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Synthesis and Antiinflammatory Activity of Alkenylphenylpropionic Acids[1)]

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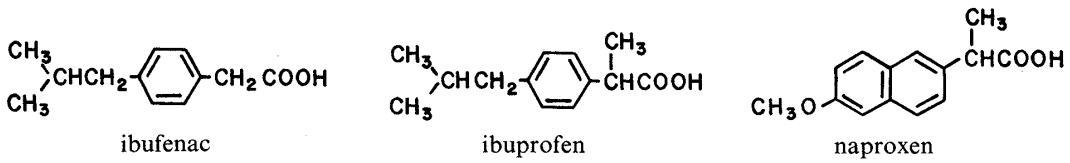
A series of 2-phenylpropionic acids substituted with a C_2—C_6 alkenyl group at the *para* position was synthesized by hydrolysis of the corresponding esters prepared by a new nickel-catalyzed coupling reaction of aryl Grignard reagents and 2-bromopropionic acid ester. Among the 2-(4-alkenylphenyl)propionic acids thus obtained, 2-[4-(2-methyl-1-propenyl)phenyl]propionic acid showed the most potent antiinflammatory activity in the carrageenin edema test, while 2-[4-(3-methyl-2-butenyl)phenyl]propionic acid showed almost the same activity and significantly lower toxicity in comparison with those of ibuprofen.

Keywords——phenylpropionic acid; 2-(4-alkenylphenyl)propionic acid; 2-[4-(3-methyl-2-butenyl)phenyl]propionic acid; Grignard reagent; nickel catalyst; antiinflammatory activity; analgesic activity; structure–activity relationship; toxicity; ibuprofen

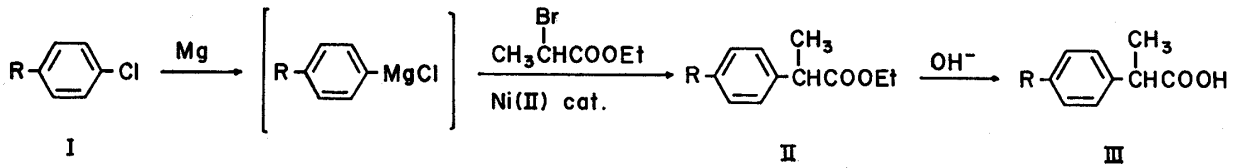
Since the discovery of 4-(2-methylpropyl)phenylacetic acid (ibufenac),[2)] many arylalkanoic acids have been synthesized for investigation of their antiinflammatory and analgesic activities. Among them, 2-[4-(2-methylpropyl)phenyl]propionic acid (ibuprofen)[3)] and 2-(6-methoxy-2-naphthyl)propionic acid (naproxen)[4)] are now widely used in the treatment of arthritis. However, very few arylalkanoic acids with alkenyl substituents have been reported.[5)]

This paper describes the synthesis of 2-(4-alkenylphenyl)propionic acids by a new Grignard coupling method, and the evaluation of their antiinflammatory and analgesic activities, together with the activities of some 2-(4-alkylphenyl)propionic acids, and some noteworthy hematological findings in a subacute toxicity study.



ibufenac ibuprofen naproxen

Fig. 1



I II III

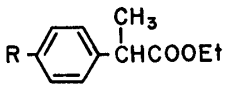
Chart 1

Synthesis

The 2-(4-alkenylphenyl)propionic acids (III) listed in Table II were synthesized by the method shown in Chart 1.

The arylation of 2-bromoalkanoic acid esters has been carried out by using arylzinc, arylcopper or arylcadmium prepared from the corresponding aryllithium or aryl Grignard reagent and an equivalent amount of transition metal halide.[6-8] In this study, we prepared the 2-(4-alkenylphenyl)propionic acid esters (II) listed in Table I by an alternative nickel-

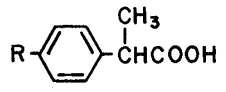
TABLE I. Physical Properties of Ethyl 2-(4-Alkenylphenyl)propionates (II)



No.	R	Yield (%)[a]	Purification[d]	Formula[e]	MS *m/e*
IIa	Ra: $-CH=CH_2$	21	H:E=50:1	$C_{13}H_{16}O_2$	204 (M^+), 131 (base), 116, 103, 91
IIb	Rb: $-CH_2CH=CH_2$	26	H:E=50:1	$C_{14}H_{18}O_2$	218 (M^+), 145 (base), 129, 117, 115, 105
IIc	Rc: $-CH=C(CH_3)_2$	37	H:E=30:1	$C_{15}H_{20}O_2$	232 (M^+), 159 (base), 143, 129, 117
IId	Rd: $-CH=CHCH(CH_3)_2$	62	H:B=1:1	$C_{16}H_{22}O_2$	246 (M^+), 173 (base), 157, 145, 129, 128, 117
IIe	Re: $-CH_2CH=C(CH_3)_2$	51, 38,[b] 43[c]	bp 128—132 °C/ 1.5 Torr	$C_{16}H_{22}O_2$	246 (M^+), 173 (base), 157, 145
IIf	Rf: $-CH_2CH_2C(CH_3)=CH_2$	68	H:B=1:1	$C_{16}H_{22}O_2$	246 (M^+), 217, 181 (base), 173, 172, 118, 117
IIg	Rg: $-C(CH_3)_2CH=CH_2$	34	H:B=1:1	$C_{16}H_{22}O_2$	246 (M^+), 173 (base), 157, 145, 143, 129
IIh	Rh: $-CH_2CH_2CH=C(CH_3)_2$	32	H:E=50:1 bp 108 °C/0.1 Torr	$C_{17}H_{24}O_2$	260 (M^+), 192, 191 (base), 119, 118

a) Nickel(II) chloride was used as a catalyst unless otherwise noted. *b*) [1,3-Bis(diphenylphosphino)propane]dichloronickel(II). *c*) Bis(acetylacetonate)nickel(II). *d*) Solvent in silica gel column chromatography: B=benzene, E=ethyl acetate, H=hexane; and boiling point in distillation. *e*) All compounds were analyzed for C and H; the analytical results were within ±0.3% of the calculated values.

