: 464.2386. Found: 464.2382.

(18) The chemical structure of **12** was determined after the conversion into γ-amino-β-ketophosphonate **13** through tosylation, desilylation, and oxidation with PDC. In ^1H the NMR spectrum (400 MHz, $CDCl_3$) of **13**, a signal ascribed to the Me group at the γ-position was observed at δ = 1.18 ppm as a doublet (*J* = 7.1 Hz) but not as a singlet corresponding to regioisomeric β-amino-γ-ketophosphonate (Scheme 7).



Scheme 7