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A Convenient Reductive Removal of Benzylic Hydroxyl and Trimethylsilyloxyl Groups with Me_3SiCl-NaI-MeCN Reagent

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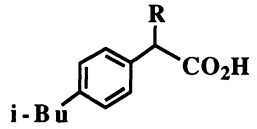
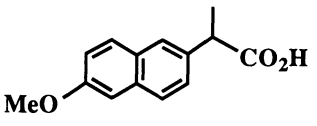
Secondary and tertiary hydroxyl groups at benzylic positions were reductively removed by treatment with 6 equivalents of Me_3SiCl-NaI-MeCN reagent in hexane at room temperature. A benzylic trimethylsilyloxyl group was also eliminated by the addition of 2 equivalents of water to the reaction system. The reduction was applied to the syntheses of precursors of such anti-inflammatory agents as ibuprofen, butibufen, naproxen, and related compounds, as well as (±)-*ar*-turmerone, an odorous sesquiterpene.

Recently, attention has been devoted to α-arylalkanoic acids and their derivatives because of their usefulness as nonsteroidal anti-inflammatory agents.[1] For example, ibuprofen (**1a**),[2] butibufen (**1b**),[3] and naproxen (**2**)[4] have been extensively utilized for medical purposes and various synthetic methods for the α-arylalkanoic acid skeleton have been developed.



1a R=Me
1b R=Et



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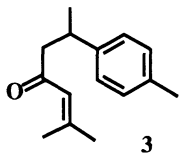
One of the straightforward approaches to them relies upon the reductive removal of such benzylic functional groups as $-OP(=O)(OEt)_2$,[2a] -OAc,[2b] $-SO_2Ph$,[2c] -OH,[3] and -SMe.[4] Therein, a convenient reduction method is still sought. It is of interest that a Me_3SiCl-NaI-MeCN reagent has been used for a variety of organic transformations.[5,6] For example, aliphatic alcohols are converted into the corresponding iodides[6,7] and α-ketols are reduced to ketones.[8] We describe here a new potential use of the reagent, in which a benzylic hydroxyl group can be reductively removed.[9] Moreover, a reduction of the benzylic trimethylsiloxyl group was also achieved by the addition of water to the system. The advantages of the present method include the reagent availability and procedural simplicity using mild conditions compared with the reported methods.[10] The synthetic utility of the method has been demonstrated by the syntheses of the precursors of racemic **1a**, **b** and **2** as well as (±)-*ar*-turmerone (**3**),[11a,b] a constituent of the essential oil from Curcuma Longa Linn.[11c]



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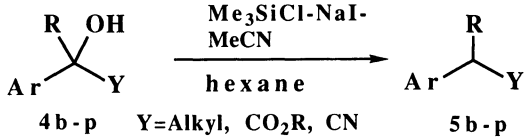
Results and Discussion

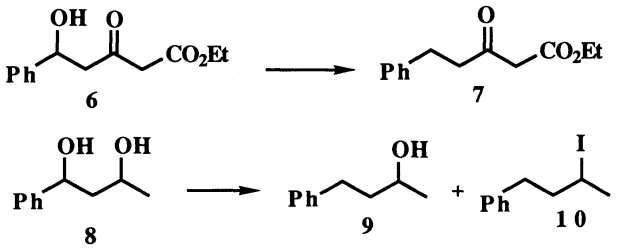
The reduction of secondary or tertiary benzylic alcohols **4b—p** with the Me_3SiCl-NaI-MeCN reagent gave products **5b—p** in good yields (Scheme 1). The results are summarized in Table 1. Optimun yields were obtained when the reaction was carried out with 6 equivalents of the reagent in hexane at room temperature. A decrease in the reagent ratio to three equivalents against **4a** resulted in a lower yield of **5b** and the partial recovery of **4b**. The obtained products were essentially pure after a simple workup, although cyanohydrins **4j** and **4k** decomposed partially to the corresponding ketones through a reverse cyanohydrin reaction under weakly acidic conditions. The reaction for menthyl ester **4m** required heating and gave a mixture of ester **5m** and its acid.

