STEREOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE E- AND Z-HOMOALLYL ALCOHOLS FROM EPOXIDES

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Abstract-Optically active E- and Z-homoallyl alcohols were prepared by Wittig and Warren olefination starting from optically active 3-hydroxyalkyltriphenylphosphonium salts, which were obtained by the reaction of epoxides with methylenetriphenylphosphorane and dibenzoyltartric acid followed by optical resolution.

Homoallyl alcohols are synthetically valuable intermediates that have been used as characterristic units of numerous macrolides and ionophore antibiotics.[1] Several groups have recently reported the stereoselective synthesis of optically active homoallyl alcohols *via* [2,3]-Wittig rearrangement, reduction, nucleophilic hydroxymethylation, asymmetric ene reaction.[2] Recently, we have reported the optical resolution of 2-hydroxyalkylphosphonium salts by using camphorsulfonic acid as a resolving agent and the preparation of optically active allyl alcohols.[3] These results prompted us to investigate the possibility of the general synthesis of optically active 3-hydroxyalkylphosphonium salts and E- and Z-homoallyl alcohols. In this communication, we now report the stereoselective synthesis of optically active E- and Z-homoallyl alcohols starting from epoxides.

First, the reaction of epoxides with methylenetriphenylphosphorane followed by the addition of dibenzoyltartaric acid (DBT) was carried out. As shown in Table 1, the optically active phosphonium salts were obtained with more than 96% ee after optical resolution. In the present method, either pure R- or S-isomers were obtained. These DBT salts were easily converted into their tetrafluoroborate salts by adding NaH followed by the addition of HBF_4 solution (Scheme 1).

Scheme 1

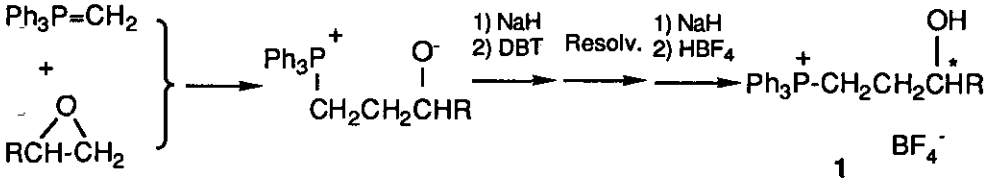


Table 1. Resolution of 3-Hydroxyalkylphosphonium Salts.

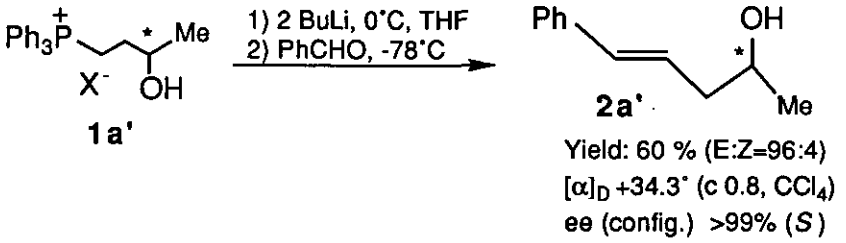
Epoxide R	Acid	Chemical Yield/%		After Resolution/%	$[\alpha]_D$ (MeOH) DBT	BF_4	ee /%[a]	Configuration
Me	L-DBT	**1a**	83	25	-68.1	-2.4	>99	R
Me	D-DBT	**1a'**	72	11	+64.5	+1.9	>99	S
Et	L-DBT	**1b**	63	36	-59.5	-1.5	>99	R
Et	D-DBT	**1b'**	49	27	+60.2	+1.1	>99	S
4-ClC_6H_4	L-DBT	**1c**	86	13	-63.4	-15.8	>98	
4-ClC_6H_4	D-DBT	**1c'**	94	21	+66.7	+14.1	>96	
$PhOCH_2$	L-DBT	**1d**	92	21	-58.1	-5.2	>99	

a) Enantiomeric excess (ee) was determined by the nmr analysis of their MTPA esters.

