Registry No. 1, 764-37-4; 2, 54560-70-2; 3, 64884-87-3; 4, 763-89-3; 5, 21019-60-3; 6, 13679-01-1; 7, 13679-00-0; 8, 96308-69-9; 9, 96308-70-2; 10, 75476-47-0; 11, 96308-71-3; 12, 20047-26-1; 13, 96206-33-6; $HO(CH_2)_2C{\equiv}CH$, 927-74-2; $HOCH(CH_3)CH_2C{\equiv}CH$, 2117-11-5; $HOCH(C_2H_5)CH_2C{\equiv}CH$, 19780-84-8; $HO(CH_2)_2C{\equiv}CCH_3$, 10229-10-4; $HO(CH_2)_2C{\equiv}CC_2H_5$, 1002-28-4; $HO(CH_2)_2C{\equiv}CC_3H_7$-*n*, 14916-79-1; $HO(CH_2)_2C{\equiv}CC_4H_9$-*n*, 14916-80-4; $HO(CH_2)_2C{\equiv}CC_5H_{11}$-*n*, 31333-13-8; $HO(CH_2)_2C{\equiv}CC_3H_7$-*i*, 96308-72-4; $HO(CH_2)_2C{\equiv}CPh$, 10229-11-5; $HOCH(C_2H_5)CH_2C{\equiv}CCH_3$, 19781-82-9.

Substituent Effects on Hydrogenation of Aromatic Rings: Hydrogenation vs. Hydrogenolysis in Cyclic Analogues of Benzyl Ethers

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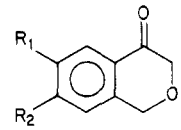
Carbalkoxy substituents are shown to retard the hydrogenation of aromatic rings over Rh/C catalyst. Hydrogenolysis predominates with acyclic (benzyloxy)acetates over this catalyst, but both hydrogenation and hydrogenolysis become sluggish with 2-isochroman-4-ones (1). However, phthalides may be cleanly hydrogenated in moderate to excellent yields without significant hydrogenolysis. Placing a benzyl ether in a ring system appears to greatly retard hydrogenolysis relative to the acyclic analogues.

As part of a plan to investigate heteroatom effects on conformational equilibria and on rate phenomena in 6- and 7-carbomethoxy-*trans*-2-heteradecalins,[1,2] we needed to prepare the 2-oxadecalin analogues. Utilization of the route previously developed[1] for the 1-oxadecalins would involve synthesis of the appropriately substituted 2-isochroman-4-ones (1) followed by reduction of the aromatic ring.



1a, $R_1 = R_2 = H$
b, $R_1 = CO_2Et$; $R_2 = H$
c, $R_1 = H$; $R_2 = CO_2Et$

Since the 2-isochromane system contains a benzyl ether function, reduction of the aromatic ring must compete effectively with hydrogenolysis of the benzyl ether C–O bond[3,4] in order for this synthesis to be feasible. Moreover, the presence of the electron-withdrawing ester groups in **1b** and **1c** might deactivate the ring toward hydrogenation,[4] thus favoring the hydrogenolysis. Increasing the amount of catalyst should increase the rate of hydrogenation, possibly overcoming the deactivating effect of the substituents.[3,4] Stocker[5] has reported the successful reductions of methyl benzyl ether and dibenzyl ether to their perhydro derivatives by using 5% Rh on charcoal at 3–4 atm of hydrogenation pressure, suggesting that this problem of hydrogenolysis may not be insurmountable.

Since literature preparations[6,7] of 2-isochroman-4-ones were somewhat lengthy, it was decided to first use simpler systems to investigate the extent to which ester substituents deactivate hydrogenation of an aromatic ring. The series of compounds **2–5** was selected because of their availability either commercially or as part of some other synthetic scheme. A methyl group and a second ester substituent were used to mimic the isochroman-4-one aromatic ring substitution pattern. Ethyl benzoate (**2**) is commercially available, while ethyl 2-methylbenzoate (**3**) was prepared in 90% yield from *o*-toluic acid. The route to diethyl 4-methylisophthalate (**4**) starts with 2,4-dichlorotoluene. The literature preparation[8] of 4-methylisophthalonitrile (**6**) presented problems until *N*-methylpyrrolidone was substituted[9] for pyridine as the solvent. Attempts to convert dinitrile **6** directly to diester **4** using 95% ethanol/concentrated H_2SO_4[10] or absolute ethanol/gaseous HCl[11] resulted in conversion only of the nitrile para to the methyl group, in line with Heppolette hypothesis[12] that the methyl groups would inhibit imido ester formation at the ortho position because the imido ester could not be coplanar with the ring as required for effective conjugation. A similar route from 2,5-dichlorotoluene produced diethyl 2-methylterephthalate (**5**).

Table I. Reduction of the Aromatic Ring of Alkyl Benzoates

no.	catalyst:substrate ratio[b]	time,[a,c] h	% yield
2	0.30	1	96
3	0.30	2.5	94
4	0.30	3	90
5	0.30	6	90

[a] Reduction carried out at room temperature. [b] 5% Rh on charcoal, purchased from Matthey Bishop Inc. (MBI). [c] Reaction stopped when calculated amount of H_2 was absorbed.

Hydrogenations of esters **2–5** were performed at room temperature over 5% Rh on charcoal. Reaction was

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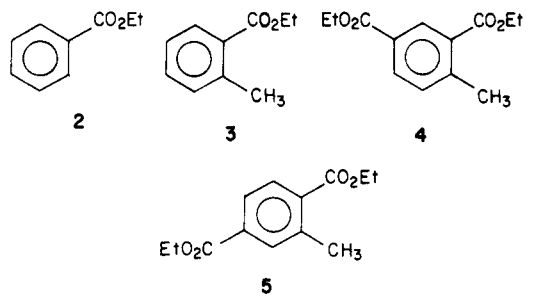
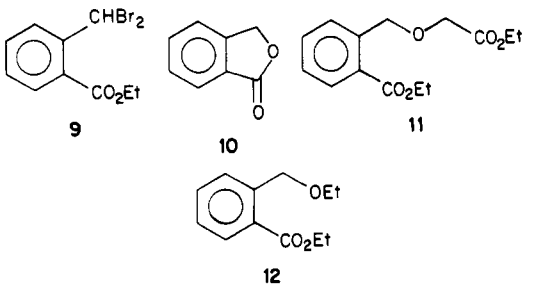


2 3 4 5

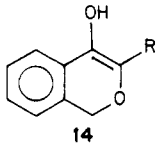
stopped when the calculated amount of hydrogen gas was absorbed. Results are reported in Table I. Clearly the carboalkoxy substituents did deactivate the aromatic ring toward reduction, especially when two esters were para to each other (**5**). Nevertheless, these substrates could all be reduced at room temperature in excellent yields and with reasonable rates.

