were washed with CH_2Cl_2, and the combined organic phases were concentrated in vacuo. The residue was stirred with 13.82 g (0.329 mol) of cyanamide in 200 ml of MeOH for 6 hr. A mixture of 27.44 g (0.395 mol) of hydroxylamine hydrochloride, 54.48 g (0.395 mol) of K_2CO_3, and 500 ml of MeOH was added. After stirring for 15 hr at 50° the reaction mixture was cooled to room temperature and filtered through Celite. The residues were washed with MeOH. The combined organics were concentrated, diluted with 500 ml of H_2O, and continuously extracted with CH_2Cl_2 to give the product, which was triturated with CH_3CN and then crystallized from MeOH–H_2O to give 27.9 g of product. Silica gel chromatography of the residues from trituration and recrystallization gave an additional 6.1 g of recrystallized product. Total yield was 34.0 g (49%), mp ca. 265° dec. The product obtained by method B was identical with that obtained by method A.

3-Cyanoimino-3-piperidinopropionitrile (4g). The portion of method A applicable to preparation of this compound was followed. A mixture of 5.00 g (0.0329 mol) of *N*-(2-cyanoacetyl)piperidine and 5.00 g (0.0338 mol) of trimethyloxonium fluoroborate[19] was first stirred in 50 ml of CH_2Cl_2[20] for 23 hr. The product was isolated and stirred with 1.38 g (0.0329 mol) of cyanamide in 25 ml of absolute EtOH for 5 hr and the mixture was concentrated in vacuo. The product mixture was chromatographed by HPLC on 30–50 μ silica gel in MeOH–$CHCl_3$ to afford 2.12 g of pure 3-cyanoimino-3-piperidinopropionitrile: mp 73–74.5°; NMR ($CDCl_3$) δ 1.75 [br, s, 6, $-CH_3-)_3$], 3.48–3.91 [m, 4, $N(CH_3)_2$], 3.93 (s, 2, CH_2); uv (EtOH) end absorption, λ_{max} 252 nm (ϵ 19000); mass spectrum *m/e* (rel intensity) 176 (749), 122 (698), 109 (999), 96 (334), 83 (556); ir (Nujol) 2260 (C≡N), 2180 (NC≡N), 1595 cm^{-1} (C=N), no N–H.

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Registry No.—**2** (R^1 = H; R^2 = Et), 15029-36-4; **2** (R^1 = H; R^2 = Bu), 39581-21-0; **2** (R^1 = H; R^2 = decyl), 52493-40-0; **2** (R^1 = H; R^2 = cyclohexyl), 15029-38-6; **2** (R^1 = R^2 = Bu), 53807-36-6; **2** (R^1 = R^2 = cyclohexyl), 56487-99-1; **2** (R^1, R^2 = piperidino), 15029-30-8; **2** (R^1, R^2 = pyrrolidino), 14227-95-3; **2** (R^1 = H; R^2 = Me), 6330-25-2; **4g**, 56488-00-7; **6a**, 55921-54-5; **6b**, 55921-55-6; **6c**, 55921-56-7; **6d**, 55921-57-8; **6e**, 55921-62-5; **6f**, 55921-63-6; **6g**, 38304-91-5; **6h**, 55921-65-8; **6i**, 55973-02-9.

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(20) Dried by passage through Woelm basic alumina, activity grade I.

A Convenient Synthesis of the Sesquiterpene (±)-α-Curcumene. VI. Application of Alkylation–Reduction to the Total Synthesis of Terpenes

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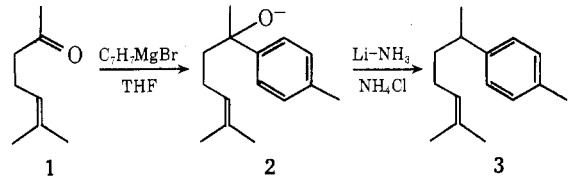
This laboratory has been developing the concept of tandem alkylation–reduction of aromatic carbonyl systems as a convenient method of preparing aromatic hydrocarbons by the lithium–ammonia–ammonium chloride reduction of benzyl alkoxides generated in situ by alkylation.[1] Recently we extended this convenient procedure to the selective synthesis of rather complex aromatic hydrocarbons in excellent isolated yields by the phenylation–reduction of appropriate aldehydes and ketones.[2] One of the purposes of that study, which demonstrated that challenging organic structures could be rapidly assembled by the proper selection of the requisite carbonyl system, was to explore the potential applicability of this simple procedure to the total synthesis of aromatic terpenes. Herein we wish to report an example of the use of the procedure, which is performed in the same reaction vessel without the isolation or purification of intermediates, for the total synthesis of (±)-α-curcumene (**3**). The entire synthesis consumed only ca. 8 hr and the overall isolated yield of the pure aromatic sesquiterpene **3** was in the range of 90–92% in repeated runs.

Addition of 6-methyl-5-hepten-2-one (**1**) to a THF solution of *p*-tolylmagnesium bromide, generated in situ from *p*-bromotoluene and a dark gray suspension of highly reactive magnesium metal[3] in THF in a metal–ammonia reaction vessel, produces the intermediate benzyl alkoxide **2**. Subsequently ammonia is distilled into the vessel, excess lithium foil is quickly added, and the resultant dark blue mixture is quenched with ammonium chloride. The latter are conditions that protonate the benzyl alkoxide **2** and then rapidly reduce the resultant benzyl alcohol to the sesquiterpene (±)-α-curcumene (**3**) before all the excess lithium is destroyed, thereby completing the synthesis.



