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# HIGHLY STEREOSELECTIVE REDUCTION OF β-OXOSULFONIUM SALTS
## ---- SYNTHESIS OF trans EPOXIDES----

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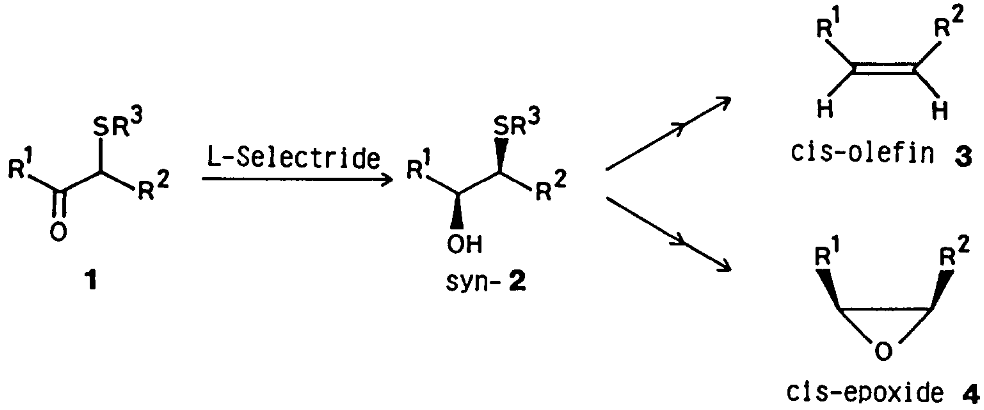
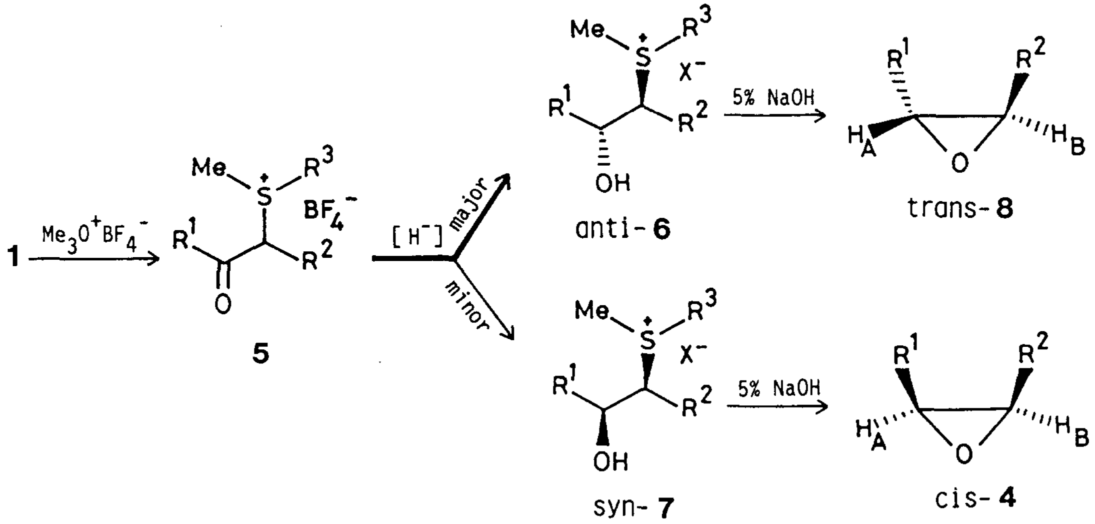
**Summary:** Alkylation of α-methylthio or α-phenylthio ketones **1** with trimethyloxonium tetrafluoroborate and the reduction of the resulting sulfonium salts **5** with $NaBH_4$ followed by the base treatment afforded trans-epoxides **8** with high stereoselectivity.

