A General and Facile Synthesis of β- and γ-Hydroxy Phosphonates from Epoxides

Zhengong Li, Saibaba Racha, Li Dan, Hussein El-Subbagh, and Elie Abushanab*

Departments of Chemistry and Medicinal Chemistry, University of Rhode Island, Kingston, Rhode Island 02881

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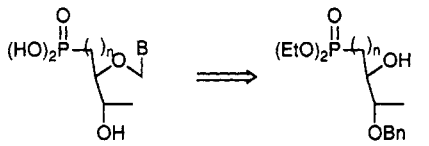
A practical and facile method for the preparation of hydroxy phosphonate esters is described. Regiospecific ring opening of monosubstituted epoxides by phosphorus and carbon nucleophiles, derived from diethyl phosphite and methanephosphonates, in the presence of BF_3·OEt_2 furnishes the corresponding β- and γ-hydroxy phosphonates, respectively. Ketals, bromides, sulfonate esters, and carbamates (compounds **12**, **13**, **15**, **16**, and **18**) are stable under the reaction conditions, but benzoate esters (**14**) behave differently. While they survive phosphite nucleophilicity, they are cleaved by phosphonates. Several chirons (**2**, **28a**, **30b**, and **31**) for the synthesis of phosphonate isosteres of nucleotides and phospholipids are also described.

Interest in phosphonate chemistry and biology is attributed to the fact that the carbon–phosphorus bond in phosphonates,[1] unlike phosphates, is not susceptible to hydrolytic actions of phosphatases, imparting stability and longer duration of action under physiological conditions. Phosphonate isosteres of biologically important phosphates can be found in carbohydrates, amino acids, phospholipids, nucleotides, etc.[2]

In connection with studies for the synthesis of phosphonate isosteres of 1′,2′-*seco*-nucleotides, an approach for introducing the phosphonate by an Arbuzov reaction[3] in individual nucleosides at a late stage in the synthesis proved to be inefficient. A more attractive alternative called for a suitable method to prepare β- and γ-hydroxybutanephosphonate esters as synthons, which can then be incorporated into individual 1′,2′-*seco*-nucleosides.



1′, 2′-*Seco*-nucleotides n = 1, 2; B = Purine or Pyrimidine

In an earlier communication[4] from our laboratory, preliminary findings on a useful reaction to prepare β- and γ-hydroxy phosphonate esters were reported. A regiospecific and nucleophilic ring opening of an epoxide catalyzed by BF_3·OEt_2 was described. Applications of this reaction in the area of phosphonolipids have recently been described.[5] We report herein a full account of the work that covers the scope of the reaction and its compatibility with other functional groups in the molecule.

Initial efforts to prepare the title compounds by the Arbuzov reaction were not successful. We then turned our attention to using epoxides, instead of alkyl halides, to form the carbon–phosphorus bond. The easy access to epoxides from polyhydroxylic and unsaturated compounds and the stereochemical predictability of their reactions make them among the most attractive starting materials in organic synthesis. Although a number of reports have appeared on ring opening reactions of epoxides involving carbon,[6] nitrogen,[7] oxygen,[8] and sulfur[9] nucleophiles, surprisingly, very few examples are known in the literature, where phosphorus or phosphorus-containing nucleophiles have been similarly used. Ethylene oxide was condensed with sodium diethyl phosphite to produce diethyl 2-hydroxyethanephosphonate.[10] The need for excess epoxide precluded the utility of this approach. In a more recent report, Lewis acid catalyzed opening of oxiranes with trimethylsilyl phosphite[11] furnished the corresponding phosphonates in good yields. Here again, the epoxide was used in 3-fold excess over the phosphite. In our hands, when this reaction was tried using equimolar quantities of TMSCl, diethyl phosphite, and epoxide **1**,[12] the desired product **2a** was obtained in about 5% yield. A silylated halohydrin was the major product obtained. A BF_3·OEt_2-catalyzed reaction using preformed trimethylsilyl phosphite resulted in recovery of the starting material.

Another epoxide opening reaction was reported to take place using the dianion of methyl acetoacetate in the

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(1) (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349. (b) Engel, R. In *The Role of Phosphonates in Living Systems*; Hilderband, R. L., Ed.; CRC Press, Inc., Boca Raton, FL, 1988. (c) Engel, R. *Synthesis of Carbon-Phosphorus Bonds*; CRC Press, Inc., Boca Raton, FL, 1988.

(2) (a) Blackburn, M. G. *Chem. Ind. (London)* **1981**, 134. (b) Blackburn, M. G.; Kent, D. E.; Folkmann, F. *J. Chem. Soc., Perkin Trans. I* **1984**, 1119. (c) Mazur, A.; Tropp, E. B.; Engel, R. *Tetrahedron Lett.* **1984**, *40*, 3949. (d) Tatsuouka, T.; Imao, K.; Suzuki, K. *Heterocycles* **1986**, *24*, 2133. (e) Padukova, N. S.; Karpeisky, M. Y.; Kolobushinka, L. I.; Mikailov, S. N. *Tetrahedron Lett.* **1989**, *20*, 3869. (f) Tanaka, H.; Fukui, M.; Haraguchi, K.; Masaki, M.; Miyasaka, T. *Tetrahedron Lett.* **1989**, *30*, 2567. (g) Flack, J. R.; Abdali, A.; Wittenberger, S. J. *J. Chem. Soc., Chem. Commun.* **1990**, 953.

(3) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.

(4) Racha, S.; Li, Z.; El-Subbagh, H. I.; Absuhanab, E. *Tetrahedron Lett.* **1992**, *33*, 5491.

(5) (a) Bittman, R.; Byun, H. S.; Mercier, B.; Saleri, H. *J. Med. Chem.* **1993**, *36*, 297. (b) Li, Z.; Saibaba, R.; Abushanab, E. *Tetrahedron Lett.* **1993**, *34*, 3539.

