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# TRIMETHYLSILYL GROUP DIRECTED WAGNER-MEERWEIN REARRANGEMENT OF BICYCLO[2.2.2]OCTAN-2-OL DERIVATIVES

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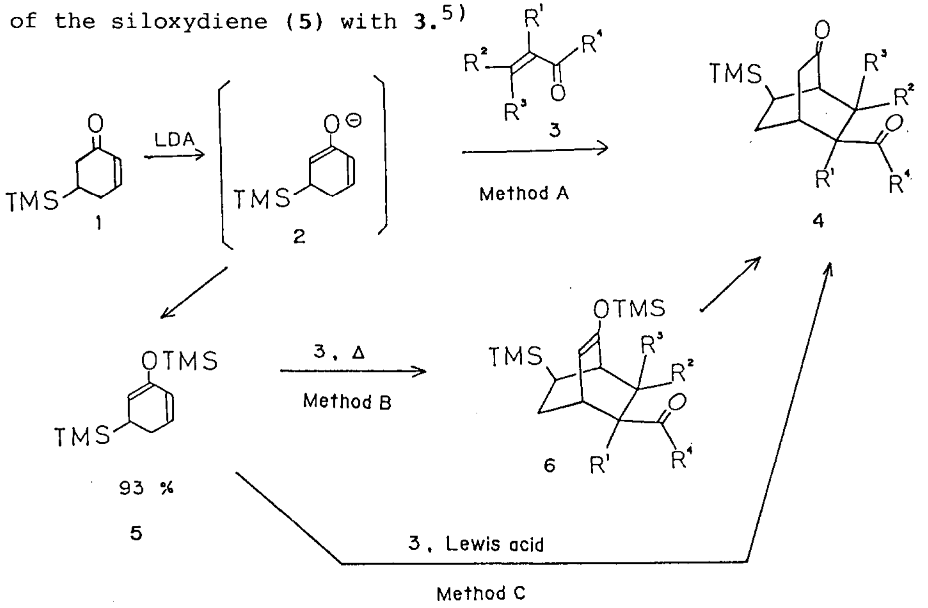
Summary: Trimethylsilyl group substituted bicyclo[2.2.2]octane derivatives were synthesized and subjected to TMS group directed Wagner-Meerwein rearrangement to give bicyclo[3.2.1]octene derivatives in high yields.

In connection with projected total syntheses of some natural products utilizing 5-trimethylsilyl-2-cyclohexenone (**1**),1) we examined the synthesis of 6-(trimethylsilyl)bicyclo[2.2.2]octan-2-ones (**4**) and Wagner-Meerwein rearrangement of their alchohol or methyl ether derivatives. It is well-known that silicon has a definite stabilizing effect on $\beta$ carbocations, and which has been utilized effectively by Fleming et al.2) in Wagner-Meerwein rearrangement of some relatively simple molecules. In our case also the presence of TMS group at the $\beta$ position to the cationic site was extremely effective to control the skeletal rearrangement into bicyclo[3.2.1]octenes.

Trimethylsilyl group substituted bicyclo[2.2.2]octane derivatives (**4**), were easyly obtained from **1** by the following three methods; method A: Sequencial Michael reaction3) with $\alpha,\beta$-unsaturated carbonyl compounds (**3**), method B: Diels-Alder reaction with **3** via trimethylsiloxy diene4) (**5**) followed by hydrolysis of the enol silyl ether (**6**), method C: Lewis acid catalyzed reaction of the siloxydiene (**5**) with **3**.5)