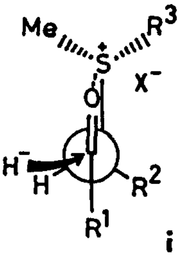
In the preceding paper, we reported that the reduction of α-methylthio and α-phenylthio ketones **1** with L-Selectride afforded the corresponding syn-alcohols **2** in high stereoselectivity.$^{1)}$ The present method is of particular significance since the resulting **2** is convertible into cis-olefins **3**$^{2)}$ or cis-epoxides **4**.$^{1,3)}$ However, in the $Zn(BH_4)_2$ reduction expected to give an anti-selectivity, excellent results were obtained only in the limited cases. Therefore, we focused our attention on the improvement of the anti-selectivity by the modification of the substrate structure.

Our working hypothesis is as follows. If the sulfides **1** are converted into the sulfonium salts **5**, the conformer **i** in which the carbonyl and the sulfonium groups are faced each other is expected to be most stable due to the charge attraction between these closely located functional groups. Therefore, the hydride anion may attack the ketone from the less hindered hydrogen side affording the desired anti-**6**, whose transformation into trans-epoxides **8** has already been reported.$^{1,3)}$

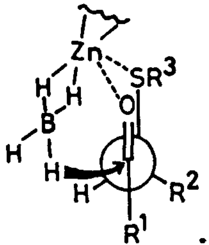




Initially, an effect of reducing agents on selectivity was examined using 5c($R^1$=Ph, $R^2$=Et, $R^3$=Ph) produced from 1c by trimethyloxonium tetrafluoroborate treatment as a substrate. Anti-selectivity to give **6c** was always excellent regardless of the reagents used, which supported the intermediacy of the transition state i in which metal cation was not contributing. The charge



**i**



**ii**

**Table 1. The Reduction of the Sulfonium Salt 5c with various Reducing Agents and the Conversion of the Resulting β-Hydroxy Sulfonium Salts 6c and 7c into Epoxides 8c and 4c(=8a and 4a)**

| Entry | Reducing Agent | Solvent | Product trans-8c : cis-4c[a] | Overall Yield(%)[b] |
|---|---|---|---|---|
| 1 | Vitride | $CH_2Cl_2$-$PhCH_3$ | 99 : 1 | 55 |
| 2 | $LiAlH_4$ | THF | 97 : 3 | 61 |
| 3 | n-$Bu_4NBH_4$ | $CH_2Cl_2$ | 96 : 4 | 67 |
| 4 | $NaBH_4$ | $CH_2Cl_2$ | 95 : 5 | 61 |
| 5 | $Zn(BH_4)_2$ | Ether | 88 : 12 | 60 |

a) The ratio was determined by 400 MHz NMR spectroscopy.
b) From 1c.

attracted cyclic transition state **i**[4)] proposed here is in sharp contrast to the metal mediated cyclic transition state **ii** proposed in the $Zn(BH_4)_2$ reduction of **1**.[1,5)] The fact that the rather unsatisfactory result was obtained by $Zn(BH_4)_2$ reduction(entry 5) suggested that the stability of i might be reduced by the prior coordination of the reagent to the carbonyl oxygen. The data were shown in **Table 1**.

The ratio of epoxides **8c** and **4c** should reflect the ratio of the reduction products **6c** and **7c** from **1c**, since anti-**6c** could be converted into trans-**8c** and syn-**7c** to cis-**4c** under virtually complete stereoselection.[1,3)] The stereochemistry of the epoxides **8c** and **4c** was assigned by the coupling constant of epoxide protons($J_{AB}$, trans-**8c** < cis-**4c**)[1,6)] shown in **Table 3**.

Then, using $NaBH_4$ as a reducing agent, a relation between ketone structure and selectivity was examined.[7)] The data were shown in **Table 2**. The structures of epoxides **8** and **4** were also assigned from NMR data(**Table 3**).[1,6)] When $R^1$ is phenyl, the anti-selectivity was excellent in every case(entry 1-4). Selectivity was not affected by the S-substituent($R^3$). It should be emphasized here that even in the case where $R^1$ was n-alkyl group a remarkably high selectivity was observed provided $R^2$ was branched alkyl group(entry 7), although in the $Zn(BH_4)_2$ reduction of the corresponding α-phenylthio ketones **1**, only unsatisfactory result was obtained.[1)] Even when $R^2$ is n-alkyl group, a fair selectivity was obtained(entry 5,6).

