Steric Effects in the Synthesis of 1,7-Dialkylindans

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Synthesis routes to 1-alkyl(CH_3, C_2H_5, *i*-C_3H_7)-6-methylindans and 1-alkyl(CH_3, C_2H_5, *i*-C_3H_7)-7-methylindans are described. Members of the latter series, especially 1-isopropyl-7-methylindan, are sterically hindered through a peri interaction. This effect manifests itself throughout the study and necessitated use of alternative synthesis routes. Yields in the Grignard, Peterson olefination, Reformatsky, and Wittig reactions as well as catalytic hydrogenation and Li/NH_3 reduction of α,β-unsaturated acids were compared.

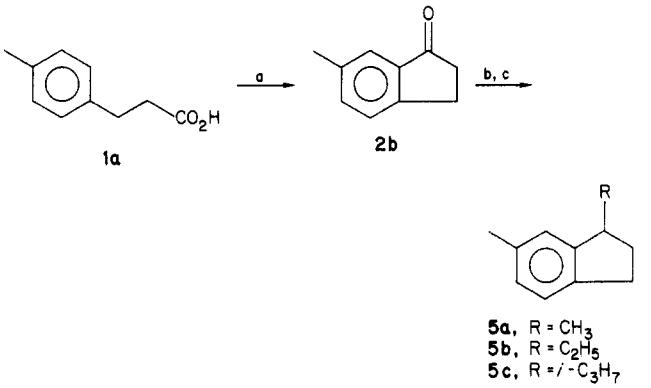
We undertook the synthesis of 1,7-dimethylindan (**4a**), 1-ethyl-7-methylindan (**4b**), and 1-isopropyl-7-methylindan (**4c**) to provide a series of indans having a graded, peri-type steric interaction of alkyl groups for use in thermodynamic[2a] and spectroscopic studies.[2b] A corresponding series of 1-alkyl-6-methylindans was prepared for comparison studies of the nonhindered isomers. This latter series (**5a**:**5b**:**5c**) was prepared in 83%, 69%, and 26% overall yield via 6-methyl-1-indanone (**2b**)[3a-c] as shown in Scheme I by using the appropriate alkylmagnesium halide. The decreased yield for **5c** is attributed to enolization induced by the Grignard reagent, and 75% of **2b** was recovered.

Despite the low yield of 1-isopropyl-6-methylindan (**5c**), we attempted the synthesis of **4a**, **4b**, and **4c** by the similar route shown in Scheme II. The first step of this route has the advantage of providing a 1:1 mixture[3d] of **2a** and **2c**, which may readily be prepared in quantity from *m*-tolualdehyde by the same procedure already used to prepare **2b**.[3a-c] The overall yields for the several steps, i.e., condensation to produce *m*-methylcinnamic acid,[3a] its hydrogenation to **1b**,[3b] and subsequent cyclization to a mixture of **2a** and **2c**[3c,e] were 88%, 87% and 84%.

The separation of **2a** and **2c** was best achieved with preparative high pressure liquid chromatography (HPLC).[4] Continuing with Scheme II provided **4a**[5a] and **4b** in 84% and 71% yields, respectively, from 7-methyl-1-indanone (**2c**). However, this procedure gave a reduced yield of **4c**.[5b] Again, we suggest the low yield (typically 13%) of the isopropyl homologue to enolization, since **2c** was recovered in 4%, 8%, and 74% yields in the reaction with methylmagnesium, ethylmagnesium, and isopropylmagnesium halides, respectively. That enolization is the chief cause of low yields in these Grignard addition reactions is supported by the data collected in Table I, which clearly show the relationship of yield and structure of Grignard reagent.

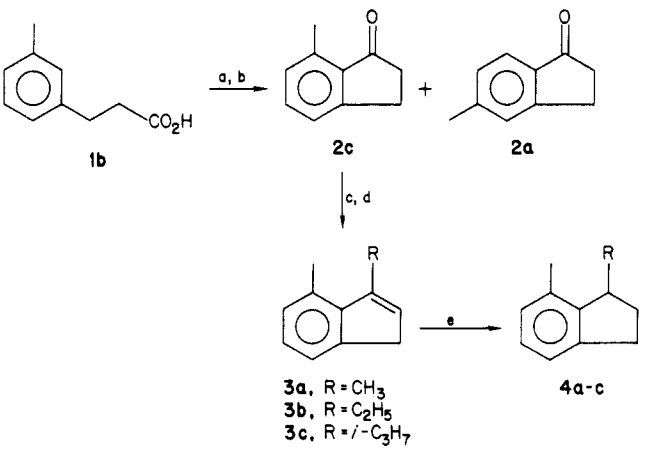
To provide enough **4c** for thermodynamic studies,[2a] it became necessary to try other routes, the best of which is shown in Scheme III. In this, the sterically interacting groups of the final product (methyl of the aromatic ring and isopropyl of the cyclopentane ring of **4c**) were in place before cyclization was attempted. The latter part of an earlier synthesis[5b] of **4c** also used this approach. Ketone **7a** was commercially available, and ketones **7b** and **7c** were

Scheme I[a]



[a] (a) PPA, Δ; (b) RMgX, ether, reflux; (c) H_2, Pd/C, CH_3CO_2H, Δ.

Scheme II[a]



[a] (a) PPA, Δ; (b) HPLC, silica, CH_2Cl_2;[4] (c) RMgX, ether; (d) oxalic acid, steam; (e) H_2, Pd/C, acetic acid.

