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Synthesis of Sterically Hindered Bicyclo[2.2.2]octanes by Lewis Acid Catalyzed Reaction of 2-(Trimethylsiloxy)-1,3-cyclohexadienes with 4-Methyl-3-penten-2-one

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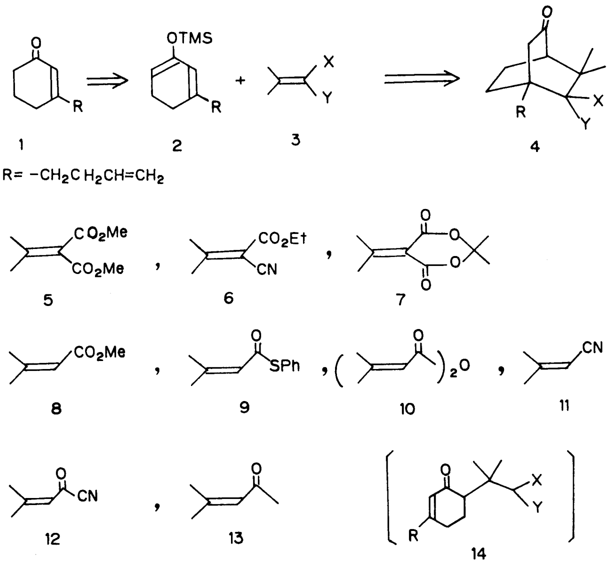
Synopsis. Dienol silyl ethers of various 2-cyclohexenones reacted with 4-methyl-3-penten-2-one(mesityl oxide) or methyl acrylate in the presence of Lewis acid to give bicyclo[2.2.2]octanes in moderate yields.

In the course of the total synthesis of (±)-eremolactone,[1] we needed to develop a new method for the construction of crowded bicyclo[2.2.2]octane skeleton.

Some reports on the synthesis of bicyclo[2.2.2]octane skeleton starting from 2-cyclohexenones using sequential Michael reaction or thermal Diels-Alder reaction via enol silyl ethers are known,[2] however, none of these methods are applicable to the construction of crowded tricyclo[5.2.2.0^{1,5}]undecane derivative suitable for the synthesis of (±)-eremolactone.

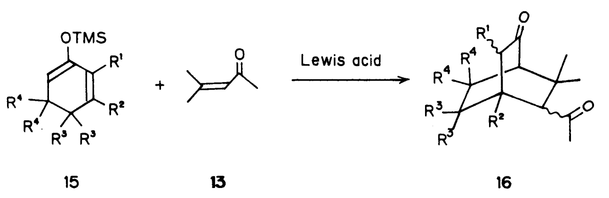
Thus, we investigated the Lewis acid catalyzed reaction of the dienol silyl ether **2** prepared from 2-cyclohexenone **1** with various 3-methyl-2-butenoic acid derivatives.



Scheme 1.

First, the reaction of dienol ether **2** with electron deficient tri- or tetra-substituted olefins (**5**—**13**) was examined in the presence of Lewis acid such as $SnCl_4$ or $TiCl_4$. In the case of the reaction of **5** or **6**, no bicyclo[2.2.2]octane but Michael adduct **14** was obtained as a major product and the attempts for the conversion of **14** to **4** under various (basic or acidic) conditions resulted in a failure. In the case of the reaction of other 3-methyl-2-butenoic acid derivatives **7**—**12**, none of desired products **4** nor **14** was obtained. When mesityl oxide (**13**) was used in the presence of $TiCl_4$, however **4** was successfully obtained in 44% yield. Then the reaction of mesityl oxide with some dienol silyl ethers derived from 2-cyclohexenones in the presence of $TiCl_4$ was carried out and the results are summarized in Table 1. The desired compounds were obtained except in the case of **15g**, in which case the reaction gave a complex mixture presumably due to the steric hindrance. As for the stereochemistry of the products, at least 2 isomers (endo- and exo-isomer) are possible, but only one isomer was isolated in the cases of **15a**, **15b**, **15e**, and **15f**, though the geometry of acetyl group is presently unknown. The dienol ether **15c** gave a mixture of two isomers and **15d** gave four isomers.[4] One of the tricyclic products synthesized from **15d** was used successfully for the synthesis of (±)-eremolactone.[1]

The mechanism of the reaction seems to involve a sequential Michael addition, because **14** was isolated when the reaction was quenched in the course of the process. For example, when the reaction of **15a** with



Scheme 2.

Table 1. Reaction of Dienol Silyl Ether (**15**) with Mesityl Oxide in the Presence of $TiCl_4$

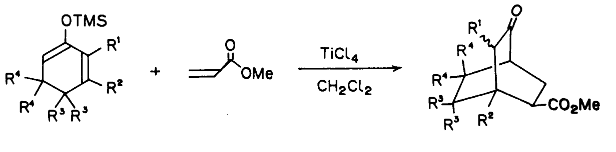
Entry		R^1	R^2	R^3	R^4	Reaction condition		Yield
						temp/°C	time/h	**16** %
1	**15a**	H	$-CH_2CH_2CH=CH_2$	H	H	−78—−30	2.5	44[a)]
2	**15b**	H	Me	H	H	−40	3	55[a)]
3	**15c**	Me	Me	H	H	−78	1.5	32[b)]
4	**15d**	$-CH(CH_3)CH_2CH_2-$		H	H	−78—−40	2	64[c)]
5	**15e**	H	H	Me	H	−40	0.5	40[a)]
6	**15f**	H	H	H	H	−78	2	12[a)]
7	**15g**	H	Me	H	Me	−78—rt	6	—[d)]

a) Single isomer. b) About one to one mixture of two geometric isomers. c) Mixture of four geometric isomers. d) Complex mixture.

