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A NEW STEREOSELECTIVE METHOD FOR SYNTHESIS OF OPTICALLY ACTIVE β-ALKYLHOMOALLYL ALCOHOLS AND γ,δ-EPOXY-β-ALKYL ALCOHOLS

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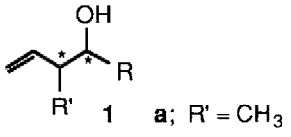
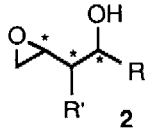
Summary : A new and general method for synthesis of optically active β-alkylhomoallyl alcohols and γ,δ-epoxy-β-alkyl secondary alcohols starting with $\Delta^{\alpha,\beta}$-butenolides having trimethylsilyl and phenylthio group at α-position, respectively, has been developed.

The synthesis of optically active β-methylhomoallyl alcohols **1a** has attracted much interest in recent years in relation to the synthesis of acyclic natural products such as macrolide and polyether antibiotics[1]. The methods for synthesis of **1a** so far reported include addition reaction of optically active crotyl metal compounds to aldehydes[2], [2,3]-Wittig sigmatropic rearrangement of optically active crotyl ethers[3], or diastereoselective addtion reaction of nucleophiles to optically active α-methyl-β-trimethylsilyl-β,γ-unsaturated carbonyl compounds[4]. The alcohols **1a** thus obtained have been further elaborated for increase of chiral centers by using the olefinic functional group presented in them. For example, the diastereoselective epoxidation of **1a** to **2a** has been used for construction of three consecutive chiral centers[5]. The reported synthetic methods of **1a**, however, are not necessarily applicable to synthesis of homoallyl alcohols having β-alkyl group other than methyl. The conversion of **1a** into **2a** also suffurs from its rather low diastereoselectivity.



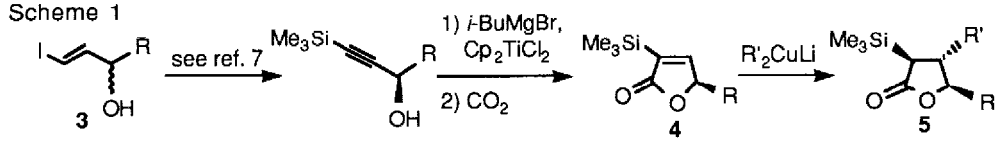
1 **a**; R' = CH_3



2 **a**; R' = CH_3

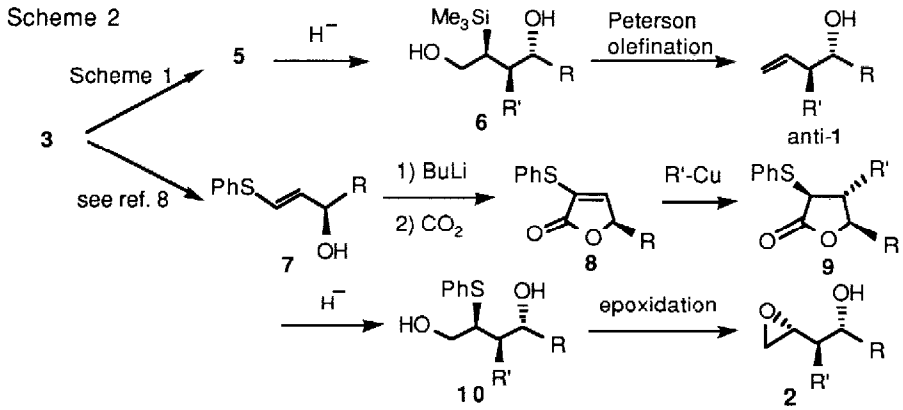
Recently we reported an efficient and practical method for synthesis of α-trimethylsilyl $\Delta^{\alpha,\beta}$-butenolides (**4**) in a chiral form starting with racemic γ-iodoallyl alcohols (**3**) and their reaction with Me_2CuLi which proceeded stereospecifically to afford **5** (R' = CH_3) (Scheme 1)[6].