TABLE II. Physical Properties of 2-(4-Alkenylphenyl)propionic acids (III)



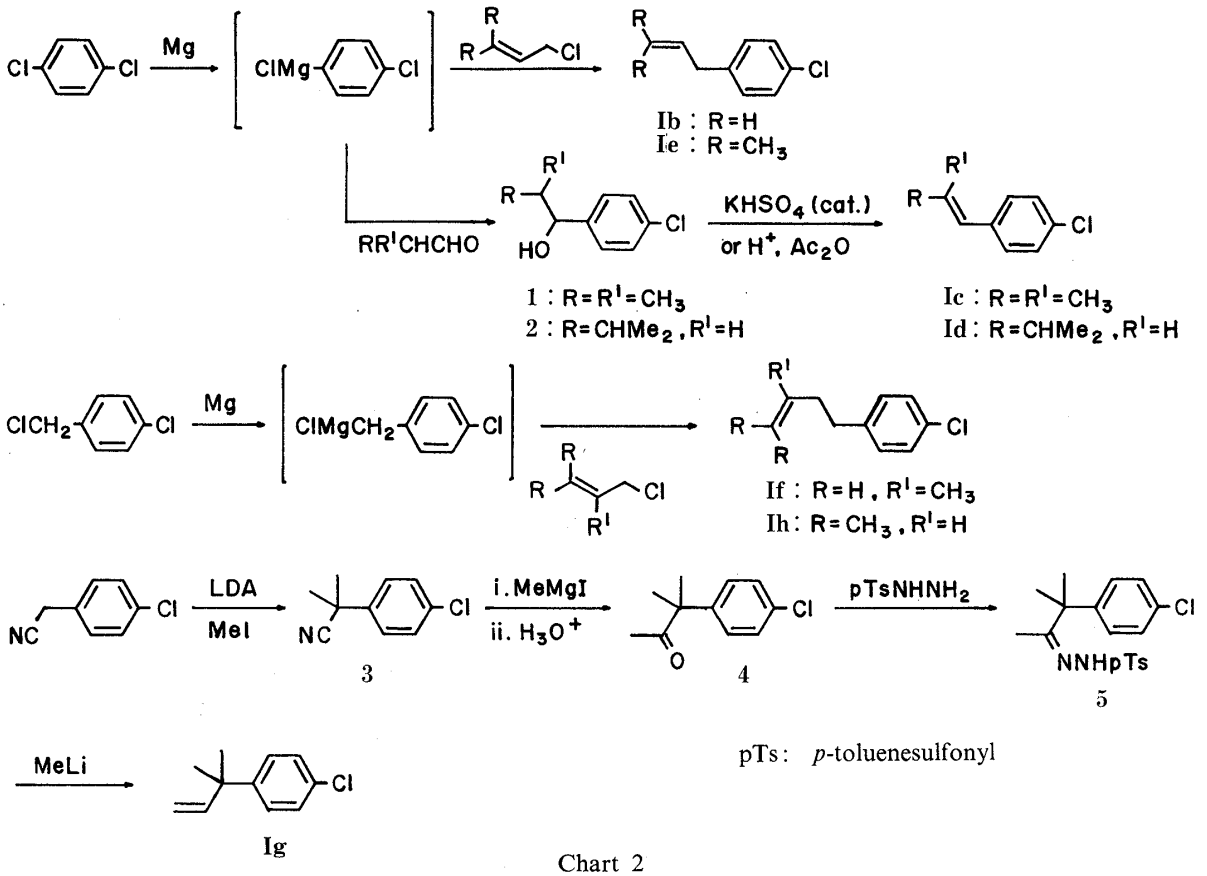
No.	R[a]	Yield (%)	mp or bp (°C)	Recrystn. solvent or pressure	Formula[b]	MS *m/e*
IIIa	Ra	89	70—71	Hexane	$C_{11}H_{12}O_2$	176 (M^+), 149, 131 (base), 116, 103, 91
IIIb	Rb	86	53—55	Hexane	$C_{12}H_{14}O_2$	190 (M^+), 173, 145 (base), 128, 117, 115, 105
IIIc	Rc	90	50—52[c]	Hexane	$C_{13}H_{16}O_2$	204 (M^+), 159 (base), 149, 128, 117, 114, 105
IIId	Rd	99	62—63	Petro. ether	$C_{14}H_{18}O_2$	218 (M^+), 173, 172, 163 (base), 149, 145, 117, 107
IIIe	Re	93	130—135	0.1 Torr	$C_{14}H_{18}O_2$	218 (M^+), 203, 173, 157, 145 (base), 129, 117, 91
IIIf	Rf	96	48—50	Hexane	$C_{14}H_{18}O_2$	218 (M^+), 173, 172, 163 (base), 149, 145, 117, 107
IIIg	Rg	86	80—82	Hexane	$C_{14}H_{18}O_2$	218 (M^+), 173, 157 (base), 145, 142, 129, 115
IIIh	Rh	87	Oil		$C_{15}H_{20}O_2$	232 (M^+), 176, 164, 163 (base), 149, 119

a) Ra—h represent the R (Ra—h) in Table I. *b*) All compounds were analyzed for C and H; the analytical results were within ±0.3% of the calculated values. *c*) Lit.[5b] mp 53—54 °C.

catalyzed coupling reaction of 2-bromopropionic acid ester and the Grignard reagents prepared from 1-alkenyl-4-chlorobenzenes (I). Nickel(II) chloride, [1,3-bis(diphenylphosphino)propane]dichloronickel (II) and bis(acetylacetonate)nickel (II) (each 1 mol% *vs.* I) effectively catalyzed the coupling reaction to afford II in moderate yields, except for IIa and IIb in which the alkenyl moieties were relatively unstable in comparison with those of the other II.

The esters II thus obtained were easily hydrolyzed to the corresponding acids III in good yields.

Syntheses of the intermediary 1-alkenyl-4-chlorobenzenes are illustrated in Chart 2.



pTs: *p*-toluenesulfonyl

Chart 2

Biological Methods

Antiinflammatory activity and analgesic activity were evaluated by using the carrageenin edema test in rats[9] and the acetic acid writhing test in mice,[10] respectively.

