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DOUBLE MICHAEL REACTION OF CARVONE AND ITS DERIVATIVES

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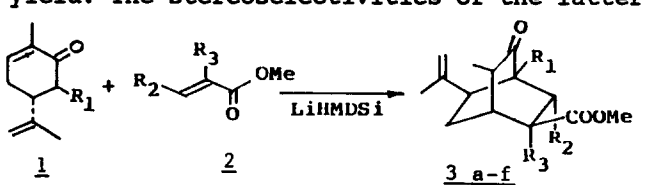
Abstract: Bicyclo[2.2.2]octane derivatives, a series of potentially useful chiron, were obtained from the double Michael reaction of carvone or methylcarvone with α,β-unsaturated esters.

Carvone has been widely used in organic synthesis as a chiral starting material[1], but there was no report on the synthesis of optically active bicyclo[2.2.2]octane compounds from carvone or its derivatives. The Diels-Alder reaction of its enol derivatives, a straightforward approach to the bicyclo[2.2.2]octane adduct, did not take place in our case. Considering the successful application of double Michael addition as an alternative approach to such adduct in recent years[2], the reaction of carvone or methylcarvone has been carried out to examine the accessibility and the stereoselectivity.

The reaction of (-)-carvone and methyl methacrylate in the presence of the usual base, such as potassium t-butoxide or LDA, could not yield any separable bicyclic adduct, but it was found that if lithium hexamethyldisilazide was used as the base in a mixed solvent system of hexane and ethyl ether, the double Michael addition occurred smoothly and the bicyclic adduct was obtained in moderate yield(Table 1). Capillary gas chromatography of the adduct showed that there were three to four components among which the major compound was more than 90%. The pure major compound could be obtained by recrystallization. Under the same condition, methyl acrylate and methyl crotonate also reacted with (-)-carvone to give the expected adducts. Methylcarvone could participate in the double Michael reaction at 0°C with somewhat better yield. The stereoselectivities of the latter reactions were



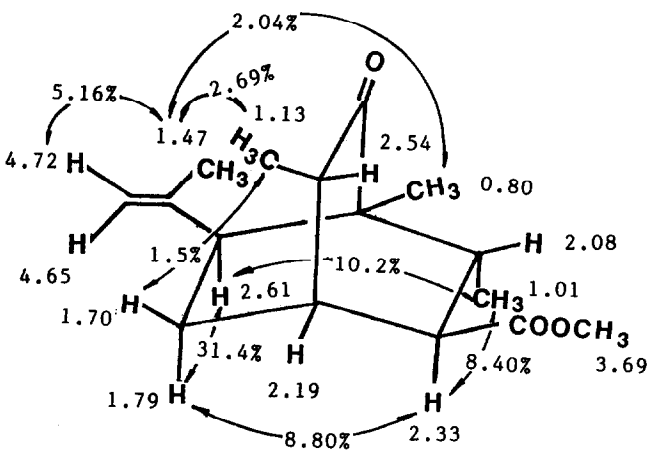
1 2 3 a-f

little lower than that of carvone and methyl acrylate. These adducts could be purified via recrystallization of their free acid and then reesterification with diazomethane.

Table 1 Double Michael Addition Reaction of (-)-Carvone and Methylcarvone

Adduct 3	R_1	R_2	R_3	Reaction Condition[3] C_6H_{14}/Et_2O	Temp.°C	Adducts Yield%	Major Adduct[4] content%	mp°C	$[\alpha]_D^{25}$(c,MeOH)
a	H	H	Me	9:1	-78--r.t.	52	94	60-61.5	-42.6(1.0)
b	H	Me	H	10:1	-78--r.t.	46	77	syrup	-42.6(1.2)
c	H	H	H	10:1	-78--r.t.	32	76	syrup	-52.8(1.2)
d	Me	H	Me	1:0	0	62	85	syrup	-37.2(0.7)
e	Me	Me	H	1:0	0	52	77	syrup	-80.7(1.1)
f	Me	H	H	1:0	0	79	87	syrup	-64.8(0.9)

Four to five chiral centers were newly built in the double Michael reaction. The stereochemistry was clarified by the analysis of NMR spectra as exemplified by compound **3e**, which has five new chiral centers. The structure of **3e** was definitely determinated by 2D-NMR and 1D NOE difference spectra as shown in the following figure, in which all the proton chemical shifts and some important NOEs were noted.

