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A NEW SYNTHETIC ROUTE OF β-HYDROXYALKYLPHOSPHONATES FROM β,γ-EPOXYALKYLPHOSPHONATES[1]

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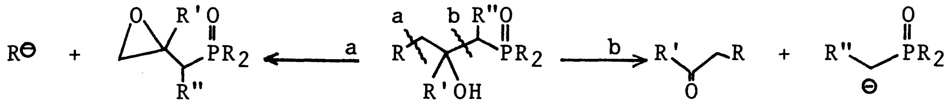
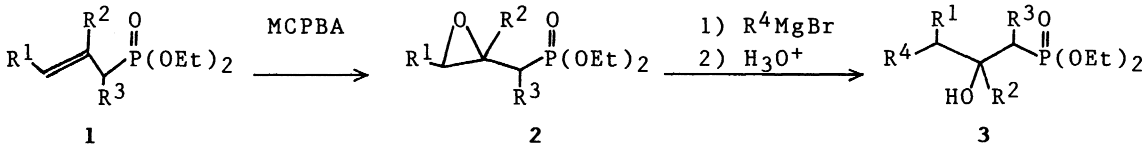
β-Hydroxyalkylphosphonates were synthesized from β,γ-epoxyalkylphosphonates and RMgX/ cat. CuI reagents, which is a new synthetic route for the various types of α- and/or γ-substituted β-hydroxyalkylphosphonates.

Synthetic modifications[2)] and applications[3)] of the Horner-Emmons olefination reaction[4)] are a current interest in organic synthesis. In these reactions, β-hydroxyalkylphosphoryl compounds are very important intermediates, however, the synthetic route to these compounds has not been so extensively studied. To our knowledge, there are only two methods;[5)] one of them is the most fundamental and well-known one, that is, the reaction of phosphoryl group stabilizing carbanion with carbonyl compound to afford directly β-hydroxyalkylphosphoryl derivative and the other is the reduction of β-ketoalkylphosphoryl compound, which is produced directly[6)] or indirectly[6a)] from α-metalloalkylphosphoryl derivative. In spite of many examinations, it is not so easy to synthesize the tert- or sec-β-hydroxyalkylphosphoryl compounds from easily enolizable aldehydes, ketones or esters.[7)] To overcome this problem, we have developed a new and promising method to prepare β-hydroxyalkylphosphonate from β,γ-epoxyalkylphosphonate.



Scheme 1.

Outline of the present method is shown in Scheme 2 and the results are



Scheme 2.

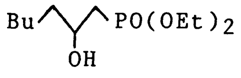
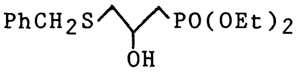
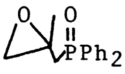
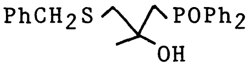
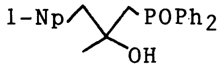
Table 1. Synthesis of **2** and **3**

1	R^1	R^2	R^3	Yield of **2** /%$^{a)}$		R^4MgBr	Yield of **3** /%$^{a)}$	
1a	H	H	H	**2a**	85	PhMgBr	**3a**	83
						1-NpMgBr$^{b)}$	**3b**	80
						1-Octyl-MgBr	**3c**	81
1b	H	Me	H	**2b**	93	PhMgBr	**3d**	76
						1-NpMgBr$^{b)}$	**3e**	80
						1-Octyl-MgBr	**3f**	73
1c	Me	H	H	**2c**	85	PhMgBr	**3g**	84
1d	H	H	Me	**2d**	94	1-NpMgBr$^{b)}$	**3h**	81
1e	H	Me	Me	**2e**	78	1-NpMgBr$^{b)}$	**3i**	83
1f	H	Me	Et	**2f**	84	1-NpMgBr$^{b)}$	**3j**	89
1g	Me	H	Me	**2g**	84	1-NpMgBr$^{b)}$	**3k**	88

a) Isolated yield. b) Np = naphthyl.

