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SYNTHESIS OF (+)-α-CURCUMENE, (+)-CURCUMONE, AND (-)-METHYL CITRONELLATE STARTING FROM OPTICALLY PURE 5-TRIMETHYLSILYL-2-CYCLOHEXENONE

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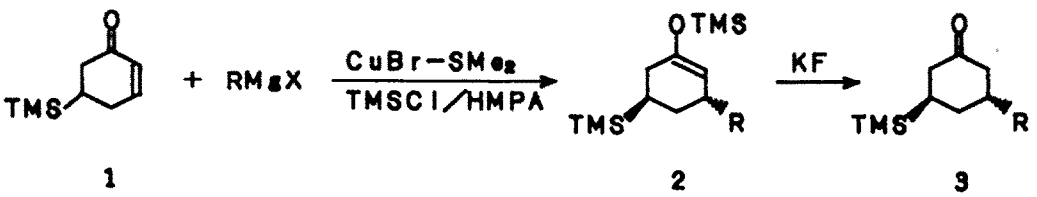
Abstract: 1,4-Addition of Grignard reagents in the presence of chlorotrimethylsilane to 5-trimethylsilyl-2-cyclohexenone (1) proceeded in a highly diastereoselective manner to give trans adducts in high yields. (+)-α-Curcumene, (+)-curcumone, and (-)-methyl citronellate were synthesized starting from optically pure 1.

In the synthesis of biologically active compounds, it is oftentimes necessary to synthesize both enantiomers with high optical purities, especially for exploring the relationship of biological activity with structure. Thus, in the development of new chiral building blocks, availability of both enantiomer is indispensable. In the last decade, various kinds of chiral building blocks have been designed[1] and used successfully for the synthesis of chiral compounds. Surprisingly, much less attention has been paid to the development of cyclohexa(e)none-type chiral building blocks, although the diastereoselective introduction of substituents to cyclohexa(e)none derivatives has been studied for a long time and conversion of the products to acyclic derivatives has also been studied. As such a chiral cyclohexenone derivative, we designed 5-trimethylsilyl-2-cyclohexenone (1) (hereafter, trimethylsilyl=TMS), and in the preceding papers[2] we reported the synthesis, optical resolution, and some reactions of 5-TMS-2-cyclohexenone (1). In this paper we wish to describe the diastereoselectivity in the 1,4-addition of Grignard reagents to 1 in detail and the synthesis of racemic and highly optically active 5-substituted 2-cyclohexenones, α-curcumene, curcumone, and methyl citronellate by utilizing 1.



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Diastereoselectivity in 1,4-addition of various alkylmetallic reagents to 5-substituted (especially 5-methyl) 2-cyclohexenone has been studied and the trans/cis ratios of the products are reported to be generally high (98/2-90/10).[3]

The results suggest that a higher level of diastereoselectivity is expected in 1,4-addition of alkylmetallic reagents to 1 which has bulky TMS group.

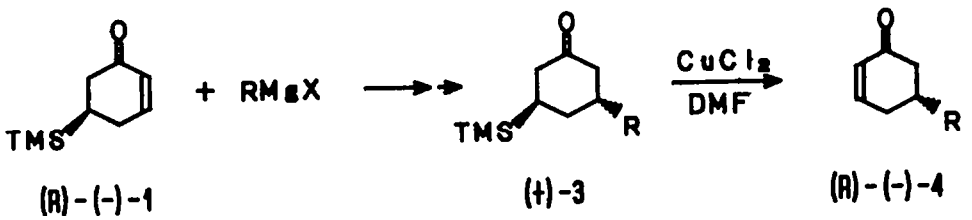
Among various alkylmetallic reagents (mainly Mg, Li, and Cu reagents) and reaction conditions examined, 1,4-addition of Grignard reagents to 1 in the presence of CuBr-SMe_2, TMSCl, and HMPA followed by the treatment with KF[4] gave the best result. As shown in Table 1, the reaction generally completed in 20-30 min at -78 °C. However, in the case of sterically hindered Grignard reagents longer reaction time (2-3 h) or large excess of Grignard reagents were required (entries 4, 5, and 6). Diastereoisomer composition of the adducts (3) was estimated by ^{13}C NMR, and in most cases the adducts were found to be of high diastereoisomeric purities since cis adducts were not detected by ^{13}C NMR (entries 1-10). However, the adducts obtained by the reaction of benzyl type Grignard reagents, were found to be diastereoisomeric mixture as shown in Table 1 (entries 11, 12, 14, and 16). In two cases, the selectivities were greatly improved by carrying out the reaction at lower (-100 °C) temperature and changing the addition mode (slow addition of a mixture of enone 1 and TMSCl to a solution of RMgX, CuBr-SMe_2, and HMPA in THF, entries 13 and 15).

