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SYNTHESIS AND UTILIZATION OF OPTICALLY ACTIVE 2-SUBSTITUTED 4-(TRIMETHYLSILYL)CYCLOPENTANONES: SYNTHESIS OF (-)-MASSOIALACTONE AND (+)-β-CUPARENONE

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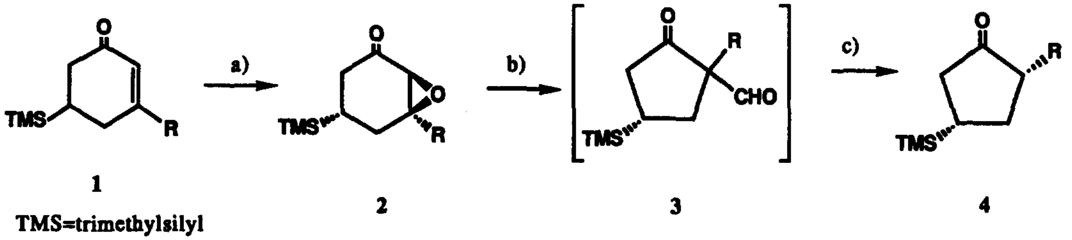
Summary: Ring contraction by $BF_3 \cdot Et_2O$ catalyzed epoxide rearrangement of 3-substituted 5-trimethylsilyl-2,3-epoxycyclohexanones gave the corresponding 2-substituted 4-(trimethylsilyl)cyclopentanones diastereoselectively. Synthesis of (-)-massoialactone and (+)-β-cuparenone utilizing the above transformation is also described.

In connection with our interest in utilizing optically active 5-trimethylsilyl-2-cyclohexenones in the natural product synthesis,1) we planned to expand our strategy, the trimethylsilyl group directed construction of chiral centers onto alicyclic compounds, to trimethylsilyl substituted cyclopentanones. Thus, the transformation of cyclohexenones **1** into the cyclopentanone derivatives **4** utilizing an epoxide rearrangement2) and utilization of the products in natural product synthesis were studied (Scheme 1).

Enones **1b**-**1g** were easily prepared from **1a** (R=H) by the reported method3) in 73-90% overall yields. The epoxidation of 3-alkyl-2-cyclohexenones **1b**-**1e** proceeded smoothly under the conventional conditions (Method A: 2 eq of 35% H_2O_2, cat. 6 M NaOH, MeOH, at 0 °C, 0.5-1.5 h)4), however, for aromatic derivatives such as 3-phenyl and 3-p-tolyl derivatives (**1g** and **1f**), a slightly modified method, use of ethanolic solution of benzyltrimethylammonium hydroxide (1 eq) in place of methanolic NaOH in the presence of large excess of 35% H_2O_2 (10 eq) at room temperature for 15 min (Method B), was necessary. The diastereoselectivity in this epoxidation was proved to be >20:1 as long as estimated by ^{13}C NMR.

The Lewis acid ($BF_3 \cdot Et_2O$) catalyzed epoxide rearrangement of **2b**-**2g** followed by base (6 M NaOH) treatment2) afforded 2-substituted 4-(trimethylsilyl)cyclopentanones **4b**-**4g** with high diastereo purity (>20:1) in good to high overall yields (61-93% from **2**). Presumably owing to the high cation stabilizing ability of the aromatic groups, the yields of **4f** and **4g** are higher than those of alkyl derivatives.

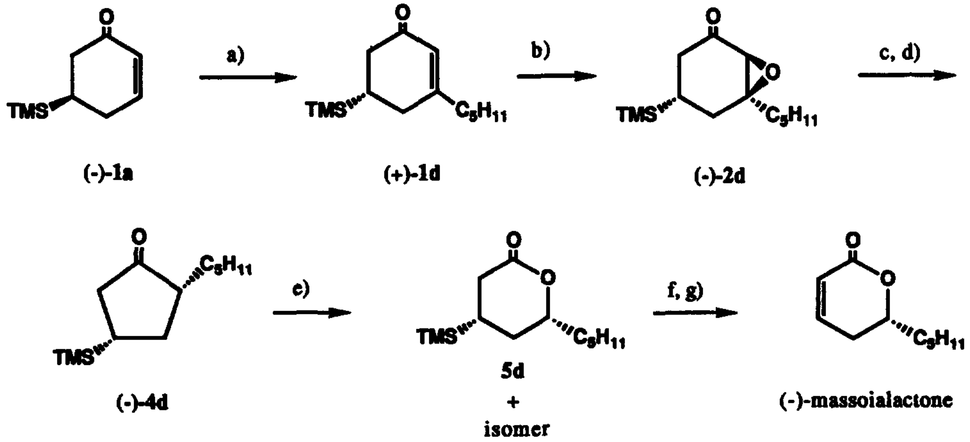


Scheme 1. a) H_2O_2, cat. base; b) $BF_3{\cdot}Et_2O$; c) NaOH.

Table 1 Epoxidation of 1 and rearrangement of 2 with $BF_3{\cdot}Et_2O$.

