

CONSTRUCTION OF CHIRAL QUARTERNARY CARBON CENTERS USING 3-SUBSTITUTED
 5-TRIMETHYLSILYL-2-CYCLOHEXENONES: SYNTHESIS OF (+)- α -CUPARENONE

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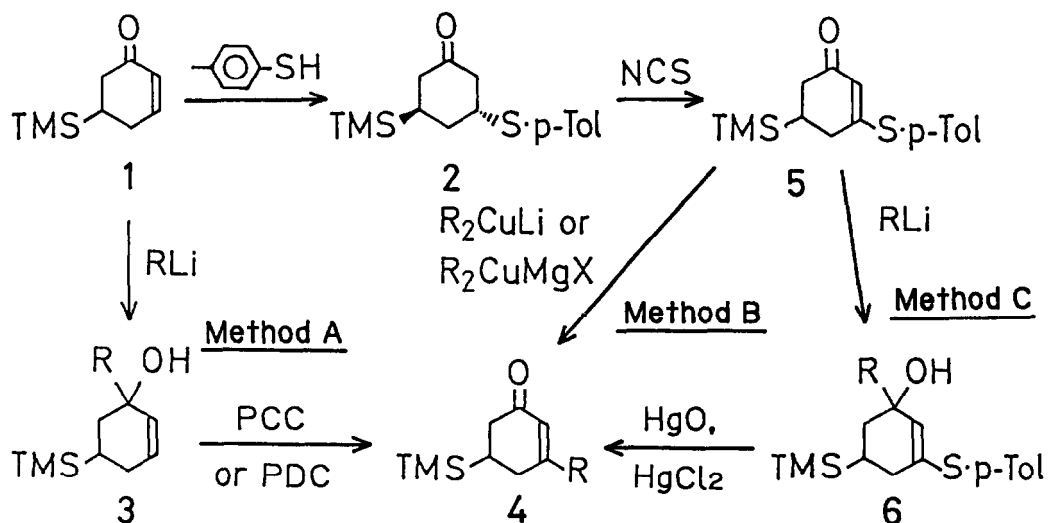
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Summary: 1,4-Addition of Grignard reagents to 3-substituted 5-trimethylsilyl-2-cyclohexenones proceeded in a highly diastereoselective manner. By utilizing the reaction, (+)- α -cuparenone was synthesized starting from enantiomerically pure 3-p-tolylthio-5-(trimethylsilyl)cyclohexanone.

In the preceding paper,¹⁾ we reported the synthesis and kinetic resolution of 5-trimethylsilyl-2-cyclohexenone (**1**) which reacted with various Grignard reagents to give 1,4-adducts with high diastereoisomeric purity. Furthermore, synthesis of (+)- α -curcumene starting from optically pure **1** was demonstrated.

In this paper we wish to report a highly stereoselective construction of quarternary carbon centers by 1,4-addition of Grignard reagents to 3-substituted 5-trimethylsilyl-2-cyclohexenones (**4** \rightarrow **8**, Scheme 2).

(\pm)-3-Substituted-5-trimethylsilyl-2-cyclohexenones (**4**) were prepared from **1** or (\pm)-3-arylthio-5-trimethylsilylcyclohexanone (**2**) by the following three methods. **Method A:** 1,2-Addition of RLi to **1** in the presence of BF₃-Et₂O²⁾ followed by oxidation with PCC or PDC.³⁾ **Method B:** 1,4-Addition of R₂CuMgBr or R₂CuLi to (\pm)-3-p-tolyl-5-trimethylsilyl-2-cyclohexenone (**5**) which is obtained in 74% yield by the oxidation of **2** with NCS in CCl₄ at 0°C. **Method C:** 1,2-Addition of RLi to **5** followed by hydrolysis in the presence of HgCl₂/HgO.