Table 1 1,4-Addition of Grignard Reagents to Enone 1

Entry	R	3	X	Time/min	Yield/%	Trans/Cis
1	Phenyl	**3a**	Br	30	90	-[a]
2	p-Tolyl	**3b**	Br	20	92	-[a]
3	p-MeO-Phenyl	**3c**	Br	30	92	-[a]
4	2,4,6-Trimethylphenyl	**3d**	Br	120	82	-[a]
5	2,4,6-Trimethylphenyl	**3d**	Br	30	92[b]	-[a]
6	1-Naphthyl	**3e**	Br	180	83	-[a]
7	2-Phenylethyl	**3f**	Br	30	92	-[a]
8	Methyl	**3g**	I	20	88	-[a]
9	t-Butyl	**3h**	Cl	30	95	-[a]
10	Hexyl	**3i**	Br	20	88	-[a]
11	p-MeO-Benzyl	**3j**	Cl	180	74	>10/1[c]
12	m-MeO-Benzyl	**3k**	Cl	80	76	1/1[c]
13	m-MeO-Benzyl	**3k**	Cl	30[d]	89	>10/1[c]
14	3,4-Dimethoxybenzyl	**3l**	Cl	20	83	1/1[c]
15	3,4-Dimethoxybenzyl	**3l**	Cl	200[d]	72	>20/1[c]
16	Benzyl	**3m**	Cl	20	89	3/1[c]

a) Cis isomer was not detected by ^{13}C NMR. b) Large excess of Grignard reagent (3 eq) and TMSCl (3.5 eq) were used. c) The ratio was estimated by ^{13}C NMR. d) A mixture of enone 1 and TMSCl was slowly added to a mixture of the other reagents at -100 °C.

The adducts (3) can easily be transformed into 5-substituted 2-cyclohexenones in high yields.[2d] In Table 2, some results of 1,4-addition of RMgX to optically pure 5-TMS-2-cyclohexenone (R)-(-)-1 and subsequent transformation to 5-substituted 2-cyclohexenones are listed.



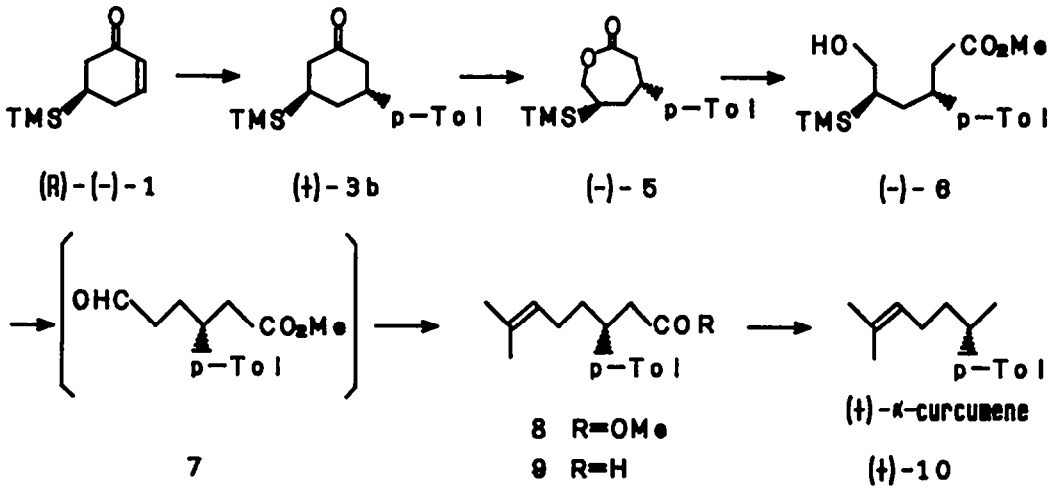
(R)-(-)-1 (+)-3 (R)-(-)-4

Table 2 Synthesis of (R)-(-)-4 from (R)-(-)-1

R	Yield/% (+)-3	Specific[a] rotation	Yield/% (R)-(-)-4	Specific[a] rotation	ee/%[b]
Ph	94	$[\alpha]_D^{20}$+10.1° c 3.00 $CHCl_3$	82	$[\alpha]_D^{25}$-45.3° c 1.29 $CHCl_3$	98
p-Tol	96	$[\alpha]_D^{22}$+13.0° c 3.00 $CHCl_3$	90	$[\alpha]_D^{20}$-43.5° c 2.61 $CHCl_3$	98
t-Bu	86	$[\alpha]_D^{20}$+91.9° c 1.20 $CHCl_3$	92	$[\alpha]_D^{20}$-26.0° c 1.20 $CHCl_3$	96[c]

a) Specific rotation of chromatographically isolated product. b) Calculated based on specific rotation. See experimental. c) Estimated by the specific rotation of cyclohexanone derivative obtained by hydrogenation.

Based on these results, syntheses of racemic and optically active α-curcumene and curcumone were carried out. TMS group directed Baeyer-Villiger reaction[5] of 3b proceeded smoothly to give crystalline 7-membered lactone 5 in high yield [(-)-5 94%, (±)-5 94%]. Base catalyzed ring opening with MeOH also proceeded in high yield [(-)-6 99%, (±)-6 99%]. PCC oxidation of hydroxy ester 6 and subsequent work-up gave desilylated aldehyde 7 which was used for the next step without further purification. Reaction of 7 with isopropylidenetriphenylphosphorane gave the ester 8 [(+)-8, 60%, (±)-8 56%, overall yields from 6].

