The Reactions of 2,3-Epoxyaldehydes with Methoxymethylenetriphenylphosphorane. Enantioselective Syntheses of (*E*)-4-Hydroxyalk-2-enals

Libing Yu and Zhiqin Wang*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Ling Ling Lu 345, Shanghai 200032, P.R. China

The reactions of 2,3-epoxyaldehydes with methoxymethylenetriphenylphosphorane in tetrahydrofuran provide directly (*E*)-4-hydroxy-2-enals with the retention of configuration.

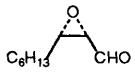
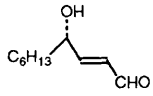
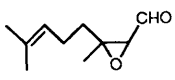
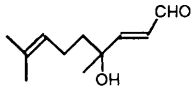
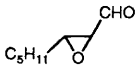
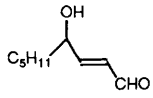
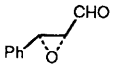
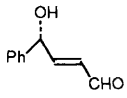
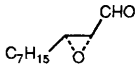
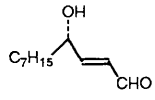
A three-carbon homologation has been reported[1,2] to synthesize (*E*)-4-hydroxy-2-enals **1**. However, no general method has been reported to prepare optically active compound **1**. Herein, we describe the first enantioselective syntheses of (*E*)-4-hydroxy-2-enols from 2,3-epoxyaldehydes with one-carbon homologation.

In the course of a total synthesis of the antibiotic 4,8-dihydroxy-2-(1-hydroxyheptyl)-3,4,5,6,7,8-hexahydro-2*H*-1-benzopyran-5-one, which was isolated from *Trichoderma koningii* and is active against soilborne plant pathogens,[3] a Wittig reaction was carried out by treatment of 2,3-epoxyaldehydes with methoxymethylenetriphenylphosphorane resulting from triphenyl(methoxymethyl)phosphonium chloride[4] and bases *e.g.* Bu^{t}OK, BuLi or NaH. Unfortunately, no expected product, 3,4-epoxy-1-methoxy-dec-1-ene (the precursor of the desired 3,4-epoxydecanal) was isolated. Instead, (*E*)-4-hydroxydec-2-enal was obtained in fairly good yield (Scheme 1).†

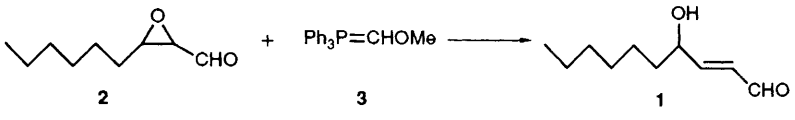
(*E*)-4-Hydroxynon-2-enal (entry 3) and its homologues, which originate from lipid peroxidation in cellular membranes, have been reported to be physiologically active[5] and

† *Typical spectroscopic data*: 4-hydroxydec-2-enal (entry 1) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J* 6 Hz, Me), 1.30 (8H, m, $4CH_2$), 1.62 (2H, m, CH_2), 2.28 (1H, br, OH), 4.44 (1H, m, CH–O), 6.31 (1H, dd, *J* 16, 8 Hz, CH=), 7.83 (1H, dd, *J* 16, 4 Hz, CH=), 9.58 (1H, d, *J* 8 Hz, CH=O). IR(film) ν/cm^{-1}: 3400(OH), 2720, 1695s, 1680, 1640. MS (*m*/*z*): 171 (M + 1), 153, 91, 55.

