Tetrahedron Letters,Vol.28,No.46,pp 5669-5672,1987	0040-4039/87 $3.00 + .00
Printed in Great Britain	Pergamon Journals Ltd.

(R)- AND (S)-5-TRIMETHYLSILYL-2-CYCLOHEXENONE: A VERSATILE CHIRAL SOURCE FOR THE SYNTHESIS OF OPTICALLY ACTIVE CYCLOHEXANONE DERIVATIVES

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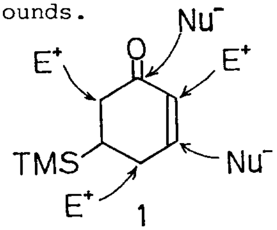
Summary: 5-Trimethylsilyl-2-cyclohexenone was synthesized from anisole and was successfully resolved to the optically pure form utilizing kinetic resolution method of the reaction with thiol in the presence of cinchonidine. (+)-α-curcumene was synthesized from (R)-(-)-5-trimethylsilyl-2-cyclohexenone.

Cyclohexenone derivatives have been widely used for the syntheses of various natural products, many of which are unfortunately racemic since the easily accessible chiral 2-cyclohexenones are restricted to a few compounds such as carvone and pulegone, furthermore, many operations are sometimes required to obain properly substituted chiral cyclohexanones from them. These facts suggest that a new widely applicable chiral cyclohexanone source would greately contribute to the chiral natural products syntheses. As such a bilding block, we designed 5-trimethylsilyl-2-cyclohexenone (**1**), since the bulky trimethylsilyl(TMS) group will lead highly stereoselective introduction of a wide variety of substituents to cyclohexenone ring as shown below. Furthermore, trimethylsilyl group would play an important role when the cyclohexanone derivatives are transformed to acyclic compounds.



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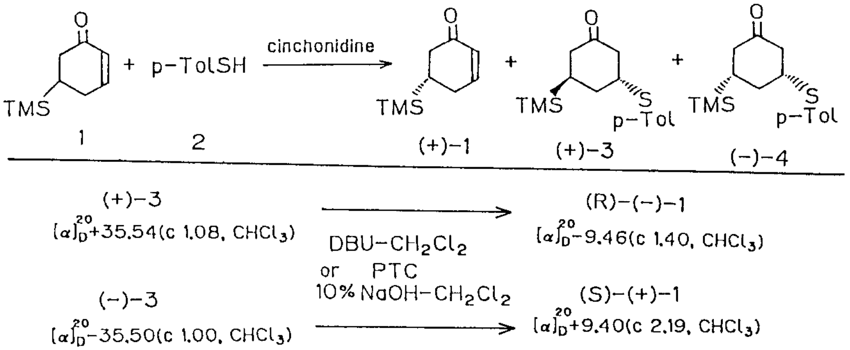
5-Trimethylsilyl-2-cyclohexenone(**1**) was easily prepared in a large scale[1)] in 65-70% overall yield from anisole via 5-trimethylsilyl-3-cyclohexenone, which was synthesized by the method of Lagerre et al.[2)]

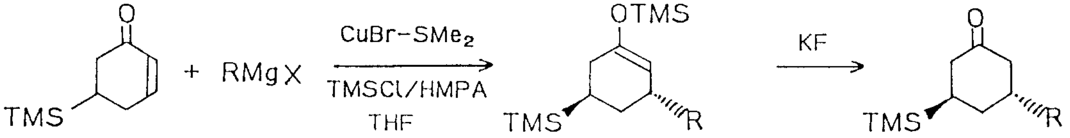
Kinetic resolution of **1** by the reaction of 0.55 eq of thiol with **1** in the presence of cinchonidine[3)] was examined. When p-toluenethiol was used,[4)] 57% ee of trans-adduct (+)-(**3**) was obtained in 50% yield together with (+)-**1**(41%, 59% ee) and a small amount



of cis-adduct [(-)-**4**, 4%, 94% ee]. Optically pure (+)-**3** was easily obtained by recrystallization. Addition of p-toluenethiol to (+)-**1** in the presence of triethylamine followed by recrystallization furnished optically pure (-)-**3**. Regeneration of optically pure **1** from (+)- and (-)-**3** was achieved in high yields (87-93%) by the treatment with diazabicycloundecene (DBU) in CH_2Cl_2 at rt or by the phase-transfer conditions (cat. trioctylmethylammonium chloride, CH_2Cl_2-10% NaOH, rt 3h). Racemic trans-adduct obtained in the course of resolution was also subjected to above operation and reused for the kinetic resolution. The absolute configurations of (+)- and (-)-**1** were confirmed by the following synthesis of (+)-α-curcumene.