Carrageenin Edema——Groups of 6 male Wistar rats weighing 140—170 g were used. The test compounds were administered orally (100 mg/kg, unless otherwise noted), 1 h before the subplantar injection (0.1 ml/rat) of 1% carrageenin suspension into the left hind paw. The paw volume was measured 3 h after the carrageenin injection. The swelling was calculated from the observed volume as compared with the pre-treatment paw volume, and the inhibitory percent was calculated by comparing the swelling with that in the control group.

Acetic Acid Writhing——Groups of 10 male ddY mice weighing 19—23 g were used. The test compounds were administered orally (100 mg/kg), 30 min before the intraperitoneal injection (10 ml/kg) of 0.7% acetic acid solution. The number of writhes by each mouse was counted during a period of 10 to 20 min after the acetic acid injection. The inhibitory percent was calculated by comparing the number of writhes with that in the untreated control group.

Acute Toxicity——Groups of 10 male Wistar rats weighing 130—160 g were used. The

test compounds were administered orally and LD_{50} values were calculated from the mortality on the eighth day by the method of Litchfield and Wilcoxon.[11]

Subacute Toxicity——Groups of 10 male Wistar rats weighing 200—220 g were used. The test compounds were administered orally once a day for 10 d. The body weight of each rat was recorded daily from day 1 to day 11. On day 10, blood samples were obtained from the orbital sinus of each rat under light ether anesthesia, and the blood cell counts and hemoglobin content were determined for each rat.

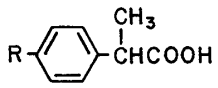
Results and Discussion

Table III shows the results of the carrageenin edema test and the acetic acid writhing test on the 2-(4-alkenylphenyl)propionic acids (IIIa—h) together with those for 2-phenylpropionic acid (IV) and some 2-(4-alkylphenyl)propionic acids (Va—c).

In the case of the antiinflammatory activity, introduction of a simple vinyl group into the parent compound IV increased the activity (entry IIIa). The most potent compound in this series was the isobutenyl compound (IIIc), 2-[4-(2-methyl-1-propenyl)phenyl]propionic acid,[5b] which showed 70.9% inhibition at a dose of 30 mg/kg. Among the compounds substituted with alkenyl groups of five carbon atoms, 2-[4-(3-methyl-2-butenyl)phenyl]-propionic acid (IIIe)[5a] showed the strongest activity (50.9% inhibition at 100 mg/kg), comparable to that of ibuprofen (Vb). When an ethylene group was inserted between the isobutenyl group and the benzene ring of IIIc, the activity was greatly decreased (entry IIIh). The alkenyl groups seemed to be equivalent (IIIa *vs.* Va and IIIe *vs.* Vc) or superior (IIIc *vs.* Vb) to the corresponding alkyl groups.

In the acetic acid writhing test, the parent compound IV showed little inhibitory activity, as was the case in the carrageenin edema test, but all the alkenyl and alkyl compounds showed significant activity. It was difficult to find any clear relationship between the structure of the substituent and the analgesic activity.

TABLE III. Antiinflammatory and Analgesic Activities of Phenylpropionic Acid Derivatives



No.	R	Inhibition % (100 mg/kg, *p.o.*)	
		Carrageenin edema	Acetic acid writhing
IIIa	$-CH=CH_2$	32.1[d]	36.7[d]
IIIb	$-CH_2CH=CH_2$	36.2[d]	66.2[e]
IIIc	$-CH=C(CH_3)_2$	70.9[b,d]	49.4[e]
IIId	$-CH=CHCH(CH_3)_2$	8.2	54.2[e]
IIIe	$-CH_2CH=C(CH_3)_2$	50.9[d]	60.0[e]
IIIf	$-CH_2CH_2C(CH_3)=CH_2$	14.5	75.5[e]
IIIg	$-C(CH_3)_2CH=CH_2$	24.1[c]	70.9[e]
IIIh	$-CH_2CH_2CH=C(CH_3)_2$	14.9	61.1[e]
IV	$-H$	8.9	13.8
Va	$-CH_2CH_3$	30.2[c]	59.5[e]
Vb[a]	$-CH_2CH(CH_3)_2$	54.8[d]	53.6[e]
Vc	$-CH_2CH_2CH(CH_3)_2$	50.6[d]	38.2[d]

a) Ibuprofen from Hokko Chemical Industry Co. *b*) 30 mg/kg, *p.o.* Statistically significant at: *c*) $p<0.05$, *d*) $p<0.01$, *e*) $p<0.001$.

TABLE IV. Body Weight Changes in Subacute Toxicity Test

Compound	Daily dose (mg/kg, *p.o.*)	Body weight (g) Mean±S.E.		
		Day 1	Day 6	Day 11
Control	—	207.4±2.8	220.3±2.8	233.3±2.7
IIIe	50	211.5±3.6	224.6±3.6	239.7±3.2
	100	210.0±2.5	226.4±2.8	238.5±2.3
	200	211.7±3.1	221.9±4.6	238.3±5.1
Ibuprofen	50	208.9±2.7	223.6±2.7	235.5±3.1
	100	209.7±2.1	222.0±2.2	231.9±2.6
	200	210.8±3.4	206.2±2.8[a)]	216.2±3.9[b)]

Statistically significant at: *a)* $p<0.01$, *b)* $p<0.001$.

TABLE V. Hematological Findings in Subacute Toxicity Test

Compound	Daily dose (mg/kg, *p.o.*)	Erythrocytes ($\times 10^4$/mm^3) Mean±S.E.	Hemoglobin (g/100 ml) Mean±S.E.
Control	—	859.9± 4.1	15.4±0.1
IIIe	50	864.2±20.2	15.2±0.1
	100	860.8± 9.5	15.1±0.2
	200	857.9±15.2	15.0±0.2
Ibuprofen	50	807.6±23.6[a)]	15.1±0.2
	100	718.2±36.3[b)]	13.9±0.2[c)]
	200	667.8±27.6[b)]	11.8±0.5[c)]

Statistically significant at: *a)* $p<0.05$, *b)* $p<0.01$, *c)* $p<0.001$.