Furthermore, δ-hydroxy β-keto ester **6** gave β-keto ester **7** in 62% yield and diol **8** was deoxygenated regioselectively, giving alcohol **9** (39% yield) and iodide **10** (7% yield) (Scheme 2). Other functional groups such as aryl, carbonyl, cyano, carboxyl, alkoxycarbonyl, and the β-keto ester moiety were scarcely affected.[12]



4b-p Y=Alkyl, CO_2R, CN **5b-p**

Scheme 1.

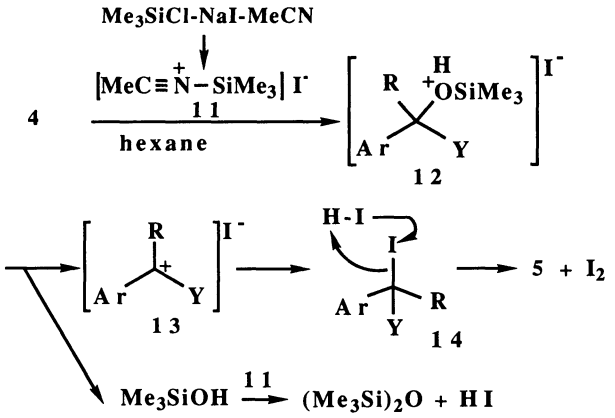


Scheme 2.

Table 1. Reductive Removal of Benzylic Hydroxyl Group Using Me_3SiCl-NaI-MeCN Reagent in Hexane[a,b]

	Alcohol 4			5	
	Ar	R	Y	Yield/%[c]	
4a[d]	Ph	H	H	e)	
4b[d]	Ph	H	Me	**5b**[d]	75
4b[d]	Ph	H	Me	**5b**[d]	57[f]
4c[d]	Ph	H	Et	**5c**[d]	99
4d	Ph	H	Pr	**5d**[d]	75
4e	Ph	H	Bu	**5e**[d]	74
4f	Piperonyl	H	Et	**5f**	57
4g	Ph	H	$-CH_2CO_2Et$	**5g**[d]	91
4h[d]	Ph	Me	Et	**5h**[d]	76
4i	Ph	Me	Pr	**5i**	82
4j	Ph	Me	CN	**5j**[d]	30[g]
4k	*p*-Isobutylphenyl	Me	CN	**5k**	77[h]
4l	*p*-Isobutylphenyl	Me	$-CO_2Et$	**5l**	85[i]
4m[j]	Ph	Me	$-CO_2$menthyl	**5m**	42[k,l]
4n[m]	Ph	Me	$-CH_2CO_2Me$	**5n**	60[l]
4o	*p*-Tolyl	Me	$-CH_2CO_2Et$	**5o**	91
4p	*p*-Tolyl	Me	$-CH_2CO_2H$	**5p**	66

a) Six equivalents of the reagent were used at room temperature for 24 h unless otherwise stated. b) All compounds listed are known. c) Isolated yield by distillation for **5b—i** or preparative TLC for **5j—p**. d) Commercially available. e) Benzyl iodide was obtained (94%). See Refs. 6 and 7. f) Three equivalents of reducing agent. Alcohol **4b** was recovered (12%). g) Acetophenone was produced (60%). h) *p*-Isobutylphenyl methyl ketone was recovered (12%). i) Reaction for 96 h. j) Diastereomeric excess of 22% (^{1}H NMR). k) Reaction for 3 days under reflux. The corresponding carboxylic acid was produced (21%). l) Racemic mixture. m) Enantiomeric excess of 70% (^{1}H NMR, Eu(hfc)$_3$).



Scheme 3.