Normant-Chefnay's route[6] to 2-isochroman-4-one (**1a**) was therefore embarked upon with some slight modifications. Benzylic bromination of ethyl 2-methylbenzoate (**3**) yielded the desired monobromo ester **8** as well as dibromo ester **9** and phthalide **10**. The relative amount of



9 10 11 12

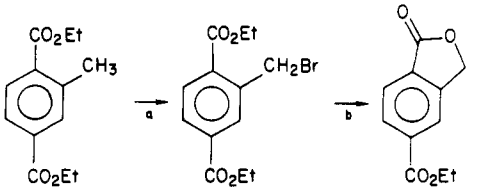
phthalide increased with an increase in temperature or with more vigorous reflux, suggesting the thermal conversion of **8** to **10**, which was directly verified. Nucleophilic attack on **8** by the sodium salt of ethyl glycolate proceeded smoothly to give diester **11** (along with small amounts of ethyl ether **12**).[13] Dieckmann cyclization[15] produced β-keto ester **13**, which was decarboxylated under basic conditions to give isochromanone **1a**. When acidic decarboxylation methods[16] were employed, extensive decomposition occurred. The product **1a** has been reported[6] to be somewhat acid sensitive. Acid-catalyzed decarboxylation would involve the enol of **1a** or the enol of **13** (**14**), which are vinyl ethers and therefore readily susceptible to hydrolysis in aqueous acidic media.



14

Isochromanone **1a** was also prepared along the lines of Thibault's route.[7] Commercially available α-bromo-*o*-tolunitrile (**15**) was converted by nucleophilic substitution to ether **16** by using the sodium salt of ethyl glycolate. Basic hydrolysis of the nitrile and ester groups produced diacid **17**, which was cyclized under Perkin's conditions[1,7]

Scheme I[a]

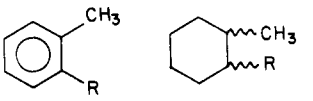


5 22

[a] (a) NBS, CCl_4, light; (b) heat.

to the enol acetate. Hydrolysis in situ yielded isochromanone **1a** in overall yields comparable to the Dieckmann route.

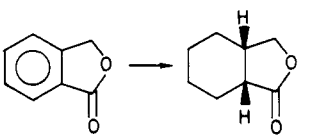
Hydrogenation of 2-isochroman-4-one (**1a**) over Rh/charcoal under a variety of conditions resulted in very little reaction other than complete hydrogenolysis of the benzylic groups, forming structures of type **18** and **19**, as shown by aromatic methyls at δ 2.6 and methyl doublets at δ 0.9 characteristic of methylcyclohexanes in the ^{1}H NMR spectra. Uptake of hydrogen was slow and practically stopped after 2–3 h. In each attempt, at least 75% of the isolated material was unreacted starting material, suggesting that neither hydrogenation nor hydrogenolysis were occurring at reasonable rates. Since esters **1b** and **1c** would be expected to be reduced even slower, hydrogenation of isochromanones did not appear to be attractive routes to 2-oxadecalins.



18 19

In order to ensure that our catalyst/solvent system was indeed effective for hydrogenation, diester **11** was subjected to the reaction conditions. After 6 h, uptake of hydrogen was almost twice that anticipated. Product consisted of hydrogenolysis products (**18**, R = CO_2Et) with methyl singlets at δ 2.66 and reduced hydrogenolysis products (**19**, R = CO_2Et) with methyl doublets at δ 0.96.

Comparison of these results with those for 2-isochroman-4-one suggested that the presence of the benzyl ether function in a ring slowed down the hydrogenolysis reaction considerably. We therefore subjected phthalide **10** to the reduction conditions. Somewhat surprisingly, phthalide **10** was reduced to the cis-fused[17] perhydro lactone[18,19] **20** almost quantitatively in about 2 h at room temperature over Rh/charcoal. This opened up the possible syntheses of 2-oxadecalins in a manner analogous to that utilized by de Waard[18] for *trans*-2-thiadecal-4-one (**21**).



10 20

Accordingly, ester-substituted phthalides **22** and **23** were prepared from diethyl 2-methylterephthalate (**5**) (Scheme I) and diethyl 4-methylisophthalate (**4**), respectively, by using similar procedures. Neither phthalide was signif-

(13) Use of anhydrous reaction conditions is strictly required. Treatment of *m*- or *p*-methylbenzyl bromide with glycolic acid in aqueous sodium hydroxide gives a very low yield of the (benzyloxy)acetic acid accompanied by a large amount of the benzyl alcohol.[14]

(14) Anzalone, L. Ph.D. Dissertation, Seton Hall University, 1984.

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(17) The stereochemical designations at the bridgeheads in the perhydro products are not meant to imply absolute configurations.

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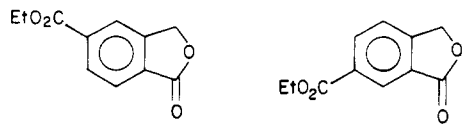
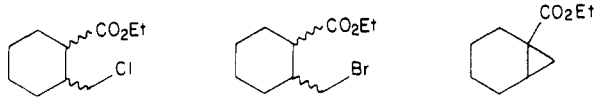


22 23

icantly reduced over Rh/C at room temperature. Reductions were subsequently performed at 60 °C with high catalyst-to-substrate ratios. Neither starting material nor products were very soluble in the various reaction media, necessitating use of large amounts of solvent and addition of tetrahydrofuran as cosolvent. The reactions required 6–12 h, with the *p*-dicarbonyl system **22** being the slower, continuing the trends found in Table I. Yields of 50% were realized after crystallization. The mother liquors were not carefully scrutinized, so the presence of hydrogenolysis products could not be excluded.

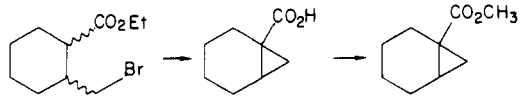
Following de Waard,[18] perhydro lactone **20** was ring opened with saturated ethanolic hydrogen chloride to give chloro ester **24**. However, attempts to displace the chloro group of **24** with the sodium salt of ethyl glycolate were unsuccessful, producing instead a product exhibiting a one-proton doublet of doublets at δ 0.63. Bromo ester **25** was similarly prepared from lactone **20**. Under the same displacement conditions, the same unusual product was obtained.