Previously, optically active (-)-(R)-3-hydroxybutyltriphenylphosphonium iodide (nearly equals to **1a**) was prepared by 5 step process starting from 1,3-butanediol.[4] The present method has several advantages; the reaction is simple and a variety of phosphonium salts were obtained. For example, salt (**1a**) was prepared by the one step reaction of propene oxide with methylenetriphenylphosphorane and D-DBT followed by optical resolution.

Since the Wittig reaction is a good method for the preparation of olefins, we then tried the reaction of these salts with bases followed by the addition of aldehydes. The corresponding E-homoallyl alcohols were obtained in good yields (Sheme 2, Table 2).

Scheme 2



In the case of butyraldehyde, E and Z isomers were obtained in 80:20 (or 62:38) ratio. However, by using benzaldehyde as a substrate, E:Z ratio was changed to 96:4. Maryanoff *et al.* studied the precise reaction mechanism of the Wittig reaction.[5] They observed that the E selectivity increased in the reaction of 3-

hydroxyalkylphosphonium salts with aromatic aldehydes, and it decreased in this reaction by using aliphatic aldehydes. Their observation agrees with ours. α,β-Unsaturated aldehyde was reacted with these ylides to give dienes in 54 and 51% yields. The obtained E alcohols were easily separated by silica gel hplc or by silver nitrate impregnated silica gel.

Table 2. Preparation of Optically Active E-Homoallyl Alcohols.

Substrate	Aldehyde	Conditions Base	Conditions Temperature/°C	Products	Yield/%	ee/%[a]	E:Z[b]
1a'	PhCHO	BuLi	-78	**2a'**	60	>99	96:4
1a'	trans-PhCH=CHCHO	BuLi	-78	**2b'**	54	>99	87:13
1a'	PrCHO	BuLi	-78	**2c'**	61	>99	62:38
1b	PhCHO	BuLi	-78	**2d**	58	>99	94:6
1b	trans-PhCH=CHCHO	BuLi	-78	**2e**	51	>99	85:15
1b	PrCHO	BuLi	-78	**2f**	77	>99	80:20

a) Enantiomeric excess was obtained by nmr analysis of their MTPA esters.
b) The ratio of E/Z was obtained by their nmr spectra.

Since optically active E-homoallyl alcohols were obtained by the Wittig reaction, we focused our attention to the synthesis of Z-homoallyl alcohols. Recently, Warren and coworkers have reported the preparation of Z-olefins by the reaction of phosphine oxides with bases followed by the addition of aldehydes.[6] The preparation of 3-hydroxyalkylphosphine oxides was carried out. As shown in Scheme 3, the corresponding optically active oxides were prepared easily. The formation of these phosphine oxides is applicable to the synthesis of Z-homoallyl alcohols. By this method, Z-homoallyl alcohols were prepared in good stereoselectivity.

Scheme 3

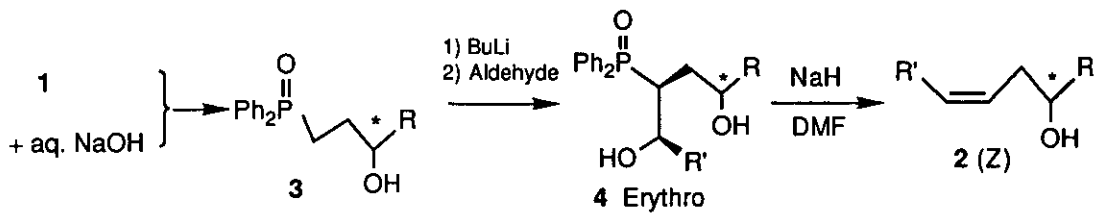


Table 3. Preparation of Optically Active 3-Hydroyalkyldiphenylphosphine Oxides and Z-Homoallyl Alcohols.