Scheme 1

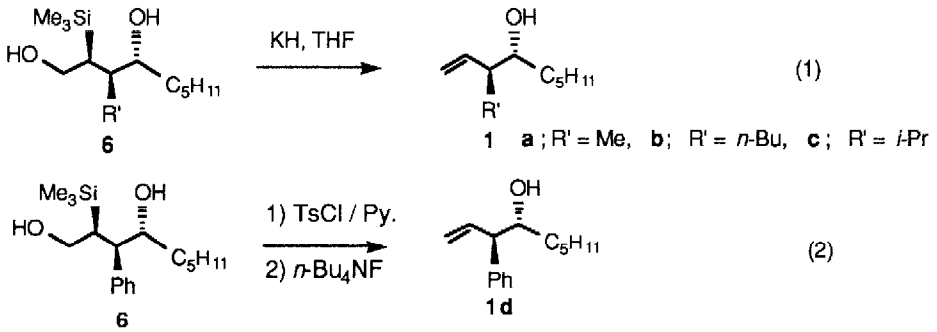


With these findings, it occurred to us that the compounds **5** might be converted into **1** via hydride reduction followed by the Peterson olefination reaction of the resulting diols **6** as shown in Scheme 2, thus providing a general method for synthesis of β-alkyl homoallyl alcohols with anti configuration. Furthermore we expected that the compound **2** could be prepared from readily available optically pure γ-phenylthio allyl alcohols (**7**)[8] via α-phenylthio $\Delta^{\alpha,\beta}$-butenolides (**8**)[9] according to the procedure also shown in Scheme 2. Herein reported is the realization of these expectations.

Scheme 2



As is the case of the reaction with Me_2CuLi, various organo copper compounds, such as *n*-Bu_2CuLi, *i*-PrMgBr/CuI, *t*-$Bu_2Cu(CN)Li_2$, and PhMgBr/CuI, reacted with **4** (R = *n*-C_5H_{11}) specifically to afford the addition products **5** in excellent yields. The reaction of the resulting **5** with $LiAlH_4$ in THF provided the diols **6** except for R' = *t*-Bu[10]. The Peterson olefination of **6** was carried out under basic conditions (KH in THF), and it was found that when R' was an alkyl group, **6** was converted into the corresponding **1** in good yields (eq 1) while when R' was phenyl group, the reaction afforded the conjugated diene $H_2C{=}C(H)C(Ph){=}CHC_5H_{11}$. Thus the synthesis of β-phenylhomoallyl alcohol **1d** was successfully carried out by selective tosylation and subsequent reaction with *n*-Bu_4NF (eq 2).



The homoallyl alcohol without β-substituent could also be prepared from **4** by the procedure shown in Scheme 3. Thus the hydrogenation of **4** (R = *n*-C_5H_{11}) followed by the reduction of the resulting saturated lactone with $LiAlH_4$ afforded the diol **6e**, which in turn was converted into the homoallyl alcohol **1e** by treatment with KH in THF.

Yields, optical rotations and NMR data of **1** thus prepared are summarized in Table 1.

Scheme 3

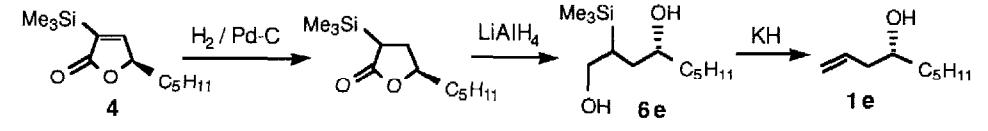


Table 1 Yields, Optical Rotations, and NMR Data of **1**

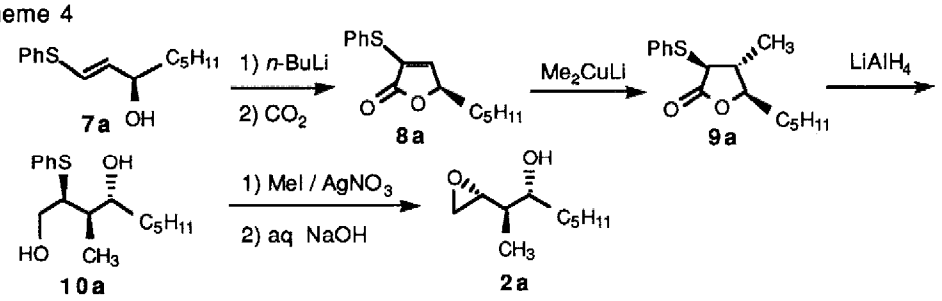
Compound	Yield[a] %	$[\alpha]^{D}_{23}$ (c, solvent)	^{1}H NMR [b]	^{13}C NMR ($CDCl_3$)
1a[c]	69	+ 14.9 (1.06, acetone)	0.82 (t, *J* = 6.3 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.1-1.5(m, 8 H), 1.98 (br s, 1 H) , 2.03-2.24 (m, 1 H), 3.27-3.38 (m, 1 H), 4.95-5.08 (m, 2 H), 5.61-5.79 (m, 1 H)	140.4, 115.8, 74.5, 43.8, 33.9, 31.7, 25.2, 22.3, 15.9,13.7
1b	84	+ 22.9 (1.0, $CHCl_3$)	0.86 (t, *J* = 6.3 Hz, 6 H), 1.1-1.6 (m, 14 H), 1.76 (br s, 1 H), 1.88-2.04 (m, 1 H), 3.37-3.48 (m, 1 H) 5.05 (dd, *J* = 18, 2.2 Hz, 1 H), 5.13(dd, *J* = 10, 2.2 Hz, 1 H), 5.61 (ddd, *J* = 18, 10, 6.8 Hz, 1 H)	139.1, 117.7, 73.6, 50.2, 34.5, 31.8, 30.3, 29.4, 25.2, 22.5, 22.4, 13.8
1c	82	+ 23.1 (1.03, $CHCl_3$)	0.82 (d, *J* = 6.6 Hz, 3 H), 0.86 (t, *J* = 6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 1.15-1.53 (m, 8 H), 1.56-1.88 (m, 3 H), 3.59-3.73 (m, 1 H), 5.13 (dd, *J* = 17, 2.4 Hz, 1 H), 5.18 (dd, *J* = 10, 2.4 Hz, 1 H), 5.66 (dt, *J* = 17, 10 Hz, 1 H)	136.7, 118.6, 71.0, 56.6, 35.0, 31.8, 27.5, 25.1, 22.4, 21.2, 19.0,13.8
1d	56	+ 14.9 (1.16, $CHCl_3$)	0.84 (t, *J* = 6 Hz, 3 H), 1.0-1.6 (m, 8 H), 1.67 (br s, 1 H), 3.13 (dd, *J* = 9, 7 Hz), 3.54-3.83 (m, 1 H), 4.99-5.31(m, 2 H), 6.11 (ddd, *J* = 18, 12, 9 Hz, 1 H), 7.06-7.46 (m, 5 H)	141.9, 138.5, 128.8, 128.5, 128.1, 126.7 118.0, 73.9,57.3, 34.2, 31.6, 25.2, 22.4, 13.8,
1e	60	+ 4.0 [d] (2.00, $CHCl_3$)	0.89 (t, *J* = 6 Hz, 1 H), 1.0-1.8 (m, 8H), 2.11 (t, *J* = 7 Hz), 3.76 (m, 1 H), 4.96-5.28 (m, 2 H), 5.66-6.18 (m, 1 H)	135.1, 118.0, 70.6, 41.7, 36.5, 13.8

