Communications to the Editor

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SYNTHESIS OF 9,9,9-TRIFLUORO-2-p-MENTHENE-1,8-DIOL. DETERMINATION OF THE STRUCTURE BY X-RAY ANALYSIS

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The ene reaction product of trifluoroacetone with cyclohexene was oxidized to 4-(1,1,1-trifluoro-2-hydroxy-2-propyl)-2-cyclohexenone, which was converted to the title compound. X-ray analysis of this compound determined the regio- and stereo-chemistries in the ene reaction, oxidation and methylation.

KEYWORDS——menthane; trifluoromethyl; ene reaction; oxidation; methylation; X-ray analysis; p-menthenediol

Previously, we reported the ene reaction of trifluoroacetone with cyclohexene gave 2-(2-cyclohexen-1-yl)-1,1,1-trifluoro-2-propanol (**1**).[1] Now, we report the derivatization of **1** to 9,9,9-trifluoro-2-menthene-1,8-diols (**4** and **5**), trifluoro analogues of menthane derivatives, and the X-ray analysis of 5.

The procedures are summarized in Chart 1.

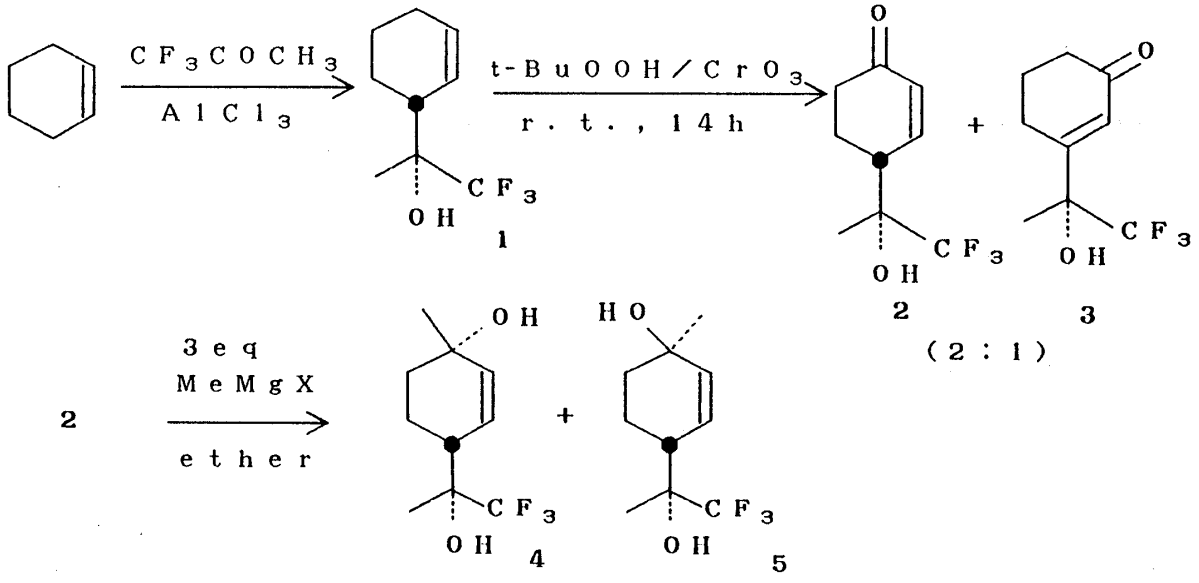

Chart 1

The first step might give two diastereoisomers concerning two chiral centers, but we had obtained one isomer, the structure of which had not been determined.[1] Recently, **1** was dehydrated with phosphorus oxychloride and pyridine to 3-(1,1,1-trifluoro-2-propylidene)cyclohexene, whose stereochemistry was tentatively assigned to a Z-form by two dimensional nuclear magnetic resonance.[2] Therefore, **1** must have the (R^*,R^*)-configuration. Oxidation of **1** with tert-butyl hydroperoxide in the presence of a catalytic amount of chromium trioxide gave 4-(1,1,1-trifluoro-2-hydroxy-2-propyl)-2-cyclohexenone (**2**) and 3-(1,1,1-trifluoro-2-hydroxy-2-propyl)-2-cyclohexenone (**3**) in a ratio of 2:1. In the formation of the latter, an allylic oxidation was followed by migration of the double bond. If such a migration occurred in the formation of the former, the structure of **2** might be 6-(1,1,1-trifluoro-2-hydroxy-2-propyl)-2-cyclohexenone. Treatment of **2** with methylmagnesium iodide gave 9,9,9-trifluoro-2-menthene-1,8-diols (**4**) and (**5**). To determine the structures of **1** to **5** unambiguously, X ray analysis of **5** was carried out. Crystal data are: Monoclinic; Space group C2/c; a=19.196(1), b=9.010(1), c=12.414(1) A; β=100.61(1)°; Z=8. The structure was determined as shown in Fig. 1. This result shows that **1** is (R^*,R^*)-isomer, **2** has the structure as shown in Chart 1 and **5** is ($1R^*$,$4R^*$,$8R^*$)-isomer. Thus, **4** is determined to be the ($1S^*$,$4R^*$,$8R^*$)-isomer.

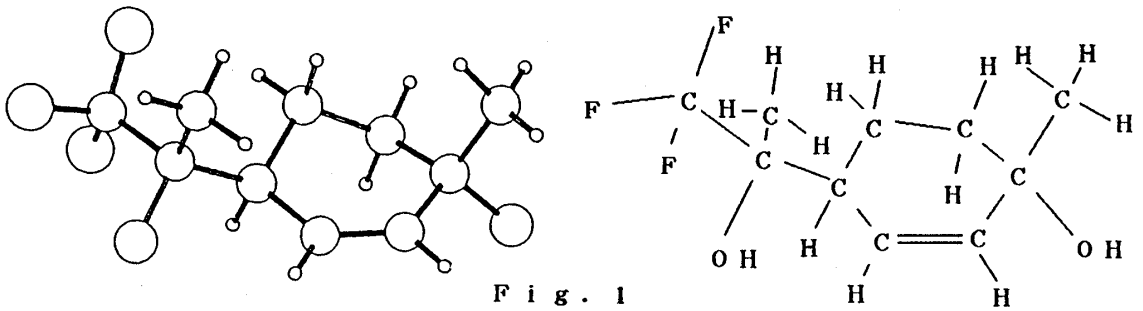

Fig. 1

The stereoselectivity in the ene reaction of trifluoroacetone with cyclohexene assumed to be due to the fact that repulsion between 3- and/or 4-protons and the trifluoromethyl group prevents formation of other isomers. The transition state for formation of **1** is shown in Fig. 2. The fact that hexafluoroacetone hardly reacted with cyclohexene supports the above assumption.

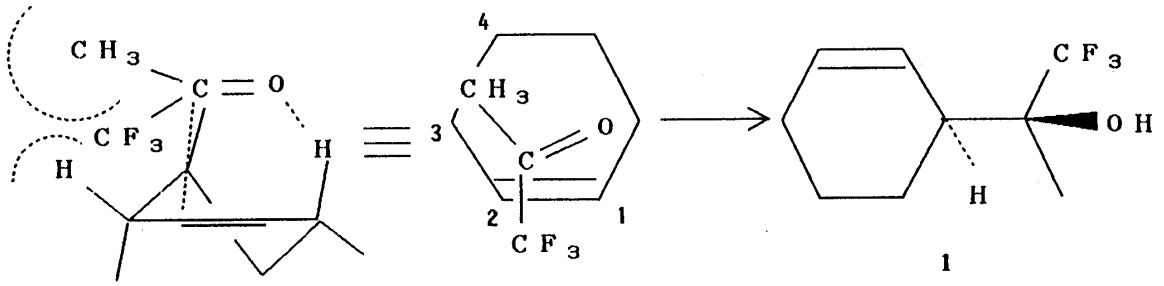

Fig. 2

REFERENCES AND NOTES

1) T. Nagai, T. Miki, I. Kumadaki, T. Miki and G. Tomizawa, Chem. Pharm. Bull., **34**, 1546 (1986).

2) T. Nagai, M. Hama, M. Yoshioka, M. Yuda, N. Yoshida, M. Koyama, A. Ando, T. Miki, and I. Kumadaki, submitted to Chem. Pharm. Bull.

3) All new compounds have been characterized by mass, ^{1}H- and ^{19}F-NMR spectra.

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