**Table 2. The Reduction of the Sulfonium Salts 5 with $NaBH_4$ in $CH_2Cl_2$ and the Conversion of the Resulting β-Hydroxy Sulfonium Salts 6 and 7 into Epoxides 8 and 4**

| Entry | Substrate | $R^1$ | $R^2$ | $R^3$ | Product trans-8 : cis-4[a] | Overall Yield(%)[b] |
|---|---|---|---|---|---|---|
| 1 | **5a** | Ph | Et | Me | 99 : 1 | 63 |
| 2 | **5b** | Ph | i-Pr | Me | 99 : 1 | 56 |
| 3 | **5c** | Ph | Et | Ph | 95 : 5 | 61 |
| 4 | **5d** | Ph | i-Pr | Ph | 99 : 1 | 67 |
| 5 | **5e** | n-Bu | n-Pr | Ph | 88 : 12 | 74 |
| 6 | **5f** | $PhCH_2CH_2$ | n-Bu | Ph | 80 : 20 | 62 |
| 7 | **5g** | $PhCH_2CH_2$ | i-Pr | Ph | >99 : <1 | 44 |
| 8 | **5h** | cyclohexyl | n-pentyl | Me | 63 : 37 | 61 |

a) The ratio was determined by 400 MHz NMR spectroscopy.
b) From **1**.

Thus, the scope of the trans-epoxide synthesis was much expanded by the present modification that the crucial ketone reduction was undertaken after initial S-alkylation of **1** with Meerwein reagent. The present results highly support the intervention of the new charge attracted cyclic transition state **i**, in the reduction of **5** where the carbonyl and the sulfonium groups are possible

**Table 3.** Chemical Shifts and Coupling Constants of $H_A$ and $H_B$ of trans-and cis-epoxides 8 and 4

| Compound | trans-Epoxide **8** Chemical Shift(δ) $H_A$ | $H_B$ | $J_{AB}$(Hz) | cis-Epoxide **4** Chemical Shift(δ) $H_A$ | $H_B$ | $J_{AB}$(Hz) |
|---|---|---|---|---|---|---|
| a(=c) | 3.61 | 2.94 | 1.95 | 4.09 | 3.17 | 4.39 |
| b(=d) | 3.66 | 2.76 | 2.20 | 4.10 | 2.86 | 4.15 |
| e | 2.68(m, centered at) | | | 2.93(m, centered at) | | |
| f | 2.70 | 2.65 | 2.20 | 2.92 | 2.97 | 4.28 |
| g | 2.46 | 2.75 | 2.32 | 2.61 | 2.99 | 4.27 |
| h | 2.72 | 2.45 | 2.20 | 2.92 | 2.62 | 4.15 |

to access closely. Further works providing more direct evidence for the transition state **i** are in progress.

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4) The counter anion of the initial alkylation product is the tetrafluoroborate anion. However, when complex metal hydrides were added, anion exchange should take place at least in part. The fact that the reduction of **5** with $NaBH_4$ proceeded smoothly even in $CH_2Cl_2$ solution might be ascribed to the formation of reactive intermediate **i**($X^-=BH_4^-$) and $NaBF_4$ by anion exchange reaction.
5) See also T. Nakata, T. Tanaka, and T. Oishi, Tetrahedron Lett., **24**, 2653 (1983); D. J. Cram and K. R. Kopecky, J. Am. Chem. Soc., **81**, 2748(1959).
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7) $NaBH_4$ was chosen since the yields of epoxides **8** and **4** were unsatisfactory when reducing agents other than $NaBH_4$ shown in **Table 1** were used particularly in the cases where $R^1$ were alkyl groups.

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