Table I. Comparison of Yields (%) in the Addition of Alkylmagnesium Halides to 1-Indanones and *o*-Tolualdehyde[a]

aldehyde or ketone	yield[b] CH_3	C_2H_5	*i*-C_3H_7
4-methyl-1-indanone	82 (4[c])	64 (6[c])	24 (45[c])
5-methyl-1-indanone (**2a**)	82 (4[c])	71 (7[c])	23 (47[c])
6-methyl-1-indanone (**2b**)	83 (3[c])	69 (7[c])	26 (47[c])
7-methyl-1-indanone (**2c**)	84 (4[c])	71 (8[c])	13 (74[c])
o-tolualdehyde	80 (0[d])	55 (33[d])	23 (62[d])

[a] Ethyl ether solvent. [b] Respective RMgX. [c] Recovered, % starting material. [d] *o*-Methylbenzyl alcohol was identified as reduction product through gas chromatography studies and isolation of *o*-toluic acid after Jones oxidation.[6]

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(4) Waters Associates PrepLC/System 500 using a silica column and dichloromethane solvent.

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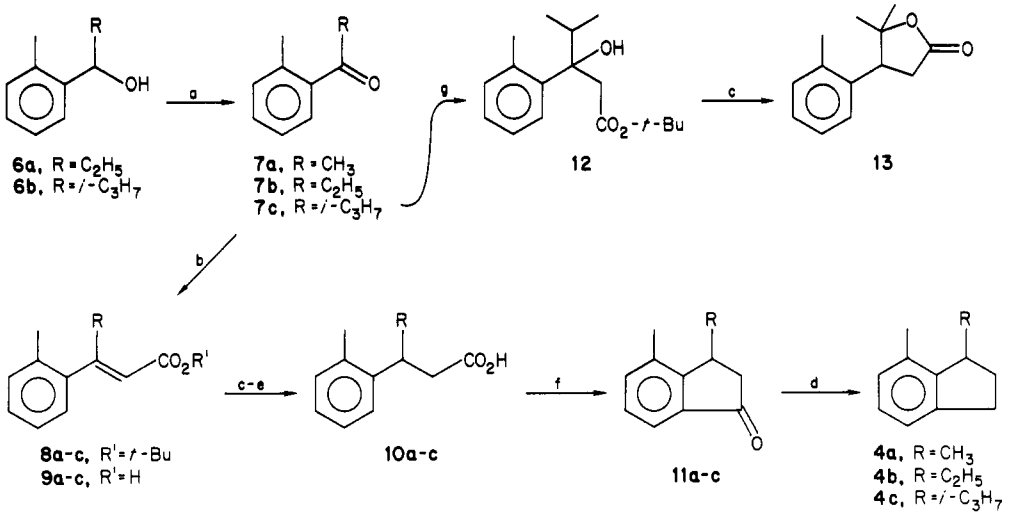
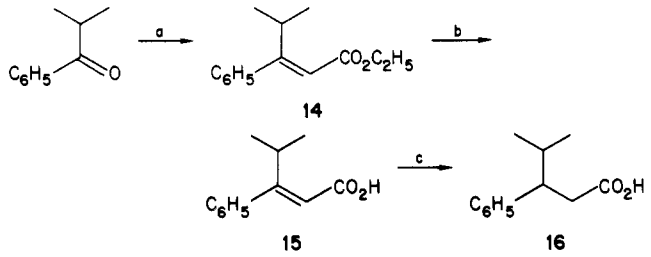
Scheme III[a]



[a] (a) CrO_3, H_2SO_4, H_2O, acetone; (b) $(CH_3)_3SiCH_2CO_2$-*t*-Bu, BuLi, diisopropylamine, THF, −78 °C; (c) CF_3CO_2H, 12 h; (d) H_2, Pd/C, acetic acid (**9a**, **11a–c**). (e) Li, NH_3, −78 °C (**9b** and **3c**). (f) PPA, 70–80 °C; (g) CH_3CO_2-*t*-Bu, LDA, THF, −78 °C.

Scheme IV[a]



[a] (a) $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, NaH, benzene; (b) 20% NaOH, reflux 12 h, H_3O^+; (c) H_2, Pd/C, acetic acid.

Table II. Comparison of Yields (%) in Two-Carbon Additions to Phenones Using the Wittig, Reformatsky, and Peterson Olefination Reactions

ketone	$(EtO)_2P(O)$-CH_2CO_2Et[a]	$BrCH_2$-CO_2Et[b]	Me_3SiC-H_2CO_2t-Bu[c]
isobutyrophenone	70[d]		
7a	71[d]	70[d]	60[d]
7b	63[e]	8–10[e]	58[e]
7c	13[e]	0	52[e]

[a] NaH, THF, reflux. [b] Zn/Cu couple, benzene, reflux. [c] BuLi, diisopropylamine, THF, −78 °C. [d] Single run. [e] Duplicate runs.

prepared as starting materials via Grignard (ethyl and isopropyl) addition to *o*-tolualdehyde and subsequent oxidation of the product with the Jones reagent[6] in 80% and 55% yields. However, before cyclization was carried out, steric interaction between aromatic methyl and side-chain alkyl groups was evident from the failure of the Reformatsky reaction[5a] applied to **7b** and the Wittig reaction[7a,b] applied to **7b** and **7c** to provide good yields, as shown in Table II. An ethyl or an isopropyl group in the side chain was not expected to present a serious steric problem particularly since isobutyrophenone (Scheme IV, Table II) reacted with triethyl phosphonoacetate,[7b] and NaH in benzene gave a 70% yield of the α,β-unsaturated ester **14**.