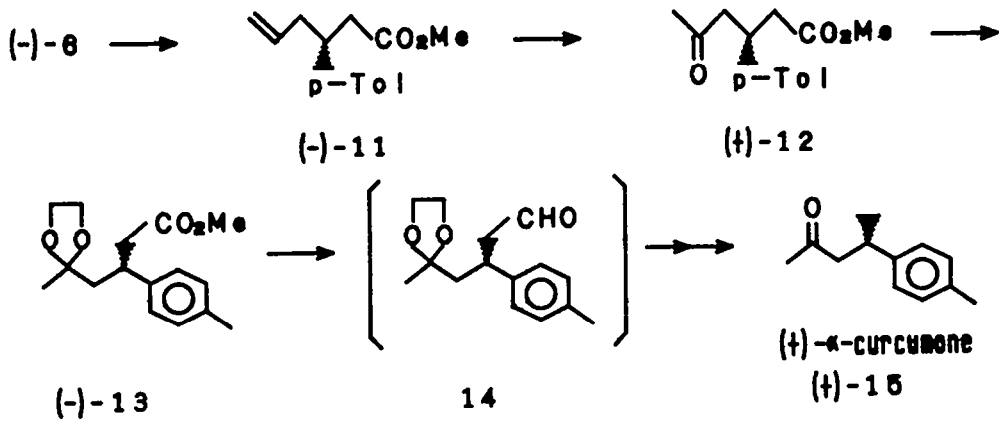


(R)-(-)-1 (+)-3b (-)-5 (-)-6

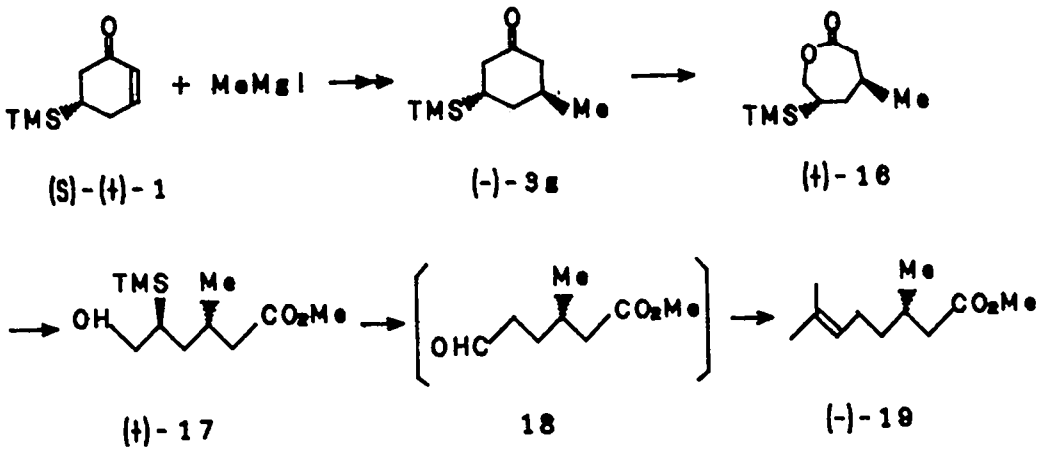
7 8 R=OMe 9 R=H (+)-α-curcumene (+)-10

Reduction of 8 with diisobutylaluminium hydride (DIBAH) at -70 °C followed by decarbonylation with Willkinson's complex [$RhCl(PPh_3)_3$] afforded (+)- and (±)-α-curcumene 10 in 84 and 80% overall yields from 8, respectively. The specific rotation of the synthesized (+)-α-curcumene was $[\alpha]_D^{22}$+42.5°(c 2.94, $CHCl_3$). The values of synthesized (+)-α-curcumene by Takano et al.[6] and that of naturally occurring curcumene[7] are reported $[\alpha]_D$+42.8°(c 1.18, $CHCl_3$) and $[\alpha]_D$+45.1°(c 0.75, $CHCl_3$), respectively.

The intermediate 6 was also used for the synthesis of curcumone (15). Treatment of 6 with trifluoroacetic acid gave terminal olefin 11 [(-)-11 94%, (±)-11 96%] which was oxidized with air in the presence of $PdCl_2$-CuCl to furnish keto ester 12 in high yield [(+)-12 94%, (±)-12 90%] along with a small amount (4-5%) of double bond migrated product. After protection of the carbonyl group with ethylene glycol, [(-)-13 98%, (±)-13 98%], reduction with DIBAH at -78 °C, decarbonylation with $RhCl(PPh_3)_3$, and subsequent deprotection gave expected curcumone 15 [(+)-15 64%, α_D^{24}+47.18°(neat, 1 dm), [lit.[8] α_D^{30}+48.21°(neat, 1 dm)], (±)-15 57% overall yield from 13].



The synthesis of (-)-methyl citronellate was also carried out by utilizing similar strategy. 1,4-Addition of methylmagnesium iodide to (S)-(+)-1 furnished (-)-3g in 92% yield. Baeyer-Villiger oxidation of (-)-3g followed by column chromatography gave 7-membered lactone (+)-16 in 88% yield as a crystalline product, which upon recrystallization from hexane gave analytically pure (+)-16 in 74% yield based on (-)-3g. Methanolysis of (+)-16 in the presence of NaOMe gave acyclic ester (+)-17 in 97% yield, which was oxidized with PCC and reacted with isopropylidenetriphenylphosphorane gave (-)-methyl citronellate (19) in 40% yield.