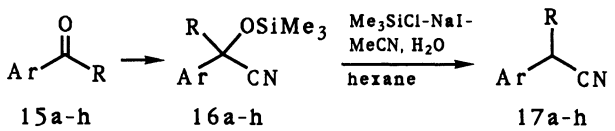
Scheme 3 illustrates a possible mechanism for the present reduction, which involves the conversion of the initially formed oxonium ion **12** to intermediate iodide **14**[6] and a subsequent reduction with an in situ generated HI, as discussed previously.[13] The proton for the reduction would, therefore, come from the original hydroxyl group. Optically active alcohols **4m** and **4n** gave racemic products **5m** and **5n**, respectively. Consequently, the present reaction seems to proceed through benzylic cation **13**. The difficulty in the formation of a primary carbonium ion from **4a** would result in the isolation of benzyl iodide.[7]

The above method leaves room for refinement in the case of cyanohydrins **4j** and **4k**. Both their yields and the product selectivity were improved by the use of

Table 2. Reductive Removal of Benzylic Trimethylsilyloxyl Group[a,b]

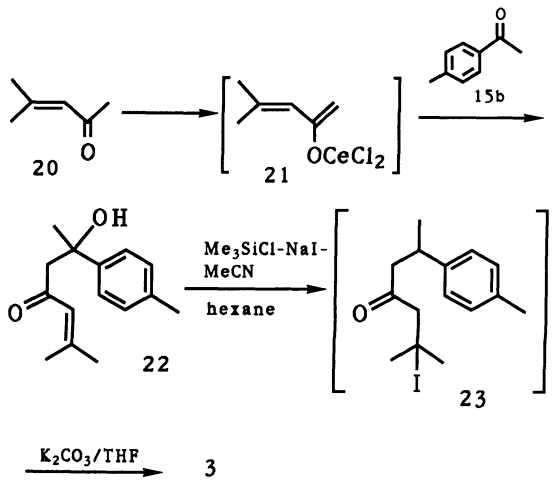
	16		17	
	Ar	R	Yield/%[c]	
16a	Ph	Me	(**5j**)[d]	74
16b	*p*-Tolyl	Me	**17b**	67
16c	*p*-Isobutylphenyl	Me	(**5k**)[d]	84
16d	*p*-Isobutylphenyl	Et	**17d**	74
16e	*p*-Isobutylphenyl	*i*-Pr	**17e**	82
16f	*p*-*t*-Butylphenyl	*i*-Pr	**17f**	24 (70)[e]
16g	6-Methoxynaphtyl	Me	**17g**	94
16h	2-Thienyl	Me	**17h**	37 (52)[e]

a) Me_3SiCl-NaI-MeCN reagent (6 equivalents) and H_2O (2 equivalents) in hexane for 24 h at room temperature. b) Known compounds except for **16c—h**. c) Isolated yields by preparative TLC. d) See Table 1. e) Overall yield from ketone without isolation of **16f** or **16h**.



Scheme 4.

α-(trimethylsilyloxy) nitriles **16a** and **16c** (Scheme 4 and Table 2), which gave **5j** and **5k** exclusively. In these cases, the addition of 2 equivalents of water is required as a proton source. Fortunately, nitriles **16** are conveniently prepared from ketones **15**.[14] Reduction using a variety of nitriles, **16b** and **16d—h**,



Scheme 5.

afforded **17b** and **17d—h** in acceptable yields, respectively. Nitriles **5k**, **17d**, and **17g** are known to be converted into **1a**, **b** and **2** by alkaline hydrolysis;[3a,10c] other nitriles are also important precursors for anti-inflammatory compounds.

By using this method, a deuterated benzylic compound was conveniently prepared. Thus, the reaction of **16b** in the presence of 2 equivalents of D_2O yielded 2-deuterio-2-*p*-tolylpropiononitrile (**18**) in 56% yield. This result supports the mechanism shown in Scheme 3.