Our initial attempts at preparing **9a**, **9b**, and **9c** in Scheme III employed ethyl (trimethylsilyl)acetate.[8] This

Table III. Comparison of Yields (%) in the Hydrogenation of α,β-Unsaturated Acids

acid	H_2, Pd/C[a]	Li, NH_3
9a	84	*c*
9b	30–40[b]	94[b]
9c	0[b]	88[b]
15	90	*c*

[a] 55 psi at 50 °C in CH_3CO_2H. [b] Dublicate runs. [c] Not attempted since H_2, Pd/C was satisfactory.

satisfactorily gave ethyl esters. However, resistance of these esters to hydrolysis, particularly the one derived from **7c**, blocked this approach. To overcome this, we used *tert*-butyl (trimethylsilyl)acetate[9a,b] because of the anticipated ease of acid-catalyzed hydrolytic removal of the *tert*-butyl group[9c] and because this reaction produces an unsaturated ester rather than a β-hydroxy ester and thus avoiding the need for hydration. An additional advantage in working with the *tert*-butyl ester is the reported inhibition of attack of base at the carbonyl group (Claisen condensation).[9a] We indeed observed this condensation as a side reaction during use of ethyl (trimethylsilyl)-acetate. Conversion of ketones **7a–c** to the acids **9a–c** via acid hydrolysis of *tert*-butyl esters **8a–c** proceeded in 58%, 60%, and 52% overall yields, respectively.[9] In contrast, the β-hydroxy *tert*-butyl ester **12**, readily prepared by addition of *tert*-butyl lithioacetate[9a] to **7c**, failed to provide a viable route to **10c**. Attempts to remove the *tert*-butyl group under acidic conditions resulted in formation of the γ-lactone **13** (Scheme III), which blocked this route. Lactone **13** is soluble in hot alkali and reforms on acidification. The yield data comparing the use of the Reformatsky,[5a] Wittig,[7a,b] and Peterson olefination[8] reactions as two carbon-extension processes are compiled in Table II.

After preparation of the unsaturated acids **9a**, **9b**, and **9c**, the final obstacle was hydrogenation of the side chains. Catalytic hydrogenation (Pd/C, acetic acid) showed a decrease in rate with increased bulk of the side-chain alkyl

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group. Whereas **9a** (R = CH_3) was hydrogenated to **10a** in 84% yield, **9b** (R = ethyl) was only partially hydrogenated to **10b** (30–40%), and no hydrogenation took place with **9c** (R = isopropyl). To overcome this problem and still avoid hydrogenation of the aromatic ring, we reduced acids **9b** and **9c** to acids **10b** and **10c** in 94% and 88% yield, respectively, with lithium in ammonia.[10] A comparison of the yields obtained by using these reduction methods is presented in Table III.

Cylcization of **10a**, **10b**, and **10c** with polyphosphoric acid (PPA) gave **11a**, **11b**, and **11c** in 88%,[5a] 93%, and 69% yields.[3c] Catalytic hydrogenolysis[11] of **11a**, **11b**, and **11c** to **4a**, **4b**, and **4c** gave satisfactory yields. However, impurities accompanied **4c**, which had to be fractionally distilled with a spinning-band column. To improve the purity of **11b**, the 2,4-dinitrophenylhydrazone was prepared, recrystallized, and hydrogenolyzed.[11] This gave a pure sample[12] of **4b** but the yield was low (41%).

Experimental Section[13]

5-Methyl-1-indanone (2a) and 7-Methyl-1-indanone (2c). Polyphosphoric acid (350 mL) at 80 °C was used to cyclize a 50 g (0.308 mol) sample of **1b**. The product was distilled (Kugelrohr) to give 38.5 g (86%) of a mixture of indanones **2a** and **2c** (1:1): bp 105 °C (3 mm).

Separation of the Indanones 2a and 2c. A Waters PrepLC/System 500 liquid chromatograph equipped with a silica column was used with CH_2Cl_2 solvent at a flow rate of 150 mL per min. In a typical run, 9.23 g of the indanone mixture in CH_2Cl_2 was injected. Fractions were collected and analyzed by analytical HPLC. The fractions, on evaporation, afforded (i) 4.5 g of pure indanone **2c** [mp 54–56 °C (lit.[14a] mp 54–56 °C); IR (KBr) 1708 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 7.46–6.98 (m, 3 H, Ar H), 3.03 (m, 2 H, $ArCH_2$), 2.6 (s, 3 H, Ar CH_3; m, 2 H, $ArCOCH_2$); ^{13}C NMR ($CDCl_3$) ppm 206.77 (CO), 155.42, 138.20, 134.08, 133.49, 128.72, 123.73, 36.51, 25.20, 18.04; mass spectrum, m/z (relative abundance) 147 (M + 1^+), 9.2, 146 (M^+, 100), 118 (46.8), 117 (69.5), 115 (30.1), 91 (28.2), 69 (40.4)], (ii) 0.8 g of a mixture of **2a** and **2c**, and (iii) 3.2 g of indanone **2a** [mp 71–73 °C (lit.[14] mp 70–71 °C); IR (KBr) 1708 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 7.54–7.1 (m, 3 H), 3.02 (m, 2 H, Ar CH_2), 2.61 (m, 2 H, $ArCOCH_2$), 2.40 (s, 3 H, Ar CH_3); ^{13}C NMR ($CDCl_3$) ppm 205.75 (CO), 155.28, 145.29, 134.52, 128.16, 126.80, 123.05, 36.18, 25.47, 21.91; mass spectrum, m/z (relative abundance) 147 (M + 1^+), 10.4), 146 (M^+ + 100), 118 (60.8), 117 (86.6), 115 (37.8), 91 (32.0), 69 (25.8)].