(6) (a) Gaylord, N. G.; Becker, E. I. *Chem. Rev.* **1951**, *49*, 413. (b) Davies, S. G.; Wollowitz, S. *Tetrahedron Lett.* **1980**, *21*, 4175.

(7) Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208.

(8) Evans, D. A.; Crawford, T. C.; Fujimoto, T. T.; Thomas, R. C. *J. Org. Chem.* **1974**, *39*, 3176.

(9) Guidon, Y.; Yong, R. N.; Frenette, R. *Synth. Commun.* **1981**, *11*, 391.

(10) Chelintsev, G. V.; Kuskov, V. K. *J. Gen. Chem. (USSR)* **1946**, *16*, 1481 (*Chem. Abstr.* **1947**, 5442).

(11) (a) Azuhata, T.; Okamoto, Y. *Synthesis* **1983**, 916. (b) Azuhata, T.; Okamoto, Y. *Synthesis* **1984**, 417.

(12) Abushanab, E.; Vemisheti, P.; Leiby, R. W.; Singh, R. W.; Mikkilineni, A. B. Wu, D. C.-J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988**, *53*, 2598.

0022-3263/93/1958-5779$04.00/0

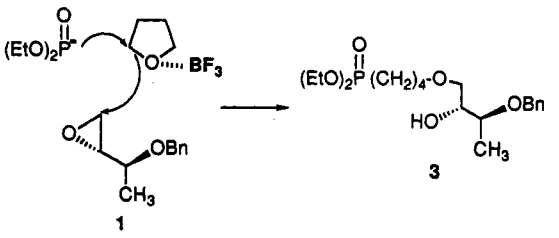
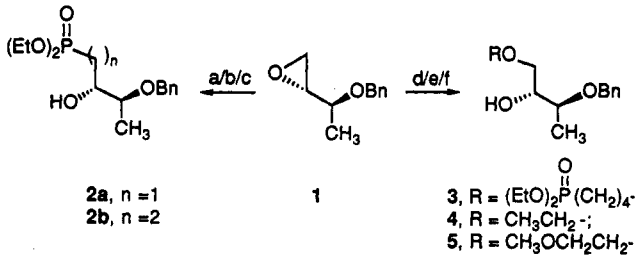


Figure 1. Rationale for ethereal solvent (THF) partitipation in epoxide opening.

Scheme I[a]



[a] (a) $(EtO)_2POSiMe_3$, ZnI_2 or Et_2AlCl, 140 °C; (b) $H(O)P(OEt)_2$, NaH, $BF_3{\cdot}OEt_2$, benzene, 0 °C; (c) $CH_3(O)P(OEt)_2$, n-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (d, e, f) same as b using instead THF, ether, and DME, respectively.

presence of $BF_3{\cdot}OEt_2$.[13] When we attempted to apply these conditions, generating the phosphite anion with NaH in THF at 0 °C, a reaction took place and a product was formed whose ^1H and ^{13}C NMR spectra suggested the involvement of the solvent in the reaction. On the basis of these and elemental analysis data, the product was assigned structure **3**. Other ethereal solvents such as ethyl ether and 1,2-dimethoxyethane led to the formation of **4** and **5**, respectively (Scheme I).

The formation of these products can be rationalized as shown in Figure 1. Initial complex formation between the solvent and $BF_3{\cdot}OEt_2$ followed by phosphite anion attack at the α-carbon of the ether generates an alkoxide ion which, in turn, reacts with the epoxide to furnish the observed products.

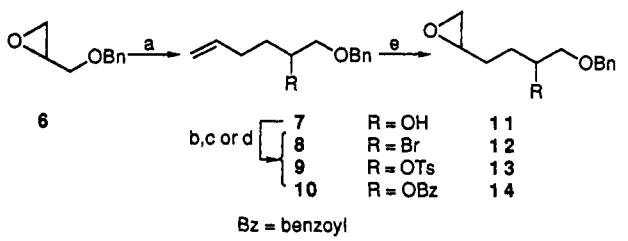
The use of a nonethereal solvent became the obvious choice. When the reaction was repeated using benzene, instead of THF, the β-hydroxy phosphonate **2a** was obtained in 65% yield along with a minor product (17%) which proved to be identical to **4**. The latter product is likely derived from ethoxide generated from the $BF_3{\cdot}OEt_2$ complex.

Our objective to prepare β- and γ-hydroxy phosphonates efficiently and in good yields was realized when we noted a report detailing the successful opening of an oxetane ring by a phosphonate anion in the presence of $BF_3{\cdot}OEt_2$.[2f] Indeed, when the anion of the same phosphonate was generated with n-BuLi in THF, followed by the sequential addition of epoxide **1** and $BF_3{\cdot}OEt_2$, the corresponding γ-hydroxy phosphonate **2b** was obtained in quantitative yield. The reaction was complete in 1 h at −78 °C. When the same reaction conditions were applied to the phosphite anion, and the temperature was maintained at −78 °C, THF did not participate in the reaction and compound **2a** was obtained in comparable yields.

The need to run the reaction at −78 °C when THF was used as the solvent detracted from its broad utility. This

(13) Lygo, B.; O'Conoor, N.; Wilson, P. R. *Tetrahedron Lett.* **1988**, *44*, 6881.

Scheme II[a]



[a] (a) C_3H_5MgBr, Li_2CuCl_4, ether, −20 °C → 0 °C; (b) CBr_4, PPh_3, THF, rt; (c) TsCl, pyridine, rt; (d) BzCl, pyridine, rt; (e) *m*-CPBA, CH_2Cl_2, 0 °C → rt.

became obvious when low temperatures reduced the solubility of the epoxide in THF, resulting in no reaction. For example, *o*-(octadecylcarbamoyl)- and *o*-hexadecylglycidol (**16** and **19**[14]) failed to undergo the desired reaction at −78 °C. However, the substitution of toluene for THF proved to be a significant improvement, allowing the reaction to be run at −30 °C and, therefore, enhancing the solubility of the starting epoxides.