In the case of α-(trimethylsilyloxy) nitriles, decreasing the amount of the reagent made the reaction rather complex. For example, the reaction of **16b** with 3 equivalents of the reagent and 2 equivalents of water in hexane gave a mixture of nitrile **17b** (33% yield), ketone **15b** (26% yield), and 2-*p*-tolylpropanamide (**19**) (26% yield). The reduction may be retarded under the conditions and accompanied by an acidic hydrolysis of the nitrile group or a reverse cyanohydrin reaction.

Finally, the present reaction was applied to an efficient synsthesis of (±)-**3**[11] from mesityl oxide (**20**) and *p*-methylacetophenone (**15b**), as communicated previously[9] (Scheme 5). Cerium enolate **21**[15] was allowed to react with **15b** to give aldol **22** in 54% yield. The reduction of **22** gave a 1:2 mixture of iodide **23** and **3** which, without isolation, was treated with K_2CO_3 in THF to afford **3** in 82% yield from **22**. This method offers one possible straightforward approaches to the synthesis of (±)-**3**.[9,11]

Experimental

General. IR spectra were taken on a JASCO A 102 spectrometer. ^{1}H NMR spectra (60 MHz) were measured with a JEOL-PMX 60 SI spectrometer. Chemical shifts are reported in value (ppm) down field from Me_4Si and *J* values are given in hertz. Preparative TLC was performed on silica gel (E. Merck, Kiesel gel 60 PF_{254}). Elemental analyses were performed by Eiichiro Amano of this laboratory using a Yanagimoto MT-3 CHN recorder.

Alcohols 4a—p. Compounds **4a—c** and **4h** are commercially available; the others were prepared according to the various methods reported.[16]

Ketones 15a—h. Compounds **15a**, **15b**, and **15h** are commercially available and **15c—g** were prepared by acylation of substituted benzene derivatives ($AlCl_3$, dichloromethane).[17]

General Procedure for Deoxygenation of Benzylic Alcohols 4a—p. To a stirred mixture of Me_3SiCl (1.54 ml, 12 mmol), NaI (1.8 g, 12 mmol), and acetonitrile (0.61 ml, 12 mmol), was added a solution of benzylic alcohol **4a—p** (2 mmol) in hexane (2 ml) at room temperature. The mixture slowly turned dark purple due to liberated iodine. After being stirred for 24 h at room temperature, the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and then concentrated under vacuum. Distillation or preparative TLC (Table 1) of the residual oil gave clean products **5a—p**,[18] whose structures were identified by using IR and ^{1}H NMR spectra.

Ethyl 3-Oxo-5-phenylpentanoate (7). Crude product from **6**[19] (236 mg, 1 mmol) was purified by preparative TLC (hexane-acetone, 3:1) to give **7**[20] (136 mg, 62% yield): R_f 0.41—0.53; IR (neat) 1745, 1715 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.20 (3H, t, *J*=7 Hz), 2.83 (4H, m), 3.23 (2H, s), 4.06 (2H, q, *J*=7 Hz), 7.10 (5H, m), 12.15 (trace, br s).

4-Phenyl-2-butanol (9)[21] **and 3-Iodo-1-phenylbutane (10).**[22] A crude product from diol **8**[23] (166 mg, 1 mmol) was separated by preparative TLC (hexane-acetone, 3:1) to give **9** (R_f 0.24—0.34, 58 mg, 39% yied) and **10** (R_f 0.78—0.90, 23 mg, 7% yield).

General Procedure for the Preparation of α-(Trimethylsilyloxy) Nitriles 16a—h. These reactions were carried out by a modification of Rasmussen's method.[14a] To a stirred suspension of NaCN (735 mg, 15 mmol), Me_3SiCl (1.02 ml, 8 mmol), and ZnI_2 (50 mg) in acetonitrile (2 ml) was added alkyl aryl ketone **15a—h** (5 mmol) at room temperature. The mixture was heated under gentle reflux for 48 h and then made basic by the addition of aqueous $NaHCO_3$; the organic layer was extracted with ether. It was then washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by vacuum distillation to give **16a—h** (5 mmol) at room temperature. The mixture was heated under gentle reflux for 48 h and then made basic by the addition of aqueous $NaHCO_3$; the organic layer was extracted with ether. It was then washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by vacuum distillation to give **16a—h**. Compound **16a**[14] was identified by a comparison of the spectral data with those reported. Those of **16b—h** are shown below.