1,7-Dimethylindan (4a).[2a] To a dry 200-mL, three-necked flask equipped with a magnetic stirrer, condenser, and nitrogen inlet and outlet was added a solution of 3.2 M methylmagnesium bromide in ether (24 mL, 0.076 mol). This solution was cooled (ice water) and 10 g (0.068 mol) of indanone **2c** in 75 mL of anhydrous ether was added slowly with stirring. After addition was complete, the mixture was stirred at room temperature for 2 h and then under reflux for 45 min, cooled to room temperature, and poured into 200 mL of ice-cold, dilute HCl. Extraction with ether and concentration gave crude product which contained recovered **2c**. This mixture was treated with an excess of acidified 2,4-dinitrophenylhydrazine reagent. The mixture was kept at room temperature for 3 h, filtered, treated with 3 g of oxalic acid, and steam distilled. The steam distillate was extracted with ether and the ether solution was dried ($MgSO_4$) and concentrated. The solid product was crystallized from 75% aqueous ethanol to give 8.3 g (84%) of indene **3a**: mp 50–51 °C; ^1H NMR ($CDCl_3$) δ 7.26–6.90 (m, 3 H, Ar H), 6.08 (m, 1 H, ArC=CH), 3.16 (m, 2 H, $ArCH_2$), 2.56 (s, 3 H, $ArCH_3$), 2.30 (d, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) ppm 145.09, 143.04, 141.17, 130.56, 129.41, 128.51, 124.34, 121.42, 37.12, 19.75; 17.53; mass spectrum m/z, calcd for $C_{22}H_{12}$ 144.0939, found M^+ 144.0937].

Indene **3a** (0.8 g, 0.05 mol) was hydrogenated over 0.8 g of 5% Pd/C catalyst in glacial acetic acid at room temperature and 30–35 psi for 1 h.[11] The mixture was filtered through Dicalite and concentrated. Isolation gave 7.4 g (91%) of indan **4a** which was distilled (Kugelrohr) at 40–45 °C (2.6 mm) [lit.[5a] bp 88 °C (16 mm)]; ^1H NMR ($CDCl_3$) δ 7.08–6.84 (m, 3 H, Ar H), 3.30 (m, 1 H, ArCh), 2.88 (m, 2 H, $ArCH_2$), 2.27 (s, 3 H, $ArCH_3$), 1.7 (m, 2 H, $ArCH_2CH_2$); ^{13}C NMR ($CDCl_3$) ppm 147.1, 142.9, 133.2, 127.4, 126.3, 121.8, 38.3, 33.5, 30.8, 19.3, 18.6; mass spectrum, m/z (relative abundance) 146 (M^+, 32.4), 121 (100), 115 (18.2), 91 (18.8), 65 (15.3).

1-Ethyl-7-methylindan (4b).[2a] **Procedure A.** Indanone **2c** (10 g, 0.068 mol), in 75 mL of anhydrous ether was reacted with a solution of 3 M ethylmagnesium bromide (24 mL, 0.072 mol). Unreacted **2c** (8–10% as shown by GC studies) was removed from the crude product by treatment with 2,4-dinitrophenylhydrazine and steam distillation as described for **3a**. The resulting indene **3b** was hydrogenated over 5% Pd/C catalyst in glacial acetic acid at room temperature and 35–40 psi.[11] The product was isolated by ether extraction and distilled (Kugelrohr), 85–90 °C (0.1 mm), to give 7.7 g (71% overall yield) of **4b**: IR (neat) 2960 and 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08–6.90 (m, 3 H, ArH), 3.10 (m, 1 H, ArCH), 2.80 (m, 2 H, $ArCH_2$), 2.29 (s, 3 H, $ArCH_3$), 2.02 (m, 2 H), 1.64–1.2 (m, 2 H), 0.96 (t, 3 H); ^{13}C NMR ($CDCl_3$) ppm 146.1, 143.2, 133.3, 127.4, 126.2, 121.7, 45.5, 31.2, 29.6, 26.2, 18.8, 12.5; mass spectrum, m/z, calcd for $C_{12}H_{16}$; 160.1252. Found: M^+ 160.1250.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 90.13; H, 9.87.

Procedure B. The semicarbazone derivative prepared from 10 g of ketone **11b** was hydrogenated at 40–45 psi for 8 h.[11] Workup as described for **4c** gave 7.8 g (84%) of hydrocarbon **4b**: bp 90–92 °C (0.1 mm). IR, ^1H and ^{13}C NMR, and mass spectrum were as previously described.

1-Isopropyl-7-methylindan (4c).[2a] **Procedure A.** Indanone **2c** (10 g, 0.068 mol) in 74 mL of anhydrous ether was reacted with 25 mL of 2.9 M (0.072 mol) isopropylmagnesium chloride. Unreacted indanone (70% by GC studies) was removed from the crude product with 2,4-dinitrophenylhydrazine and steam distillation as described for **3a**. The indene **3c** was hydrogenated over 5% Pd/C catalyst in acetic acid at room temperature (35–40 psi)[11] and isolated by ether extraction and distillation (Kugelrohr, air temperature, 110 °C (0.8 mm); [lit.[5b] bp 80–82 °C (2.5 mm)] to give 1.6 g (13% overall yield) of **4c**:[5b] IR (neat) 2800 and 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04–6.84 (m, 3 H, Ar H), 3.16 (m, 1 H, ArCH), 2.80 (m, 2 H, $ArCH_2$), 2.30 (s, 3 H, $ArCH_3$), 2.18–1.86 (m, 3 H), 1.05 (m, 6 H); ^{13}C NMR ($CDCl_3$) ppm 144.9, 143.8, 133.4, 127.4, 126.2, 121.5, 50.0, 31.2, 30.8, 25.1, 21.1, 19.1, 16.6; mass spectrum, m/z (relative abundance) calcd for $C_{13}H_{18}$ 174.1408, found M^+ 174.1405 (63), 116 (57), 115 (100), 91 (48).