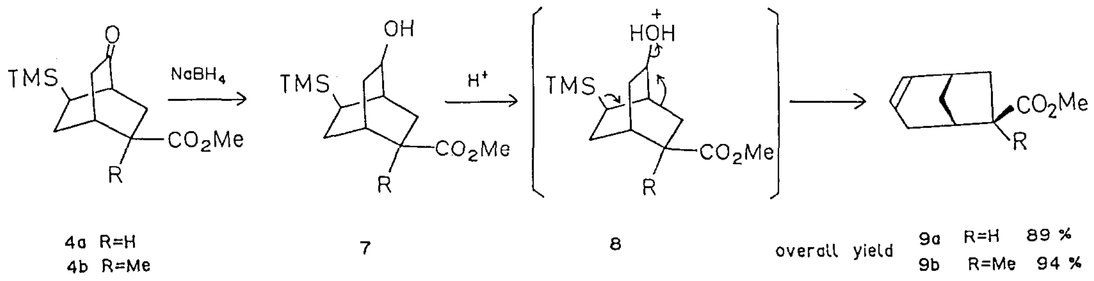
As shown in table 1, when unsaturated esters, methyl acrylate and methyl methacrylate, were used as **3**, method A was proved to be most effective. In the case of these esters, method B required vigorous reaction conditions (neat, 100-105°C, 22-28 h) and resulted **4** was contaminated with a small amount of diastereoisomer and/or unidentified by-product. On the contrary, in the case of more reactive dienophile, N-phenylmaleimide and maleic anhydride, method B gave the corresponding **4** successfully, though maleic anhydride gave final product in a moderate yield presumably due to the hydrolysis of anhydride moiety in the second step. Method C gave the most satisfactory results when unsaturated ketones were used. As for the stereochemistry of the products **4** shown in table 1 (**4a-4f**), each of them was obtained as a single diastereoisomer. On the basis of mechanstic aspects of the three methods,[3-5] the stereostructure of the products were tentatively proposed as shown in the schemes.

Table 1. Synthesis of **4**

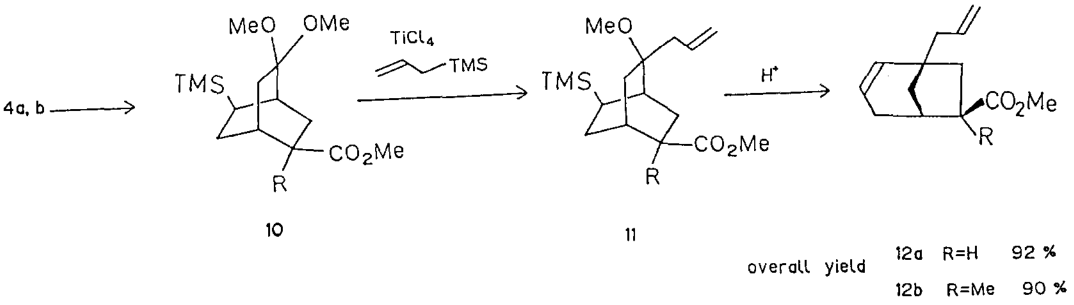
| $R^1$ | $R^2$ | $R^3$ | $R^4$ | Method | Reaction conditions | **4** | Yield(%) | mp(°C) |
|---|---|---|---|---|---|---|---|---|
| H | H | H | OMe | A | -70~-5°C 2.5 h | **4a** | 71 | 86-7 |
| Me | H | H | OMe | A | -40~10°C 3 h | **4b** | 63 | 59.5-60.5 |
| H | Me | H | OMe | A | -70~-10°C 2.5 h | -- complex mixture -- | | |
| H | H | -CO-NPh- | | B[a)] | rt 2 days | **4c** | 90[c)] | ~229-236 (sublime) |
| H | H | -CO-O- | | B[a)] | rt 16 h | **4d** | 65[c)] | ~204-209 (sublime) |
| H | H | H | OMe | C[b)] | -70~-60°C 2 h | **4a** | 63[c)] | 86-7 |
| H | H | H | Me | C[b)] | -70°C 1 h | **4e** | 91[c)] | 69-70 |
| H | Me | Me | Me | C[b)] | -70°C 7 h | **4f** | 48[c)] | 85-85.5 |
| Me | H | H | Me | C[b)] | -70°C 1 h | -- complex mixture -- | | |

a) Reaction was carried out in benzene and then crude **6** was treated with KF in acetone. b) Reaction was carried out in $CH_2Cl_2$ using $SnCl_4$ as a catalyst. c) Yield was calculated based on **5**.