Substrate	Phosphine Oxide 3	Yield/%	Aldehyde	4 (Erythro)	Yield/%	Z-Homoallyl Alcohol 2	Yield/%	ee/%[a]	E:Z[b]
1a'	**3a'**	88	PhCHO	**4a'**	72	**2a'**	65	>99	4:96
			PrCHO	**4b'**	60	**2c'**	60	>99	19:81
1b	**3b**	95	PhCHO	**4c**	56	**2d**	66	>99	4:96

a) Enantiomeric excess was obtained by nmr analysis of their MTPA esters.
b) The ratio of E/Z was obtained by their nmr spectra.

The present result provides a new method for the preparation of optically pure homoallyl alcohols.

Efforts to explore the chemistry of hydroxyalkylphosphonium salts and to expend it to the synthesis of natural products containing homoallyl alcohol moiety are in progress in our laboratories.

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7 Satisfactory elemental analyses or mass spectra were obtained for all new compounds. Spectral data of **2b'**(E): ^{1}H Nmr ($CDCl_3$) δ=1.23 (d, J=5.9 Hz, 3H, Me), 2.24-2.38 (m, 2H, CH_2), 3.89 (sextet, J=5.9 Hz, 1H, CH-O), 5.82 (dt, J=14.7 and 7.3 Hz, 1H, CH=), 6.30 (dd, J=11.0 and 15.4 Hz, 1H, CH=), 6.50 (d, J=16.1 Hz, 1H, PhCH=), 6.77 (dd, J=11.0 and 16.1 Hz, 1H, CH=), 7.19-7.39 (m, 5H, Ph). $[\alpha]_D$ +31.6° (c 0.62, CCl_4). **2c'** (E): ^{1}H Nmr ($CDCl_3$) δ=0.90 (t, J=7.6 Hz, 3H), 1.19 (d, J=6.1 Hz, 3H), 1.39 (sextet, J=7.3 Hz, 2H), 2.01 (quintet, J=7.0 Hz, 2H), 2.07-2.13 (m, 1H), 2.17-2.22 (m, 1H), 3.79 (sextet, J=6.1 Hz, 1H), 5.37-5.45 (m, J_{trans}=15.0 Hz, 1H, CH=), 5.51-5.58 (m, J_{trans}=15.0 Hz, 1H, CH=). $[\alpha]_D$ +11.2° (c 0.24, CCl_4). **2d**(E): ^{1}H Nmr ($CDCl_3$) δ=0.98 (t, J=7.3 Hz, 3H, Me), 1.48-1.61 (m, 2H, $CH_3C\underline{H}_2$), 2.26-2.34 (m, 1H, =C-CH_2), 2.42-2.47 (m, 1H, =C-CH_2), 3.65 (quintet, J=5.1 Hz, 1H, CH-O), 6.23 (dt, J=15.4 and 7.3 Hz, 1H, =CH), 6.47 (d, J=15.4 Hz, 1H, PhCH=), 7.19-7.37 (m, 5H, Ph). $[\alpha]_D$ -22.7° (c 2.0, CCl_4). **2e**(E): $[\alpha]_D$ -28.9° (c 1.64, CCl_4). **2f**(E): $[\alpha]_D$ -4.3 (c 0.65, CCl_4). **2a'**(Z): $[\alpha]_D$ -39.7° (c 2.2, CCl_4). **2c'** (Z): ^{1}H Nmr ($CDCl_3$) δ=0.91 (t, J=7.3 Hz, 3H), 1.21 (d, J=6.1 Hz, 3H, Me), 1.38 (sextet, J=7.3 Hz, 2H), 2.04 (q, J=7.3 Hz, 2H, CH_2), 2.17-2.29 (m, 2H, CH_2), 3.80-3.85 (m, 1H, CH-OH), 5.38-5.44 (m, J_{cis}=11.0 Hz, 1H, CH=), 5.54-5.61 (m, J_{cis}=11.0 Hz, 1H, CH=). $[\alpha]_D$ +5.4° (c 0.40, CCl_4). **2d**(Z): $[\alpha]_D$ +39.7° (c 2.2, CCl_4).

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