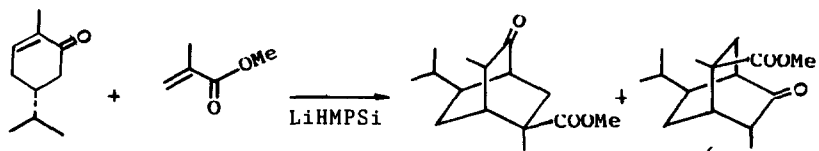


3e

The contents and the structures of the major products indicated that the double Michael addition of carvone or methylcarvone occurred with satisfactory selectivity. It was proposed that the acrylate accessed the car-

vone molecule preferentialy from the opposite side of the isopropenyl group. The structure also revealed that the methoxycarbonyl group of acrylate and carbonyl group of carvone were in the same side, a result correspounds to the endo addition of Diels-Alder reaction. This result was also similar to that of other double Michael reactions reported in recent literatures[2a,2b].

The minor adducts of these reactions were too few to be identified. When carvotanacetone **4** was treated with methyl methacrylate in the same condition, another adduct was presented in the crude adduct as much as one third of the major product. With careful column chromatography, two compounds **5** and **6** were obtained in pure form. The major product **5**[5] was identical with the hydrogenation product of **3a**, while compound **6**[6] had similar physical data to those of **5**, except the Cotton effect of CD spectra. It was proposed that compound **6** arose from attacking of methyl methacrylate in the same side of isopropyl group as shown in the following scheme.



4 5 6

In summary, we found that the double Michael reaction of carvone and methylcarvone could be carried out in highly stereoselectivity manner. The procedure described here provided an efficient route to the syntheses of optically active compounds with bicyclo[2.2.2]octane skeleton, which were potentially useful precursors to a number of natural products. A formal synthesis of natural (-)-patchouli alcohol from **3f** will be reported in due time.

ADDENDUM While this manuscript was being prepared, a double Michael reaction of (+)-carvone and α,β-unsaturated ester for systhesis of taxane diterpene appeared in a symposium (Nagaoka,H., Fujita,S., Yoshinaga,Y., Kobayashi,K., Okue,M., Yamada,Y., 31st symposium papers P.96).

ACKNOWLEDGEMENT We thank the National Natural Science Fundation of China for financial support.

References and Notes

1. For example:
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2.a) Asaoka,M., Takei,H., Tetrahedron Lett.,1987, **28** 6343.

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c) Ihara,M., Ishida,Y., Abe,M., Toyota,M., Fukumoto,K., J.Chem.Soc. Perkin Trans I, 1988,1155.

d) Ihara,M., Takahashi,T., Shimizu,N., Ishida,Y., Sudow,I., Fukumoto,K., Kametani,T., ibid 1989, 529.

3. Typical procedure for preparation of bicyclic adducts:

To a solution of hexamethyldisilazane (8.6 mL, 30.5 mmol) in dry hexane (60 mL) was charged n-butyllithium (30.5 mmol) at 0°C. After stirring for 15 min, a solution of methylcarvone (5 g, 30.5 mmol) in hexane (50 mL) was added and then after 45 min, methyl acrylate (3.3 mL, 30.5 mmol) was added.The reaction mixture was stirred for additional 1h, and then passed through a silica gel column. The crude product from the eluate was purified by chromatography to give 5.86g of an oily adduct duct **3f** in 79% yield (69% for pure **3f**).

4. All new compounds gave satisfactory spectroscopic (IR, NMR, MS) and analytical data.

5. Compound **5**: mp 71.5-73°C; $[\alpha]_D^{25}$=-41.1° (c=1.1, MeOH), IR ν_{max}(nujol) 1712 cm^{-1}; ^1H NMR δ_{ppm}(200MHz, $CDCl_3$) 3.70(3H,s), 1.41(3H,s), 1.09(3H,d, J=7Hz), 0.89,0.88(3Hx2,d,J=6.3Hz); MS m/z 253(M^++1); CD $\Delta\varepsilon^{MeOH}_{277nm}$=-0.37, $\Delta\varepsilon^{MeOH}_{311nm}$=+0.02; Anal. calcd. for $C_{15}H_{24}O_3$: C,71.39; H,9.58, Found: C,71.15; H,9.53.

6. Compound **6**: mp 101.5-102.5°C; $[\alpha]_D^{25}$=-35.1°(c=0.6, MeOH); IR ν_{max}(nujol) 1712 cm^{-1}; ^1H NMR δ_{ppm}(400MHz, $CDCl_3$) 3.65(3H,s), 1.37(3H,s), 1.12(3H,d, J=7.4Hz), 0.94,0.83(3Hx2,d,J=6.4Hz); MS m/z 252(M^+); CD $\Delta\varepsilon^{MeOH}_{290nm}$=+0.54; Anal. calcd. for $C_{15}H_{24}O_3$: C,71.39; H,9.58, Found: C, 71.45; H, 9.70.

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