Entry	1	R	Method	Yield of **2** (%)	Yield of **4** (%)
1	**1b**	Me	A	76	69
2	**1c**	Et	A	76	67
3	**1d**	n-C_5H_{11}-	A	90	77
4	**1e**	n-C_9H_{19}-	A	83	61
5	**1f**	Ph	B	58	91
6	**1g**	p-Tol	B	68	93

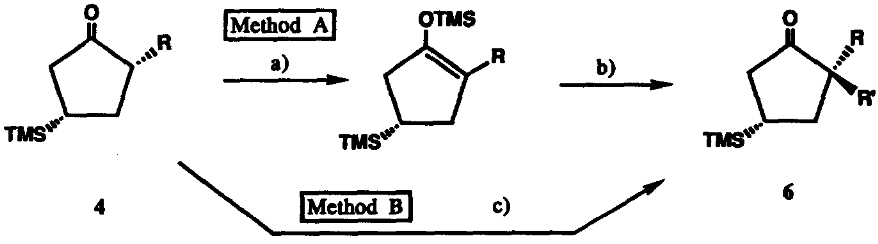
To confirm the diastereostructure of **4** and to estimate the utility of **4** in natural product synthesis, the synthesis of (-)-massoialactone[5,6] starting with (-)-**1a** was carried out (Scheme 2).



Scheme 2. a) Ref. 3; b) H_2O_2, cat. base; c) $BF_3{\cdot}Et_2O$; d) NaOH; e) m-CPBA; f) LDA, Br_2; g) Bu_4NF.

After the transformation of (-)-**1a** into (-)-**4d** as described above, the Baeyer-Villiger oxidation of (-)-**4d** (m-CPBA, 0 °C, Na_2HPO_4, CH_2Cl_2-H_2O) gave an approximately 4:1 mixture of lactones (**5d** and the alternative possible regio-isomer) in 87% yield which was subsequently transferred into (-)-massoialactone [$[\alpha]_D^{19}$-96.3°(c 1.26, $CHCl_3$); lit. $[\alpha]_D^{25}$-99.4°(c 1.04, $CHCl_3$),[6] $[\alpha]_D$-110.5°(c 2.5, $CHCl_3$),[7a] and $[\alpha]_D^{36}$-108.4°(c 2.7, $CHCl_3$)[7b]] by bromination followed by debromosilylation with tetrabutylammonium fluoride (31% overall yield from the mixture of lactones). It is apparent from the above results, that the stereochemistry of **4** is cis and the cyclopentanones **4** prepared by this method possess enough optical purity for the enantioselective synthesis of natural products.

As a further application of **4** to the natural product synthesis, diastereoselectivity in the alkylation at 2-position was examined. Two methods were used for the alkylation of **4**. For the aryl group substituted cyclopentanones (**4f**-**4g**), base (NaH) treatment followed by methylation gave successful results. However, in the case of alkyl group substituted derivatives (**4b**-**4c**), alkylation of lithium enolate, generated via enol silyl ether, in the presence of trimethylaluminum[8] was used. ^{13}C NMR spectra of **6** show the high diastereo purities (>20:1->10:1) of the products.



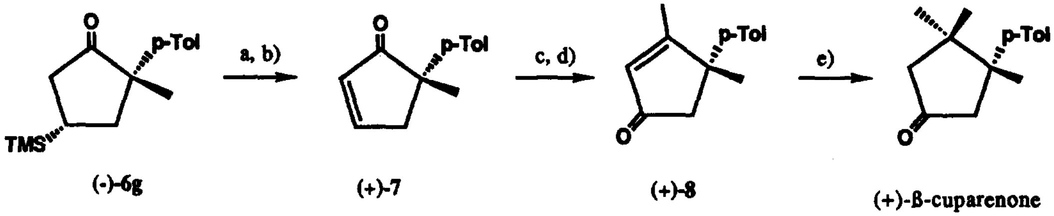
Scheme 3. a) i-Pr_2NMgBr, TMSCl; b) MeLi, Me_3Al, R'X; c) NaH, R'X.

Table 2 Alkylation of **4**.

Entry	4	R'X	Method	Yield of **6** (%)
1	**4b**	Prenyl-Br[a]	A	70
2	**4c**	Prenyl-Br[a]	A	68
3	**4f**	Me-I	B	77
4	**4g**	Me-I	B	85

a) Prenyl: 3-methyl-2-butenyl.

To confirm the diastereo structure of **6**, the synthesis of (+)-β-cuparenone starting with (-)-**1a** was carried out.



Scheme 4. a) $C_5H_5NHBr_3$; b) Bu_4NF; c) MeLi; d) PDC; e) $MeCu\text{-}BF_3$.

Bromination of (-)-**6g**, which was prepared from (-)-**1a** as described above, with pyridinium bromide perbromide followed by treatment with tetrabutylammonium fluoride gave enone (+)-**7** in 78% yield. Addition of methyllithium and subsequent oxidation with PDC gave (+)-**8** in 97% yield. 1,4-Addition of methylcopper reagent in the presence of BF_3 9) afforded (+)-β-cuparenone [$[\alpha]_D^{23}+44.4°$(c 2.47, $CHCl_3$), lit. $[\alpha]_D^{29}+45°$(c 1.4, $CHCl_3$) 10) and $[\alpha]_D^{30}+48.0°$($CHCl_3$) 11)] in 64% yield.

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