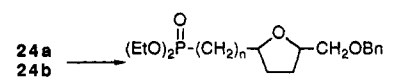
In an attempt to widen the scope of this reaction, we decided to examine the compatibility of other functional groups with the reaction conditions. Thus, the stability of halides and sulfonate and benzoate esters was examined. The preparation of these compounds is outlined in Scheme II.

The condensation of *o*-benzylglycidol (**6**) with allylmagnesium bromide furnished alcohol **7** which was converted to derivatives **8**–**10** using standard procedures. Epoxidation of the latter compounds with *m*-CPBA gave the corresponding epoxides **12**–**14**. Attempts to oxidize **7** to **11** were not successful since, under the reaction conditions, the free hydroxyl group participated in acid-catalyzed opening of the resulting epoxide.

The results of reacting epoxides **12**–**14** with phosphite and phosphonate anions are shown in Table I. It can be seen that all three functionalities are stable to the reaction conditions, when the phosphite anion was used, resulting in the formation of products **23a**, **24a**, and **25a**, respectively. However, the same is not true for the methanephosphonate anion. While the reaction with bromo epoxide **12** led to the expected γ-hydroxy phosphonate **23b**, the other tosylate (**13**) and benzoate (**14**) epoxides did not give the expected compounds. The ^1H NMR spectrum of the crude product obtained from **13**, when the reaction was quenched with a pH 4 buffer solution, strongly supported the formation of the expected tosylate **24b**. However, attempts to purify the compound by chromatography on either silica gel or neutral alumina resulted in intramolecular displacement of the tosylate group and formation of the tetrahydrofuran **33b**.[15] Similarly, cleavage of the benzoate ester took place in the reaction of **14**. In addition to the

(14) (a) Hirch, G.; Barner, R. *Helv. Chim. Acta* **1982**, *65*, 1059. (b) Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J. Org. Chem.* **1988**, *53*, 6005.

(15) For reasons that are not entirely clear, product **24b** underwent spontaneous intramolecular cyclization to give **33b**. However, β-hydroxy phosphonate **24a** was stable to purification and its cyclization to **33a** was effected using NaH in THF (see Experimental Section).

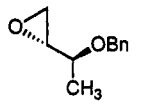
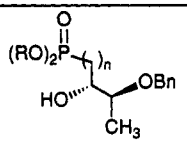
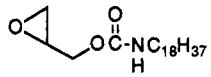
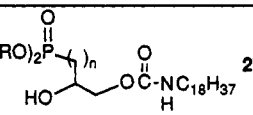
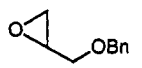
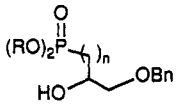
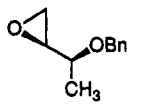
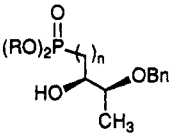
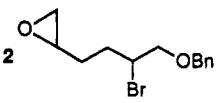
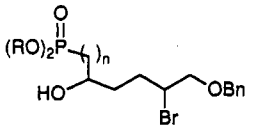
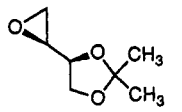
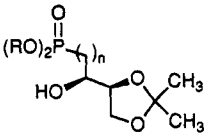
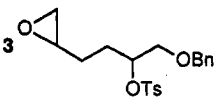
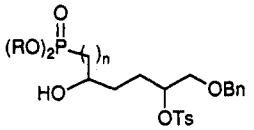
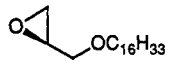
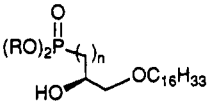
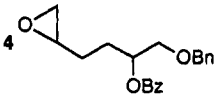
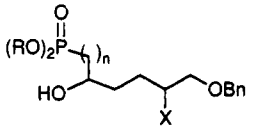
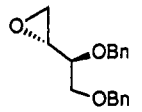
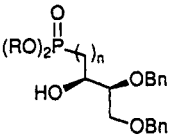
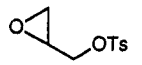
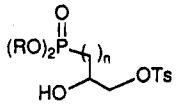
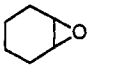
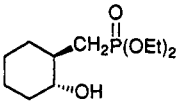


33a, n = 1
33b, n = 2

Table I

Epoxide $\xrightarrow[BF_3 \cdot OEt_2,\ THF,\ -78°C]{\text{Nucleophile}^a,\ n\text{-BuLi}}$ Product

a series: R = Et, n = 1 **c** series: R = Me, n = 2
b series: R = Et, n = 2 **d** series: R = Bn, n = 2

epoxide no.	epoxide structure	product structure	product no.	yield, %	epoxide no.	epoxide structure	product structure	product no.	yield, %
1			**2a**	100	16[≠]			**27b**	94
			2b	100					
			2c	95					
			2d	84					
6			**22b**	94	17			**28a**	100
12			**23a**	65	18			**29a**	64
			23b	84				**29b**	65
13			**24a**	65	19[≠]			**30b**	86
			24b	90[#]					
14			**25a** (X = OBz)	72	20			**31a**	77
			25b (X = OH)	90				**31b**	100
								31c	96
								31d	61
15			**26b**	79	21			**32**	83

[a] Nucleophiles: **a**, $H(O)P(OEt)_2$; **b**, $CH_3(O)P(OEt)_2$; **c**, $CH_3(O)P(OMe)_2$; **d**, $CH_3(O)P(OBn)_2$. Reaction run in toluene; yield of compound **33b**.[15]

formation of dihydroxy compound **25b**, diethyl benzoylmethanephosphonate was also formed as a byproduct. This type of reaction has been previously used for the preparation of β-keto phosphonates.[16] While carboxylate esters are cleaved by phosphonate anions, carbamates seem to be stable to these conditions. This is illustrated by the reaction of **16** to form the expected product **27b** in excellent yield.

