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DIASTEREO-DIFFERENTIATING SIMMONS-SMITH REACTION USING A NEW CHIRAL AUXILIARY

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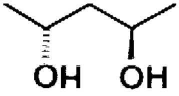
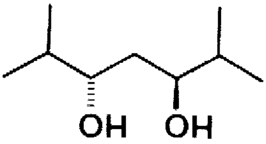
Summary: Diastereo-differentiating Simmons-Smith reactions of enol ethers of various ketones were carried out by using (3S,5S)-2,6-dimethyl-3,5-heptanediol as a new chiral auxiliary. The diastereomer excess of these reactions reached to be >99%.

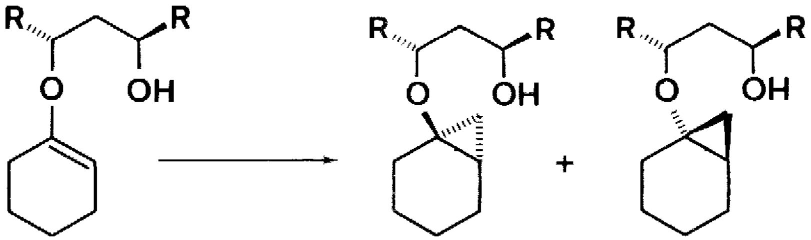
In a preceding communication[1] we have reported that the diastereo-differentiating Simmons-Smith cyclopropanation of enol ether of cyclohexanone with optically active 2,4-pentanediol(**2a**), smoothly proceeded in giving a mixture of **3a** and **4a** with 95% of diastereomer excess(d.e.=([**3**]-[**4**])x100 /([**3**]+[**4**])) and 55% of chemical yield when DME was employed as a solvent(Eq.1, R=Me). However by the use of hexane or ether as a solvent, the d.e. of the reaction became 40% or -8%, respectively. The results were suggestive that the diastereo-face of substrate was not fixed with 2,4-pentanediol(**1a**) unless a particular solvent provided a certain substrate/reagent/solvent complex. One approach to exclude this solvent effect is to design an efficient chiral auxiliary having bulky groups on its chiral centers. In this communication, we wish to show the effectiveness of a new chiral auxiliary, (3S,5S)-2,6-dimethyl-3,5-heptanediol(**1b**), designed as a bulky analogue of **1a**.



(2R,4R)-**1a**



(3S,5S)-**1b**



(eq. 1)

2a : R=Me
2b : R=i-Pr

3a
3b

4a
4b

Optically pure (3S,5S)- and (3R,5R)-**1b** were prepared by the enantio-differentiating hydrogenation of 2,6-dimethyl-3,5-heptanedione over (R,R)- and (S,S)-tartaric acid modified Raney nickel catalyst, respectively, followed by three recrystallizations.[2,3]

Enol ether(**2b**) was obtained from cyclohexanone and (3S,5S)-**1b** by the ketallization(87% yield) with collidinium tosylate in benzene under refluxing followed by the isomerization (98% yield) with triisobutylaluminium in CH_2Cl_2/hexane at 0°C.

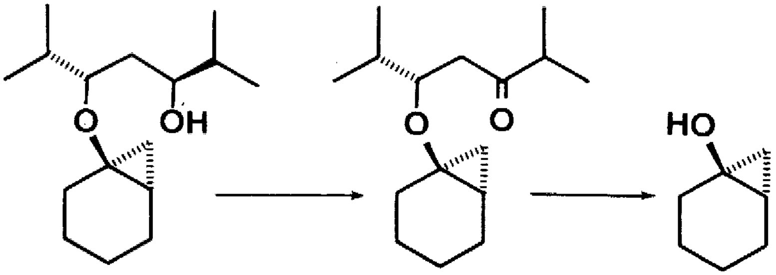
Simmos-Smith reaction was carried out as follows; to a solution of 333 mg of **2b** in 10 ml of the solvent stated in Table 1 was added Et_2Zn (7 ml, 1 molar solution in hexane) and then was added CH_2I_2 (1.2 ml) dropwise at the same temperature. The reaction mixture was allowed to stand for several hours under stirring. After quenching of the reaction mixture with saturated aqueous solution of NH_4Cl, the product was extracted with ether. The concentrated extract was subjected to MPLC purification on silica gel to give 191-304 mg of the product. The ratio of **3b** and **4b** in the product was determined by GLC analysis(PEG-20M fused silica capillary column, 0.25mm x 50m, 110°C).[4] The results of the reactions under different conditions are listed in Table 1.

Table 1 The results of Simmons-Smith reactions of **2b**

No.	solvent	temp.(°C)	time(hr)	yield(%)	d.e.(%)
1	hexane	0	1.5	54.3	98.8
2	hexane	-40 0	2.5[a]	75.3	98.8
3	ether	20	1.5	86.4	>99.5
4	ether	0	3	72.0	99.4
5	ether	-40	27	59.3	95.0
6	THF	20	2.5	69.0	95.8

a) The mixture was kept for 0.5 hr at -40°C, warmed up to 0°C over 1.5 hr, and then kept for 0.5 hr at 0°C.

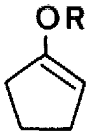
In all cases, both d.e. and chemical yield of the products increased considerably by comparing with the results of **2a**[1]. Under optimum conditions, **3b** essentially freed from **4b** was obtained(Table 1, No.3).