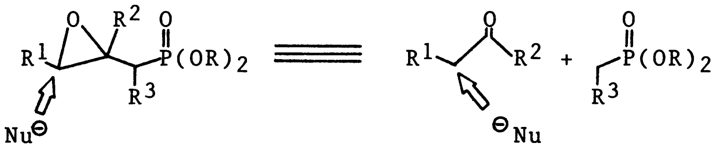
summarized in Table 1. General procedure is as follows: Diethyl 2-propenylphosphonates (**1a**–**c**) prepared by the Becker reaction of diethyl phosphite with allylic halides were treated with lithium diisopropylamide (1 equiv.)$^{8)}$ and then alkyl iodides (1.2-1.5 equiv.) to afford 1-alkyl-2-propenylphosphonates (**1d**–**g**) in almost quantitative yields. Successive oxidation of **1** with m-chloroperbenzoic acid (MCPBA) (1.2 equiv.) in dichloromethane at room temperature gave β, γ-epoxyalkylphosphonates as a single product (**2a**–**c**) or a diastereomeric mixture (**2d**–**g**).$^{9)}$ These epoxides were treated with the Grignard reagent (1.1 equiv.) in the presence of CuI (0.1 equiv.)$^{10)}$ to produce β-hydroxyalkylphosphonate (**3**) with high regioselectivity$^{11)}$ and with the same diastereomeric ratio (**3h**–**k**).$^{9)}$ In place of the Grignard reagent, another nucleophiles could be also utilized and these results were summarized in Table 2. Under much more vigorous reaction condition, the direct conversion of **3** to the corresponding olefins was unsuccessful even when KH,

Table 2. Synthesis of Other β-Hydroxyalkylphosphoryl Derivatives

Substrate	Nucleophile	Product		Yield/%
2a	Bu_2CuLi		**3l**	83
	$KSCH_2Ph$		**3m**	80
 **4**	$KSCH_2Ph$		**5**	79
	1-NpMgBr cat.CuI		**6**	90

NaH, and ^{t}BuOK were used as base.[12]

The characteristic features of the present procedure are to introduce various substituent groups at the α and/or γ-position(s) of the phosphorus atom and to prepare β-hydroxy derivatives from "the unique synthetic blocks,"[4] that is, β,γ-epoxyalkylphosphonates and nucleophiles, which have never been used in this type of reaction. This method is very suitable for the synthesis of the sec- and tert-β-hydroxyalkylphosphonate which can not be so readily prepared in the previous way. And also in the present reaction, the γ-position of β,γ-epoxyalkylphosphonates were selectively attacked by nucleophiles, indicating overall reactivity umpolung of the α-position of carbonyl group (Scheme 3).



Scheme 3.

References

1) A part of this work was presented at the 48th National Meeting of the Chemical Society of Japan at Sapporo, August, 1983 and at the 44th Symposium of the Synthetic Organic Chemistry of Japan at Tokyo, November, 1983.
2) a) T. Kawashima, T. Ishii, and N. Inamoto, Tetrahedron Lett., 24, 739 (1983); b) Idem, Chem. Lett., 1983, 1375; c) C. R. Johnson and R. C. Elliott, J. Am. Chem. Soc., 104, 7041 (1982).
3) C. Earnshaw, R. S. Torr, and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1983, 2893 and references cited therein.
4) These reactions are usually thought of the conversion of carbonyl compounds into olefins and so as "the synthetic blocks" of these reaction are always used carbonyl compounds and α-metalloalkylphosphoryl derivatives.
5) Very recently another synthetic route to β-siloxyalkylphosphonates has been developed: T. Azuhata and Y. Okamoto, Synthesis, 1983, 916.
6) a) E. J. Corey and G. T. Kwiatkowski, J. Am. Chem. Soc., 90, 6816 (1968); b) P. Savignac and F. Mathey, Tetrahedron Lett., 1976, 2829; c) Idem, Synthesis, 1976, 766; d) Idem, Tetrahedron, 34, 649 (1978); e) E. E. Abovjaovck and N. Colliginon, Synthesis, 1983, 634.
7) For example, the reaction of dimethyl α-lithioethylphosphonate with dibenzyl and diisopropyl ketones in THF gave the corresponding β-hydroxyalkylphosphonates in only 47 and 0% yields, respectively: T. Kawashima, T. Ishii, and N. Inamoto, unpublished results.
8) If butyllithium is used as base, only a complex mixture is obtained. The main product was the double bond migrated vinylphosphonate.
9) Diastereomeric ratio was ca. 3 : 1 to 4 : 1, which was determined by the ^{31}P-