[a] Isolated overall yields from the butenolide **4**. [b] Recorded in $CDCl_3$ for **1a**~**c** and in CCl_4 for **1d, e** [c] Enantiomerical purity was confirmed to be > 99% ee by ^{1}H NMR analysis of the derived MTPA ester. [d] $[\alpha]^{20}_{D}$ +2.37° (*c* 2.3, $CHCl_3$) for 60% enantiomeric purity was repoted : K. Tamao, R. Kanatani, and M. Kumada, *Tetrahedron Lett.*, **25**, 1913 (1984).

Next we describe the synthesis of optically pure α-phenylthio $\Delta^{\alpha,\beta}$-butenolide **8a** and its conversion into **2a** (Scheme 4). The successive treatment of homochiral **7a**[8] with *n*-BuLi and solid CO_2 furnished **8a** ($[\alpha]^{20}_{D}$ +72.2° (*c* 1.48, $CHCl_3$)) in 87% yield[11], which upon reaction with Me_2CuLi provided **9a** ($[\alpha]^{23}_{D}$ -2.0° (*c* 1.0, $CHCl_3$)) as the sole product[9]. Reduction of **9a** with $LiAlH_4$ gave the diol **10a** in 84% yield

(based on **8a**). Finally the reaction of **10a** with MeI in the presence of $AgNO_3$ followed by addtion of aqueous NaOH to the reaction mixture furnished the epoxide **2a** ($[\alpha]^{26}_D$ +17.7° (*c* 1.35, $CHCl_3$)) exclusively in 65% yield. The ^1H NMR spectrum of **2a** thus prepared was in good agreement with that of the major product obtained by epoxidation of **1a** with *t*-BuOOH/$VO(acac)_2$[5].

Scheme 4



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9) Synthesis of racemic α-phenylthio $\Delta^{\alpha,\beta}$-butenolides and their reaction with Me_2CuLi to afford the γ-lactones having the relative configuration identical with that of **9a** was reported : M. Watanabe, M. Tsukazaki, Y. Hirakawa, M. Iwao, and S. Furukawa, *Chem. Pharm. Bull.*, **37**, 2914 (1989).

10) Reduction of **5** (R' = *t*-Bu) with $LiAlH_4$ afforded the corresponding hemiacetal as major product ; no further efforts to obtain the diol were made.

11) Preparation of **8a** was accomplished as follows : To a solution of **7a** (3.38 g, 14.3 mmol) and dipyridyl (ca 5 mg) in THF (100 ml) was added *n*-BuLi (19.5 ml, 1.85 M in hexane, 35.8 mmol) at -70 °C. The solution was warmed to -10 °C over 2 h and poured into a mixture of dry ice (ca 30 g) and Et_2O (100 ml) to give **8a** (3.26 g, 87 %) after chromatography on silica gel.

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