The upfield position of the ^1H NMR signals suggested the formation of a cyclopropyl ring, with **26** as the unexpected product. Precedent was found in the conversion[20]



24 25 26

of 5-chloro-2-pentanone to cyclopropyl methyl ketone with base. Presumably the alkoxide ion is acting as a base rather than as a nucleophile toward either **24** or **25**. To verify this thinking, bromo ester **25** was treated with sodium hydride in Me_2SO. Aqueous workup produced acid **27**, which was esterified with diazomethane to give **28**. Mass spectral data and elemental analysis supported these structural assignments. The difference between these results and those of de Waard[18] lies in the greater nucleophilicity of the thioglycolate anion.



25 27 28

Efforts along these lines toward the syntheses of 2-oxadecalins were abandoned since another route[21] proved successful.

Summary. Hydrogenolysis of acyclic benzyl ethers (e.g., **11**) over Rh/C catalyst is facile. However, when the ether is part of a six-membered ring, as in 2-isochroman-4-ones (**1**), hydrogenolysis becomes sluggish and occurs at rates comparable to the hydrogenation of the aromatic ring.

On the other hand, when the benzyl ether is part of a five-membered ring, as in phthalides (e.g., **10**), aromatic hydrogenation becomes dominant. This method of preparation of hexahydrophthalides provides a satisfactory alternative to the previously utilized method involving a Diels–Alder reaction and subsequent alkene hydrogenation.

(20) Bartsch, R. A.; Cook, D. M. *J. Org. Chem.* **1970**, *35*, 1714.
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Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 567 Grating Infrared Spectrophotometer. ^1H NMR spectra were routinely obtained with a Varian T-60 instrument, and, in certain cases, with a Varian XC-200 NMR spectrometer. Unless otherwise noted, all spectra were recorded with $CDCl_3$ as solvent. Chemical shifts are reported in parts per million downfield from tetramethylsilane as the internal reference. ^{13}C NMR spectra were measured on a JEOL-MX90 Fourier Transform NMR. Mass spectral analysis were determined on a LKB Model 9000 at 70 eV. "Flash chromatography" refers to the technique developed by Still,[22] and the silica used was E. Merck 230–400 mesh. Thin-layer chromatography was performed on precoated silica gel glass plates (E. Merck). Spots were visualized under 254 nm U.V. light and/or by spraying with a solution of 3% aqueous ceric ammonium sulfate in 10% sulfuric acid or a solution of 5% ethanolic phosphomolybdic acid or a saturated potassium permanganate solution. VPC analysis were performed on Varian 5020 Thermal Conductivity GC instrument. The columns used were SE-30 and Carbowax 20M. Elemental analyses were performed by the Mikroanalytisches Laboratorium, Elbach, West Germany. Reduced pressure refers to water aspirator pressure followed by a short time under vaccum pump pressure. Solvents were purified according to Armarego.[23]

Ethyl 2-Methylbenzoate (3). A mixture of *o*-toluic acid (Aldrich, 23.5 g, 0.17 mol) and concentrated H_2SO_4 (6 mL) in absolute EtOH was refluxed for 21 h. Once cooled, the mixture was partitioned between CH_2Cl_2 (200 mL) and H_2O (100 mL), and the layers separated. The organic layer was washed with H_2O, 5% aqueous $NaHCO_3$ solution, and saturated NaCl solution and dried over $MgSO_4$, and the solvent evaporated. Distillation at 56 °C (0.25 mm) gave 25.5 g (90.7%) of the product as a clear liquid:[24] IR 1735 cm^{-1} (C=O); NMR δ 7.90 (m, 1 H), 7.30 (m, 3 H), 4.33 (q, 2 H, J = 7), 2.61 (s, 3 H), 1.35 (t, 3 H, J = 7).

4-Methylisophthalonitrile (6). This compound was prepared according to the method of Newman[9] in 64% yield after sublimation at 110 °C (0.03 mm). Recrystallization from anhydrous ethanol gave needle-like crystals: mp 140–142 °C (lit.[8] mp 142–144 °C; NMR δ 7.78 (m, 3 H, aromatic), 2.68 (s, 3 H, $ArCH_3$); IR a very sharp absorption at 2230 cm^{-1} (C≡N).

4-Methylisophthalic Acid (7). A stirred mixture of NaOH (11.25 g, 0.28 mol) and dinitrile **6** (10 g, 0.07 mol) in 125 mL of diethylene glycol with trace amounts of H_2O was refluxed for 8 h. The cooled mixture was diluted with 100 mL of H_2O and acidified to pH 1 with 10% HCl. The tan precipitate was redissolved in 10% aqueous NaOH, and the solution decolorized with Norite. Reacidifying and recrystallizing the precipitate from methanol, followed by drying at 110 °C overnight, gave 10 g (79.3%) of product (mp 338–340 °C dec) (lit.[8] mp 330–332 °C); NMR δ 8.15 (m, 3 H, aromatic), 2.65 (s, 3 H, $ArCH_3$), 13.23 (br, s, 2 H, COOH disappeared with D_2O); IR (nujol) broad absorption in the –OH region (3300–3000 cm^{-1}), 1730 (C=O), 765 cm^{-1} (aromatic).

Diethyl 4-Methylisophthalate (4). A solution of 9.9 g of 4-methylisophthalic acid (**7**) (55.2 mmol) was esterified as for *o*-toluic acid (above). Distillation at 110 °C (0.2 mm) yielded 8.8 g of colorless oil (67.5%); IR 1730 cm^{-1} (C=O); NMR δ 8.05 (m, 3 H, aromatic), 4.42 (q, 4 H, J = 7, CO_2CH_2), 2.63 (s, 3 H, $ArCH_3$), 1.42 (t, 6 H, J = 7, $CO_2CH_2CH_3$).

Alcoholysis of Dinitrile 6. Trial I.[10] A stirred solution of dinitrile **6** (2.7 g, 19.2 mmol) in 10 mL of 95% EtOH and concentrated H_2SO_4 (catalytic amount) was refluxed for 22 h. Workup consisted of adding 20 mL of CH_2Cl_2 and 10 mL of water to the cooled reaction mixture, and separating the layers. The organic layer was washed with water, 5% aqueous $NaHCO_3$ solution and saturated NaCl solution and dried over anhydrous Na_2SO_4, and the solvent evaporated to obtain 2.26 g of an oil. Chromatography on silica gel with a 1:1 EtOAc/CH_2Cl_2 solvent mixture gave 1.8

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(23) Perrin, D. P.; Armarego, W. F. L.; Perrin, D. R. "Purification of Laboratory Chemicals"; Pergamon Press: New York, 1966.
(24) Theilacker, W.; Wessel-Ewald, M. L. *Ann. Chem.* **1955**, *594*, 229.

g of a clear oil: IR 2240 (C≡N) and 1725 cm^{-1} (C=O); NMR δ 7.33 (m, 3 H, aromatic), 4.41 (q, 2 H, J = 7), 2.66 (s, 3 H), 1.41 (t, 3 H, J = 7).