Since IIIe and ibuprofen showed almost the same antiinflammatory and analgesic activities, we compared their acute and subacute toxicities in rats. The acute oral LD_{50} values in male Wistar rats for IIIe and ibuprofen were 1437 and 711 mg/kg, respectively. In the subacute toxicity test, the body weight gain of the rats receiving ibuprofen at a dose of 200 mg/kg/d were decreased significantly as compared with that of control rats, whereas IIIe did not affect the body weight gain at any dose used (Table IV). Ibuprofen significantly reduced erythrocyte counts at 50 mg/kg/d (similar anemic signs have been reported in animals treated with many other non-steroidal antiinflammatory drugs[12)]), whereas IIIe did not affect the hematological findings even at 200 mg/kg/d (Table V). Accordingly, IIIe was selected for further studies.[13)]

Experimental

All reactions were carried out under a nitrogen or argon atmosphere. The extracted organic solutions were dried over $MgSO_4$ and concentrated on a rotary evapolator under reduced pressure. All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Jasco DS-701G spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 or EM-390 spectrometer in $CDCl_3$ unless otherwise noted, and are reported in δ from tetramethylsilane (TMS) or hexamethyldisiloxane (HMS). Mass spectra (MS) were recorded on a Shimadzu LKB-9000 or JEOL-D300 mass spectrometer.

Preparation of 1-Alkenyl-4-chlorobenzenes (I)

1-Allyl-4-chlorobenzene (Ib)——Bromoethane (1 ml) was added to a stirred mixture of magnesium turnings (Mg; 8.0 g, 0.33 mol), a few pieces of iodine and 10 ml of tetrahydrofuran (THF) at room temperature. After the iodine coloration disappeared, a solution of 1,4-dichlorobenzene (44.1 g, 0.30 mol) in THF (40 ml) was added dropwise to

the stirred mixture at 80—90 °C over 1 h. The reaction mixture was stirred for an additional 4 h, then cooled to room temperature and diluted with THF (200 ml). A solution of allyl chloride (23.7 g, 0.31 mol) in THF (100 ml) was added dropwise to the stirred Grignard solution at 10—15 °C over 1 h. The reaction mixture was stirred for an additional 2 h at room temperature, then poured into 10% aq. NH_4Cl (200 ml). The organic layer was separated and the aqueous layer was extracted with hexane (100 ml × 3). The combined organic layer was washed with 10% aq. NaCl (200 ml × 3), dried and concentrated to leave an oil, which was distilled under reduced pressure to give Ib (14.2 g, 31%), bp 91—93 °C/21 Torr, [lit.[14] bp 52 °C/0.8 Torr].

1-(4-Chlorophenyl)-2-methylpropan-1-ol (1)——A solution of 2-methylpropanal (54 g, 0.75 mol) in THF (50 ml) was added dropwise to a stirred solution of 4-chlorophenylmagnesium chloride [prepared from 1,4-dichlorobenzene (110 g, 0.75 mol) and Mg (18 g, 0.74 mol)] in THF (600 ml) at 5—10 °C over 1 h. After being stirred for an additional 2.5 h at room temperature, the mixture was poured into 10% aq. NH_4Cl. The aqueous solution was extracted with Et_2O (500 ml × 3). The ethereal solution was washed, dried, and concentrated, and the residue was distilled to give **1** (81 g, 59%), bp 88—92 °C/0.3 Torr, [lit.[15] bp 147 °C/25 Torr].

1-Chloro-4-(2-methyl-1-propenyl)benzene (Ic)——A mixture of **1** (15.7 g, 85 mmol), acetic anhydride (11.1 g, 109 mmol) and conc. H_2SO_4 (0.5 ml) was refluxed for 4 h, then cooled to room temperature and poured into 10% aq. NaOH (100 ml). The aqueous solution was extracted with Et_2O (50 ml × 3). The ethereal solution was washed, dried, and concentrated, and the residue was distilled to give Ic (8.47 g, 60%), bp 122—125 °C/21 Torr, [lit.[16] bp 102 °C/11 Torr].

1-(4-Chlorophenyl)-3-methylbutan-1-ol (2)——A solution of 3-methylbutanal (10.3 g, 0.12 mol) in THF (10 ml) was added dropwise to a stirred solution of 4-chlorophenylmagnesium chloride [prepared from 1,4-dichlorobenzene (17.6 g, 0.12 mol) and Mg (3.4 g, 0.14 mol)] in THF (120 ml) at 5—10 °C over 30 min. After being stirred for an additional 2 h at room temperature, the mixture was poured into 10% aq. NH_4Cl. The aqueous solution was extracted with Et_2O (50 ml × 3). The ethereal solution was washed, dried, and concentrated, and the residue was distilled to give **2** (11.9 g, 50%), bp 90—95 °C/0.2 Torr. IR ν_{max}^{neat} cm^{-1}: 3330, 2945, 1594, 1488, 1090, 1012, 826. MS *m/e*: 200 ($M^+ + 2$), 198 (M^+), 180, 167, 165, 143, 141 (base), 113, 107. NMR δ TMS: 0.96 (6H, d, $J = 7$ Hz), 1.36—1.56 (1H, m), 1.62—1.84 (2H, m), 1.89 (1H, d, $J = 4$ Hz, OH), 4.67—4.81 (1H, m), 7.26—7.45 (4H, m). *Anal.* Calcd for $C_{11}H_{15}ClO$: C, 66.50; H, 7.61. Found: C, 66.27; H, 7.57.

1-Chloro-4-(3-methyl-1-butenyl)benzene (Id)——A mixture of **2** (11.3 g, 57 mmol) and $KHSO_4$ (0.2 g, 1.5 mmol) was stirred at 130 °C for 2 h, then cooled to room temperature. Et_2O (100 ml) was added to the reaction mixture, which was washed, dried, and concentrated. The residue was distilled to give Id (6.7 g, 65%), bp 91—95 °C/3 Torr, [lit.[17] bp 128 °C/15 Torr]. IR ν_{max}^{neat} cm^{-1}: 3025, 2960, 1485, 1083, 1006, 960, 847, 800. MS *m/e*: 182 ($M^+ + 2$), 180 (M^+), 167, 165 (base), 145, 130. NMR δ TMS: 1.00 (6H, d, $J = 7$ Hz), 2.10—2.55 (1H, m), 5.83—6.33 (2H, m), 7.00—7.30 (4H, m).