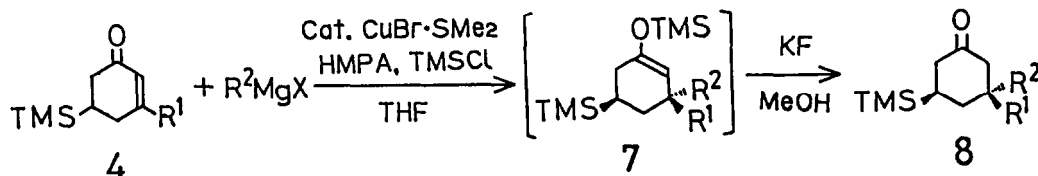
Scheme 1

Table 1. Synthesis of **4**

Entry	R	Method	Yield 4 (%)
1	Me	A	77 ^{a)}
2	n-Bu	A	73 ^{a)}
3	Ph	A ^{b)}	53 ^{a)}
4	n-Bu	B ^{c)}	100 ^{d)}
5	Ph	B ^{e)}	87 ^{d)}
6	Me	B ^{c)}	92 ^{d)}
7	n-Hex	B ^{e)}	89 ^{d)}
8	PhCH ₂ CH ₂ -	B ^{e)}	95 ^{d)}
9	p-MeO-C ₆ H ₄ -	B ^{e)}	64 ^{d)}
10	n-Bu	C	64 ^{d)}
11	Ph	C	47 ^{d)}

a) Based on **1**. b) Without BF₃-Et₂O. c) R₂CuLi. d) Based on **5**.
e) R₂CuMgBr.

Next, 1,4-addition of Grignard reagents⁴⁾ to the enones (**4**) was examined. The reaction of Grignard reagents (2 eq) to **4** in the presence of 5 mol% CuBr-SMe₂, TMSCl (2.5 eq), HMPA (2 eq) in THF at -78°C for 1-1.5 h and subsequent KF catalyzed hydrolysis of the products, enol silyl ethers (**7**), gave expected 1,4-adducts (**8**) as shown in Table 2.



Scheme 2

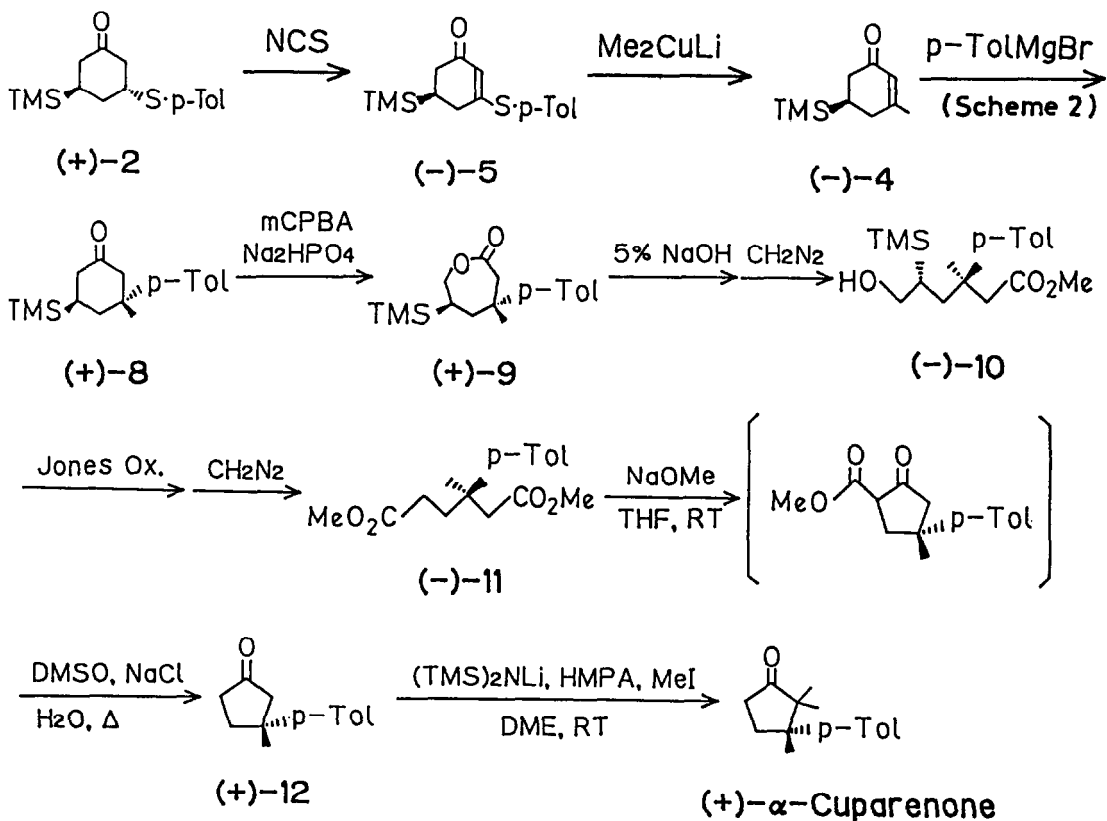
Table 2. 1,4-Addition of Grignard reagents to **4**