The regiospecificity of this reaction is undoubtedly due to the ability of the nucleophile to attack the least hindered site of the oxirane ring. The successful opening of cyclohexene oxide **21** to give **32** (Table I) further broadens the utility of this reaction to 1,2-disubstituted epoxides. However, the regioselectivity or regiospecificity in unsymmetrical epoxides is yet to be determined.

The original objective of this work, namely, the preparation of chiral phosphonate synthons, has been met as shown in Table I (compounds **1**, **17–20**). These phosphonates, and especially the dibenzyl esters (**2d** and **31d**) which can be reductively cleaved, have been or are in the process of being converted to phosphonate isosteres of biologically important nucleotides and phospholipids. The synthesis and biological activity will be reported elsewhere.

Experimental Section

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on either a Varian EM-390 or Bruker 300-MHz spectrometer. Chemical shifts are in parts per million with respect to TMS. Unless otherwise indicated, optical rotations were measured in absolute EtOH on a Perkin-Elmer Model-141 digital readout polarimeter. Silica gel (Merck grade 60, 230–400 mesh, 60 Å) suitable for column chromatography was purchased from Aldrich. All solvent proportions are by volume. Unless otherwise indicated, yields are given in Table I. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

General Procedure. A 2.5 M solution of n-BuLi in hexanes (12 mL, 30 mmol) was added dropwise to a stirred solution of phosphorus-containing nucleophile (**a**, **b**, **c**, or **d**, Table I, 30 mmol) in dry THF (30 mL) at −78 °C under a nitrogen atmosphere. After 15 min of stirring, a solution of the epoxide (10 mmol) in THF (5 mL) was added dropwise, followed by $BF_3 \cdot OEt_2$ (5.68 g, 40 mmol) which was slowly introduced, while maintaining the temperature below −70 °C. After the solution was stirred for two more hours, the reaction was quenched with saturated aqueous NH_4Cl and was allowed to warm up to rt. The residue obtained, after evaporation under reduced pressure, was dissolved in ether.

(16) Tank, K.-C.; Coward, J. K. *J. Org. Chem.* **1983**, *48*, 5001.
(17) Abushanab, E.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1984**, *35*, 3841.

The solution was washed with brine, dried ($MgSO_4$), and concentrated, and the residue was chromatographed on silica gel (hexane-EtOAc 3:1) to yield the pure hydroxy phosphonate ester.

Diethyl (2*R*,3*S*)-3-(benzyloxy)-2-hydroxybutanephosphonate (2a) was prepared from 1 by following the general procedure: $[\alpha]^{25}_D$ +25.9° (*c* = 1.84); ^{1}H NMR δ 1.25 (t, *J* = 6 Hz, 6H), 1.36 (d, *J* = 6 Hz, 3 H), 1.75–2.22 (m, 2H), 3.26–3.68 (m, 2H, 1H, D_2O exchangeable), 3.76–4.30 (m, 5H), 4.54 (q_{AB}, *J* = 9 Hz, 2H), 7.28 (s, 5H). Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.95; H, 7.97; P, 9.79. Found: C, 56.86; H, 8.10; P, 9.66.

Diethyl (3*R*,4*S*)-4-(benzyloxy)-3-hydroxypentanephosphonate (2b) was prepared from 1 by following the general procedure: $[\alpha]^{25}_D$ +27.6° (*c* = 0.530); ^{1}H NMR δ 1.02–2.20 (m, 13H), 3.22–3.78 (m, 3H), 3.82–4.32 (m, 4H), 4.32–4.76 (m, 2H), 7.23 (s, 5H). Anal. Calcd for $C_{16}H_{27}O_5P$: C, 58.17; H, 8.24; P, 9.38. Found: C, 58.38; H, 8.07; P, 9.18.

Dimethyl (3*R*,4*S*)-4-(benzyloxy)-3-hydroxypentanephosphonate (2c) was prepared from 1 by following the general procedure: $[\alpha]^{25}_D$ +36.9° (*c* = 0.225); ^{1}H NMR δ 1.22 (d, *J* = 6 Hz, 3H), 1.54 (m, 4H), 3.04 (br s, 1H, D_2O exchangable), 3.30–4.12 (m, 2H), 3.70 (d, *J* = 9 Hz, 6H), 4.40–4.72 (m, 2H), 7.26 (s, 5H). Anal. Calcd for $C_{14}H_{23}O_5P$: C, 55.62; H, 7.67. Found: C, 55.53; H, 7.50.

Dibenzyl (3*R*,4*S*)-4-(benzyloxy)-3-hydroxypentanephosphonate (2d) was prepared from 1 by following the general procedure: $[\alpha]^{25}_D$ +18.1° (*c* = 0.900, CH_2Cl_2); ^{1}H NMR δ 1.10 (t, *J* = 6 Hz, 3H), 1.40–2.22 (m, 4H), 2.61 (d, *J* = 5 Hz, 1H, D_2O exchangeable), 2.75–3.25 (m, 2H), 4.28–4.68 (q, *J* = 12 Hz, 2H), 4.75–5.15 (m, 4H), 7.10–7.43 (m, 15H). Anal. Calcd for $C_{26}H_{31}O_5P$: C, 68.70; H, 6.77; P, 6.82. Found: C, 68.58; H, 6.81; P, 6.74.

