Tetrahedron Letters, Vol.32, No.41, pp 5789-5792, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Synthesis of Optically Active γ-Trimethylsilyl-β,γ-epoxy Tertiary Alcohols by the Diastereoselective Addition Reaction of β-Trimethylsilyl-α,β-epoxyketones with Grignard Reagents

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Key Words : Sharpless kinetic resolution; β-trimethylsilyl-α,β-epoxyketone; diastereoselective addition; optically active tertiary alcohol

Summary : The reaction of β-trimethylsilyl-α,β-epoxyketones, readily prepared in a chiral form by using the Sharpless kinetic resolution of γ-trimethylsilyl secondary allylic alcohols as a key reaction,with Grignard reagents proceeds highly diastereoselectively to afford optically active γ-trimethylsilyl-β,γ-epoxy tertiary alcohols.

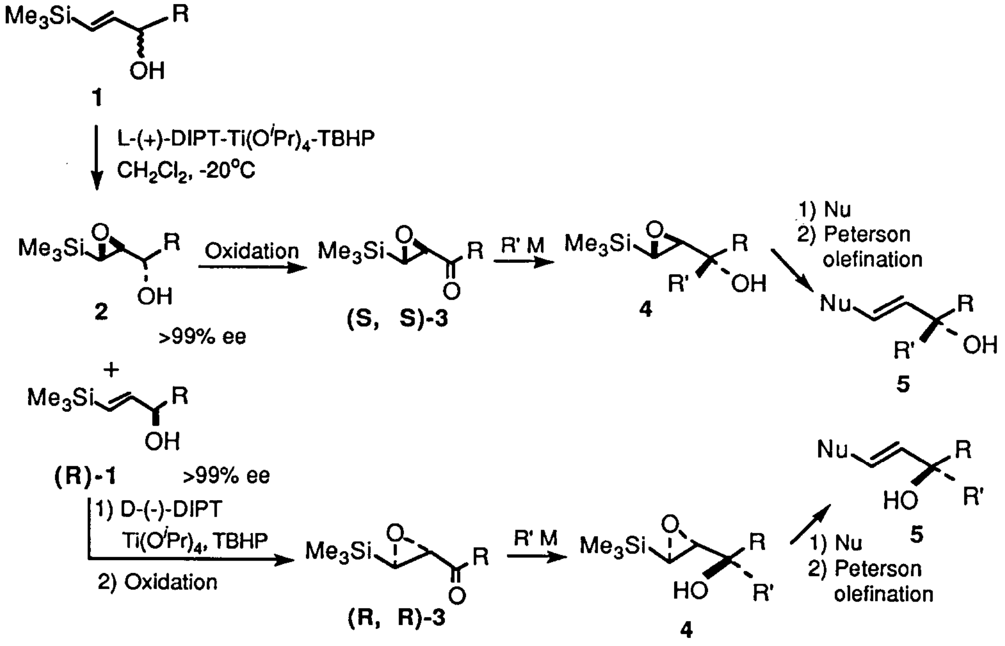
Tertiary allylic alcohols are incorporated in the structures of a variety of natural products and commercially important pharmaceuticals. Equally significant is the latent faculties of tertiary allylic alcohols as versatile synthetic intermediates. Only a few methods, however, are available for preparation of them in a chiral form and these methods so far developed suffer from some disadvantages such as low optical purity and/or lack of generality.[1]

Recently we have reported that the Sharpless kinetic resolution of γ-trimethylsilyl secondary allylic alcohols **1** proceeds with very large rate differences for the two enantiomers to afford optically active **1** and the epoxy alcohols **2** with respectively >99% ee.[2] It occurred to us that **1** and **2** thus obtained might be converted into the corresponding optically active tertiary allylic alcohols **5** according to the procedure shown in Scheme 1, thus providing a general method for preparation of optically pure tertiary allylic alcohols.

In starting with the reactions of Scheme 1, our greatest concern was the diastereoselectivity of the reaction of the epoxy ketones **3** with organometallic compounds, because, to the best of our knowledge, no research has been carried out on the diastereoselectivity of the reaction of an epoxy ketone with an organometallic compound.[3] We have now succeeded in carrying out the reaction of **3** with organometallic compounds highly diastereoselectively to afford **4**, which is the subject of this paper, and in the following paper[4] we will report the conversion of **4** into the optically active tertiary allylic alcohols **5**.

The oxidation of **2** with DMSO and $(COCl)_2$ afforded the corresponding ketones (*S*,*S*)-**3** in 83~96% yields, while (*R*)-**1** was converted into (*R*,*R*)-**3** in 90~96% yields by epoxidation with D-(-)-DIPT-$Ti(O^iPr)_4$-TBHP at -20 °C in CH_2Cl_2 followed by Swern oxidation of the resulting epoxy alcohols.

Scheme 1



The results of the reaction of optically pure **3** thus obtained with organolithium compounds or Grignard reagents are summarized in Table 1. It can be seen from Table 1 that the diastereoselectivity of the reaction depends not only on the organometallic compound applied but also on the solvent, and, when the reaction with Grignard reagents was carried out in THF and/or in THF-HMPA, one diastereoisomer was obtained exclusively except in the case of R = CH_3. The lower diastereoselectivity observed in the case of R = CH_3 (83% d.s.) is presumably due to the lower steric demand of the methyl group. The configuration of the major addition products **4** was confirmed to be that shown in Scheme 1 (and Table 1) by converting into the corresponding tertiary allylic alcohols **5** (see the following paper [4]).