Procedure B. Ketone **11c** (60 g), dissolved in 150 mL of glacial acetic acid, was hydrogenated in the presence of Pd/C catalyst at 50 psi for 5 h at room temperature.[1] The mixture was filtered through Dicalite and concentrated. Isolation gave 53 g (97%) of **4c** purified by fractional distillation. IR, ^1H and ^{13}C NMR, and mass spectrum were as previously described.

1,6-Dimethylindan (5a).[2a] Reaction of indanone **2b** (6 g, 0.04 mol) with 13 mL (0.042 mol) of a 3.2 M solution of methylmagnesium bromide in ether, followed by catalytic hydrogenation as described for the synthesis of **4a**, gave 5 g (83%) of 1,6-dimethylindan (**5a**):[3a,c] bp 60–62 °C (1.0 mm) [lit.[14b] bp 210 °C (740 mm)]; ^1H NMR ($CDCl_3$) δ 7.08–6.88 (m, 3 H, Ar H), 3.10 (m, 1 H, ArCH), 2.78 (m, 2 H, $ArCH_2$), 2.30 (s, 3 H, $ArCH_3$), 1.60 (m,

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(12) Combustion analysis by National Institute for Petroleum and Energy Research, Bartlesville, Oklahoma 74005, showed 99.9% + theoretical CO_2 for $C_{12}H_{16}$.

(13) All melting and boiling points are uncorrected. Vacuum distillations were carried out on a Kugelrohr apparatus. IR spectra were obtained with a Perkin-Elmer 681 instrument and ^1H and ^{13}C NMR spectra were obtained with a Varian XL-100A and/or a Varian XL-300 superconducting FT NMR spectrometer using $CDCl_3$ and internal Me_4Si standard. Mass spectra were recorded with a CEC 21-110B high resolution mass spectrometer and Data General DS-505 data system. Gas chromatographic analyses were obtained with a Varian 3700 capillary gas chromatograph and a Varian Aerograph, Model 500. Analytical and preparative high pressure LC separations were performed on a Waters Associates analytical system and PrepLC/System 500. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN.

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2 H), 1.24 (d, 3 H); ^{13}C NMR ($CDCl_3$) ppm 148.6, 140.5, 135.3, 126.7, 123.8, 123.7, 39.3, 34.9, 31.0, 21.2, 19.8.

1-Ethyl-6-methylindan (5b).[2a] Reaction of indanone **2b** (5 g, 0.32 mol) with 3 M ethylmagnesium bromide (12 mL, 0.36 mol) in anhydrous ether, followed by catalytic hydrogenation as described for **4a**, gave 3.7 g (69%) of **5b**: bp 70–79 °C (1.6 mm); ^{1}H NMR ($CDCl_3$) δ 7.10–6.88 (m, 3 H, Ar H), 3.00 (m, 1 H, ArCH), 2.80 (m, 2 H, $ArCH_2$), 2.30 (s, 3 H, $ArCH_3$), 2.14–1.20 (m, 4 H), 0.97 (t, 3 H); ^{13}C NMR ($CDCl_3$) ppm 147.3, 140.7, 135.0, 126.8, 124.1, 123.8, 46.4, 31.8, 30.9, 27.7, 21.2, 11.9.

1-Isopropyl-6-methylindan (5c).[2a] Reaction of 6-methyl-1-indanone (**2b**) (9 g, 0.06 mol) with 2.9 M isopropylmagnesium chloride (22 mL, 0.063 mol) in anhydrous ether, followed by catalytic hydrogenation as described for **4a**, gave 2.8 g (26%) of **5c**: bp 55–58 ° C (0.05 mm) [lit.[15] bp 60–65 °C (0.4 mm)]; ^{1}H NMR ($CDCl_3$) δ 7.70–6.88 (m, 3 H, Ar H), 3.02 (m, 1 H, ArCH), 2.88 (m, 2 H, $ArCH_2$), 2.32 (s, 3 H, $ArCH_3$), 2.28–1.10 (m, 3 H), 0.98 (d, 3 H), 0.76 (d, 3 H); ^{13}C NMR ($CDCl_3$) ppm 146.0, 141.1, 134.8, 126.8, 124.7, 123.8, 51.0, 31.3, 30.8, 26.8, 21.2, 21.2, 17.7.

1-(2-Methylphenyl)-1-propanol (6a). Reaction of 150 g (0.83 mol) of *o*-tolualdehyde with 333 mL (1.0 mol) of a 3 M solution of ethylmagnesium bromide in ether, as described below under **7c**, gave 108.7 g (87%) of **6a**: IR (neat) 3600 and 3010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.5–6.9 (m, 4 H), 4.8–4.5 (t, 1 H), 2.12 (s, 3 H), 1.8–1.4 (m, 2 H), 1.0–0.7 (t, 3 H); ^{13}C NMR ($CDCl_3$) ppm 142.7, 134.1, 129.9, 126.6, 125.8, 125.3, 71.5, 30.8, 18.9, 10.2. Anal. Calcd for $C_{10}H_{14}O$; C, 79.95; H, 9.39. Found: C, 79.64; H, 9.44.