1-Chloro-4-(3-methyl-2-butenyl)benzene (Ie)——Ie was prepared in the same manner as Ib. 1-Chloro-3-methyl-2-butene (343 g, 3.3 mol) was added dropwise to a stirred solution of 4-chlorophenylmagnesium chloride [prepared from 1,4-dichlorobenzene (438 g, 3.0 mol) and Mg (80 g, 3.3 mol)] in THF (2.5 l) at 10—15 °C over 2 h. After being stirred for an additional 3 h at room temperature, the reaction mixture was poured into 10% aq. NH_4Cl (1.0 l). The aqueous solution was extracted with Et_2O (500 ml × 3). The ethereal solution was washed , dried, and concentrated, and the residue was distilled to give Ie (361 g, 67%). bp 64—65.5 °C/0.38 Torr, [lit.[18] bp 84—88 °C/1.5 Torr].

1-Chloro-4-(3-methyl-3-butenyl)benzene (If)——A mixture of Mg (120 g, 4.9 mol), bromoethane (2 ml), a few pieces of iodine and Et_2O (240 ml) was stirred at room temperature until the iodine coloration disappeared. A solution of 4-chlorobenzyl chloride (403 g, 2.5 mol) in Et_2O (2.0 l) was added dropwise to the above mixture with stirring at 25—30 °C over 5 h. The stirred mixture was refluxed for 1 h and cooled to 20 °C, then CuBr (16 g, 0.11 mol) was added. Next, a solution of 3-chloro-2-methylpropene (217 g, 2.4 mol) in THF (1.0 l) was added dropwise over 3 h under reflux. The mixture was stirred overnight at room temperature, then poured into 10% aq. NH_4Cl (2.0 l). The organic layer was separated, washed, dried, and concentrated, and the residue was distilled to give If (334 g, 77%), bp 62—70 °C/1.5 Torr. IR ν_{max}^{neat} cm^{-1}: 3070, 2930, 1640, 1485, 1085, 1010, 890, 805. MS *m/e*: 182 ($M^+ + 2$), 180 (M^+), 145, 127, 125 (base). NMR δ HMS: 1.66 (3H, s), 2.00—2.30 (2H, m), 2.40—2.70 (2H, m), 4.55—4.75 (2H, m), 6.85—7.20 (4H, m). *Anal.* Calcd for $C_{11}H_{13}Cl$: C, 73.13; H, 7.25. Found: C, 73.01; H, 7.18.

4-Chloro-α,α-dimethylphenylacetonitrile (3)——A solution of lithium diisopropylamide (LDA) was prepared from diisopropylamine (20 g, 0.20 mol) in THF (70 ml) and butyllithium (100 ml of 1.60 M hexane solution from Aldrich Co., 0.16 mol) at −40 °C. A half of the LDA solution was added dropwise to a stirred solution of 4-chlorophenylacetonitrile (10.6 g, 70 mmol) in THF (30 ml) at −20 °C over 25 min, then iodomethane (11.4 g, 80 mmol) in THF (10 ml) was added. The reaction mixture was warmed to 0 °C, and cooled again to −20 °C, then the other half of LDA solution was added at −20 °C with stirring. Iodomethane (11.4 g, 80 mmol) in THF (10 ml) was added. The mixture was warmed to room temperature and poured into 1 N HCl (200 ml). The aqueous solution was extracted with Et_2O (200 ml × 3). The ethereal solution was washed, dried, and concentrated, and the residue was distilled to give **3** (11.8 g, 94%), bp 81—83 °C/1 Torr. IR ν_{max}^{neat} cm^{-1}: 3070, 2985, 2240, 1490, 1100, 1010, 825, 730. MS *m/e*: 181 ($M^+ + 2$), 179 (M^+), 166, 164 (base), 137, 128. NMR δ HMS: 1.63 (6H, s), 7.15—7.45 (4H, m). *Anal.* Calcd for $C_{10}H_{10}ClN$: C, 66.86; H, 5.61; N, 7.80. Found: C, 66.60; H, 5.54; N, 7.75.

3-(4-Chlorophenyl)-3-methylbutan-2-one (4)——A solution of methylmagnesium iodide [prepared from iodomethane (17.0 g, 0.12 mol) and Mg (3.4 g, 0.14 mol)] in THF (80 ml) was added dropwise to a stirred solution of **3** (18.0 g, 0.10 mol) in benzene (100 ml) at 50—55 °C over 30 min. The reaction mixture was refluxed for 2 h, then cooled to room temperature and poured into 10% aq. NH_4Cl (200 ml). The organic layer was separated and 2 N HCl (50 ml) was added. The mixture was refluxed for 1 h, then cooled. The organic layer was separated, washed, dried, and concentrated, and the residue was distilled to give **4** (17.8 g, 91%), bp 73—75 °C/0.5 Torr. IR ν_{max}^{neat} cm^{-1}: 2980, 1710, 1490, 1121, 1100, 1010, 825. MS *m/e*: 198 ($M^+ + 2$), 196 (M^+), 155, 153 (base), 127, 125. *Anal.* Calcd for $C_{11}H_{13}ClO$: C, 67.18; H, 6.66. Found: C, 67.26; H, 6.51.

***p*-Toluenesulfonylhydrazone of 4 (5)**——A solution of **4** (16.7 g, 85 mmol), *p*-toluenesulfonylhydrazide (14.9 g, 80 mmol) and conc. H_2SO_4 (0.5 ml) in EtOH (50 ml) was refluxed for 2 h, then allowed to stand overnight at room temperature. Benzene (100 ml) was added, and the whole was concentrated under reduced pressure. The residue was dissolved in Et_2O (200 ml). The solution was washed with H_2O (100 ml × 3), dried and concentrated to leave a crystalline solid. Recrystallization from MeOH–H_2O gave **5** (15.7 g, 51%) as colorless needles, mp 135—137 °C. IR ν_{max}^{KBr} cm^{-1}: 3220, 2975, 1590, 1480, 1340, 1160, 1085, 1030, 905, 830. MS *m/e*: 366 ($M^+ + 2$), 364 (M^+), 211, 209 (base), 180, 165, 153, 145, 139. NMR δ (DMSO-d_6)TMS: 1.27 (6H, s), 1.50 (3H, s), 2.43 (3H, s), 7.01 (2H, d, J=9 Hz), 7.32 (2H, d, J=9 Hz), 7.47 (2H, d, J=9 Hz), 7.82 (2H, d, J=9 Hz), 9.92 (1H, s). *Anal.* Calcd for $C_{18}H_{21}ClN_2O_2S$: C, 59.25; H, 5.80; N, 7.68. Found: C, 59.08; H, 5.72; N, 7.59.