Table 2. Reaction of Dienol Silyl Ether (**15**) with Methyl Acrylate in the Presence of $TiCl_4$

Entry		R_1	R_2	R_3	R_4	Reaction condition		Yield **18**[a)]
						temp/°C	time/h	%
1	**15b**	H	Me	H	H	−78—−40	8	52[b)]
2	**15c**	Me	Me	H	H	−78	6	55[c)]
3	**15h**	H	H	H	Me	−78—−40	7	54[b)]
4	**15i**	Me	H	H	H	−78	3	39[c)]
5	**15g**	H	Me	H	Me	−78—rt	6	—[d)]
6	**15f**	H	H	H	H	−78	5	10[b)]

a) The structure was confirmed by comparison with authentic sample prepared by the method in Ref. 2. b) Single isomer. c) About two to one mixture of geometric isomers. d) Complex mixture.



15 17 18

Scheme 3.

13 was carried out at −78 °C for 2 h, almost all the starting materials were consumed and 38% yield of **14** (X=Ac, Y=H) was obtained along with **16a** (29%). To make clear the scope and limitation, the reactions of dienol silyl ethers **15** with α,β-unsaturated esters were also examined. Although methyl crotonate gave no cyclo-adduct, methyl acrylate afforded the corresponding [2.2.2]bicyclo-products in moderate yields as shown in Table 2. We assigned all of the major products as endo-isomers by the comparison with authentic samples prepared by the methods[2)] which are reported to give endo-isomers predominantly.

In conclusion, Lewis acid catalyzed reaction of dienol silyl ethers derived from 2-cyclohexenones with α,β-unsaturated carbonyl compounds is effective for the synthesis of crowded bicyclo[2.2.2]- or tricyclo-[5.2.2.$0^{1,5}$]-derivatives. In addition, this method is of importance especially when base labile compounds are subjected to such type of the reactions,[3)] since this reaction proceeds under acidic conditions.

Experimental

Nuclear magnetic resonance spectra were taken on a JEOL PS-100 (100 MHz) or Hitachi R-24B (60 MHz). Infrared spectra were recorded on a Hitachi 260-50 spectrophotometer.

Typical Procedure: To a mixture of 1-methyl-3-trimethylsiloxy-1,3-cyclohexadiene **15b** (184 mg, 1 mmol), mesityl oxide (196 mg, 2 mmol) in dichloromethane (5 ml) was added $TiCl_4$ (2 mmol) in dichloromethane (5 ml) at −40 °C under an argon atmosphere. The solution was stirred at the temperature for 3 h, mixed with aqueous K_2CO_3 solution, and then extracted with dichloromethane. The extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography to give **16b** (114 mg, 55%); mp 94—96 °C. IR (KBr) 1700 and 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=0.84 (3H, s), 0.94 (3H, s), 1.34 (3H, s), 2.21 (3H, s), 2.58 (1H, d, J=2 Hz), 3.14 (1H, dd, J=2 and 18 Hz), 1.14—2.30 (6H, m). Found: C, 75.16; H, 9.69%. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%.

16a: Mp 73—74 °C. IR (KBr) 1730, 1710 cm^{-1} (C=O) and 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ=0.71 (3H, s), 1.22 (3H, s), 2.18 (3H, s), 2.51 (1H, d, J=2 Hz), 2.95 (1H, dd, J=2 and 18 Hz), 4.60—5.12 (2H, m), 5.25—5.70 (1H, m), 0.55—2.63 (10H, m). Found: C, 77.45; H, 9.74%. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74%.

16c: IR (KBr) 1700 and 1718 cm^{-1} (C=O); ^1HNMR ($CDCl_3$) δ=0.85 (1.5H, s), 0.90 (1.5H, s), 1.33 (1.5H, s), 2.20 (1.5H, s), 1.05 (1.5H, d, 8 Hz), 1.15—3.36 (7H, m), 0.88 (1.5H, s), 1.02 (1.5H, s), 1.10 (1.5H, s), 2.18 (1.5H, s), 1.08 (1.5H, d, 8 Hz). Found: C, 75.61; H, 9.85%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

16e: Mp 87—88.5 °C. IR (KBr) 1695 and 1712 cm^{-1} (C=O); ^1HNMR ($CDCl_3$) δ=0.90 (3H, s), 0.98 (3H, s), 1.12 (3H, s), 1.38 (3H, s), 2.25 (3H, s), 1.50—2.10 (4H, m), 2.53 (1H, dd, J=2 and 4 Hz), 2.75 (1H, d, J=2 Hz), 2.98 (1H, m). Found: C, 75.69; H, 9.94%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

16f: Mp 68—70 °C. IR (KBr) 1700 and 1712 cm^{-1} (C=O); ^1HNMR ($CDCl_3$) δ=0.88 (3H, s), 1.38 (3H, s), 2.23 (3H, s), 0.80—3.20 (9H, m). Found: C, 74.22; H, 9.20%. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%.

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4) The X-ray analysis and the chemical transformation of **16d** proved that exo-products are formed predominantly in this case. The stereoselectivity is opposite to the results shown in Table 2, presumable due to the steric hindrance.