(eq. 2)

The structure of a major diastereomer was determined to be **3b** by chemical correlation with (+)-(1S,6S)-1-bicyclo[4.1.0]heptanol[1] as shown in eq. 2. Thus, Simmons-Smith reagent attacked from si-re face of (3S,5S)-**2b** in a similar manner as (2R,4R)-**2a**.

Diastereo-differentiating Simmons-Smith reaction was also successfully applied to enol ethers of **1b** with various ketones shown below.



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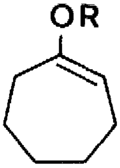

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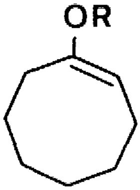

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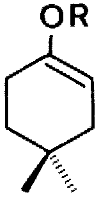

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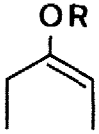

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R=(3S,5S)-**1b**-moiety

In all cases, enol ethers were obtained from the corresponding ketones and **1b** by the same process as the case of **2b** in favorable yields(for two steps, 60 to 90%).[5] The cyclopropanations of the enol ethers were carried out under the optimized conditions(Table 1, No 3) to give products in yields of 80.7, 77.2, 58.2, 80.0, 57.1, from **5**, **6**, **7**, **8**, **9**, respectively. The capillary GLC of each product showed a single peak and no detectable peak corresponding to its diastereomer. The ^{1}H and ^{13}C NMR spectra also indicated the homogeneity of each product. Thus, the d.e.'s of all reactions were considered to be more than 99%. The stereochemistry of these products were only confermed in the case of **6** and **7** to be (1S,7S) and (1S,8S), respectively.[6] On extention of these results, Simmons-Smith reagent was expected to attack to si-re face of the enol ether in all cases.

Through the present study, effectiveness of **1b** as a chiral auxilialy for the Simmons-Smith reaction was confirmed. It is noteworthy that the order of reactivity of **1b** and the all compounds containing **1b** moiety was the same as those of **1a** under the same reaction conditions.

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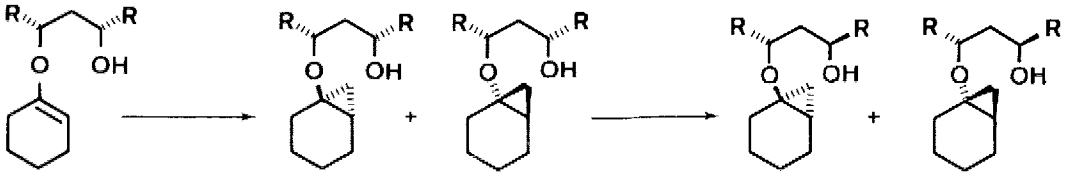
References and Notes

1. T. Sugimura, T. Futagawa and A. Tai, Tetrahedron Lett., **29**, 5775(1988)
2. A. Tai, K. Ito and T. Harada, Bull. Chem. Soc. Jpn., **54**, 223(1981)

3. Colorless needles, mp 91.5-92.0°C, (3S,5S)-**1**; $[\alpha]_D^{20}$= -63.8 (c 1.0, methanol), (3R,5R)-**1**; $[\alpha]_D^{20}$=63.2 (c 1.0, methanol). Each sample was found to be free from its antipode both by ^{1}H-NMR of its monoacetate with a chiral shift reagent and by HPLC of its dibenzoate on Chiralpak OT+. Details of the synthetic procedure and the determination of stereochemistry will be published elsewhere.
4. Since the amount of a minor diastereomer was too small to confirm its structure by spectroscopic methods, a mixture of racemic **3b** and **4b** in a ratio of 81.7:18.3 was prepared from enol ether of cyclohexanone with meso-2,6-dimethyl-3,5-heptanediol(**1c**) as a reference material. That is, **2c** was cyclopropanated with Simmons-Smith reagent in THF, then the product was epimerized to a mixture of racemic diastereomers having the same relative configuration of **3b** and **4b** by the Mitsunobu method. The capillary GLC analysis showed that the retention times of the obtained each diastereomer was matched with that of **3a** and **4b**, respectively. The ^{1}H and ^{13}C NMR spectra of the mixture were consisted with those expected from a mixture of diastereomers.



2c R=i-Pr **3b**(racemi) **4b**(racemi)

5. 3-Pentanone exclusively gave E-enolate when its ketal was treated with Al(i-Bu)$_3$ at -50°C for 6 hours. The stereochemistry of the compound was confirmed by its NOEZY NMR spectra.
6. The stereochemistry of cyclopropanes was determined by chemical correlation with (R)-2-methylcycloalkanones, which was derived from cyclopropanes by acid treatment in benzene containing water in the case of **6** and **7**. Cyclopropane from **5** did not afford 2-methlcyclopentanone, but yielded cyclohexanone under these conditions. The stereochemistry of 2,4,4-trimethylcyclohexanone was unknown. Reference for (-)-(R)-2-methylcycloheptanone; C. D. Gutsche, and C. T. Cheng, *J. Am. Chem. Soc.*, **84**, 2263(1962), for (-)-(R)-2-methylcyclooctanone; A. C. Cope, E. Ciganek, and J. Lazar, *J. Am. Chem. Soc.*, **84**, 2591(1962)

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