1-Chloro-4-(1,1-dimethyl-2-propenyl)benzene (Ig)——A solution of methyllithium (60 ml of 1.56 M ethereal solution from Aldrich Co., 94 mmol) was added dropwise to a stirred solution of **5** (14.6 g, 40 mmol) in Et_2O (120 ml) at room temperature over 20 min. The reaction mixture was stirred for an additional 1 h and poured into H_2O (200 ml). The organic layer was separated, washed, dried, and concentrated, and the residue was distilled to give Ig (5.28 g, 73%), bp 42—45 °C/0.2 Torr. IR ν_{max}^{neat} cm^{-1}: 3090, 2970, 1490, 1095, 1010, 910, 820. MS *m/e*: 182 ($M^+ + 2$), 180 (M^+), 167, 165 (base), 145, 130. NMR δ HMS: 1.31 (6H, s), 4.83—5.10 (2H, m), 5.75—6.13 (1H, m), 7.20 (4H, s). *Anal.* Calcd for $C_{11}H_{13}Cl$: C, 73.13; H, 7.25. Found: C, 73.29; H, 7.22.

1-Chloro-4-(4-methyl-3-pentenyl)benzene (Ih)——A solution of 1-bromo-3-methyl-2-butene (9.2 g, 62 mmol) in THF (40 ml) was added dropwise to a stirred solution of 4-chlorobenzylmagnesium chloride [prepared from 4-chlorobenzyl chloride (10.0 g, 62 mmol) and Mg (1.51 g, 62 mmol)] in Et_2O (65 ml) at a rate sufficient to maintain spontaneous reflux, over 20 min. The stirred solution was refluxed for an additional 45 min, then cooled to 20 °C. The solution was poured into 10% aq. NH_4Cl (100 ml) and extracted with Et_2O (100 ml × 2). The ethereal solution was washed, dried and concentrated to give an oil, which was chromatographed on silica gel with hexane to give a mixture (9.1 g, 75%) of Ih and its isomer [1-chloro-4-(2,2-dimethyl-3-butenyl)benzene]. NMR indicated the ratio to be 7 : 1. The mixture was used for the next reaction without further purification. IR ν_{max}^{neat} cm^{-1}: 3025, 2910, 1490, 1090, 1015, 820. MS *m/e*: 196 ($M^+ + 2$), 194 (M^+), 154, 152, 141, 139, 125 (base). NMR δ TMS: 1.54 (3H, s), 1.68 (3H, s), 2.19—2.36 (2H, m), 2.54—2.68 (2H, m), 5.08—5.20 (1H, m), 7.11 (2H, d, J=8 Hz), 7.24 (2H, d, J=8 Hz).

NMR δ TMS for the isomer: 0.98 (6H, s), 2.54 (2H, s), 4.84 (1H, dd, J=2, 11 Hz), 4.92 (1H, dd, J=2, 17 Hz), 5.82 (1H, dd, J=11, 17 Hz), 7.04 (2H, d, J=9 Hz), 7.22 (2H, d, J=9 Hz).

Preparation of 2-(4-Alkenylphenyl)propionates (II)

Ethyl 2-(4-Vinylphenyl)propionate (IIa)——A solution of 4-chlorostyrene (13.9 g, 0.10 mol) in THF (50 ml) was added dropwise to a stirred mixture of Mg (2.92 g, 0.12 mol; activated with 1,2-dibromoethane and iodine) in THF (20 ml) at 60—65 °C over 1 h. The stirred mixture was refluxed for 1 h, then cooled to room temperature. The Grignard solution was added dropwise to a stirred mixture of ethyl 2-bromopropionate (18.1 g, 0.10 mol), $NiCl_2$ (0.13 g, 1.0 mmol) and THF (40 ml) at 20—25 °C over 30 min. The mixture was stirred for an additional 4 h, then poured into 10% aq. NH_4Cl (100 ml), and the whole was extracted with Et_2O (100 ml × 3). The ethereal solution was washed with 10% aq. NaCl (100 ml × 2), dried and concentrated. The residue was extracted with hexane (30 ml × 3). The hexane solution was concentrated and chromatographed on silica gel with hexane–EtOAc (50 : 1) to give IIa (4.3 g, 21%). The physical properties of IIa are summarized in Tables I and VI.

Ethyl 2-(4-Allylphenyl)propionate (IIb)——A solution of Ib (30.5 g, 0.20 mol) in THF (20 ml) was added dropwise to a stirred mixture of Mg (5.8 g, 0.24 mol; activated with 1,2-dibromoethane and iodine) in THF (10 ml) over 1 h under vigorous reflux. The reaction mixture was stirred at 100—110 °C for 2 h, then cooled and diluted with THF (100 ml). The Grignard solution was added dropwise to a stirred mixture of ethyl 2-bromopropionate (36.2 g, 0.20 mol), $NiCl_2$ (0.26 g, 2.0 mmol) and THF (100 ml) at room temperature over 30 min. The reaction mixture was stirred for an additional 4 h, then worked up as described for IIa to give IIb (11.3 g, 26%).

The following compounds (IIc—h) were prepared similarly. The physical properties of IIb—h are summarized in Tables I and VI.

Ethyl 2-[4-(2-Methyl-1-propenyl)phenyl]propionate (IIc).

Ethyl 2-[4-(3-Methyl-1-butenyl)phenyl]propionate (IId).

Ethyl 2-[4-(3-Methyl-2-butenyl)phenyl]propionate (IIe).

Ethyl 2-[4-(3-Methyl-3-butenyl)phenyl]propionate (IIf).