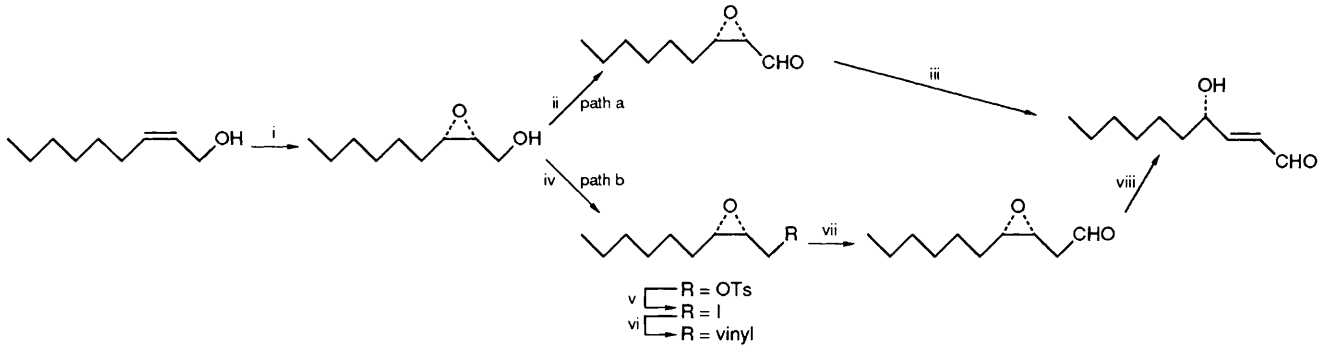
Table 1

Entry	Substrates	[α][a]	Products[c]	[α][a]	J/Hz[b]	Isolated yield (%)[e]
1					16	77
2					16	81
3					16	83
4[d]		+86.0 *c* 2.1		+222.9 *c* 0.73	16	80
5[d]		+86.4 *c* 1.2		+35.4 *c* 2.3	16	76

[a] $CHCl_3$ as solvent at 25 °C. [b] Coupling constant of the two H of vicinal double bond hydrogens. [c] All products were identified by satisfactory ^1H NMR, IR and mass spectroscopy. [d] Optically pure substrates were prepared by Sharpless asymmetric epoxidation of respective allylic alcohols followed by recrystallization and Swern oxidation with an overall yield of >75%. 300 MHz ^1H NMR analysis of the derived MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] esters of the products showed e.e. >95%. [e] General procedure: Wittig salt (2 mmol) and Bu^tOK (2 mmol) in THF at −40 °C provided an orange solution. 2,3-epoxy aldehyde (1 mmol) was added at −78 °C. The reaction mixture was allowed to warm to room temp. and then poured into water. Extraction followed by concentration and column chromatography afforded pure product.

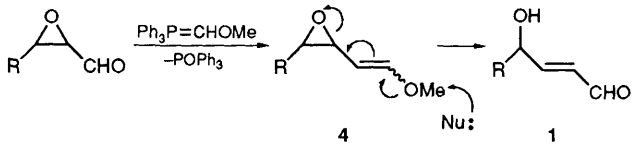


Scheme 1



Scheme 2 *Reagents and conditions*: i, $Ti(OPr^i)_4$, Bu^tOOH, (−)-DET (diethyl tartrate), CH_2Cl_2, −20 °C; ii, $(COCl)_2$, Me_2SO, Et_3N; iii, refer to Table 1; iv, TsCl, Py, 0 °C; v, NaI, DMF (dimethylformamide), 80 °C; vi, CuI (cat.), CH_2=CHMgCl, HMPA (hexamethylphosphoramide), THF (tetrahydrofuran), −25 °C; vii, OsO_4 (cat.), $NaIO_4$, dioxane, H_2O (3:1); viii, Et_3N, CH_2Cl_2, room temp.

along with optically active **1** are potential intermediates in the synthesis of natural products. We, therefore, extended this reaction to some other 2,3-epoxyaldehydes. Table 1 summarizes five examples of this reaction. We found both *syn* and *anti* epoxides afforded *trans* enals, which were assigned by the coupling constants of the two vicinal double-bond hydrogens. When optically pure epoxides were used as substrates, optically pure products (entry 1, 4 and 5) were obtained. In order to investigate the stereochemistry of the chiral centre, (*E*)-4-hydroxydec-2-enal (entry 1) was also prepared from the same starting material (2*S*,3*S*)-2,3-epoxyaldehyde through path b, which should give unambiguous 4*S* configuration. The optical rotation $[\alpha]_D^{25}$ +43.5 (*c* 2.0, $CHCl_3$) compared with the value of the compound $[\alpha]_D^{25}$ +42.6 (*c* 1.8, $CHCl_3$) obtained through path a (Scheme 2), we found that this reaction proceeds with retention of the C-3 configuration. ^1H NMR



Scheme 3

spectroscopic analysis of the derived MTPA esters of 4*S* and racemic compounds (entries 4 and 5) showed that the enantiomeric excess (e.e.) value exceeded 95%. Because triphenylphosphine oxide was isolated from the reaction mixture and the work up was very mild, we suggest that the methoxy group of the normal Wittig reaction product was attacked by nucleophile (Cl^- or OH^-) to afford the ultimate product (Scheme 3).

We consider that this reaction, coupled with Sharpless asymmetric epoxidation[6] and Swern oxidation of allylic alcohols, would be an efficient and convenient approach to chiral (*E*)-4-hydroxy-2-enals.

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