and ^{13}C-NMR spectroscopies. Spectral data for **2**, for example, **2d**; ^{31}P-NMR ($CDCl_3$):δ_P29.3 (anti), 30.1 (syn) ppm (from 85% H_3PO_4); ^{13}C-NMR ($CDCl_3$): anti: δ_C 11.12 (d, ^2J_P= 5.49 Hz, $-CH_3$), 16.44 (d, ^3J_P= 6.10 Hz, P-O-C-$\underline{C}H_3$), 36.09 (d, ^1J_P= 139.16 Hz, -CH-P), 47.12 (d, ^3J_P= 3.05 Hz, $-CH_2$-O-), 52.11 (d, ^2J_P= 2.44 Hz, -CH-O) , and 62.12 ppm (d, ^2J_P= 6.71 Hz, P-O-CH_2-); syn: δ_C 8.95 (d, ^2J_P= 5.49 Hz), 16.44 (d, ^3J_P= 6.10 Hz, P-O-C-$\underline{C}H_3$), 33.76 (d, ^1J_P= 140.99 Hz), 44.81 (d, ^3J_P= 9.16 Hz), 50.95 (d, ^2J_P=2.44 Hz), and 62.12 ppm (^2J_P= 6.71 Hz, P-O-CH_2-); High resoln MS: Found: m/e 208.0885, Calcd for $C_8H_{17}O_4P$: 208.0865.

10) The ring opening reaction occurred even if the Grignard reagent was used without the catalyst. But in these cases, the reaction was much slower and side reactions, for example, nucleophilic attack at the phosphorus atom and abstraction of the -proton in **2**, were competed.

11) According to the ^{1}H-, ^{13}C-, and ^{31}P-NMR data, the ratio of β- and γ-hydroxy derivatives is more than 20 : 1. Spectral data for **3**, for example, **3d**: ^{1}H-NMR ($CDCl_3$): δ 1.31 (dt, J= 7.03 Hz, ^4J_P= 0.22 Hz, 6H), 1.32 (d, ^4J_P= 0.88 Hz, 3H), 1.99 (d, ^2J_P= 18.46 Hz, 2H), 2.89 (d, ^4J_P= 1.54 Hz, 2H), 3.49 (s, -OH, 1H), 4.09 (quintet, J= 7.03 Hz, ^3J_P= 7.03 Hz, 4H), and 7.26 (s, 5H); ^{31}P-NMR ($CDCl_3$): δ_P 29.7 ppm; ^{13}C-NMR ($CDCl_3$): δ_C 16.33 (d, ^3J_P= 6.10 Hz, P-O-C-$\underline{C}H_3$), 28.13 (d, ^3J_P= 6.72 Hz, $-CH_3$), 37.31 (d, ^1J_P= 136.10 Hz, CH_2-P), 49.42 (d, ^3J_P= 11.59 Hz, $-CH_2$-Ph), 63.65 (d, ^2J_P= 6.11 Hz, P-OCH_2), 70.83 (d, ^2J_P= 3.66 Hz, -C-OH), 126.47, 128.01, 130.72, and 137.41 ppm (aromatics); High resoln MS: Found: m/e 286.1302, Calcd for $C_{14}H_{23}O_4P$: 286.1332.

12) Generally, it is very difficult to convert these "non-activated" β-hydroxyalkylphosphonates to the corresponding olefins, see B. J. Walker, "Organophosphorus Reagents in Organic Synthesis," ed by J. I. G. Cadogan, Academic Press, New York (1979), pp. 155-205. But all these β-hydroxyalkylphosphonates could be converted into the corresponding olefins in good or moderate yields under the conditions as we have described before, see Ref. 2b.

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