Ethyl 2-[4-(1,1-Dimethyl-2-propenyl)phenyl]propionate (IIg).

Ethyl 2-[4-(4-Methyl-3-pentenyl)phenyl]propionate (IIh).

TABLE VI. IR and NMR Data for Ethyl 2-(4-Alkenylphenyl)propionates (II)

No.	IR ν_{max}^{neat} cm^{-1}	NMR (δ in $CDCl_3$ from TMS or HMS[a])
IIa	1725, 1206, 1175, 862	TMS: 1.20 (3H, t, J=7 Hz), 1.48 (3H, d, J=7 Hz), 3.70 (1H, q, J=7 Hz), 4.01—4.22 (2H, m), 5.23 (1H, dd, J=11, 1 Hz), 5.73 (1H, dd, J=18, 1 Hz), 6.70 (1H, dd, J=18, 11 Hz), 7.27 (2H, d, J=9 Hz), 7.38 (2H, d, J=9 Hz)
IIb	1726, 1205, 1173, 862	TMS: 1.20 (3H, t, J=7 Hz), 1.47 (3H, d, J=7 Hz), 3.38 (2H, d, J=7 Hz), 3.68 (1H, q, J=7 Hz), 4.01—4.23 (1H, m), 5.01—5.17 (2H, m), 5.86—6.09 (1H, m), 7.16 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz)
IIc	1725, 1205, 1171, 870	TMS: 1.20 (3H, t, J=7 Hz), 1.48 (3H, d, J=7 Hz), 1.85 (3H, d, J=0.5 Hz), 1.88 (3H, d, J=1 Hz), 3.69 (1H, q, J=7 Hz), 4.05—4.24 (1H, m), 6.24 (1H, br s), 7.19 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz)
IId	1724, 1200, 1169	TMS: 1.00 (6H, d, J=7 Hz), 1.11 (3H, t, J=7 Hz), 2.39 (3H, d, J=7 Hz), 2.1—2.6 (1H, m), 3.57 (1H, q, J=7 Hz), 4.01 (2H, q, J=7 Hz), 5.9—6.4 (2H, m), 7.05—7.33 (4H, m)
IIe	1725, 1160 1200, 860	HMS: 1.10 (3H, t, J=7 Hz), 1.39 (3H, d, J=7 Hz), 1.55—1.75 (6H, m), 3.23 (2H, d, J=7 Hz), 3.58 (1H, q, J=7 Hz), 4.02 (2H, q, J=7 Hz), 5.10—5.40 (1H, m), 6.97—7.30 (4H, m)
IIf	1729, 1199, 1167	HMS: 1.32 (3H, t, J=7 Hz), 1.41 (3H, d, J=7 Hz), 1.7 (3H, s), 2.05—2.4 (2H, m), 2.5—2.8 (2H, m), 3.6 (1H, q, J=7 Hz), 4.04 (2H, q, J=7 Hz), 4.66 (2H, s), 7.0—7.25 (4H, m)
IIg	1731, 1203, 1168	HMS: 1.1 (3H, t, J=7 Hz), 1.32 (6H, s), 1.39 (3H, d, J=7 Hz), 3.6 (1H, q, J=7 Hz), 4.03 (2H, q, J=7 Hz), 4.8—5.1 (2H, m), 5.77—6.13 (1H, m), 7.06—7.33 (4H, m)
IIh	1730, 1200, 1160, 862	TMS: 1.21 (3H, t, J=7 Hz), 1.49 (3H, d, J=7 Hz), 1.58 (3H, s), 1.70 (3H, s), 2.22—2.41 (2H, m), 2.55—2.73 (2H, m), 3.69 (1H, q, J=7 Hz), 4.05—4.26 (2H, m), 5.12—5.27 (1H, m), 7.04—7.37 (4H, m)

a) Internal standard: TMS = tetramethylsilane, HMS = hexamethyldisiloxane.

TABLE VII. IR and NMR Data for 2-(4-Alkenylphenyl)propionic Acids (III)

No.	IR ν_{max} cm^{-1}	NMR (δ in $CDCl_3$ from TMS or HMS[a])
IIIa	Nujol: 3220—2540, 1696, 1405, 1235, 912	TMS: 1.50 (3H, d, J=7 Hz), 3.75 (1H, q, J=7 Hz), 5.24 (1H, d, J=11 Hz), 5.73 (1H, d, J=18 Hz), 6.70 (1H, dd, J=18, 11 Hz), 7.29 (2H, d, J=9 Hz), 7.39 (2H, d, J=9 Hz), 10.7 (1H, br s)
IIIb	Neat: 3250—2550, 1710, 1415, 1230, 862	TMS: 1.48 (3H, d, J=7 Hz), 3.37 (2H, d, J=7 Hz), 3.71 (1H, q, J=7 Hz), 5.01—5.17 (2H, m), 5.84—6.07 (1H, m), 7.16 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz)
IIIc	Nujol: 3350—2550, 1697, 1420, 1285, 1210, 755	TMS: 1.50 (3H, d, J=7 Hz), 1.84 (3H, d, J=1 Hz), 1.88 (3H, d, J=0.5 Hz), 3.72 (1H, q, J=7 Hz), 6.24 (1H, br s), 7.19 (2H, d, J=9 Hz), 7.28 (2H, d, J=9 Hz)
IIId	Nujol: 3180—2657, 1701, 1510, 1420, 1235, 970	TMS: 1.0 (6H, d, J=7 Hz), 1.4 (3H, d, J=7 Hz), 2.1—2.6 (1H, m), 3.6 (1H, q, J=7 Hz), 5.9—6.4 (2H, m), 7.1—7.35 (4H, m), 11.23 (1H, br s)
IIIe	Neat: 3450—2500, 1700, 1225, 850	HMS: 1.45 (3H, d, J=7 Hz), 1.66—1.80 (6H, m), 3.32 (2H, d, J=7 Hz), 3.68 (3H, q, J=7 Hz), 5.2—5.45 (1H, m), 7.05—7.35 (4H, m), 11.83 (1H, s)
IIIf	Nujol: 3245—2600, 1702, 1412, 1233, 862	HMS: 1.4 (3H, d, J=7 Hz), 1.7 (3H, s), 2.05—2.4 (2H, m), 2.5—2.8 (2H, m), 3.61 (1H, q, J=7 Hz), 4.66 (2H, s), 7.0—7.27 (4H, m), 11.13 (1H, s)
IIIg	Nujol: 3115—2600, 1705, 1415, 1232, 916	HMS: 1.33 (6H, s), 1.42 (3H, d, J=7 Hz), 3.63 (1H, q, J=7 Hz), 4.85—5.1 (2H, m), 5.8—6.15 (1H, m), 7.23 (4H, s), 11.2 (1H, br s)
IIIh	Neat: 3210—2600, 1705, 1415, 1230, 862	TMS: 1.49 (3H, d, J=7 Hz), 1.56 (3H, s), 1.69 (3H, s), 2.21—2.37 (2H, m), 2.55—2.69 (2H, m), 3.72 (1H, q, J=7 Hz), 5.12—5.24 (1H, m), 7.16 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz)