Trial II.[11] Hydrogen chloride gas was bubbled through a cold solution of 2.0 g of dinitrile **6** (0.014 mol) and 2 mL of absolute EtOH (0.035 mol) in 25 mL of dry dioxane for 45 min. The temperature was kept slightly above the freezing point of dioxane (11 °C) during the gas addition. The reaction mixture was stirred for three days at room temperature and then allowed to stand at −20 °C for 1 day. After the mixture was raised to room temperature, a white precipitate was separated, filtered, dried, and weighed (1.6 g): mp 196–200 °C; IR (nujol) 2220 (C≡N), 1760 cm^{-1} (C=NH_2Cl); NMR (Me_2SO-d_6, DSS internal standard) δ 8.48 (m, 3 H, aromatic), 4.76 (q, 2 H, J = 7), 2.66 (s, 3 H), 1.55 (t, 3 H, J = 8).

2-Methylterephthalonitrile. A mixture[8,9] of 2,5-dichlorotoluene (Aldrich, 24.57 g, 152.5 mmol) and dry cuprous cyanide (50 g, 558.1 mmol) in freshly distilled *N*-methylpyrrolidone (Fisher, 130 mL) was heated under reflux (200–216 °C) for 24 h. While hot (110 °C), the mixture was poured into a flask containing 260 mL of 50% aqueous NH_4OH solution and 100 mL of toluene and shaken to try to break up the lumps. After the mixture was cooled to room temperature, ether (100 mL) was added to the mixture, and the resulting mixture was filtered through cloth. The dark filtrate was poured into a 1000 mL separatory funnel and the layers were separated with the aid of additional ether (100 mL). The organic layer was washed with aqueous 10% NH_4OH solution (5 × 110 mL, until the basic layer was no longer blue), with H_2O (100 mL), 10% HCl solution (2 × 100 mL), H_2O (100 mL), and saturated NaCl solution. After drying ($MgSO_4$), evaporation of the solvent gave 16.3 g of product as buff colored powder. The original aqueous layer was extracted with a 50:50 ether–chloroform solvent mixture (2 × 100 mL) and worked-up as before to give an additional 1.2 g of product: total 17.5 g (80% yield); mp 144–147 °C (lit.[25] mp 150–152 °C); IR (nujol) 2230 cm^{-1} (C≡N); NMR δ 7.73 (m, 3 H, aromatic) 2.61 (s, 3 H).

2-Methylterephthalic Acid. A sample of 2-methylterephthalonitrile (16.0 g, 112.6 mmol) was added to a solution of NaOH (18 g, 450.6 mmol) and water (few drops) in diethylene glycol (DEG, 300 mL). The reaction mixture was slowly heated at reflux (200 °C) for 42 h (a white precipitate formed around the flask during the refluxing period which necessitated addition of more DEG). The cooled alkaline solution (dark brown) was acidified to pH 1. The paste-like precipitate was filtered, washed with several portions of cold absolute EtOH, and dried under vacuum. It weighed 19.5 g (94% yield): mp 334–336 °C dec (lit.[25] mp 328–330 °C); IR (nujol) 3300–3000 (OH), 1730 cm^{-1} (C=O); NMR (Me_2SO-d_6, DSS) δ 8.33 (very broad singlet, 2 H, disappeared with D_2O), 8.0 (s, 3 H), 4.30 (s, 3 H).

Diethyl 2-Methylterephthalate (5). Diacid 2-methylterephthalic acid (19.5 g, 0.106 mol) was esterified in a manner analogous to *o*-toluic acid (above). Vacuum distillation at 105–115 °C (0.2–0.15 mm) gave 19.6 g (78%) of clear, pleasant-smelling liquid: IR (film) 1725 cm^{-1} (C=O); NMR δ 7.91 (s, 3 H), 4.40 (q, 4 H, J = 7), 2.63 (s, 3 H), 1.40 (t, 6 H, J = 7).

Reduction Studies. The catalyst used for the following hydrogenations was 5% Rh/C (Matthey Bishop, Inc., lot no. MB10-5-0105). To insure that the reaction mixture was only under an atmosphere of hydrogen, the Parr bottle was flushed three times while in place before shaking was started.

Reduction of Ethyl Benzoate (2). A mixture of MeOH (11 mL), ethyl benzoate (2.4 g, 0.18 mol), and acetic acid (0.1 mL) was added slowly to a 250-mL Parr bottle containing 0.33 g of 5% Rh/C catalyst. The mixture was shaken for 1 h at room temperature, and the required amount of H_2 was adsorbed. The mixture was then filtered through a bed of Celite and concentrated to yield a clear liquid (yield 96%), which was identical with a sample of ethyl cyclohexanecarboxylate (P & B).

Reduction of Diethyl 2-Methylterephthalate (5). A solution of diethyl 2-methylterephthalate (**5**) (0.48 g, 2.03 mmol) in anhydrous MeOH (7 mL) and glacial acetic acid (0.05 mL) was added slowly to a 250-mL Parr bottle containing 0.19 g of 5% Rh/C catalyst. The mixture was shaken for 6 h at room temperature (the required amount of H_2 was adsorbed). The mixture was then filtered through Celite, the catalyst was washed with $CHCl_3$ several times, and the solvent evaporated from the combined filtrates to yield 0.48 g of slightly yellow liquid: IR (neat) 1730 cm^{-1} (C=O ester); NMR δ 4.1 (broad q, 4 H, J = 6.5), 2.56 (broad s, 2 H), multiplet centered at 1.8 (7 H), 1.26 (broad t, J = 6.5), 1.0 (d, 3 H, J = 4).

Reduction of Diethyl 4-Methylisophthalate (4). Diethyl 4-methylisophthalate (**4**) (0.5 g, 2.05 mmol) was reduced in the same manner as the above isomer. Reaction time was 3 h. Workup resulted in 0.49 g of a sweet smelling liquid: IR (neat) 1730 cm^{-1} (C=O ester); NMR δ 4.14 (q, 2 H, J = 7), 4.16 (q, 2 H, J = 7), 2.43 (m, 2 H), 1.73 (m, 7 H), 1.46 (t, 6 H, J = 7), 0.90 (d, 3 H, J = 7).