2-*p*-Tolyl-2-(trimethylsilyloxy)propiononitrile (16b):[24] bp 140—152 °C (9 mmHg, 1 mmHg=133.322 Pa); IR (neat) 2225 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.13 (9H, s), 1.76 (3H, s), 2.31 (3H, s), 7.06 (2H, d, *J*=8 Hz), and 7.32 (2H, d, *J*=8 Hz).

2-(*p*-Isobutylphenyl)-2-(trimethylsilyloxy)propiononitrile (16c): bp 115—130 °C (0.2 mmHg); IR (neat) 2230 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.14 (9H, s), 0.89 (6H, d, *J*=6 Hz), 1.08 (3H, s), 1.5—2.6 (1H, m), 2.46 (2H, d, *J*=8 Hz), 7.05 (2H, d, *J*=9 Hz), and 7.37 (2H, d, *J*=9 Hz). Found: C, 69.71; H, 8.82; N, 5.12%. Calcd for $C_{16}H_{25}NOSi$: C, 69.82; H, 9.09; N, 5.09%.

2-(*p*-Isobutylphenyl)-2-(trimethylsilyloxy)butyronitrile

(**16d**): bp 110—130 °C (0.2 mmHg); IR (neat) 2240 cm^{-1}; ^1H NMR (CCl_4) δ=0.10 (9H, s), 0.89 (6H, d, J=6 Hz), 0.96 (3H, t, J=7 Hz), 1.5—2.2 (3H, m), 2.46 (2H, d, J=7 Hz), 7.03 (2H, d, J=8 Hz), and 7.30 (2H, d, J=8 Hz). Found: C, 70.66; H, 9.37; N, 4.64%. Calcd for $C_{17}H_{27}NOSi$: C, 70.59; H, 9.34; N, 4.84%.

2-(*p*-Isobutylphenyl)-3-methyl-2-(trimethylsilyloxy)butyronitrile (16e): bp 140—155 °C (0.3 mmHg); IR (neat) 2250 cm^{-1}; ^1H NMR (CCl_4) δ=0.14 (9H, s), 0.80—0.36 (12H, m), 1.45—2.35 (2H, m), 2.52 (2H, d, J=7 Hz), and 7.24 (4H, m). Found: C, 71.53; H, 9.59; N, 4.76%. Calcd for $C_{18}H_{29}NOSi$: C, 71.29; H, 9.57; N, 4.62%.

2-(*p*-*t*-Butylphenyl)-3-methyl-2-(trimethylsilyloxy)butyronitrile (16f): bp 105—120 °C (0.3 mmHg); IR (neat) 2350 cm^{-1}; ^1H NMR (CCl_4) δ=0.14 (9H, s), 0.87 (3H, d, J=7 Hz), 1.11 (3H, d, J=7 Hz), 1.38 (9H, s), 1.4—2.7 (2H, m), and 7.35 (4H, s). Found: C, 71.42; H, 9.31; N, 4.50%. Calcd for $C_{18}H_{29}NOSi$: C, 71.29; H, 9.57; N, 4.62%.

2-(6-Methoxy-2-naphthyl)-2-(trimethylsilyloxy)propiononitrile (16g): bp 145—155 °C (0.18 mmHg); IR (neat) 2229 cm^{-1}; ^1H NMR (CCl_4) δ=0.15 (9H, s), 1.85 (3H, s), 3.80 (3H, s), and 7.0—8.0 (5H, m). Found: C, 68.47; H, 6.84; N, 4.55%. Calcd for $C_{12}H_{21}NO_2Si$: C, 68.23; H, 7.02; N, 4.68%.