Experimental

Proton NMR spectra were taken on a Hitachi R-24B(60MHz) and ^{13}C NMR spectra were taken on a JEOL FX-90Q. Infrared spectra were recorded on a Hitachi 260-50 spectrophotometer. Optical rotations were measured on a Horiba SEPA-200 automatic polarimeter.

(R)-(-)- and (S)-(+)-5-Trimethylsilyl-2-cyclohexenone 1: Synthesis and optical resolution of 1 were carried out as described in ref. 2a. Recrystallization of trans-3-p-tolylthio-5-(trimethylsilyl)cyclohexanone was carried out by using ethanol as a solvent and generation of 1 was achieved as follows. Method A: To optically pure trans-3-p-tolylthio-5-(trimethylsilyl)cyclohexanone (25 g, 85.6 mmol) dissolved in dichloromethane (900 ml), was added diazabicycloundecene (DBU, 14.3 g, 94,2 mmol) and the reaction mixture was left at rt overnight. The solution was washed with 2 M HCl and dried over $MgSO_4$. After removal of the solvent, distillation of the residue gave slightly impure 1 which was further purified by flash column chromatography (solvent: hexane/AcOEt=12/1) to give optically pure 1 (12.6 g, 88%). Method B: To a solution of trans-3-p-tolylthio-5-(trimethylsilyl)cyclohexanone (13.5 g, 46.2 mmol) in dichloromethane (100 ml), was added 100 ml of aqueous 10% NaOH and methyltrioctylammonium chloride (1.5 g). The two phase mixture was stirred vigorously at rt for 3 h. The reaction mixture was extracted with dichloromethane. After removal of the solvent, the residue was purified by flash column chromatography followed by distillation (bp 72-73°C/3 mmHg) to give optically pure 1 (7.24 g, 93%).

Typical procedure for the 1,4-addition of Grignard reagents to 5-trimethylsilyl-2-cyclohexenone: To a stirred solution of 1 (168 mg, 1 mmol) in dry THF (17 ml) were added CuBr-SMe_2 (10 mg), HMPA (0.35 ml), and TMSCl (0.38 ml) under Ar. Phenylmagnesium bromide solution in THF (1.11 M, 2.3 ml) was added to the cooled (-78 °C) solution and the reaction mixture was stirred at that temperature for 0.5 h. Hexane (50 ml) was added to the mixture and the solution was warmed to rt. The organic layer was washed with water and brine. The crude enol silyl ether obtained by removal of the solvent was dissolved in methanol (15 ml) and treated

with a small amount of KF at rt for several minutes. Water (100 ml) was added to the reaction mixture and the product was extracted with CH_2Cl_2. Purification of the adduct by tlc (solvent: hexane/ether=6/1) gave 3-phenyl-5-(trimethylsilyl)-cyclohexanone (3a) (222 mg, 90%): mp 65.0-65.5 °C. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.8-1.5(1H, m), 2.70(2H, d, J=5Hz), 3.50(1H, quint, J=5Hz), 7.23(5H, s); ^{13}C NMR ($CDCl_3$) δ=-3.4, 20.6, 32.9, 41.6, 41.9, 45.5, 126.2, 127.1, 128.4, 144.2, 211.7, IR(KBr) 1700 cm^{-1}(C=O). Found: C, 73.26; H, 9.10%. Calcd for $C_{15}H_{22}OSi$: C, 73.11; H, 9.00%.

3-p-Tolyl-5-(trimethylsilyl)cyclohexanone **3b**: Mp 77.0-77.5 °C. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.8-1.5(1H, m), 2.28(3H, s), 1.7-2.9(6H, m), 3.45(1H, quint, J=6Hz), 7.00(4H, s); ^{13}C NMR ($CDCl_3$) δ=-3.4, 20.6, 20.9, 33.0, 41.6, 41.8, 45.6, 127.1, 129.1, 135.7, 141.1, 212.6; IR (KBr) 1695 cm^{-1}(C=O). Found: C, 73.83; H, 9.31%. Calcd for $C_{16}H_{24}OSi$: C, 73.78; H, 9.29%.

3-p-Methoxyphenyl-5-(trimethylsilyl)cyclohexanone **3c**: Mp 42.0-43.5 °C. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.8-1.5(1H, m), 1.8-2.5(4H, m), 2.70(2H, d, J=5Hz), 3.50(1H, quint, J=5Hz), 3.75(3H, s), 6.77(2H, d, J=9Hz), 7.10(2H, d, J=9Hz); ^{13}C NMR ($CDCl_3$) δ=-3.4, 20.5, 33.1, 41.3, 41.9, 45.7, 55.2, 113.8, 128.2, 136.2, 157.9, 212.6; IR (KBr) 1700 cm^{-1}. Found: C, 69.40; H, 8.70%. Calcd for $C_{16}H_{20}O_2Si$: C, 69.51; H, 8.75%.