Diethyl (2*S*,3*S*)-4-(3benzyloxy)-2-hydroxy-1-butoxy)butanephosphonate (3). Diethyl phosphite (1.38 g, 10 mmol) in dry THF (5 mL) was added dropwise to a cold (0 °C), stirred suspension of NaH (0.240 g, 10 mmol), previously washed three times with dry hexane, in THF (40 mL) under a nitrogen atmosphere. After the solution was stirred for 30 min, a solution of epoxide 1 (0.890 g, 5 mmol) in dry THF (5 mL), followed by BF_3·OEt_2 (2.270 g, 16 mmol), was added, and the resulting mixture was allowed to warm up to rt while stirring overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL), and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (hexane–EtOAc 1:1) to provide 3 (0.794 g, 41%): $[\alpha]^{25}_D$ +6.94° (*c* = 0.865); ^{1}H NMR δ 0.98–1.42 (m, 9H), 1.44–2.16 (m, 6H), 3.22–3.74 (m, 7H), 3.76–4.24 (m, 4H), 4.50 (q_{AB}, *J* = 9 Hz, 2H), 7.21 (s, 5H). Anal. Calcd for $C_{19}H_{33}O_6P$: C, 58.75; H, 8.56; P, 7.97. Found: C, 58.47; H, 8.59; P, 8.17.

(2*S*,3*S*)-3-*O*-Benzyl-1-*O*-ethylbutane-1,2,3-triol (4) was isolated in 66% yield when the reaction was carried out as described for 3, except that Et_2O was used in place of THF: ^{1}H NMR δ 1.16 (t, J = 6 Hz, 3H), 1.20 (d, J = 6 Hz, 3H), 2.32–2.76 (br s, 1H, D_2O exchangeable), 3.34–3.78 (m, 6H), 4.56 (q_{AB}, *J* = 9 Hz, 2H), 7.26 (s, 5H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.49; H, 8.78.

(2*S*,3*S*)-3-*O*-Benzyl-1-*O*-(2-methoxyethyl)butane-1,2,3-triol (5) was isolated in 66% yield when the reaction was carried out as described for 3, except that DME was used in place of THF: ^{1}H NMR δ 1.20 (d, *J* = 6 Hz, 3H), 2.75 (s, 1H, D_2O exchangeable), 3.34 (s, 3H), 3.38–3.88 (m, 8H), 4.52 (q_{AB}, *J* = 9 Hz, 2H), 7.22 (s, 5H). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.08; H, 8.95.

1-*O*-Benzylhex-5-ene-1,2-diol (7). To a stirred suspension of Mg (1.20 g, 50 mmol) in dry ether (5 mL) cooled by an ice bath was added dropwise a solution of freshly distilled allyl bromide (4.84 g, 40 mmol) in ether (10 mL). The mixture was stirred at room temperature for 1 h. The Grignard reagent was siphoned into a solution of *O*-benzylglycidol (6) (3.28 g, 20 mmol) and Li_2CuCl_4 (4.82 g, 22 mmol) in THF (50 mL) at −78 °C. The reaction mixture was allowed to stir at −78 °C for 1 h, brought to rt, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether, and the organic phase was successively washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated. Distillation of the resulting residue at reduced pressure yielded 7 (3.87 g, 94%): ^{1}H NMR δ 1.30–1.72 (m, 2H), 1.88–2.32 (m, 2H), 2.52 (br s, 1H, D_2O exchangeable), 3.14–4.06 (m, 3H), 4.48 (s, 2H), 4.78–5.14 (m, 2H), 5.42–6.02 (m, 1H), 7.20 (s, 5H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.56; H, 7.76.

6-(Benzyloxy)-5-bromo-1-hexene (8). To a stirred solution of 7 (2.47g, 12 mmol) and 2,6-lutidine (0.32 g, 3 mmol) in dry THF (30 mL) were added PPh_3 (3.93 g, 15 mmol) and CBr_4 (4.81 g, 14.5 mmol). The mixture was stirred overnight at rt, diluted with hexane (50 mL), and filtered. The filter cake was washed with hexane/ether (1:1, 50 mL). The filtrate was concentrated and the residue was chromatographed on silica gel (hexane–EtOAc 95:5) to provide 8 (3.20 g, 99%): ^{1}H NMR δ 1.68–2.40 (m, 4H), 3.56–4.26 (m, 3H), 4.48 (s, 2H), 4.82–5.18 (m, 2H), 5.46–5.98 (m, 1H), 7.24 (s, 5H). Anal. Calcd for $C_{13}H_{17}BrO$: C, 58.01; H, 6.37, Br, 29.68. Found: C, 58.28; H, 6.40; Br, 29.81.

6-(Benzyloxy)-5-(*p*-toluenesulfonyloxy)-1-hexene (9). A mixture of the alcohol 7 (2.0 g, 10 mmol) and *p*-toluenesulfonyl chloride (2.29 g, 12 mmol) in pyridine (10 mL) was stirred at room temperature for 36 h, treated with ice–water, and extracted with ether. The organic phase was successively washed with water, cold dilute HCl, and brine, dried ($MgSO_4$), and concentrated. The resulting residue was chromatographed on silica gel (hexane–EtOAc 95:5) to give 9 (3.24 g, 90%): ^{1}H NMR δ 1.62–2.20 (m, 4H), 2.44 (s, 3H), 3.48 (d, J = 6 Hz, 2H), 4.40 (s, 2H), 4.46–5.14 (m, 3H), 5.46–5.96 (m, 1H), 7.02–7.44 (m, 7H), 7.72 (d, J = 7 Hz, 2H). Anal Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71; S, 8.89. Found: C, 66.55; H, 6.80; S, 8.65.

5-(Benzyloxy)-6-(benzyloxy)-1-hexene (10) was prepared from 7 in 93% yield by following the same procedure described for 9, except that benzoyl chloride was used in place of *p*-tgoluenesulfonyl chloride: ^{1}H NMR δ 1.70–2.25 (m, 4H), 3.60 (d, *J* = 6 Hz, 2H), 4.52 (s, 2H), 4.85–5.12 (m, 3H), 5.52–6.00 (m, 1H), 7.25–7.52 (m, 8H), 8.01 (dd, *J* = 7.5 and 1.5 Hz, 2H). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.15. Found: C, 77.55; H, 7.27.