***o*-Methylpropiophenone (7b).** Jones oxidation of 105 g of the alcohol **6a** in acetone at 20–30 °C gave 98.4 g (95%) of ketone **7b**.[5] This was purified by distillation: bp 75 °C (0.3 mm) (lit.[16] bp 219–220 °C); IR (neat) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.7–7.0 (m, 4 H), 3.0–2.7 (q, 2 H), 2.5 (s, 3 H), 1.3–1.0 (t, 3 H); ^{13}C NMR ($CDCl_3$) ppm 202.9, 136.6, 136.8, 130.8, 130.4, 130.0, 124.7, 33.6, 20.4, 7.5.

***o*-Methylisobutyrophenone (7c).** Isopropylmagnesium bromide was prepared by addition of 86.1 g (1 mol) of isopropyl bromide to 24.32 g (1 mol) of magnesium turnings in 200 mL of anhydrous ether in a 2-L, three-necked flask equipped with overhead mechanical stirrer, nitrogen inlet, and pressure relief. To the cooled (ice water) flask was added 300 mL of anhydrous ether and then 100 g (0.83 mol) of *o*-tolualdehyde in 100 mL of anhydrous ether was added dropwise with vigorous stirring for 30 min. The reaction mixture was stirred for 1 h at room temperature and then heated at reflux for 2 h. After cooling, the product was poured into a mixture of 5% HCl and crushed ice. After separation of layers, the aqueous layer was extracted with ether and the combined ether extracts were washed twice with water, dried ($MgSO_4$), and concentrated to give a mixture of product **6b** and starting material.

The crude mixture (115 g) was oxidized with Jones reagent[6] to give the crude ketone **7c** (75 g; 55%): bp 78 °C (0.4 mm); IR (neat) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.6–7.0 (m, 4 H, Ar H), 3.6–3.1 (m, 1 H), 2.4 (s, 3 H), 1.3–1.0 (d, 6 H); ^{13}C NMR ($CDCl_3$) ppm 207.3, 137.7, 136.5, 130.7, 129.6, 126.6, 124.7, 37.9, 19.9, 17.8 (2C). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.10; H, 8.49.

Synthesis of Acids 9a, 9b, 9c from 8a, 8b, 8c and 7a, 7b, 7c Using *tert*-Butyl (Trimethylsilyl)acetate and Trifluoroacetic Acid Solvolysis. A. 3-(2-Methylphenyl)-2-butenoic Acid (9a). Acid **9a** was prepared as described below for **9c** to give 15.3 g (58%) of a mixture of the cis and trans isomers of **9a**: identified through IR (Nujol) 1690, 1640, and 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.2–6.8 (aromatic protons), 5.95 (vinyl proton of major isomer), 5.75 (vinyl proton of minor isomer), 2.5–2.2 (methyl groups); ^{13}C NMR ($CDCl_3$) ppm 172 (C=O, minor isomer), 170.7 (C=O, major isomer); and mass spectrum, *m/z* (relative abundance) calcd for $C_{11}H_{12}O_2$ M^+ 176.0837, found M^+ 176.0811 (34), 161 (80), 130 (64), 129 (43), 115 (100), 91 (58). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 75.00; H, 6.96.

B. 3-(2-Methylphenyl)-2-pentenoic Acid (9b). Acid **9b** also was prepared as described below for **9c** to give crude acid in 60% yield. This acid was used as such in the Birch reduction described below.

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C. *tert*-Butyl 3-(2-Methylphenyl)-4-methyl-2-pentenoate (8c) and 3-(2-Methylphenyl)-4-methyl-2-pentenoic Acid (9c). A 2-L, three-necked flask equipped with magnetic stirrer, nitrogen inlet, and pressure relief was flushed with nitrogen and immersed in an ice-water bath. The flask was charged with 447 mL of 1.7 M solution of butyllithium in hexane (0.76 mol) and 77 g (0.76 mol) of diisopropylamine was added over 10 min. The lithium diisopropylamide thus formed was diluted with dry THF and the flask immersed in a dry ice–acetone bath. *tert*-Butyl (trimethylsilyl)acetate (0.76 mol) was added dropwise over 15 min at −78 °C and the mixture was stirred for a further 15 min. *o*-Methylisobutyrophenone (**7c**) (120 g, 0.74 mol) in 100 mL of dry THF was then added dropwise over 30 min. The reaction mixture was stirred for 30 min more at −78 °C and then allowed to warm slowly to room temperature and quenched with 5% HCl. Extraction with ether gave 115 g (60%) of crude ester **8c**.[8d]

The crude ester was treated dropwise with 50 mL of trifluoroacetic acid in an ice water bath and the mixture was stirred at room temperature for 12 h.[9c] The mixture was then diluted with water and extracted with ether, and the ether extract was washed several times with water to remove trifluoroacetic acid. The organic solution was then extracted with 10% NaOH and the alkaline extract was acidified with dilute HCl. Extraction with ether gave 78.5 g (52%) of **9c**: mp 105–106 °C; IR (Nujol) 1700, 1690, and 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.2–6.7 (m, 4 H), 5.88 (s, 1 H), 2.7–2.3 (m, 1 H), 2.15 (s, 3 H), 1.2–1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) ppm 171.0, 167.4, 139.4, 134.0, 129.4, 126.8, 126.4, 124.7, 115.4, 37.5, 20.9, 20.7, 19.4; mass spectrum, *m/z* (relative abundance) calcd for $C_{13}H_{16}O_2$ M^+ 204.1150, found M^+ 204.2233 (80), 180 (41), 129 (40), 128 (36), 117 (40), 115 (100), 91 (37).

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.31; H, 7.96.