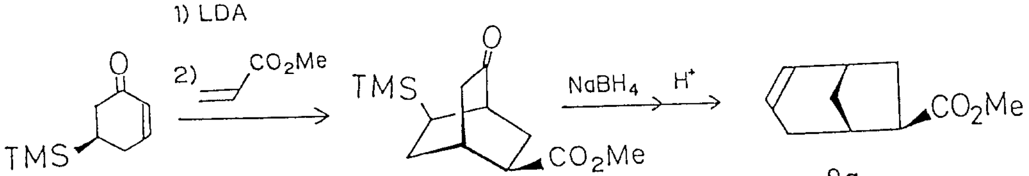
Using **4a,b** , trimethylsilyl group directed skeletal rearrangement via their alcohol derivatives was examined. After the reduction of **4a,b** with $NaBH_4$, treatment of the crude trimethylsilyl substituted bicyclo[2.2.2]octanol derivatives **7a** and **7b**, with p-toluenesulfonic acid (PTS) on silica gel[6)] in dry benzene under reflux for 45 min gave expected **9a** and **9b** in 89 and 94% overall yields from **4**, respectively.[7)]



Introduction of some substituents in the course of above transaformation was also envisioned. First, the reaction of **4a** with $Me_4Ti$ was examined at -78°C~rt but **4a** was almost inert toward the reagent under these conditions. Then Lewis acid catalyzed electophilic reaction of **4a,b** via acetal derivatives were carried out. Acetalization of **4a,b** [MeOH, $HC(OMe)_3$, Amberlite IR 112, rt, 2 days] followed by the reaction with excess allyltrimethylsilane in the presence of $TiCl_4$ ($CH_2Cl_2$, -70~-10°C, 6-10 h) and usual work-up afforded almost pure **11a** and **11b** which were used without further purification for the next step. Treatment of **11a,b** with PTS on silica gel in refluxing benzene for 10 minutes furnished rearranged products **12a** and **12b** in 92 and 90% overall yields from **4**.7)



Finally, the synthesis of optically active **9a** was also examined starting from optically pure **1**.1) The specific rotations of (-)- and (+)-**4a** as well as those of (+)- and (-)-**9a** showed good agreement of the absolute values and $^{13}$C NMR spectra of the final products [(+)- and (-)-**9a**] showed their homogeneity.7) These results are shown below.



1 4a 9a

| | | | | |
|---|---|---|---|---|
| (R)-(−) | 73 % | $[\alpha]_D^{22}$ −98.2° (c 1.00, $CHCl_3$) | 87 % | $[\alpha]_D^{22}$ +16.7° (c 1.20, $CHCl_3$) |
| (S)-(+) | 83 % | $[\alpha]_D^{22}$ +98.0° (c 1.00, $CHCl_3$) | 81 % | $[\alpha]_D^{22}$ −16.8° (c 1.20, $CHCl_3$) |

In conclusion, this method provided prospective route for the synthesis of various optically active bicyclo[3.2.1]octene derivatives which would be useful intermediates for the synthesis of chiral natural poroducts.

## References and Notes

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4) The enolate **2** was generated by the treatment with LDA in THF at -70°C for 3 h and the reaction with chlorotrimethylsilane was carried out at -70°C for 15 min to give siloxydiene **5** (bp 69-71°C/2.0-2.5 mmHg) in 93% yield. As for the synthesis and the Diels-Alder reaction of similar siloxydiene ,see a) G. M. Rubottom and D. S. Krueger, Tetrahedron Lett., **1977**, 611; b) M. E. Jung, C.A.McCombs, Y. Takeda, and Y-G, Pan, J. Am. Chem. Soc., **103**, 6677 (1981).

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7) All the bicyclo[3.2.1]octenes synthesized here are oily compounds and their structures were confirmed by their spectral (NMR and IR) data and elemental analysis. Both of (-)- and (+)-**4a** showed the same mp 47.5-8.5°C.

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