3-(2,4,6-Trimethylphenyl)-5-(trimethylsilyl)cyclohexanone **3d**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H,s), 1.2-2.0(1H, m), 2.15(3H, s), 2.30(6H, s), 2.0-3.2(6H, m), 3.2-3.8(1H, m), 6.7(2H, s); ^{13}C NMR ($CDCl_3$) δ=-3.2, 20.3, 20.4, 21.1, 27.8, 39.5, 42.9, 130.2, 135.3, 135.5, 136.7, 212.3; IR (neat) 1720 cm^{-1}(C=O). Found: C, 75.01; H, 9.89%. Calcd for $C_{18}H_{28}OSi$: C, 74.94; H, 9.78%.

3-(1-Naphthyl)-5-(trimethylsilyl)cyclohexanone **3e**: Mp 69-71 °C. ^{1}H NMR ($CDCl_3$) δ=-0.1(9H, s), 0.7-1.4(1H, m), 1.9-2.5(4H, m), 2.23(2H, d, J=5Hz), 4.23(1H, quint, J=5Hz), 7.0-8.1(7H, m); ^{13}C NMR ($CDCl_3$) δ=-3.4, 20.8, 31.5, 37.8, 41.8, 46.1, 123.0, 124.4, 125.3, 125.5, 126.0, 127.2, 129.2, 131.0, 134.1, 140.1, 212.6,; IR (KBr) 1710 cm^{-1}(C=O). Found: C, 77.01; H, 8.31%. Calcd for $C_{19}H_{24}OSi$: C, 76.97; H, 8.16%.

3-(2-Phenylethyl)-5-(trimethylsilyl)cyclohexanone **3f**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.8-2.8(12H, m), 7.3(5H, s); ^{13}C NMR ($CDCl_3$) δ=-3.7, 21.6, 30.0, 33.4, 34.8, 37.2, 41.9, 46.4, 125.8, 128.2, 141.8, 212.0,; IR (KBr) 1710 cm^{-1}(C=O). Found: C, 74.49; H, 9.70%. Calcd for $C_{17}H_{26}OSi$: C, 74.39; H, 9.55%.

3-Methyl-5-(trimethylsilyl)cyclohexanone **3g**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.95(3H, d, J=6Hz), 0.7-2.8(8H, m); ^{13}C NMR ($CDCl_3$) δ=-3.5, 19.3, 21.5, 32.1, 32.7, 42.0, 48.3, 212.4; IR (neat) 1720 cm^{-1}(C=O). Found: C, 65.00; H, 10.71%. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94%.

3-t-Butyl-5-(trimethylsilyl)cyclohexanone **3h**: Mp 31.0-32.5 °C. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.87(9H, s), 0.7-2.6(8H, m); ^{13}C NMR ($CDCl_3$) δ=-2.6, 20.8, 25.6, 27.1, 32.9, 40.3, 41.8, 44.3, 214.4,; IR (KBr) 1720 cm^{-1}(C=O). Found: C, 68.63; H, 11.64%. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57%.

3-Hexyl-5-(trimethylsilyl)cyclohexanone **3i**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.5-2.7(21H, m); ^{13}C NMR ($CDCl_3$) δ=-3.5, 14.1, 21.6, 22.7, 27.2, 29.4, 31.8, 32.9, 37.8, 42.1, 46.9, 213.1; IR (neat) 1720 cm^{-1}(C=O). Found: C, 71.08; H, 12.08%. Calcd for $C_{15}H_{30}OSi$: C, 70.79; H, 11.88%

3-p-Methoxybenzyl-5-(trimethylsilyl)cyclohexanone **3j**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.9-1.9(4H, m), 1.9-2.90(6H, m), 3.81(3H, s), 6.96(4H, q); ^{13}C NMR ($CDCl_3$) δ=-3.6, 21.6, 29.4, 38.4, 40.4, 42.1, 45.9, 55.0, 113.7, 129.9, 132.0, 158.0, 211.8; IR (neat) 1715 cm^{-1}(C=O). Found: C, 70.43; H, 9.12%. Calcd for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02%.

3-m-Methoxybenzyl-5-(trimethylsilyl)cyclohexanone **3k**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.87-1.9(4H, m), 1.9-3.1(6H, m), 3.76(3H, s), 6.53-6.90(3H, m), 6.90-7.38(1H, m); ^{13}C NMR ($CDCl_3$) δ=-3.6, 21.6, 29.4, 39.3, 40.1, 42.1, 46.1, 54.9, 111.4, 114.7, 121.4, 129.2, 141.6, 159.7, 211.6; IR (neat) 1710 cm^{-1}(C=O). Found: C, 70.47; H, 9.51%. Calcd for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02%.

3-(3,4-Dimethoxy)-5-(trimethylsilyl)cyclohexanone **3l**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.81-1.90(4H, m), 1.90-2.76(6H, m), 3.81(3H, s), 3.83(3H, s), 6.44-6.88(3H, m); ^{13}C NMR ($CDCl_3$) δ=-3.5, 21.7, 29.4, 38.9, 40.5, 42.1, 45.9, 55.8, 111.5, 112.6, 121.0, 132.7, 147.5, 148.9, 211.7; IR (neat) 1705 cm^{-1}(C=O). Found: C, 67.28, H, 8.83%. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81%.