6-(Benzyloxy)-5-bromo-1,2-epoxyhexane (12). A solution of 8 (1.80 g, 6.69 mmol) and *m*-CPBA (2.76 g, 50%; 8 mmol) in CH_2Cl_2 (30 mL) was stirred overnight at rt. After dilution with ether (100 mL), the mixture was successively washed with saturated solutions of $NaHCO_3$, $NaHSO_3$, $NaHCO_3$, and brine, and the organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (hexane–EtOAc 95:5) to afford 12 (1.78 g, 93%): ^{1}H NMR β 1.42–2.32 (m, 4H), 2.34–2.62 (m, 1H), 2.64–3.04 (m, 2H), 3.52–3.90 (m, 2H), 3.94–4.32 (m, 1H), 4.50 (s, 2H), 7.26 (s, 5H). Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01, Br, 28.02. Found: C, 54.60; H, 6.23; Br, 28.11.

6-(Benzyloxy)-5-(*p*-toluenesulfonyloxy)-1,2-epoxyhexane (13) was prepared from 9 in 88% yield by following the same procedure as described for 12: ^{1}H NMR δ 1.37–1.95 (m, 4H), 2.28–2.46 (m, 4H), 2.59–2.70 (m, 1H), 2.71–2.89 (m, 1H), 3.49 (d, *J* = 6 Hz, 2H), 4.39 (s, 2H), 4.62–4.95 (m, 1H), 7.08–7.28 (m, 7H), 7.73 (d, J = 7.5 Hz, 2H). Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43; S, 8.50. Found: C, 63.66; H, 6.63; S, 8.39.

5-(Benzyoyloxy)-6-(benzyloxy)-1,2-epoxyhexane (14) was prepared from 10 in 91% yield by following the same procedure as described for 12: ^{1}H NMR δ 1.42–2.05 (m, 4H), 2.32–2.42 (m, 1H), 2.56–2.78 (m, 1H), 2.80–3.02 (m, 1H), 3.65 (d, *J* = 6 Hz, 2H), 4.55 (s, 2H), 5.17–5.50 (m, 1H), 7.28–7.53 (m, 8H), 8.00 (dd, *J* = 7.5 and 1.5 Hz, 2H). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.80; H, 6.74.

***O*-(Octadecylcarbamoyl)glycidol (16).** To a solution of octadecyl isocyanate (0.500 g, 1.69 mmol) and glycidol (0.160 g, 2.16 mmol) in anhydrous CH_2Cl_2 (7 mL) was added one drop of pyridine. After the solution was stirred overnight at rt, the solvents were evaporated and the residue was chromatographed on silica gel (hexane–EtOAc 95:5) to provide 16 (0.581 g, 93%): mp 76.2–76.4 °C; ^{1}H NMR δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.25 (s, 28H), 1.50 (m, 4H), 2.64 (dd, *J* = 2.6 and 4.84 Hz, 1H), 2.83 (t, *J* = 4.5 Hz, 1H), 3.18 (m, 3H), 3.87 (dd, *J* = 6.4 and 12.1 Hz, 1H), 4.42 (dd, *J* = 2.7 and 12.1 Hz, 1H), 4.73 (br s, 1H, D_2O exchangeable). Anal. Calcd for $C_{22}H_{43}NO_3$: C, 71.54; H, 11.65, N, 3.79. Found: C, 71.71, H, 11.45, N, 3.84.

Diethyl 4-(benzyloxy)-3-hydroxybutanephosphonate (22b) was prepared from 6 by following the general procedure: ^{1}H NMR δ 1.30 (t, *J* = 6 Hz, 6H), 1.53–2.02 (m, 4H), 3.15–3.40 (m, 3H, 1H D_2O exchangeable), 3.64–4.15 (m, 5 H), 4.53 (s, 2H), 7.32 (s, 5H). Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.95; H, 7.97; P, 9.79. Found: C, 56.95; H, 7.84; P, 9.67.

Diethyl 6-(benzyloxy)-5-bromo-2-hydroxyhexanephosphonate (23a) was prepared from **12** by following the general procedure: ^{1}H NMR δ 1.12–2.36 (m, 12H), 3.54–4.44 (m, 9H), 4.52 (s, 2H), 7.28 (s, 5H). Anal. Calcd for $C_{17}H_{28}BrO_5P$: C, 48.24; H, 6.67; Br, 18.88; P, 7.32. Found: C, 48.51; H, 6.49; Br, 19.02; P, 7.23.

Diethyl 7-(benzyloxy)-6-bromo-3-hydroxyheptanephosphonate (23b) was prepared from **12** by following the general procedure: ^{1}H NMR δ 1.27 (t, J = 6 Hz, 6H), 1.45–2.22 (m, 8H), 2.89 (br s, 1H, D_2O exchangeable), 3.68 (d, J = 6 Hz, 2H), 3.82–4.27 (m, 6H), 4.53 (s, 2H), 7.32 (s, 5H). Anal. Calcd for $C_{18}H_{30}O_5$-BrP: C, 49.44; H, 6.92; Br, 18.27; P, 7.08. Found: C, 49.45; H, 6.80; Br, 18.11; P, 7.04.

Diethyl 6-(benzyloxy)-2-hydroxy-5-(*p*-toluenesulfonyloxy)hexanephosphonate (24a) was prepared from **13** by following the general procedure: ^{1}H NMR δ 1.35 (t, J = 6 Hz, 6H), 1.43–2.01 (m, 6H), 2.40 (s, 3H), 3.45 (d, J = 6 Hz, 2H), 3.76–4.27 (m, 6H), 4.30 (s, 2H), 4.48–4.76 (m, 1H), 7.06–7.31 (m, 7H), 7.68 (d, J = 7 Hz, 2H). Anal. Calcd for $C_{24}H_{35}O_8PS$: C, 56.02; H, 6.86; P, 6.02; S, 6.23. Found: C, 55.80; H, 6.62; P, 5.88; S, 5.96.