1 2 3

Although there have been numerous methods reported for the total synthesis of this racemic sesquiterpene,[4] the best overall yield starting from commercially available material seems to be ca. 35%.[4d]

Since α-curcumene has previously been reduced to β-curcumene in sodium–ammonia–ethanol (92% yield)[4d] and cyclized in phosphoric acid to calamenene (80% yield),[5] this tolylation–reduction procedure constitutes a convenient method for the preparation of these sesquiterpenes as well.

Experimental Section[6]

General Comments. The entire reaction sequence was performed under a static argon (prepurified) atmosphere, which is connected by a T tube to the assembly and to a soda lime drying trap that is connected in series to an oil bubbler, and is operated at a moderate flow rate throughout the synthesis. All glassware was oven dried and cooled to room temperature in a large box desiccator, and then quickly assembled. Anhydrous magnesium chloride was weighed in a nitrogen atmosphere. Potassium metal was wiped

free of oil, cut into small pieces, and rinsed in petroleum ether just prior to use. Lithium wire (0.32 cm, high purity, Foote Mineral Co.) was wiped free of oil, hammered flat between sheets of aluminum foil, cut into 0.5-cm pieces, and rinsed in petroleum ether just prior to use. Tetrahydrofuran (THF) was freshly distilled under nitrogen from $LiAlH_4$. Commercially available *p*-bromotoluene and 6-methyl-5-hepten-2-one (1) were redistilled. Anhydrous ammonia was distilled, through a tower of potassium hydroxide pellets, directly into the reaction vessel. Gas chromatography (GLC) analyses were performed on a 100 × 0.4 cm (i.d.) glass column, packed with 3% silicon gum rubber OV-17 (methyl phenyl) supported on 80–100 mesh HP Chromosorb W, using a 40 ml/min carrier gas flow rate, with a Hewlett-Packard Model 7610A (flame detector) chromatograph. Purification of the product by column chromatography was accomplished on chromatographic grade activated alumina (80–325 mesh, Matheson Coleman and Bell) by elution with petroleum ether. Evaporative distillations were performed in a Kügelrohr oven. The boiling point is uncorrected.

(±)-α-Curcumene (3). A stirred mixture containing 7.08 g (74.4 mmol) of magnesium chloride and 5.20 g (133 mg-atoms, five pieces) of potassium in 180 ml of THF was refluxed (oil bath, 78–80°) for 2 hr. After the dark gray suspension was allowed to cool to 25° (ca. 30 min), a solution of 5.80 g (33.9 mmol) of *p*-bromotoluene in 15 ml of THF was slowly added (ca. 5 min). After 25 min the stirred mixture was cooled to ca. −78° (Dry Ice–acetone bath) and then a solution of 3.15 g (25.0 mmol) of 6-methyl-5-hepten-2-one (1) in 15 ml of THF was added dropwise (ca. 10 min). After 20 min at −78°, the cooling bath was removed and the stirred mixture was allowed to warm to 25°. After 1 hr, 210 ml of ammonia was carefully distilled (ca. 30 min) into the reaction vessel and then 0.694 g (100 mg-atoms, 40 pieces) of lithium foil was quickly added. After ca. 10 min, the dark blue color of the reaction mixture was discharged by the rather continuous addition (ca. 15 min) of excess ammonium chloride[7] (ca. 23 g) and then the ammonia was allowed to evaporate. After the residue had been taken up in water, adjusted to pH 7 with 1 *N* HCl, and extracted with ether, the organic phase was dried ($MgSO_4$), filtered, and concentrated at water aspirator pressure. The resultant colorless oil (4.85–5.00 g, 96–99%) exhibited one product peak on GLC (6-min retention time at 120°). Following column chromatography 4.55–4.65 g (90–92%) of (±)-α-curcumene (3) was obtained as a colorless oil: bp 125–127° (15 mm); $n^{26}D$ 1.4996; ir (film) 3095, 3050, 3025, 2965, 2925, 2865, 1515, 1450, 1375, 810, 720 cm^{-1}; NMR (100 MHz, $CDCl_3$, 250 scans) δ 7.08 (4 H, s), 5.09 (1 H, apparent t, *J* = *ca.* 7 Hz), 2.65 (1 H, apparent sextet, *J* = 6.8 Hz), 2.31 (3 H, s), 2.0–1.7 (2 H, m), a broad multiplet at 1.7–1.3 (2 H, m) on which is superimposed two perturbed singlets at 1.66 (3 H, s) and 1.52 (3 H, s), 1.21 (3 H, d, *J* = 6.8 Hz); mass spectrum *m/e* (rel intensity) 202 (M^+, 17), 188 (5), 173 (2), 159 (3), 145 (22), 132 (76), 131 (41), 119 (100), 105 (55), 91 (33), 83 (21), 77 (17), 69 (26), 55 (48), 41 (81), 39 (29).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.92; H, 10.95.

The physical and spectral data are consistent with those available in the literature.[4b-d]

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Registry No.—1, 110-93-0; 3, 3649-81-8; *p*-bromotoluene, 106-38-7;

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(7) The ammonium chloride is most conveniently introduced by attaching a glass bulb tube filled with the salt to a side arm by means of tygon tubing. When the ammonium chloride is to be added, the bulb is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and sometimes even the vigorous stirring should be momentarily stopped to avoid an eruption.