2-(2-Thienyl)-2-(trimethylsilyloxy)propiononitrile (16h): bp 143—157 °C (15 mmHg); IR (neat) 3125, 3100, 3000, 2250 cm^{-1}; ^1H NMR (CCl_4) δ=0.16 (9H, s), 1.91 (3H, s), 6.78 (1H, m), and 7.16 (2H, m). Found: C, 53.14; H, 6.44; N, 6.13%. Calcd for $C_{10}H_{15}NOSSi$: C, 53.33; H, 6.67; N, 6.22%.

General Procedure for the Reductive Removal of α-Trimethylsilyloxyl Group of 16a—h. Nitriles **16a—h** (0.5 mmol) were added to a mixture of Me_3SiCl (0.38 ml, 3 mmol), NaI (450 mg, 3 mmol), acetonitrile (0.19 ml, 3 mmol), and hexane (1 ml). After the addition of water (18 mg, 1 mmol), the mixture was stirred for 24 h at room temperature. The usual workup, followed by purification with preparative TLC on silica gel (hexane–acetone, 3:1) gave α-aryl nitriles **17a—h**. IR and ^1H NMR data of **17g** were identical with those reported.[25b,e] Those of others, which are not given in the literature, are shown below.

2-*p*-Tolylpropiononitrile (17b):[25a] R_f 0.48—0.60; IR (neat) 2250 cm^{-1}; ^1H NMR (CCl_4) δ=1.53 (3H, d, J=7 Hz), 2.31 (3H, s), 3.64 (1H, q, J=7 Hz), and 7.11 (4H, m).

2-(*p*-Isobutylphenyl)butyronitrile (17d):[25b] R_f 0.61—0.72; IR (neat) 2240 cm^{-1}; ^1H NMR (CCl_4) δ=0.90 (6H, d, J=6 Hz), 1.05 (3H, t, J=7 Hz), 1.5—2.3 (3H, m), 2.46 (2H, d, J=7 Hz), 3.61 (1H, t, J=6 Hz), and 7.10 (4H, m).

2-(*p*-Isobutylphenyl)-3-methylbutyronitrile (17e):[25c] R_f 0.56—0.81; IR (neat) 2250 cm^{-1}; ^1H NMR (CCl_4) δ=0.85—1.28 (12H, m), 1.3—2.7 (2H, m), 2.45 (2H, d, J=7 Hz), 3.54 (1H, d, J=6 Hz), and 7.09 (4H, m).

2-(*p*-*t*-Butylphenyl)-3-methylbutyronitrile (17f):[25d] R_f 0.44—0.60 (hexane–acetone, 5:1); IR (neat) 2250 cm^{-1}; ^1H NMR (CCl_4) δ=0.99 (3H, d, J=7 Hz), 1.03 (3H, d, J=7 Hz), 1.29 (9H, s), 2.10 (1H, m), 3.05 (1H, d, J=6 Hz), and 7.26 (4H, m).

2-(2-Thienyl)propionitrile (17h):[25f] R_f 0.41—0.49; IR (neat) 3130, 3020, 2960, 2260 cm^{-1}; ^1H NMR (CCl_4) δ=1.69 (3H, d, J=7 Hz), 4.09 (1H, q, J=7 Hz), 6.3—7.4 (3H, m).

2-Deuterio-2-*p*-tolylpropiononitrile (18). Nitrile **16b** (233 mg, 1 mmol) was added to a mixture of 6 equivalents of a Me_3SiCl–NaI–MeCN reagent in 1 ml of hexane, and then D_2O (99.6%, 36 mg, 2 mmol) was introduced. The mixture was treated in the usual way, giving **18** (81 mg, 55% yield): IR (neat) 2250 cm^{-1}; ^1H NMR (CCl_4) δ=1.52 (3H, m), 2.29 (3H, s), 3.26 (0.27H, q, J=7 Hz), 7.09 (4H, m); ^{13}C NMR ($CDCl_3$) δ=21.0 (q), 21.3 (q), 30.5 (t from C-D), 30.8 (d, C-H, trace), 121.7 (s), 126.5 (d), 129.7 (d), 134.1 (s), 137.8 (s). The ^1H NMR data indicates the deuterated ratio is 91%.

