2,5- or 1,4-twist form, depending on the location of the geminal substitution in position 2 or 4, respectively. The chair–twist enthalpy difference for the 1,4-twist form appears to be ca. 5 kJ mol^{-1} smaller than that for the 2,5-twist form. Two small discrepancies between our present results and Burkert's molecular mechanics calculations still remain. First we conclude that compounds **4–6** exist predominantly if not exclusively in the 2,5-twist form whereas according to Burkert's calculations the chair form has an appreciable contribution. Second, the question about the influence of the substitution on the chair–twist enthalpy difference cannot be exactly answered. This is not, however, crucial since the experimental results[3,4b,12] apply very well to those cases where the twist form really has an important role whereas Burkert's calculations[4a] deal with the unsubstituted ring.

(iii) Last but not least we emphasize the importance of different experimental approaches like thermochemistry,[3a,c,d,f–h,4b] mass spectrometry,[3e] ^{1}H and ^{13}C NMR spectroscopy,[2,5,6,11,12] X-ray results,[9] and succesful molecular mechanics calculations[4a] in defining the detailed molecular structures.

Registry No. 3, 21589-58-2; 4, 20268-00-2; 5, 28231-59-6; 6, 36376-78-0; 7, 56444-60-1; 8, 32560-29-5; 9, 35776-46-6; 10, 35776-45-5; 11, 35776-44-4; 12, 83115-78-0.

Ester Enolates from α-Acetoxy Esters. Synthesis of Aryl Malonic and α-Aryl Alkanoic Esters from Aryl Nucleophiles and α-Keto Esters

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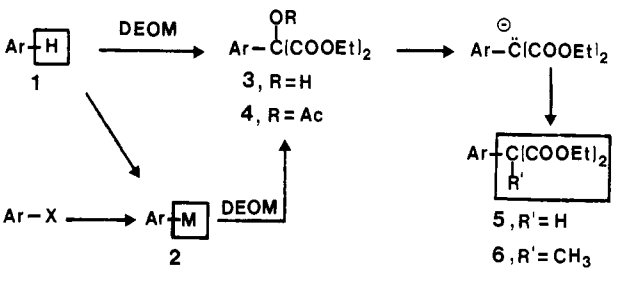
Received February 9, 1982

Ester enolates are generated by reductive α-deacetoxylation of α-acetoxy-α-arylmalonic esters or α-acetoxy-α-arylalkanoic esters with lithium in liquid ammonia or sodium α-(dimethylamino)naphthalenide in hexamethylphosphoramide–benzene. Since the requisite α-acetoxy esters are available from aryl nucleophiles, the reductions provide effective new synthetic routes to arylmalonic esters and α-arylalkanoic esters. For example, 2-(*p*-isobutylphenyl)propionic acid (ibuprofen, a commercially important nonsteroidal antiinflammatory agent) is obtained in 73% yield overall from isobutylbenzene. Arenes, aryllithiums, or arylmagnesium halides react with α-keto esters, e.g., diethyl oxomalonate, ethyl pyruvate, methyl phenylglyoxalate, or alkyl glyoxylates, to afford α-hydroxy esters. These are acetylated with acetic anhydride–triethylamine and *p*-(dimethylamino)pyridine as a catalyst. Reductive α-deoxygenation then allows replacement of the acetoxy group by hydrogen or an alkyl group.

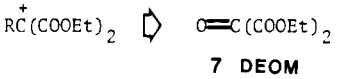
Arylmalonic acid esters are important rudimentary synthons inter alia for preparation of medicinally valuable nonsteroidal antiinflammatory agents and barbiturates.[1] Arylation of malonic ester carbanions is of limited utility since electrophilic arylating agents are not generally available. We now report widely applicable new synthetic methodology which exploits diethyl oxomalonate (DEOM) as a malononium equivalent for construction of diethyl arylmalonates **5** or **6** from aryl nucleophiles **1** or **2** (Scheme I). The conversion depends on our recent discovery of effective methods for reductive deoxygenation and reductive alkylation of α-acetoxymalonates **4**.[2] We also report analogous syntheses of α-arylalkanoic esters from α-oxoalkanoic esters.

Construction of arylmalonic esters from aryl *electrophiles* and malonate carbanions is sometimes achievable via benzyne intermediates.[3] However, this approach is unattractive for preparing ring-substituted arylmalonates because it produces positional isomers. Thus, electrophilic attack occurs nonselectively at both carbons of the formal C≡C bond. Regiospecific replacement of the aryl nucleofuge by a malonate nucleophile does occur, by an addition–elimination sequence, if ortho or para electron-withdrawing substituents such as nitro or acyl groups are present.[4-6] Aryl bromo substituents situated ortho to a carboxylate group exhibit a unique susceptibility in the presence of copper(I) salts toward substitution by malonate carbanions.[7] Copper(I) salts promote a more general replacement of aryl iodo substituents by malonate carbanions, especially in hexamethylphosphoric triamide solutions.[8]

Scheme I



In view of the wide availability of aromatic *nucleophiles*, it is remarkable that no synthetic method is known which exploits these synthons in reactions with a carbon electrophile to produce diethyl arylmalonates. This gap in synthetic methodology prompted us to explore the possibility that diethyl oxomalonate (DEOM, **7**) can serve a malononium ion equivalent.