3-Benzyl-5-(trimethylsilyl)cyclohexanone **3m**: Oil. ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.89-1.90(4H, m), 1.90-2.89(6H, m), 7.14(5H, s); ^{13}C NMR ($CDCl_3$) δ=-3.6, 21.5, 29.3, 39.2, 40.2, 41.9, 46.0, 125.9, 128.1, 128.8, 140.0, 211.3; IR (neat) 1710 cm^{-1}(C=O). Found: C, 73.73; H, 9.35%. Calcd for $C_{16}H_{24}OSi$: C, 73.78; H, 9.29%.

Typical procedure for the 1,4-addition of Grignard reagentS to 5-trimethylsilyl-2-cyclohexenone at -100 °C: To a solution of Grignard reagent (3.7 mmol in 16 ml THF) cooled to -100 °C, CuBr-Me_2S (25 mg, 10 mol%), and HMPA (0.42 ml, 2 eq) were added and then THF solution (0.5 ml) of **1** (206 mg, 1.23 mmol) and TMSCl (0.46 ml, 3 eq) was slowly added over a period of 5 min. The reaction mixture was stirred at that temperature for 30 min. The same work-up described before and purification by tlc gave **3k** in 89% yield.

Synthesis of optically active 5-substituted-2-cyclohexenone: 1,4-Addition of phenylmagnesium bromide to (R)-(-)-**1** was carried out as described before. Mixture of the adduct (338 mg, 1.37 mmol) and anhydrous $CuCl_2$ (553 mg, 4.11 mmol) in commercial grade DMF (5.5 ml) was heated at 60°C for 40 min. After cooled to rt the mixture was diluted with water (20 ml) and filtered through short pad of celite. The filtrate was extracted with Et_2O. Removal of the solvent followed by isolation by tlc (solvent: hexane/Et_2O=3/1) gave (R)-(-)-5-phenyl-2-cyclohexenone, (R)-(-)-**4a** (194 mg, 82%): $[\alpha]_D^{25}$-45.3°(c 1.29, $CHCl_3$). Recrystallization from pentane gave optically pure (R)-(-)-**4a**: mp 60.5 °C; $[\alpha]_D^{23}$-46.4°(c 5.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ=2.35-2.92(4H, m), 2.98-3.58(1H, m), 6.00(1H, dt, J=2 and 10Hz), 6.70-7.10(1H, m), 7.10(5H, s); IR (KBr) 1680 cm^{-1}(C=O). Found: C, 83.63; H, 7.04%. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02%. In a similar manner, (R)-(-)-5-p-tolyl-2-cyclohexenone, (R)-(-)-**4b**: $[\alpha]_D^{20}$-43.5°(c 2.61, $CHCl_3$), was obtained in 90% yield, and optically pure sample was obtained by recrystallization from

pentane. Mp 53.5-4 °C; $[\alpha]_D^{20}$-44.5°(c 1.70, $CHCl_3$). ^1H NMR (CDCl) δ=2.32(2H, s), 2.20-3.70(5H, m), 5.95(1H, d, J=12Hz), 7.10(4H, s), 6.70-7.20(1H, m). IR (KBr) 1680 cm^{-1}(C=O). Found: C, 83.99; H, 7.49%. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58%. (R)-(-)-5-t-Butyl-2-cyclohexenone, (R)-(-)-4c: oil; $[\alpha]_D^{20}$-26.0°(c 1.20, $CHCl_3$), was obtained in 92% yield. ^1H NMR ($CDCl_3$) δ=0.93(9H, s), 1.8-2.7(5H, m), 5.98(1H, dt, J=2 and 10Hz), 6.80-7.16(1H, m). IR (neat) 1680cm^{-1}(C=O). Found: C, 78.66; H, 10.62%. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59%. Hydrogenation of the enone in AcOEt at rt under H_2 in the presence of Pd-C gave (R)-(+)-3-t-butylcyclohexanone, $[\alpha]_D^{22}$+23.14°(c 2.80, $CHCl_3$), which optical purity was evaluated as 96% ee based on the value $[\alpha]_D$+24.1°.[9]

4-p-Tolyl-6-trimethylsilyl-2-oxepanone (-)-5: To a mixture of (+)-3b (5.20 g, 20 mmol) in CH_2Cl_2 (50 ml) and Na_2HPO_4 (5.68 g, 40 mmol) in water (50 ml), was added mCPBA (30 mmol) and the mixture was stirred at rt for 2.5 h. After the addition of saturated Na_2SO_3 solution, the reaction mixture was extracted with CH_2Cl_2. Removal of the solvent and purification of the residue by flash column chromatography (solvent: hexane/AcOEt=8/1) gave (-)-5 (5.19 g, 94%). Recrystallization from hexane gave 4.17 g (76%) of (-)-5: mp 85.0-85.5 °C. $[\alpha]_D^{22}$ -23.5°(c 2.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.13(9H, s), 1.0-1.7(1H, m), 1.9-2.2(2H, m), 2.30(3H, s) 2.7-3.3(3H, m), 4.3-4.5(2H, m), 7.05(4H, s); IR (KBr) 1720cm^{-1}(C=O). Found: C, 69.11; H, 8.51%. Calcd for $C_{16}H_{24}O_2Si$: C, 69.51; H, 8.75%. (±)-5: 94%, mp 91.0-92.0 °C.