Entry	R ¹	R ²	X	Yield 8 (%)
1	Me	Ph	Br	94
2	Ph	Me	I	56 ^{a)}
3	Me	n-Bu	Br	91
4	n-Bu	Me	I	80
5	Me	PhCH ₂ CH ₂	Br	86
6	PhCH ₂ CH ₂	Me	I	90
7	Me	p-Tol	Br	90

a) Diastereoisomeric mixture (97:3, evaluated by ¹³C NMR).

When substituent R^1 in **4** is alkyl group, adducts **8** were obtained in high yields and the presence of diastereoisomers were not discernible by ^{13}C NMR, although when R^1 is phenyl group, the yield of the adduct was low and it contained a small amount of diastereoisomer (entry 2). Thus, 1,4-addition of various Grignard reagents to optically pure **4** is evaluated to be a prospective method to construct a highly optically pure quarternary carbon center on cyclohexane ring. Furthermore, TMS group of the products can be used for the further elaboration such as regiospecific Baeyer-Villiger reaction.⁵⁾

To demonstrate the utilities of this strategy and to confirm the stereochemistry of quarternary carbon centers, synthesis of (+)- α -cuparenone was carried out. Oxidation of optically pure ketone (+)-**2** [mp 112.5-113°C, $[\alpha]_{\text{D}}^{22}$ +33.50°, c 2.00, CHCl_3]¹⁾ with NCS in CCl_4 gave (-)-**5** [mp 99.5-100°C, $[\alpha]_{\text{D}}^{22}$ -102.4°, c 1.00, CHCl_3] in 82% yield. Reaction of Me_2CuLi with (-)-**5** in THF at -78°C gave (-)-**4** (74%) which afforded (+)-**8** in 98% yield by the reaction with *p*-tolMgBr. TMS group directed regiospecific Baeyer-Villiger oxidation⁵⁾ gave 7-membered lactone (+)-**9** in 74% yield after recrystallization from hexane [mp 83.5°C, $[\alpha]_{\text{D}}^{23}$ +11.9°, c 4.00, CHCl_3].



Scheme 3

The lactone showed unexpected stability under the methanolysis conditions (MeOH-NaOMe at rt) to give the mixture of the lactone (9) and acyclic ester (10) (1:1.3). Hydrolysis with NaOH, acidification, and treatment with CH_2N_2 gave (-)-10 in 80% yield, which was converted to diester (-)-11 (55%) by Jones oxidation and subsequent treatment with CH_2N_2 . Dieckmann condensation of (-)-11 with NaOMe in THF at rt afforded mixture of β -ketoesters which was treated with NaCl in wet DMSO at 130-140°C 3.5 h to give 3,3-disubstituted cyclopentanone (+)-12 as a crystalline product in 61% yield after recrystallization from pentane [mp 45.0-45.5°C, $[\alpha]_{\text{D}}^{23} +13.3^\circ$, c 4.00, CHCl_3]. Direct dimethylation⁶⁾ of (+)-12 with 5 equivalents of MeI in the presence of $\text{LiN}(\text{TMS})_2$ in dimethoxyethane at rt gave (+)- α -cuparenone in 26% yield [mp 55.0-56.5°C $[\alpha]_{\text{D}}^{26} +167.7^\circ$, c 0.457, CHCl_3].^{7,9)}

By the above synthesis, absolute configuration of quarternary carbon center of (+)-8 was confirmed as (R), therefore, geometric structures of (+)-8 were deduced as depicted in Scheme 2.

References and notes

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- 7) The reported specific rotation of natural (+)- and (-)-cuparenone⁸⁾ in CHCl_3 are $[\alpha]_{\text{D}}^{30} +177.1^\circ$ and $[\alpha]_{\text{D}}^{20} -169.9^\circ$.
- 8) G. L. Chetty and S. Dev, *Tetrahedron Lett.*, **1964**, 73; V. Benesova, *Collect. Czech. Chem. Commun.*, **41** 3812 (1976).
- 9) Structures of the new compounds depicted in Scheme 1, 2, and 3 are confirmed by their spectral (IR, NMR) data and elemental analyses.

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