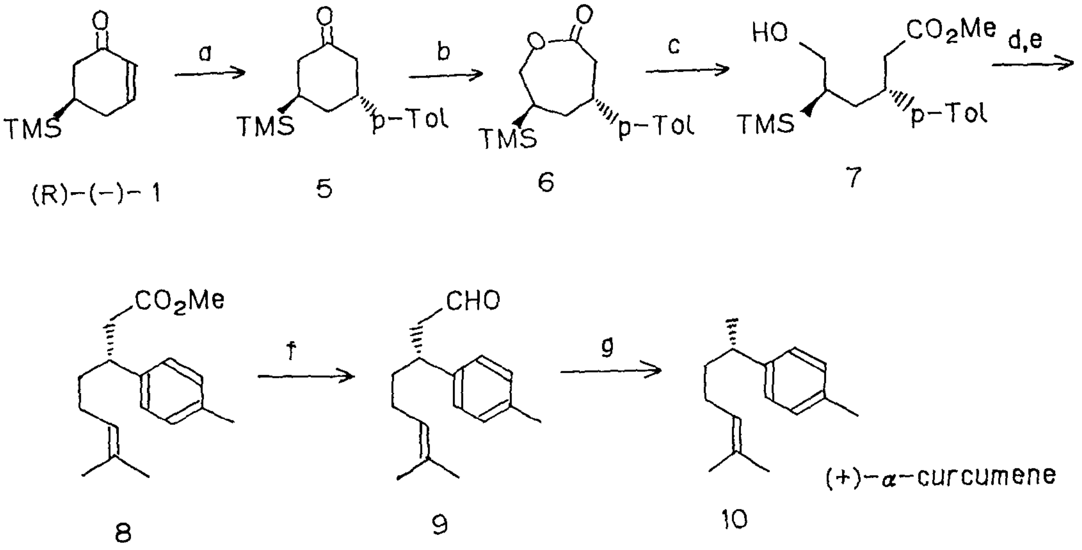
<u>Kinetic resolution of 5-trimethylsilyl-2-cyclohexanone</u> (**1**): 5-Trimethylsilyl-2-cyclohexenone(90 g, 0.536 mol) and p-toluenethiol(36.6 g, 0.295 mol) were added to 2.8 l of dry benzene (or toluene) solution of cinchonidine (1.58 g, 5.36 mmol). After standing at rt overnight, the reaction mixture was concentrated under reduced pressure until the total volume became about 1 l, washed with 2M HCl, and dried over $MgSO_4$. After removal of the solvent, pentane(200 ml) was added to the residue and the mixture was allowed to stand below 0°C for 12 h. Filtration of the crystal gave trans-adduct (+)-**3** (60% ee, 66.5 g, 43%). Distillation of the filtrate gave (+)-**1**(54% ee, 38.0 g, 42%) which was converted to trans-adduct (-)-**3** by triethylamine catalyzed addition of p-toluenethiol. Recrystallization of (+)-**3** and (-)-**3** from hexane gave enantiomerically pure (+)-**3** (33.4 g, 21%, $[\alpha]_D^{20}$+35.54° c 1.08, $CHCl_3$) and (-)-**3** (24,5 g, 16%, $[\alpha]_D^{20}$-35.50° c 1.00, $CHCl_3$). From the mother liquor of above recrystallization, further crop of pure (+)-**3** (3%) and (-)-**3** (3%) were obtained by fractional recrystallization .

Initially, diastereoselectivity in 1,4-addition of Grignard reagents to **1** in the presence of CuBr-Me_2S, TMSCl, and HMPA$^{5)}$ was examined. Both of aromatic and aliphatic Grignard reagents such as phenyl-, p-tolyl-, 2-phenylethyl-, methyl-, tert-butyl-, and hexyl-magnesium halide reacted with (±)-**1** smoothly in a highly diastereoselective manner to give corresponding trans-1,4-adducts in high yields (88-95%) and the absence of cis-isomer was confirmed by their ^{13}C NMR spectra.