Ethyl 2-(Bromomethyl)benzoate (8). A stirred mixture of ethyl 2-methylbenzoate (**3**) (20 g, 121.9 mmol) and NBS (25.7 g, 144.3 mmol) in CCl_4 (600 mL) was heated under gentle reflux for 18 h while a 150-W bulb situated 2 cm away was shining on the reaction flask. The cooled reaction mixture was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$, and the solvent concentrated. Distillation of the yellow oil at 90–95 °C (0.15 mm) yielded 26.2 g (88%) of bromide **8** as a clear liquid: IR 1720 cm^{-1} (C=O) (lit.[26] 1730 cm^{-1}); NMR δ 7.46 (m, 3 H), 5.00 (s, 2 H), 4.1 (q, 2 H, J = 7), 1.40 (t, 3 H, J = 7).

In one of the runs when the mixture was not refluxed gently there were two other products isolated by chromatography through silica gel (3:1 hexane–EtOAc as the eluent) in addition to the desired bromide **8** (which constituted 54% of the reaction product).

(1) Ethyl 2-(Dibromomethyl)benzoate (9): IR 1720 cm^{-1} (C=O); NMR (100 MHz) δ 8.18 (d of d, 1 H, J = 2 and 7), 8.07 (s, 1 H), 7.90 (d of d, 1 H, J = 2 and 7), 7.64 (t of t, 1 H, J = 2 and 7), 7.32 (t of t, 1 H, J = 2 and 7), 4.34 (q, 2 H, J = 7), 1.34 (t, 3 H, J = 7); MS, *m/e* (relative intensity) 322 (4), 277 (8), 241 (30), 133 (100). Anal. Calcd for $C_{10}H_{10}Br_2O_2$: C, 37.39; H, 3.13. Found: C, 38.51; H, 3.41.

(2) Phthalide (10): IR 1765 cm^{-1} (C=O); NMR δ 7.36 (m, 4 H), 5.10 (s, 2 H). These spectra are similar to those of the compound purchased from Aldrich. Heating bromide **8** at boiling for a few minutes[26] with a Bunser burner provided an 80% yield of phthalide (**10**).[27]

Ethyl [(2-Carbethoxybenzyl)oxy]acetate (11). The procedure was similar to the one reported[6] except that the bromo compound **8** was utilized instead of the chloro starting material. Distillation under vacuum gave 3 fractions. The first (2.4 g) boiled at 28–40 °C (0.05 mm) and was a mixture of Me_2SO and ethyl glycolate. The second (0.5 g) boiled at 60–90 °C (0.05 mm) and was identified as the ethyl ether **12**: IR 1410 (C–O); NMR δ 7.72 (m, 4 H, aromatic), 5.12 (s, 2 H, $ArCH_2$), 4.31 (q, 2 H, J = 7, OCH_2CH_3), 1.32 (t, 3 H, J = 7, OCH_2CH_3). And the third fraction (16 g) boiled at 128–140 °C (0.05 mm) (lit.[6] bp 155–160 °C (0.5 mm)) and was the desired product **11** (a clear liquid, 75.2% yield): IR 1750 (C=O of the aliphatic ester), 1710 cm^{-1} (C=O of the benzylic ester) (lit.[6] 1750–1700 cm^{-1}); NMR δ 7.66 (m, 4 H), 5.08 (s, 2 H), 4.35 and 4.22 (two q, 4 H), 4.15 (s, 2 H), 1. 38 and 1.28 (two t, 6 H).

3-Carbethoxyisochroman-4-one (13). This material was prepared by the method of Normant-Chefnay.[6] Chromatography of 3.44 g of yellow-amber oil on silica gel with 50:1 CH_2Cl_2–EtOAc as the solvent mixture gave 2.70 g (54.5% yield) of slightly yellow oil as a mixture of enol and keto form (a deep purple color upon testing with 1% methanolic $FeCl_3$). An attempt to isolate a single spot was not successful: IR 3420 (OH, enolic), 1740 (C=O, ester), 1700 (C=O, keto), 1650 (C=O, enolic), 1600 cm^{-1} (C=C, enolic) (lit.[6] 3350, 1750, 1700 cm^{-1}); NMR δ 10.46 (s, 0.5 H, disappeared with D_2O), 8.06 (d of d, 0.5 H), 7.36 (m, 3.5 H), 5.23 (d of d, 1 H), 5.0 (s, 1 H), 4.9 (s, 0.5 H), 4.33 (q of q, 2 H, J = 7 and 7), 1.33 (t of t, 3 H, J = 7 and 7). The benzylic proton spin–spin couplings are due to different protons in the enol form. (Lit.[6] δ 5.18 and 4.78 (ABq, 2 H, J = 15), 4.78 (s, 1 H), 4.22 (q, 2 H, J = 7), 1.23 (t, 3 H, J = 7)).

Other reaction conditions were attempted: (1) Sodium in hot Me_2SO according to Thibault[7] yielded 45% of the product after

(25) Hodgson, H. H.; Heyworth, F. *J. Chem. Soc.* **1949**, 1131.

(26) Pifferi, G.; Testa, E. *Tetrahedron* **1966**, *22*, 2107.

(27) Davies, W.; Perkin, W. H. *J. Chem. Soc.* **1922**, *121*, 2202.

chromatography and (2) KO-*t*-Bu (potassium *tert*-butoxide) in cold toluene (according to Sief[15]) gave a 40% yield of the β-keto ester.

Ethyl [(2-Cyanobenzyl)oxy]acetate (16). The sodium salt of ethyl glycolate was prepared with NaOEt (0.08 mol) and ethyl glycolate (0.16 mol) in Me_2SO (5 mL), as previously. A solution of α-bromo-*o*-tolunitrile (**15**) (Aldrich, 15.6 g, 0.08 mol) in 15 mL of dry Me_2SO was added dropwise to the basic mixture over a 45-min period. The mixture was stirred at room temperature until it solidified (1 h) and then at 56–70 °C for 5 h. Once cold, the mixture was quenched with ice (20 g) and extracted with ether (4 × 50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. Distillation of the resulting amber oil at 120–128 °C (0.05 mm) yielded 11.9 g (71.2%) of product: IR (film) 2230 (C≡N), 1752 (C=O), 1210 cm^{-1} (O–CH_2); NMR δ 7.66 (m, 4 H), 4.86 (s, 2 H), 4.25 (m, 4 H), 1.33 (t, 3 H, J = 7). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.73; H, 5.97; N, 6.38. Found: C, 65.57; H, 5.93; N, 6.24.