a) Internal standard: TMS = tetramethylsilane, HMS = hexamethyldisiloxane.

Preparation of 2-(4-Alkenylphenyl)propionic Acids (III)

2-(4-Vinylphenyl)propionic Acid (IIIa)——A solution of IIa (10.2 g, 50 mmol) in EtOH (100 ml) was added to a solution of NaOH (4.0 g, 0.10 mol) in H_2O (10 ml), and the mixture was stirred for 6 h at room temperature. The EtOH was removed under reduced pressure, then the aqueous mixture was poured into H_2O (50 ml) and washed with Et_2O (50 ml × 2). The aqueous layer was acidified with 1 N HCl (105 ml), then extracted with Et_2O (100 ml × 3). The extract was washed with 10% aq. NaCl (30 ml × 3), dried and concentrated to leave a crystalline solid IIIa (7.8 g, 89%).

The following compounds (IIIb—h) were prepared similarly. The physical properties of IIIa—h are summarized in Tables II and VII.

2-(4-Allylphenyl)propionic Acid (IIIb).
2-[4-(2-Methyl-1-propenyl)phenyl]propionic Acid (IIIc).
2-[4-(3-Methyl-1-butenyl)phenyl]propionic Acid (IIId).
2-[4-(3-Methyl-2-butenyl)phenyl]propionic Acid (IIIe).
2-[4-(3-Methyl-3-butenyl)phenyl]propionic Acid (IIIf).
2-[4-(1,1-Dimethyl-2-propenyl)phenyl]propionic Acid (IIIg).
2-[4-(4-Methyl-3-pentenyl)phenyl]propionic Acid (IIIh).

Preparation of 2-(4-Alkylphenyl)propionic Acid (V)

Ethyl 2-(4-Ethylphenyl)propionate (6)——A solution of 1-bromo-4-ethylbenzene (37.0 g, 0.20 mol) in THF (100 ml) was added dropwise to a stirred mixture of Mg (5.3 g, 0.22 mol; activated with 1,2-dibromoethane and iodine) and THF (20 ml) at 60—65 °C over 30 min. The stirred mixture was refluxed for 4 h. The Grignard solution was cooled and added dropwise to a stirred mixture of ethyl 2-bromopropionate (36.2 g, 0.20 mol), $NiCl_2$ (0.26 g, 2.0 mmol) and THF (70 ml) at room temperature over 30 min. The mixture was stirred for an additional 4 h, then poured into 10% aq. NH_4Cl (200 ml) and extracted with Et_2O (200 ml × 3). The ethereal solution was washed, dried, and concentrated, and the residue was distilled to give **6** (21.1 g, 51%), bp 105—108 °C/2.5 Torr. IR ν_{max}^{neat} cm^{-1}: 2960, 1725, 1513, 1445, 1200, 1160, 860. MS *m/e*: 206 (M^+), 134, 133 (base), 117, 105. NMR δ TMS: 1.20 (3H, t, J=7 Hz), 1.22 (3H, t, J=7 Hz), 1.47 (3H, d, J=7 Hz), 2.63 (2H, q, J=7 Hz), 3.68 (1H, q, J=7 Hz), 4.02—4.23 (2H, m), 7.16 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.80; H, 8.74.

2-(4-Ethylphenyl)propionic Acid (Va)——In the same manner as described for to IIIa, **6** was hydrolyzed to give Va. Distillation under reduced pressure gave a quantitative yield of Va, bp 135 °C/3.5 Torr. IR ν_{max}^{neat} cm^{-1}: 3200—2600, 1705, 1513, 1457, 1411, 1230, 857. MS *m/e*: 178 (M^+), 163, 134, 133 (base), 117, 105. NMR δ TMS: 1.22 (3H, t, J=7 Hz), 1.50 (3H, d, J=7 Hz), 2.64 (2H, q, J=7 Hz), 3.72 (1H, q, J=7 Hz), 7.18 (2H, d, J=9 Hz), 7.26 (2H, d, J=9 Hz), 10.5 (1H, br s). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.94; H, 7.88.

2-[4-(3-Methylbutyl)phenyl]propionic Acid (Vc)——A mixture of IIIe (21.8 g, 0.10 mol), 5% Pd on carbon (0.20 g) and 0.5 N NaOH (220 ml) was stirred at room temperature under a hydrogen atmosphere. After absorption of hydrogen had ceased, the catalyst was removed by filtration. Then 10% aq. NH_4Cl (100 ml) was added to the filtrate, and the whole was extracted with hexane (100 ml × 3). The organic solution was washed, dried, and concentrated, and the residue was distilled to give Vc (20.0 g, 91%), bp 125—128 °C/0.1 Torr. IR ν_{max}^{neat} cm^{-1}: 3200—2600, 1705, 1513, 1457, 1411, 1230, 1071, 937, 857. MS *m/e*: 220 (M^+), 176, 175 (base), 164, 163, 108. NMR δ TMS: 0.91 (6H, d, J=5 Hz), 1.47 (3H, d, J=7 Hz), 1.32—1.68 (3H, m), 2.40—2.78 (2H, m), 3.67 (1H, q, J=7 Hz), 7.15 (4H, s), 11.73 (1H, br s). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.23; H, 9.37.

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