Reduction of Acids 9a, 9b, and 9c. A. Hydrogenation of 9a to 3-(2-Methylphenyl)butanoic Acid (10a). Acid **9a** (5 g, 0.028 mol), as a mixture of the cis and trans isomers, was hydrogenated at 45 psi in acetic acid with 0.5 g Pd/C catalyst.[11] After 1.5 h, hydrogen uptake ceased. The mixture was filtered through Dicalite and most of the acetic acid was evaporated under reduced pressure. The concentrated solution was then poured onto crushed ice and the resulting white solid was filtered out, washed with water, dried, and recrystallized from hexane to give 4.2 g (84%) of the butanoic acid (**10a**): mp 46–47 °C; IR (Nujol) 1718 and 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.9 (br s, 1 H), 7.15 (m, 4 H), 2.5 (m, 1 H), 2.7–2.5 (m, 2 H), 2.35 (s, 3 H), 1.27 (d, 3 H); ^{13}C NMR ($CDCl_3$) ppm 178.8, 143.3, 134.9, 130.2, 126.1, 125.9, 124.7, 41.7, 31.1, 21.1, 19.29; mass spectrum, *m/z* (relative abundance) calcd for $C_{11}H_{14}O_2$ M^+ 178.0993, found M^+ 178.0957 (12), 119 (100), 117 (13), 115 (15), 91 (24), 85 (15). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.15; H, 7.75.

B. Li/NH_3 Reduction of 9b to 3-(2-Methylphenyl)pentanoic Acid (10b) and of 9c to 3-(2-Methylphenyl)-4-methylpentanoic Acid (10c). The crude unsaturated acid **9b** (40 g, 0.2 mol), in anhydrous ether, was added dropwise with stirring to a solution of lithium (0.6 mol) in 250 mL of liquid ammonia under nitrogen. The mixture was stirred for 45 min at −78 °C and then quenced with NH_4Cl. Ether was added and ammonia was allowed to evaporate. The residue was acidified with 10% HCl and extracted with ether, and the ether solution was extraced with 10% NaOH. Acidification and extraction gave 38 g (94%, overall from ketone **7b**; 58%) of the saturated acid **10b** as a white solid from isooctane; mp 62–64 °C; IR (Nujol) 1718 and 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.58 (s, 1 H), 7.2–7.0 (m, 4 H), 3.5–3.15 (m, 1 H), 2.7–2.5 (d, 2 H), 2.35 (s, 3 H), 1.85–1.4 (m, 2 H), 0.9–0.65 (t, 3 H); ^{13}C NMR ($CDCl_3$) ppm 179.0, 141.7, 136.0, 130.1, 126.0, 125.8, 125.1, 40.7, 37.7, 29.0, 19.7, 11.6; mass spectrum, *m/z* (relative abundance) calcd for $C_{12}H_{16}O_2$ M^+ 192.1150, found M^+ 192.1142 (37), 163 (25), 133 (41), 121 (100), 117 (39), 105 (75). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39 Found: C, 74.96; H, 8.20.

Acid **9c** (78.5 g, 0.384 mol) was reduced under similar Birch conditions to give 70 g (88%) of 3-(2-methylphenyl)-4-methylpentanoic acid (**10c**):[5b] mp 44–45 °C (from isooctane); [lit.[5b] (mp not given)]; IR (Nujol) 1718 and 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.3 (s, 1 H), 7.2–7.0 (m, 4 H), 3.4–4.0 (m, 1 H), 2.8–2.5 (m, 2 H), 2.35 (s, 3 H), 2.0–1.6 (m, 1 H), 0.95 (d, 3 H), 0.75 (d, 3 H); ^{13}C NMR ($CDCl_3$) ppm 179.2, 141.6, 136.3, 130.0 (2C), 125.7 (2C), 42.7, 28.1, 22.6, 20.7, 20.0, 19.9; mass spectrum, *m/z* (relative abun-

dance) calcd for $C_{13}H_{18}O_2$ M^+ 206.1306, found M^+ 206.1300 (15), 163 (28), 121 (100), 105 (22), 91 (22). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.52; H, 9.01 (lit.[5b] C, 75.62; H, 8.64).

Cyclization of Acids 10a, 10b, and 10c to 3,4-Dialkyl-1-indanones 11a, 11b, and 11c. A. 3,4-Dimethyl-1-indanone (11a). Indanone **11a** was previously prepared by PPA cyclization.[5a]

B. 3-Ethyl-4-methyl-1-indanone (11b). Acid **10b** (85 g) was cyclized in 1 L of PPA at 75–80 °C for 1 h. The reaction was worked up as described for **11c** to give 71 g (93%) of ketone **11b**: bp 90–95 °C (0.1 mm); IR (Nujol) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5–7.0 (m, 3 H), 3.4–3.1 (m, 1 H), 3.0–2.5 (m, 2 H), 2.35 (s, 3 H), 1.5–1.1 (m, 2 H), 0.9–0.7 (t, 3 H); ^{13}C NMR ($CDCl_3$) ppm 204.2, 155.1, 135.8, 134.5, 134.4, 126.3, 119.5, 41.6, 37.7, 26.4, 16.9, 10.0; mass spectrum, m/z (relative abundance) calcd for $C_{12}H_{14}O$ M^+ 173.0966, found M^+ 173.0954 (13), 172 (100), 157 (28), 128 (56), 115 (52).