Methyl 6-hydroxy-3-p-tolyl-5-(trimethylsilyl)hexanoate (-)-6: After the addition of NaH (55% in oil, 63 mg, 1.45 mmol) to 30 ml of MeOH, lactone (-)-5 (4.00 g, 14.5 mmol) was added to the solution and the mixture was stirred at rt for 1 h. Reaction was quenched with saturated aq. NH_4Cl solution and the product was extracted with CH_2Cl_2. Removal of solvent in vacuo and purification of the residue by flash column chromatography (solvent: hexane/AcOEt=8/1) gave (-)-6 (4.42 g, 99%): oil. α_D^{22}-19.43°(neat, 1 dm), ^1H NMR ($CDCl_3$) δ=0.00(9H, s), 0.5-0.9(1H, m), 1.30(1H, s), 1.80(2H, t, J=7Hz), 2.30(3H, s), 2.53(1H, d, J=8Hz), 2.55(1H, d, J=7Hz), 2.8-3.4(1H, m), 3.50(3H, s), 3.4-3.8(2H, m), 7.05(4H, s); IR (neat) 1740 (C=O), 3100-3700 cm^{-1}(OH). Found: C, 66.03; H, 9.24%. Calcd for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15%. (±)-6: 99%, oil.

Methyl 7-methyl-3-p-tolyl-6-octenoate (+)-8: To a solution of (-)-6 (2.0 g, 6.49 mmol) in dry CH_2Cl_2 was added PCC (2.10 g, 9.74 mmol) and the mixture was stirred at rt for 2 h. Ether was added and the reaction mixture was filtered through a short pad of silica gel. After removal of solvent, the crude aldehyde was dissolved in dry THF (40 ml) and added to a solution of isopropylidene-triphenylphosphorane (6.49 mmol) in THF (60 ml) at 0 °C. Stirring was continued at 0 °C for 0.5 h and at rt for 2 h. After the addition of aq. NH_4Cl, the reaction mixture was extracted with ether. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (solvent: hexane/Et_2O=12/1) to give 1.01 g (60%) of (+)-8: oil. $[\alpha]_D^{22}$+9.19°(c 2.13, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.45(3H, s), 2.15(3H, s), 1.9-2.5(4H, m), 2.30(3H, s), 2.52(2H, d, J=6Hz), 2.7-3.4(1H, m), 3.50(3H, s), 4.7-5.2(1H, m), 7.00(4H, s); IR (neat) 1740 cm^{-1}(C=O). Found: C, 78.43; H, 9.51%. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29%. (±)-8: 56%, oil.

(+)-α-Curcumene **10:** To a solution of (+)-**8** (676 mg, 2.6 mmol) in dry CH_2Cl_2 cooled to -78 °C, hexane solution of diisobutylaluminium hydride (1.0 M, 2.6 mmol) was added. After 15 minutes, MeOH (1.5 ml) was added to the solution and the reaction mixture was warmed to rt. After the addition of water, the reaction mixture was extracted with Et_2O. Removal of volatiles in vacuo gave crude aldehyde **9** which was used for the next step without further purification. To a solution of **9** in dichloroethane (20 ml) was added Wilkinson's complex (2.40 g, 2.6 mmol) and the solution was heated under reflux for 40 minutes. The reaction mixture was cooled to rt and filtrated through celite. Solvent was removed in vacuo and the residue was purified by tlc (solvent: pentane), to give (+)-**10** (442 mg, 84%: oil. $[\alpha]_D^{22}$+42.5°(c 2.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.20(3H, d, J=7Hz), 1.50(3H, s), 1.65(3H, s), 1.35-2.10(4H, m), 2.30(3H, s), 2.4-3.0(1H, m), 4.8-5.4(1H, m), 7.00(4H, s); IR (neat) 730, 810, 910 cm^{-1}. Found: C, 88.87; H, 10.79%. Calcd for $C_{15}H_{22}$: C, 89,04; H, 10.96%. (±)-**10**: 80%, oil.

Methyl 3-p-tolyl-5-hexanoate (-)-**11:** Trifluoroacetic acid (2 ml) was added to hydroxy ester (-)-**6** (1.66 g, 5.39 mmol) and resulted solution was concentrated in vacuo immediately. Small amount of dry benzene was added and evaporated in vacuo in order to remove trace amount of trifluoroacetic acid. Flash column chromatography of the residue (solvent: hexane/Et_2O=12/1) gave (-)-**11** (1.10 g, 94%): oil. $[\alpha]_D^{22}$-19.82°(c 4.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=2.27(3H, s), 2.1-2.8(4H, m), 2.9-3.4(1H, m), 3.50(3H, s), 4.7-5.1(2H, m), 5.2-5.9(1H, m), 7.00(4H, s); IR (neat) 1740 cm^{-1}(C=O). Found: C, 76.99; H, 8.58%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%. (±)-**11**: 96%, oil.