The selective production of **4** can be explained by assuming that the reaction proceeds via Cram's cyclic model (Fig 1). It should be noted that it is very fortunate to find the conditions to get only one diastereoisomer in many cases, since two diastereoisomers have very similar *Rf* values on TLC and eventually mutual separation is almost impossible.[6]

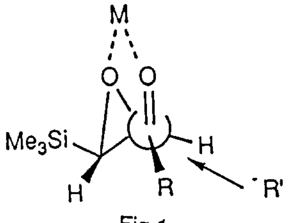
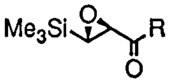
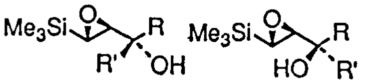
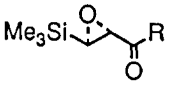
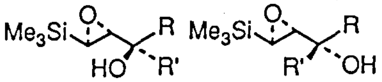


Fig 1

Table 1 Reaction of the epoxy ketone **3** with organometallic compounds (R'-Met.)[a]

		4[c]		
3	R' - Met[b] / solvent	diastereomer ratio [d]	yield, % [e]	$[\alpha]_D$ (c)[f]
				
R = n-Bu	MeLi / THF	2 : 1	98[h]	
n-Bu	MeMgI / THF	4 : 1	99[h]	
n-Bu	MeMgI / THF - HMPA[g]	>99 : 1	91	-15.9° (c 1.31)
n-Bu	EtMgBr / THF	>99 : 1	89	-19.0° (c 1.11)
n-Bu	PhMgI / THF	>99 : 1	98	-11.4° (c 2.82)
Me	n-BuMgBr / THF - HMPA[g]	5 : 1	90[h]	
Et	n-BuMgBr / THF	>99 : 1	94	-16.2° (c 1.32)
n-Am	MeMgI / THF - HMPA[g]	>99 : 1	90	-13.9° (c 3.00)
				
R = n-Bu	MeMgI / THF - HMPA[g]	>99 : 1	90	+15.9° (c 1.13)
n-Am	MeMgI / THF - HMPA[g]	>99 : 1	90	+13.6° (c 3.18)

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[a] All reactions were carried out at -78 °C to 0 °C under argon atmosphere. [b] Organometallic reagents were prepared in Et_2O (0.8 - 1.5 M). [c] For ^1H NMR data ; see note 5. [d] Determined by ^1H and ^{13}C NMR analysis ; >99 : 1 means that the other diastereoisomer was not detected. [e] Isolated yield. [f] In $CHCl_3$ at 25 °C. [g] THF - HMPA = 3 : 1. [h] Total yield of both diastereoisomers.

In conclusion we have now succeeded in developing highly efficient method for synthesis of γ-trimethylsilyl-β, γ-epoxy tertiary alcohols **4**. Though we have synthesized **4** as a precursor of tertiary allylic alcohols **5**, α, β-epoxysilanes can also be readily converted into carbonyl compounds by isomerization or into epoxides by protodesilylation, thus the compounds **4** are potentially versatile intermediates for organic synthesis and the synthetic use of them is now undergoing in our laboratory.

References and Notes

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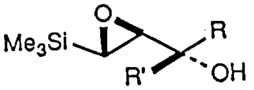
2) Y. Kitano, T. Matsumoto, and F. Sato, *J. Chem. Soc. Chem. Commun.*, 1323 (1986)..*idem*, *Tetrahedron*, **44**, 4073 (1988).
3) Selective reduction of α,β-epoxy ketones with metal hydrides was reported : P. Chautemps, and J. L. Pierre, *Tetrahedron*, **32**, 549 (1976). T. Oishi, and T. Nakata, *Acc. Chem. Res.*, **17**, 338 (1984). α-Trimethylsilyl α,β-epoxy aldehydes were reported to react with Grignard reagents highly diastereoselectively thanks to the presence of the trimethylsilyl group at α-position : Y. Takeda, T. Matsumoto, and F. Sato, *J. Org. Chem.* **51**, 4728 (1986).
4) S. Okamoto, T. Yoshino, H. Tsujiyama, and F. Sato, *Tetrahedron Lett.*, following paper.
5) ^{1}H NMR data (CCl_4, 90 MHz) of ;



R = Bu, R'= Me ; δ 0.02 (s, 9H), 1.00 (t, *J* = 6.3 Hz, 3H), 1.31 (s, 3H), 1.20-1.84 (m, 6H), 2.32 (d, *J* = 3.8 Hz, 1H), 2.62 (d, *J* = 3.8 Hz,1H). **R = Bu, R'= Et** ; δ 0.23 (s, 9H), 0.83-1.22 (m, 6H), 1.22-2.05 (m, 8H), 2.29 (d, *J* = 3.6 Hz, 1H), 2.68 (d, *J* = 3.6 Hz, 1H). **R = Bu, R' = Ph** ; δ 0.26 (s, 9H), 0.98 (t, *J* = 6.0 Hz, 3H), 1.13-2.10 (m, 6H), 2.44 (d, *J* = 3.9 Hz, 1H), 3.14 (d, *J* = 3.9 Hz, 1H), 7.05-7.55 (m, 5H). **R = Et, R'= Bu** ; δ 0.45 (s, 9H), 0.80-1.79 (m, 14H), 2.26 (d, *J* = 3.8 Hz, 1H), 2.64 (d, *J* = 3.8 Hz, 1H). **R = Am, R' = Me** ; δ 0.21 (s, 9H), 1.00 (t, *J* = 6.2 Hz, 3H), 1.20-1.72 (m, 8H), 1.31 (s, 3H), 2.34 (d, *J* = 3.8 Hz, 1H), 2.63 (d, *J* = 3.8 Hz, 1H).

6) It should be note that the alcohol shown in Fig 2 (and its antipode) is the only one which can not be obtained purely due to the lower diastereoselectivity of the reaction.

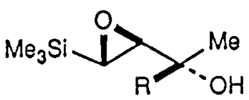


Fig 2

(Received in Japan 22 May 1991)