Diethyl 7-(benzyloxy)-3-hydroxy-6-(*p*-toluenesulfonyloxy)heptanephosphonate (24b) was prepared from **13** by following the general procedure: ^{1}H NMR δ 1.30 (t, J = 6 Hz, 6H), 1.47–2.04 (m, 8H), 2.40 (s, 3H), 3.45 (d, J = 6 Hz, 2H), 3.78–4.80 (m, 9H), 7.04–7.28 (m, 7H), 7.64 (d, J = 7 Hz, 2H). Attempts to purify this compound by column chromatography resulted in the formation of **33b**.

Diethyl 5-(benzoyloxy)-6-(benzyloxy)-2-hydroxyhexanephosphonate (25a) was prepared from **14** by following the general procedure: ^{1}H NMR δ 1.27 (t, J = 6 Hz, 6H), 1.50–2.02 (m, 6H), 3.61 (d, J = 6 Hz, 2H), 3.87–4.23 (m, 6H), 4.51 (s, 2H), 5.32 (br 1H, D_2O exchangeable), 7.12–7.48 (m, 8H), 7.98 (dd, J = 7.5 and 1.5 Hz, 2H). Anal. Calcd for $C_{24}H_{33}O_7P$: C, 62.06; H, 7.16. Found: C, 62.04; H, 7.13.

Diethyl 7-(benzyloxy)-3,6-dihydroxyheptanephosphonate (25b) was prepared from **14** by following the general procedure: ^{1}H NMR δ 1.27 (t, J = 6 Hz, 6H), 1.44–2.12 (m, 8H), 3.28–4.23 (m, 10H), 4.52 (s, 2H), 7.30 (s, 5H). Anal. Calcd for $C_{18}H_{31}O_6P$: C, 57.74; H, 8.35; P, 8.27. Found: C, 57.56; H, 8.39; P, 8.01.

Diethyl 3-hydroxy-4-(*p*-toluenesulfonyloxy)butanephosphonate (26b) was prepared from **15** by following the general procedure: ^{1}H NMR δ 1.20 (t, J = 6 Hz, 6H), 1.46–2.25 (m, 4H), 2.44 (s, 3H), 3.52–4.20 (m, 8H), 7.52 ($q_{A_2B_2}$, J = 6 Hz, 4H). Anal. Calcd for $C_{15}H_{25}O_7PS$: C, 47.36; H, 6.62; S, 8.43. Found: C, 47.40; H, 6.51; S, 8.61.

Diethyl 3-hydroxy-4-(octadecylcarbamoyl)butanephosphonate (27b) was prepared from **16b** by following the general procedure: mp 46.5–48.2 °C; ^{1}H NMR δ 0.88 (t, J = 7 Hz, 3H), 1.25 (br s, 28H), 1.33 (t, J = 7 Hz, 6H), 1.46–1.53 (m, 4H), 1.71–2.01 (m, 4H), 3.16 (m, 2H), 3.86 (m, 1H), 3.96–4.03 (m, 6H), 4.72 (br s, 1H, D_2O exchangeable), 4.88 (br s, 1H, D_2O exchangeable). Anal. Calcd for $C_{27}H_{56}NO_6P$: C, 62.15; H, 10.82; N, 2.68; P, 5.94. Found: C, 61.98; H, 10.52; N, 2.57; P, 5.71.

Diethyl (2*S*,3*S*)-3-(benzyloxy)-2-hydroxybutanephosphonate (28a) was prepared from **17**[17] by following the general procedure: $[\alpha]^{25}_D$ +30.95° (c = 1.26); ^{1}H NMR δ 1.24 (t, J = 6 Hz, 6H), 1.34 (d, J = 6 Hz, 3H), 1.76–2.12 (m, 2H), 3.29 (br d, 1H D_2O exchangeable), 3.36–3.70 (m, 1H), 3.82–4.28 (m, 5H), 4.52 (q_{AB}, J = 9 Hz, 2H), 7.30 (s, 5H). Anal. Calcd for $C_{15}H_{25}O_5P$: C, 56.95; H, 7.97; P, 9.79. Found: C, 57.11; H, 7.89; P, 9.62.

Diethyl (2*S*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxybutanephosphonate (29a) was prepared from **18**[12] by following the general procedure: $[\alpha]^{25}_D$ −10.2° (c = 0.610); ^{1}H NMR δ 1.32 (t, J = 6 Hz, 6H), 1.34 (s, 3 H), 1.46 (s, 3H), 1.96 (dd, J = 16 and 6 Hz, 2H), 2.80–3.40 (m, 1H, D_2O exchangeable), 3.68–4.26 (m, 8H). Anal. Calcd for $C_{11}H_{23}O_6P$: C, 46.81; H, 8.21; P, 10.97. Found: C, 46.71; H, 8.16; P, 11.19.

Diethyl (2*S*,3*S*)-3,4-*O*-isopropylidene-2,3,4-trihydroxypentanephosphonate (29b) was prepared from **18** by following the general procedure: $[\alpha]^{25}_D$ −15.7° (c = 1.08); ^{1}H NMR β 1.38 (t, J = 6 Hz, 6H), 1.44 (s, 6H), 1.68–2.32 (m, 4H), 2.96 (br s, 1H,D_2O exchangable), 3.62–4.42 (m, 8H). Anal. Calcd for $C_{12}H_{25}$-O_6P: C, 48.64; H, 8.50; P, 10.45. Found: C, 48.81; H, 8.33; P, 10.36.