Methyl 5-oxo-3-(p-tolyl)hexanoate (+)-**12:** To an air bubbling mixture of $PdCl_2$ (73 mg, 0.414 mmol), CuCl (559 mg, 4.14 mmol), H_2O (1 ml), and DMF (10 ml) was added DMF solution (10 ml) of (-)-**11** (903 mg, 4.14 mmol) over a period of 6 h. Bubbling of air was continued for 4 h after the completion of the addition. To the reaction mixture was added 2M HCl and the mixture was extracted with ether. Solvent was removed in vacuo and the residue was purified by flash column chromatography (solvent: hexane/AcOEt=6/1) to give (+)-**12** (914 mg, 94%): mp 59.5-60.5 °C. $[\alpha]_D^{22}$+20.8°(c 5.00, benzene); ^{1}H NMR ($CDCl_3$) δ=2.00(3H, s), 2.26(3H, s), 2.58(2H, d, H=7Hz), 2.76(2H, d, J=7Hz), 3.55(3H, s), 3.3-3.9(1H, m), 7.00(4H, s); IR (neat) 1710, 1720 cm^{-1}(C=O). Found: C, 71.35; H, 7.97%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%. (±)-**12**: 90%, mp 39.0-40.0°C.

Methyl 5-oxo-3-(p-tolyl)hexanoate (-)-**13:** A mixture of (+)-**12** (807 mg, 3.45 mmol), ethylene glycol (430 mg), PPTS (173 mg) in dry benzene (100 ml) was heated under reflux for 6 h with removal of water azeotropically. The reaction mixture was cooled to rt, washed with aq. $NaHCO_3$ solution and brine. After removal of the solvent in vacuo, purification by flash column chromatography (solvent: hexane/AcOEt=8/1) gave (-)-**13** (940 mg, 98%): oil. $[\alpha]_D^{22}$-12.78°(c 6.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.20(3H, s), 2.00(2H, d, J=6Hz), 2.27(3H, s), 2.72(2H, d, J=6Hz), 2.9-3.6(1H, m), 3.50(3H, s), 3.83(4H, s), 7.00(4H, s); IR (neat) 1740 cm^{-1}(C=O). (±)-**13**: 98%, oil).

(+)-Curcumone (+)-**15:** Reduction and decarbonylation of (-)-**13** (816 mg, 2.94 mmol) were carried out as described in the synthesis of (+)-curcumene (**10**). The crude product was treated with a catalytic amount of PTS in acetone under reflux

for 0.5 h. The mixture was extracted with CH_2Cl_2, and the solvent was removed. Purification by tlc (solvent: hexane/Et_2O=10/1) furnished (+)-15 (336 mg, 64%): oil. $[\alpha]_D^{23}$+40.2°(c 2.35, $CHCl_3$), α_D^{24}+47.18°(neat, 1 dm), ^{1}H NMR ($CDCl_3$) δ=1.20(3H, d, J=7Hz), 2.00(3H, s), 2.27(3H, s), 2.63(1H, d, J=9Hz), 2.65(1H, d, J=7Hz), 2.9-3.6(1H, m), 7.00(4H, s); IR (neat) 1720 cm^{-1}(C=O). Found: C, 81.93; H, 9.11%. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15%. (±)-15: 57%, oil.

3-Methyl-5-(trimethylsilyl)cyclohexanone (-)-3g: 1,4-Addition of methylmagnesium iodide to (S)-(+)-1 was carried out at -78 °C as described before. (-)-3g: oil. $[\alpha]_D^{20}$-92.32°(c 2.10, $CHCl_3$).

4-Methyl-6-trimethylsilyl-2-oxepanone (+)-16: Mp. 74.0-75.0 °C. $[\alpha]_D^{20}$+72.5°(c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.00(9H, s), 0.95(3H, d, J=6Hz), 0.8-2.3(4H, m), 2.5-2.8(2H, m), 4.0-4.25(2H, m); IR (KBr) 1720 cm^{-1}(C=O). Found: C, 59.79; H, 9.87%. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06%.

Methyl 6-hydroxy-3-methyl-5-(trimethylsilyl)hexanoate (+)-17: Oil. $[\alpha]_D^{22}$+5.34°(c 1.00, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ=0.03(9H, s), 0.7-1.16(4H, m), 1.2-1.7(2H, m), 1.30(1H, s), 1.9-2.5(3H, m), 3.63(3H, s), 3.5-3.8(2H, m); IR (neat) 1740 cm^{-1}(C=O). Found: C, 57.01; H, 10.48%. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41%.

Methyl citronellate (-)-19: Oil. $[\alpha]_D^{22}$-6.70(c 2.28, $CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ=0.90(3H, d, J=6Hz), 1.60(3H, s), 1.67(3H, s), 1.1-2.5(7H, m), 3.60(3H, s), 4.83-5.28(1H, m). IR (neat) 1740 cm^{-1}(C=O). Found: C, 70.58; H, 10.92%. Calcd for $C_{11}H_{22}O_2$: C, 71.70; H, 10.94%.

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