C. 3-Isopropyl-4-methyl-1-indanone (11c). PPA (1 L) was stirred at 60 °C and 103 g of acid **10c** was added in portions over 20 min. After addition, the mixture was stirred for 1 h at 80 °C, cooled, and poured onto crushed ice, and the product was isolated by filtration. This procedure gave 70 g (69%) of indanone **11c**.[5b] Purification by distillation (Kugelrohr) 105 °C (0.1 mm) [lit.[5b] bp 108–110 °C (1.3 mm)] and recrystallization from isooctane gave colorless **11c**: mp 55–56 °C; IR (Nujol) 1720 cm–1; ^1H NMR ($CDCl_3$) δ 7.65–7.1 (m, 3 H), 3.5 (m, 1 H), 2.44 (d, 2 H), 2.45 (s, 3 H), 2.3 (m, 1 H), 1.1 (d, 3 H), 0.42 (d, 3 H); ^{13}C NMR ($CDCl_3$) ppm 206.3, 145.7, 142.9, 133.0, 127.1, 126.0, 121.4, 45.2, 30.9, 29.4, 26.0, 18.5, 12.2; mass spectrum, m/z (relative abundance) calcd for $C_{13}H_{16}O$ M^+ 188.1201, found M^+ 188.1183 (32), 146 (83), 145 (100), 115 (48), 91 (22).

Preparation of *tert*-Butyl 3-Hydroxy-4-methyl-3-(2-methylphenyl)pentanoate (12). A three-necked, 500-mL flask fitted with nitrogen inlet, thermometer, and dropping funnel was charged with 15.4 g (0.085 mol) of dicyclohexylamine in 200 mL of dry THF. The stirred solution was cooled to –78 °C and treated with 50 mL of a 1.7 M solution of butyllithium in hexane. After 15 min, *tert*-butyl acetate (9.86 g, 0.085 mol) was added dropwise at –78 °C and the solution was stirred for 30 min. *o*-Methylisobutyrophenone (**7c**) (11 g, 0.07 mol), dissolved in dry THF, was then added dropwise, and a mixture was stirred at –78 °C for 1 h, at –25 °C to 0 °C for 1 h, and finally at room temperature for 1 h. It was then poured into 5% HCl and crushed ice and extracted with ether. Isolation gave 17 g (90%) of the β-hydroxy ester **12**: IR (neat) 3500 and 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5–7.0 (m, 4 H), 4.3 (s, 1 H, OH), 3.05 (d, 1 H, J = 14 Hz), 2.7 (d, 1 H, J = 14 Hz), 2.5 (s, 3 H), 1.45 (m, 1 H), 1.13 (s, 9 H), 0.95 (d, 3 H), 0.81 (d, 3 H); ^{13}C NMR ($CDCl_3$) ppm 171.2, 141.7, 133.9, 131.2, 126.3, 125.5, 123.9, 80.5, 78.3, 42.9, 35.5, 27.3 (3C), 22.4, 16.9 (2C).

5,5-Dimethyldihydro-4-(2-methylphenyl)-2(3*H*)-furanone (13). The hydroxy ester **12** (17.3 g, 0.08 mol) was added to trifluoroacetic acid coooled in an ice bath. The mixture was stirred at room temperature for 24 h and then poured into ice-cold 10% NaOH. The alkaline mixture was washed with ether and acidified with dilute HCl (no precipitate obtained). The ether layer was washed with water, dried ($MgSO_4$), and concentrated to give 15 g (94%) of lactone **13**: mp 85–86 °C (from hexane); IR (KBr) 1770 and 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3–7.1 (m, 4 H), 3.8 (t, 1 H), 2.95 (m, 2 H), 2.35 (s, 3 H), 1.55 (s, 3 H), 1.1 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 175.7, 136.5, 135.9, 130.6, 127.0, 126.29, 126.24, 87.4, 45.1, 36.4, 28.8, 23.8, 20.2; mass spectrum, m/z (relative abundance) calcd for $C_{13}H_{16}O_2$ M^+ 204.1170, found M^+ 204.1168 (5), 116 (44), 91 (100), 77 (33), 65 (35), 63 (23). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.72; H, 7.64.

4-Methyl-3-phenylpentanoic Acid (16). Triethyl phosphonoacetate (44.9 g, 0.2 mol) was added dropwise at 30–35 °C to a stirred suspension of sodium hydride (0.2 mol) in dry benzene under nitrogen. After stirring for 1.5 h, 20 g (0.135 mol) of isobutyrophenone was added dropwise during 30 min. The mixture was then heated at 60–65 °C for 15 min and stirred overnight at room temperature. Water and ether were added and the layers were separated. the organic layer was washed with water, dried ($MgSO_4$), and concentrated to give 47 g (70%) of a cis and trans mixture of ester **14**. The crude ester was hydrolyzed by refluxing with 20% NaOH for 12 h converted to the unsaturated acid **15** which was hydrogenated with Pd/C catalyst at 50 psi in glacial acetic acid[11] as described for **10a**. Concentration of the dried ($MgSO_4$) ether extract gave 38 g (65% overall yield) of acid **16**: mp 50–51 °C (from hexane); IR (Nujol) 1718 and 1465 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.0 (m, 5 H), 3.0–2.4 (m, 3 H), 2.0–1.6 (m, 1 H), 0.95 (d, 3 H), 0.75 (d, 3 H); ^{13}C NMR ($CDCl_3$) ppm 179.0, 142.2, 128.1, 128.0, 127.9, 127.8, 126.1, 48.2, 38.1, 32.9, 20.5, 20.7; mass spectrum, m/z (relative abundance) calcd for $C_{12}H_{16}O_2$ M^+ 192.1150, found M^+ 192.1137 (12), 150 (21), 132 (30), 130 (23), 107 (100), 91 (49), 79 (23), 77 (24). Anal. Calcd for $C_{12}H_{16}O$: C, 74.96; H, 8.39. Found: C, 75.01; H, 8.42.

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