Diethyl 4-(hexadecyloxy)-3-hydroxybutanephosphonate (30b) was prepared from **19** by following the general procedure to afford a low-melting solid: $[\alpha]_D^{25}$ −10.2° (c = 0.850); ^{1}H NMR δ 0.88 (t, J = 6.7 Hz, 3H), 1.26 (s, 26H), 1.32 (t, J = 7 Hz, 6H), 1.57 (m, 2H), 1.69–2.01 (m, 4H), 3.28–3.47 (m, 5H, 1H exchangeable D_2O), 3.79 (m, 1H), 4.04–4.15 (m, 4H). Anal. Calcd for $C_{24}H_{51}O_5P$: C, 63.97; H, 11.41; P, 6.87. Found: C, 63.74; H, 11.17; P, 7.09.

Diethyl (2*R*,3*S*)-3,4-bis(benzyloxy)-2-hydroxybutanephosphonate (31a) was prepared from **20** by following the general procedure: $[\alpha]^{25}_D$ +7.04° (c = 4.64); ^{1}H NMR δ 1.26 (t, J = 6 Hz, 6H), 1.80–2.30 (m, 2H), 3.32–3.84 (m, 4H, 1H D_2O exchangeable), 3.86–4.32 (m, 5H), 4.50 (s, 2H), 4.66 (q_{AB}, J = 9 Hz, 2H), 7.27 (s, 10H). Anal. Calcd for $C_{22}H_{31}O_6P$: C, 62.55; H, 7.40; P, 7.33. Found: C, 62.72; H, 7.39; P, 7.12.

Diethyl (3*R*,4*S*)-4,5-bis(benzyloxy)-3-hydroxypentanephosphonate (31b) was prepared from **20** by followng the general procedure: $[\alpha]^{25}_D$ +17.3° (c = 0.370); ^{1}H NMR δ 1.22 (t, J = 6 Hz, 6H), 1.54–2.14 (m, 4H), 3.08 (br s, 1H, D_2O exchangeable), 3.36–4.24 (m, 8H), 4.50 (s, 2H), 4.59 (q_{AB}, J = 9 Hz, 2H), 7.26 (s, 10H). Anal. Calcd for $C_{23}H_{33}O_6P$: C, 63.29; H, 7.62; P, 7.10. Found: C, 63.36; H, 7.45; P, 6.96.

Dimethyl (3*R*,4*S*)-4,5-bis(benzyloxy)-3-hydroxypentanephosphonate (31c) was prepared from **20** by following the general procedure: $[\alpha]^{25}_D$ +17.9° (c = 1.87); ^{1}H NMR δ 1.50–2.08 (m, 4H), 2.56 (br m, 1H, D_2O exchangeable), 3,22–4.22 (m, 4H), 3.68 (d, J = 9 Hz, 6H), 4.46 (s, 2H), 4.58 (q_{AB} J = 9 Hz, 2H), 7.22 (s, 10H). Anal. Calcd for $C_{21}H_{29}O_6P$: C, 61.76; H, 7.16; P, 7.58. Found: C, 61.66; H, 7.19; P, 7.43.

Dibenzyl (3*R*,4*S*)-4,5-bis(benzyloxy)-3-hydroxypentanephosphonate (31d) was prepared from **20** by following the general procedure: $[\alpha]^{25}_D$ +11.3° (c = 1.26); ^{1}H NMR δ 1.55–2.06 (m, 4H), 3.17 (br m, 1H, D_2O exchangeable), 3.41 (q, J = 9 Hz, 1H), 3.60 (d, J = 5 Hz, 2H), 3.63–3.72 (m, 1H), 4.44 (s, 2H), 4.54 (q_{AB}, J = 12 Hz, 2H), 4.82–5.04 (m, 4H), 7.24 (s, 20H). Anal. Calcd for $C_{33}H_{37}O_6P$: C, 70.70; H, 6.65; P, 5.53. Found: C, 70.51; H, 6.68; P, 5.71.

Diethyl (2-hydroxycyclohexanyl)methanephosphonate (32) was prepared from cyclohexene oxide **21** in 83% yield by following the general procedure: ^{1}H NMR δ 0.95–2.14 (m, 17H), 3.10–4.28 (m, 6H, 1H D_2O exchangeable). Anal. Calcd for $C_{11}H_{23}O_4P$: C, 52.95; H, 9.26; P, 12.38. Found: C, 52.61; H, 9.13; P, 12.18.

Diethyl (5-((Benzyloxy)methyl)tetrahydrofuran-2-yl)-methanephosphonate (33a). To the stirred suspension of NaH (0.043 g, 60%, 1.07 mmol), previously washed three times with dry hexane, in dry THF (10 mL) at 0 °C, was added dropwise a solution of **24a** (0.500g, 0.97 mmol) in THF (5 mL). After the solution was stirred for 30 min at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated and the residue was chromatographed on silica gel (hexane–EtOAc 4:6) to yield **33a** (0.313 g, 94%): ^{1}H NMR δ 1.27 (t, J = 6 Hz, 6H), 1.51–2.23 (m, 6H), 3.41 (d, J = 6 Hz, 2H), 3.79–4.29 (m, 6H), 4.53 (s, 2H), 7.30 (s, 5H). Anal. Calcd for $C_{17}H_{27}O_5P$: C, 59.64; H, 7.95; P, 9.05. Found: C, 59.42; H, 7.90; P, 8.97.

Diethyl (5-((benzyloxy)methyl)tetrahydrofuran-2-yl)-ethanephosphonate (33b) was isolated in 90% yield when the reaction was carried for the preparation of **24b** by following the general procedure using **13**: ^{1}H NMR δ 1.27 (t, J = 6 Hz, 6H), 1.52–2.27 (m, 8H), 3.42 (d, J = 6 Hz, 2H), 3.74–4.28 (m, 6H), 4.53 (s, 2H), 7.30 (s, 5H). Anal. Calcd for $C_{18}H_{29}O_5P$: C, 60.66; H, 8.20; P, 8.69. Found: C, 60.42; H, 8.03; P, 8.77.