Based on the results, the synthesis of (+)-α-curcumene from (R)-(-)-**1** was carried out. The trans-adduct (+)-**5** was obtained in 96% yield by the 1,4-addition of p-tolylmagnesium bromide to (R)-(-)-**1** . Baeyer-Villiger oxidation$^{6)}$ of (+)-**5** gave lactone [(-)-**6**, 94% (by column chromatography), 76%

oxidation$^{6)}$ of (+)-**5** gave lactone [(-)-**6**, 94% (by column chromatography), 76% (recryst. from hexane, $[\alpha]_D^{22}$-23.5°, c 2.00, $CHCl_3$)] which was converted to acyclic derivative [(-)-**7**] in 99% yield by the treatment with NaOMe in MeOH. Oxidation of (-)-**7** with PCC followed by Wittig reaction(0°C-rt, 2.5h) gave ester (+)-**8** in 60% overall yield. Reduction of (+)-**8** with DIBAH (CH_2Cl_2, -78°C, 15 min) and subsequent decarbonylation with Wilkinson's reagent ($ClCH_2CH_2Cl$, reflux 40 min) afforded (+)-α-curcumene($[\alpha]_D^{22}$+42.5° *c* 2.94, $CHCl_3$) in 84% overall yield.$^{7)}$

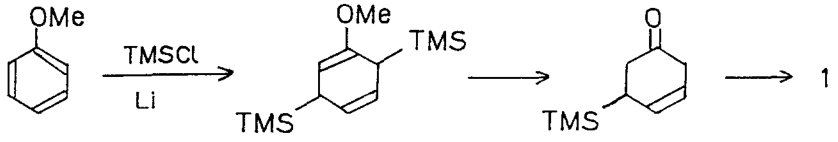


a) p-TolMgBr, $CuBr-Me_2S$, TMSCl, HMPA b) mCPBA c) NaOMe, MeOH d) PCC
e) PPh_3=< f) DIBAH g) $RhCl(PPh_3)_3$

References and notes

1) The synthesis of 5-trimethylsylil-3-cyclohexenone (**12**) from anisole and its partial isomerization to **1** under acidic conditions is reported briefly by Lagerre et al$^{2)}$, however, all our trials for the isomerization of **12** to **1** under various acidic conditions resulted **1** only in poor yields. The isomerization was successfully achieved with DBU. The large scale preparation of **1** was carried out as shown blow.

To a suspension of Li powder (100 g of 30% dispersion in oil, 4.39 mol) in THF (800 ml) cooled to -35~-25°C, is added dropwise a mixture of anisole (210 g, 1.94 mol) and TMSCl (750 ml). The temperature of reaction mixture is kept at -10~-20°C during the addition. After the completion of the addition the mixture is stirred at rt overnight. Filtration under argon, removal of volatiles and subsequent distillation of the residue (95-105°C/6 mmHg) gave crude cyclohexadiene **11**(431-473 g) which is used without further purification. Half of the diene dissolved in 400 ml of ether is placed in three necked flask (3 l) attached with three efficient condensers. To the solution, is added 35 ml of 2M HCl. After stirring at rt for about 15 min, exothermic reaction occurs and ether refluxes vigorously (Caution! moderate exothermic reaction; cooling with cold water after the initiation of reflux is recommended). Stirring is continued for 0.5 h after the reflux subsided. Extraction with ether, neutralization of organic layer, and removal of solvent gives crude 5-trimethylsylil-3-cyclohexenone (**12**). The rest of the diene is also hydrolyzed similarly. The combined crude 3-cyclohexenone is dissolved in 1400 ml of CH_2Cl_2-Et_2O(1:1) and to the solution is added DBU (10 g). After standing at rt for 2-3 weeks, usual work-up followed by fractional distillation with efficient column gives **1** in 65-70% overall yield (212-230 g, Bp 65.5-67°C/2.0 mmHg).



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4) Use of p-tert-butylbenzenethiol also gave similar results, but when benzenethiol was used, the optical purities of adducts and recovered enone became worse. p-Toluenethiol is of much advantage than p-tert-butylbenzenethiol, since p-toluenethiol is commercially available, and recrystallization of optically enriched **3** gives optically pure **3** much easily.

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7) Specific rotation of synthesized **10** by Takano et al[8)] and that of naturally occurring **10**[9)] are $[\alpha]_D$+42.8° (c 1.18, $CHCl_3$) and $[\alpha]_D$+45.1° (c 0.75, $CHCl_3$), respectively.

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(Received in Japan 16 May 1987)