Reaction of 16b with 3 Equivalents of the Reducing Agent. Crude product from **16b** (233 mg, 1 mmol) was separated by preparative TLC (hexane–acetone 3:1) to give nitrile **17b** (R_f 0.42—0.73, 48 mg, 33% yield), amide **19** (R_f 0.03—0.16, 42 mg, 26% yield), and ketone **15b** (R_f 0.22—0.42, 15.5 mg, 11% yield). Compound **19**: IR (KBr) 3350, 3200, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.34 (3H, d, J=7 Hz), 2.26 (3H, s), 3.37 (1H, q, J=7 Hz), 5.80 (1H, br s), 6.97 (4H, m). Found: C, 73.41; H, 7.84; N, 8.64%. Calcd for $C_{10}H_{13}ON$: C, 73.62; H, 7.98; N, 8.59%.

6-Hydroxy-2-methyl-6-*p*-tolyl-2-hepten-4-one (22).[26] To a cooled (−78 °C) solution of LDA (4.4 mmol) [diisopropylamine (0.62 ml, 4.4 mmol) and 1.59 mol dm^{-3} BuLi hexane solution (2.75 ml, 4.4 mmol)] in THF (4 ml) in an acetone–Dry Ice bath, was added dropwise a solution of mesityl oxide (392 mg, 4 mmol) in THF (1 ml). After sitrring for 1 h at −78 °C, a suspension of $CeCl_3$ (1.16 g, 4.7 mmol) in THF (5 ml) was slowly added. The mixture was stirred for 1 h to form a cerium enolate anion. A solution of *p*-methylacetophenone (**15b**) (536 mg, 4 mmol) in THF (1 ml) was then added dropwise through a syringe. Stirring was continued for an additional 3 h at −78 °C. The resulting mixture was poured into water and acidified with 10% HCl. The organic layer was extracted with ether, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was subjected to vacuum distillation to give **22** (505 mg) as a clean oil: 54% yield; bp 140—150 °C (5 mmHg); IR (neat) 3475, 1675, 1610 cm^{-1}; ^1H NMR (CCl_4) δ=1.37 (3H, s), 1.80 (3H, s), 2.00 (3H, s), 2.24 (3H, s), 2.72 (1H, s), 2.81 (1H, s), 4.41 (1H, brs), 5.81 (1H, m), 6.94 (2H, d, J=8 Hz), and 7.21 (2H, d, J=8 Hz).

(±)-*ar*-Turmerone (3).[11] Compound **22** (101 mg, 0.43 mmol) was treated with Me_3SiCl (0.39 ml, 3 mmol), NaI (450 mg, 3 mmol), acetonitrile (0.15 ml, 3 mmol) in hexane (1 ml) in the usual manner and 116 mg of oily product was obtained. ^1H NMR analysis showed that it was a 1:2 mixture of 2-iodo-2-methyl-6-*p*-tolyl-4-heptanone (**23**)[27] and **3**, which was then stirred with K_2CO_3 (36 mg, 0.26 mmol) in THF (2 ml) for 20 h at room temperature. After the addition of water, the organic layer was extracted with ether, washed with aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and then concentrated. The residual oil was subjected to vacuum distillation to give **3** (76 mg): 82% yield from **22**; bp 150—160 °C (7 mmHg); IR (neat) 1685, 1620, 1515, 819 cm^{-1}; ^1H NMR (CCl_4) δ=1.31 (3H, d, J=7 Hz), 1.81 (3H, s), 2.05 (3H, s), 2.22 (3H, s), 2.54 (2H, m), 3.15 (1H, m), 5.85 (1H, m), and 6.94 (4H, s). The spectral data are consistent with those reported.[11]

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