[(2-Carboxybenzyl)oxy]acetic Acid (17). Sodium hydroxide (0.73 g, 18.2 mmol) was dissolved in diethylene glycol (20 mL) and water (few drops) with the aid of heat. Ester **16** (1.0 g, 4.56 mmol) was added in one portion, and the mixture was refluxed for 12 h. The cooled amber solution was acidified to pH 1. A tan solid precipitated as the solution became acidic. The solid was filtered and dissolved in saturated aqueous Na_2CO_3 solution. The resulting solution was decolorized and reacidified. The white precipitate was filtered and dried in a vacuum oven at 60 °C. The solid weighed 0.4 g (42%) and melted at 154–156 °C (lit.[6] mp 160 °C): IR (nujol) 1740 (C=O), 1675 cm^{-1} (C=O aromatic); NMR δ 11.16 (br s, 2 H, disappeared with D_2O), 7.5 (m, 3 H), 5.0 (s, 2 H), 4.18 (s, 2 H). Spectra match those reported,[7] and those of the compound obtained by saponification of the corresponding diethyl ester **11**.

2-Isochroman-4-one (1a). Method I. Decarboxylation of β-Keto Ester 13. The procedure of Normant-Chefnay[6] was followed. Recrystallization from hexane gave 0.5 g of solid: mp 50–53 °C (lit.[6] mp 54.5 °C); IR (nujol) 3340 (OH enolic), 1690 (C=O), and 1600 cm^{-1} (C=C, enolic); NMR δ 8.0 (m, 1 H), 7.3 (m, 3 H), 4.81 (s, 2 H), 4.3 (s, 2 H).

Since the mother liquor generated a purple color upon testing with $FeCl_3$, it was stripped of solvent and decarboxylated with base, as was done previously. Workup yielded an additional 0.14 g of solid (total 0.64 g, 44%). The basic layer was acidified and extracted with ether. However, evaporation of the solvent led to no residue.

Decarboxylation under acidic conditions (10% aqueous HCl) was also attempted, yielding a 30% mixture of starting material and product (mostly product). Presumably the enol form of the β-keto ester, being an enol ether, undergoes hydrolysis and therefore ring cleavage.

Method II. Perkin Condensation of Diacid 17. A procedure patterned after that of Thibault[7] was adopted. A mixture of diacid **17** (0.7 g, 3.3 mmol) and freshly fused potassium acetate (1.4 g, 14.2 mmol) in acetic anhydride (10 mL) was heated at reflux for 1 h. After evaporation of the excess acetic anhydride, the white residue was dissolved in water and extracted with ether (4 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and saturated NaCl solution and dried over Na_2SO_4, and the solvent was evaporated to yield 0.43 g of yellow oil, presumably 4-acetoxyisochromene. Treatment of this oil with 10 mL of 5% ethanolic KOH at room temperature for 2 h led to 0.12 g of product with the same physical properties and spectral data as above.

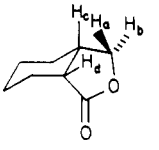
Attempt To Reduce 2-Isochroman-4-one (1a). To a 250-mL Parr bottle containing 0.4 g of the 5% Rh/C catalyst was added, slowly, a solution of 0.5 g of **1a** in 20 mL of absolute EtOH. The mixture was shaken for 12 h. There was no visible hydrogen uptake after 6 h (amount absorbed less than the calculated amount). The catalyst was then removed by filtration through a Celite bed, and the filtrate concentrated to yield 0.45 g of yellow semisolid material, which was triturated with warm cyclohexane and filtered. The resulting yellow solution was concentrated and the residue was analyzed by GLC (Carbowax 20M, 190 °C). The chromatogram of this material gave 4 peaks (one of which, consisting of 75% of the mixture, corresponded to starting material): IR (neat) 3300 (OH), 1730 cm^{-1} (C=O). The NMR spectrum showed signals similar to those of the starting material in addition to a small asymmetric singlet at δ 2.6 ($ArCH_3$) and a multiplet at δ 0.90 (alicyclic CH_3). The solid, insoluble in $CDCl_3$, was not identified (mp 180–185 °C).

When the reduction was carried out with smaller catalyst-to-substrate ratio, and/or for a longer time, the only variable was the amount of starting material in the product mixture. This was at its lowest with the reaction conditions described above.

Attempt To Reduce Ethyl [(2-Carbethoxybenzyl)oxy]acetate (11). A solution of diester **11** (1.5 g, 5.5 mmol) in 30 mL of absolute EtOH was stirred at room temperature with two teaspoons of Ra Ni (W-2, Grace) for 0.5 h and then filtered. Evaporation of the solvent left 1.46 g of a liquid with a rather pleasant odor. In addition to the signals of the diester, the NMR spectrum of the liquid displayed another singlet at δ 2.66 characteristic of methyl groups attached to an aromatic ring. A solution of this material in anhydrous MeOH (13 mL) was slowly added to a 250-mL Parr bottle containing 0.8 g of the 5% Rh/C catalyst and shaken for 6 h (uptake of H_2 was almost twice that of the calculated amount). The catalyst was removed by filtration through a Celite mat and rinsed several times with chloroform. The combined filtrate was concentrated to yield 0.64 g of yellow residue. Flash chromatography of the residue using 4:1 hexane–EtOAc yielded 0.50 g of clear liquid: IR (neat) 1730 cm^{-1} (C=O); NMR δ 4.66 (q, 2 H, J = 7), 2.5 (br m, 1 H), 1.56 (br m, 9 H), 1.3 (t, 3 H, J = 7), 0.96 (d, 3 H, J = 7).

When the reductions were carried out with either lower catalyst-to-substrate ratio or shorter time, the results were either no reaction or a mixture of hydrogenolysis and reduced hydrogenolysis products.

***cis*-Hexahydrophthalide (20).** A solution consisting of MeOH (40 mL), glacial acetic acid (0.5 mL), and phthalide (**10**) (Aldrich, 5.0 g, 37 mmol) was slowly added to a 500-mL Parr bottle containing 1.2 g of 5% Rh/C. After this mixture was shaken at room temperature for 2.2 h, the required amount of H_2 was adsorbed, and the catalyst was removed by filtration thru a Celite bed. Concentration of the solution led to 5.05 g of reduced material. Distillation at 70 °C (0.2 mm) (lit.[28] bp 131–132 °C (18 mm)) yielded 4.8 g (92%) of the product as a clear liquid: IR (film) 1770 cm^{-1} (C=O lactone) (lit.[28] 1786 cm^{-1}); NMR a sharp multiplet centered at δ 4.13 (7 peaks) accounting for the H_a and H_b (see below), a broad multiplet at 2.66 (H_c and H_d), and a very broad multiplet between 2.0 and 1.0 accounting for the remaining 8 protons.



This reduction also occurred without the acetic acid in the same time span.

Diethyl 2-(Bromomethyl)terephthalate. Benzylic bromination was effected with NBS in 90% yield. Recrystallization from hexane gave a white solid which had a mp 49–51 °C: IR (nujol) 1730 cm^{-1} (C=O); NMR δ 8.03 (m, 3 H), 5 (s, 2 H), 4.46 (2 H, J = 7), 4.44 (q, 2 H, J = 7), 1.45 (t, 3 H, J = 7), 1.43 (t, 3 H, J = 7). Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.53; H, 4.79. Found: C, 49.31; H, 4.74.

5-Carbethoxyphthalide (22). A flask containing the above bromo diester (3.3 g, 10.4 mmol) was immersed in an oil bath (preheated to 190–200 °C) and allowed to remain there for 1 h. The dark residue was recrystallized from a 95% ethanol–hexane mixture, giving 1.53 g of yellow solid. After dissolving in chloroform, treating with decolorizing charcoal, and recrystallizing with absolute ethanol, 1.23 g (57%) of product, as needle-like crystals, was obtained: mp 148–150 °C; IR (film) 1750 (C=O lactone), 1720 cm^{-1} (C=O ester); NMR δ 7.82 (m, 3 H, aromatic), 5.41 (sharp s, 2 H), 4.46 (q, 2 H, J = 7), 1.43 (t, 3 H, J = 7). Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.00; H, 5.01. The gas which evolved from the reaction was trapped (dry ice/isopropyl alcohol trap), and an NMR spectrum of the resulting

(28) Christol, H.; Donche, A.; Plenat. F. *Bull. Soc. Chim. Fr.* **1966**, 2535.

liquid was obtained: δ 3.43 (q, 2 H, J = 6), 1.66 (t, 3 H, J = 6), consistent with ethyl bromide. The liquid evaporated on standing.

Diethyl 4-(Bromomethyl)isophthalate. This material was prepared as before from **4** and NBS in a 65% yield after recrystallization from hexane: mp 74–76 °C; IR (nujol) 1720 cm^{-1} (C=O); NMR δ 8.6 (br s, 1 H), 8.13 (br d, 1 H, J = 9), 7.53 (d, 1 H, J = 9), 5.0 (s, 2 H), 4.56 (d of d, 4 H, J = 1, 7), 1.52 (t of t, 6 H, J = 1, 7). Anal. Calcd for $C_{13}H_{15}BrO_4$: C, 49.53; H, 4.79. Found: C, 49.39; H, 4.74.

6-Carbethoxyphthalide (23). The above bromo diester (1.2 g, 3.8 mmol) in a 5-mL round-bottomed flask was heated in an oil bath (preheated at 180 °C) for 1 h. Once cooled, the dark residue was recrystallized from 95% ethanol to yield 0.4 g (51%) of fine needle-like crystals: mp 118–119 °C; IR (film) 1755 (C=O lactone), 1715 cm^{-1} (C=O ester); NMR δ 7.93 (m, 3 H, aromatic), 5.41 (sharp s, 2 H), 4.43 (q, 2 H, J = 7), 1.43 (t, 3 H, J = 7); MS, *m/e* (relative intensity) 206 (20), 178 (20), 161 (100), 149 (46).

5-Carbethoxyhexahydrophthalide. Phthalide **22** (1.25 g, 6.06 mmol) was dissolved with the aid of heat in absolute ethanol (90 mL). Tetrahydrofuran (10 mL) was added to the hot solution. Once cooled (no precipitate), the solution was added to a 250-mL Parr bottle containing 0.77 g of 5% Rh/C catalyst. The bottle was shaken for 12 h while the mixture was kept at 60 °C by means of a thermocouple immersed into the mixture. The cooled mixture was filtered, and the catalyst was washed several times with $CHCl_3$ to yield 1.2 g of yellow solid. Recrystallization from ether/hexane produced 0.80 g (62%) of needle-like crystals: mp 72–74 °C; IR (film) 1760 (C=O lactone), 1725 cm^{-1} (C=O ester); NMR (100 MHz) δ 4.24 (d of d, 1 H, J = 4, 5), 4.14 (q, 2 H, J = 7), 4.09 (d, 1 H, J = 9), 2.77 (t, 1 H, J = 5), 2.54 (sextet, 1 H, J = 5), multiplet between 2.2 and 1.32 (7 H), and 1.24 (t, 3 H, J = 7); MS *m/e* (relative intensity) 212 (30), 167 (35, M – 45), 139 (32, M – 73), 95 (100, M – 117). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.59. Found: C, 62.35; H, 7.52.

6-Carbethoxyhexahydrophthalide. Phthalide **23** (0.6 g, 2.9 mmol) was dissolved with the aid of heat in absolute ethanol (60 mL). While still hot, tetrahydrofuran (5 mL) was added. The reaction conditions were the same as above, yielding 55% of product as a slightly yellow solid (mp 50–54 °C after recrystallization from ether/hexane solvent mixture): IR (film) 1760 (C=O lactone), 1730 cm^{-1} (C=O ester); NMR δ 4.20 (broad s, 1 H), 4.15 (q, 2 H, J = 7), 4.05 (d, 1 H, J = 10), 2.75 (m, 1 H), 2.5–1.65 (8 H), 1.3 (t, 3 H).

Ethyl *cis*-2-(Chloromethyl)cyclohexanecarboxylate (24). The published procedure[18] was slightly modified. A solution of reduced phthalide **20** (4.18 g, 29.8 mmol) in absolute ethanol (30 mL) was cooled to 0 °C, and, at this temperature, gaseous HCl was bubbled through for a 2-h period. The solution was left stirring at 0 °C for 19 h and then warmed to room temperature. The solvent was evaporated and the yellowish residue was dissolved in $CHCl_3$ and evaporated again to remove residual HCl. The yellowish oil was dissolved in ether and the solution was dried ($MgSO_4$) and concentrated to yield 4.48 g of yellow oil. Flash chromatography with 3:1 hexane–EtOAc as the solvent mixture gave 4.3 g (70%) of clear liquid: IR (neat) 1720 cm^{-1} (C=O ester); NMR δ 4.16 (q, 2 H, J = 7), 3.6 (d, 2 H, J = 7), 2.83 (m, 1 H), 1.51 (m, 9 H), 1.23 (t, 3 H, J = 7).

Ethyl *cis*-2-(Bromomethyl)cyclohexanecarboxylate (25). A solution of hexahydrophthalide **20** (1.25 g, 8.9 mmol) in absolute ethanol (40 mL) was cooled to 0 °C, and then HBr gas was bubbled through for $3^1/_2$ h, the solution turning yellow. After workup as above, 1.9 g of yellowish liquid was obtained. Flash chromatography using 3:1 hexane–EtOAc as the eluting solvent gave 1.7 g (76%) of product as slightly yellowish liquid (very pleasant odor): IR (neat) 1725 cm^{-1} (C=O ester); NMR δ 4.16 (q, 2 H, J = 7), 3.45 (d, with shoulder, 2 H, J = 7), 2.83 (broad s, 1 H, W/2 = 10), 1.63 (m, 9 H), 1.26 (t, 3 H, J = 7); MS *m/e* (relative intensity) 251 (1.5), 249 (1.5), 169 (3), 141 (5), 123 (21), 95 (100).

Attempted Preparation of Ethyl [(2-Carbethoxyperhydrobenzyl)oxy]acetate. To a flask containing sodium hydride (0.42 g, 17.5 mmol, previously washed twice with benzene) was added dry Me_2SO (10 mL). Then at 18 °C a solution of ethyl glycolate (Eastman, 1.45 g, 13.9 mmol) in dry Me_2SO (15 mL) was added dropwise. After stirring for 2 h (the NaH had dissolved after 1 h), the mixture turned amber in color. The γ-chloro ester **24** (3.0 g, 14.6 mmol) dissolved in Me_2SO (10 mL) was added slowly to the amber mixture, and stirred for 18 h at room temperature. GLC showed no starting material. The mixture was poured into ice cold H_2O (150 mL) and extracted with ether (10 × 20 mL). The combined ether solutions were washed with H_2O (9 × 20 mL) and saturated NaCl solution and dried ($MgSO_4$), and the solvent was evaporated to yield 2.42 g of yellow liquid (sweet odor). Distillation at 37 °C (0.2 mm) yielded 2.2 g of clear liquid (a mixture as per GLC (SE-30, 170 °C) and TLC). Flash chromatography (3:1 hexane–EtOAc) of 1.0 g of the liquid gave 0.80 g of a single component: IR (neat) 3070, 1725 cm^{-1}; NMR (100 MHz) δ 4.10 (q, 2 H, J = 7), 2.48 (quintet, 1 H, J = 4), 1.90 (quintet, 1 H, J = 4), 1.62 (m, 4 H), 1.30 (m, 4 H), 1.23 (t, 3 H, J = 7), 0.63 (d of d, 1 H, J = 4); MS *m/e* (relative intensity) 168 (30), 139 (18), 123 (34), 95 (100); ^{13}C NMR δ 175.9 (C=O ester), 60.1, 24.07, 23.0, 22.12, 21.47, 21.0, 20.5, 20.3, 14.0. Anal. Calcd for $C_{10}H_{16}O_2$ (ethyl bicyclo(4.1.0.)heptanecarboxylate (**26**)): C, 71.39; H, 9.58. Found: C, 71.3; H, 9.52.

Employing the same procedure as for the synthesis of the benzyloxy acetate **11** a product with the same spectral properties as described above was obtained. Upon changing the solvent to DME, the recovery was not as good as in the case of Me_2SO. When a mixture of bromide **25** and ethyl glycolate in HMPA was heated to 60 °C for 30 h, no reaction was detected. Upon workup only 40% of the starting material was recovered.

Methyl Bicyclo[4.1.0]heptanecarboxylate (28). A mixture of NaH (50% dispersion in mineral oil, 0.13 g, 2.5 mmol, previously washed twice with hexane) and ethyl 2-(bromomethyl)cyclohexane-1-carboxylate (**25**) (0.5 g, 2 mmol) in Me_2SO (5 mL) was stirred at room temperature for 16 h. Once cooled, the mixture was quenched with ice cold H_2O and acetic acid. Workup consisted of extracting with ether (5 × 10 mL), washing the combined organic layers with H_2O (3 × 10 mL) and saturated NaCl solution, drying ($MgSO_4$), and evaporating the solvent to furnish 0.38 g of yellow oil as a mixture of starting material and acid **27**. The crude product was dissolved in ether and cooled to 5 °C, and an ethereal solution of diazomethane was added until the bright yellow color persisted. Evaporation of the solvent gave 0.35 g of liquid. Its NMR spectrum exhibited a multiplet at δ 0.7 typical of cyclopropyl derivatives and was otherwise similar to the ethyl ester previously obtained.

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Registry No. **1a**, 20924-56-5; **2**, 93-89-0; **3**, 87-24-1; **4**, 96259-57-3; **5**, 96259-58-4; **6**, 1943-88-0; **7**, 3347-99-7; **8**, 7115-91-5; **9**, 96259-59-5; **10**, 87-41-2; **11**, 20924-53-2; **12**, 96259-60-8; **13**, 32521-19-0; **15**, 22115-41-9; **16**, 96259-61-9; **17**, 20924-54-3; **19**, 56532-18-4; **20**, 6939-71-5; **22**, 23405-31-4; **23**, 96259-62-0; **24**, 90976-97-9; **25**, 96259-63-1; **26**, 96259-64-2; **27**, 96259-65-3; **28**, 92984-25-3; ethyl 3-cyano-4-methylbenzoate, 96259-68-6; 4-(acetyloxy)-(1*H*)-2-benzopyran, 20924-55-4; *o*-toluic acid, 118-90-1; 2,4-dichlorotoluene, 95-73-8; 2-methylterephthalonitrile, 55984-93-5; 2,5-dichlorotoluene, 19398-61-9; 2-methylterephthalic acid, 5156-01-4; ethyl cyclohexanecarboxylate, 3289-28-9; ethyl glycolate sodium salt, 38233-96-4; diethyl 2-(bromomethyl)terephthalate, 96259-69-7; diethyl 4-(bromomethyl)isophthalate, 96259-71-1; 5-carbethoxyhexahydrophthalide, 96259-70-0; 6-carbethoxyhexahydrophthalide, 96259-72-2; ethyl [(2-carbethoxyperhydrobenzyl)oxy]acetate, 96259-73-3; ethyl glycolate, 623-50-7; ethyl 2-methylcyclohexanecarboxylate, 56532-18-4; diethyl 4-methyl-1,3-cyclohexanedicarboxylate, 96259-66-4; diethyl 2-methyl-1,4-cyclohexanedicarboxylate, 96259-67-5.