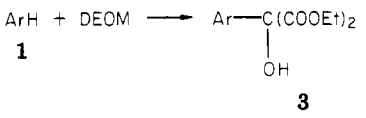
7 DEOM

(1) Lednicer, D.; Mitcher, L. A. "The Organic Chemistry of Drug Synthesis"; Wiley: New York, 1977; Vo. 1, pp 85–92, 267–77; 1980, Vol. 2, pp 63–82.
(2) Pardo, S. N.; Ghosh, S.; Salomon, R. G. *Tetrahedron Lett.* **1981**, *22*, 1885.
(3) Leake, W. W.; Levine, R. *J. Am. Chem. Soc.* **1959**, *81*, 1629.
(4) Sen, A. B.; Bhargava, P. M. *J. Indian Chem. Soc.* **1947**, *24*, 371.
(5) Atkinson, J. G.; et al. *Tetrahedron Lett.* **1979**, 2857.
(6) Williams, H. W. R.; et al. *J. Org. Chem.* **1979**, *44*, 4060.
(7) Hurtly, W. R. H. *J. Chem. Soc.* **1929**, 1870.
(8) Semmelhack, M. F.; et al. *J. Am. Chem. Soc.* **1975**, *97*, 2507.

0022-3263/82/1947-4692$01.25/0

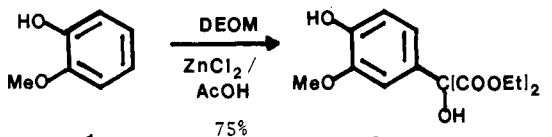
Results and Discussion

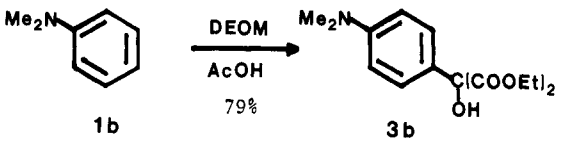
Synthesis of Diethyl Aryltartronates. (A) Electrophilic Aromatic Substitution. Diethyl aryltartronates (3, α-aryl-α-hydroxymalonates) can be pre-



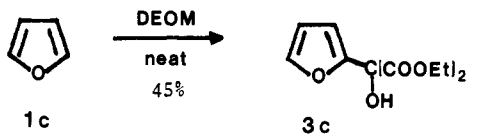
1 3

pared in good to excellent yields from arenes by reactions with DEOM.[9-13] Phenols in acetic acid solution react readily in the presence of zinc chloride, a mild Lewis acid catalyst,[9] whereas *N,N*-dimethylaniline (**1b**) in acetic acid

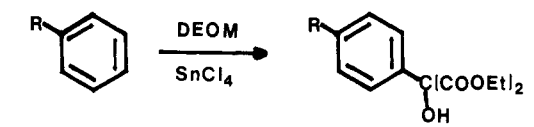


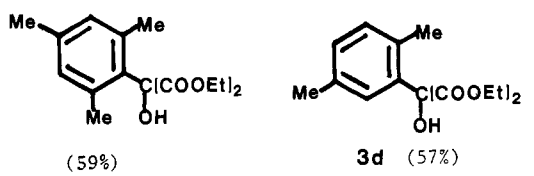


solution reacts in the absence of catalyst.[10] The hydroxyl and dimethylamino substituents strongly orient the substitution to the para position. Pure **3a** or **3b** are isolated in high yields by simple crystallization.[9,10] Furan undergoes substitution in the 2-position to give isomerically pure **3c**



by reaction with DEOM in the absence of solvent.[11] Also, highly regioselective C–C bond formation para to alkyl substituents is observed in $SnCl_4$-catalyzed reactions of DEOM with alkylbenzenes.[12] Ortho substitution is found

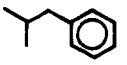
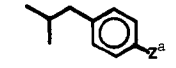
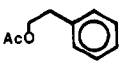
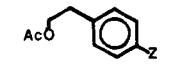
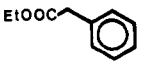
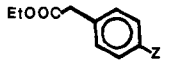
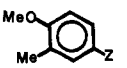
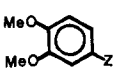
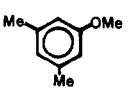
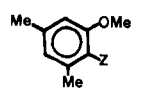
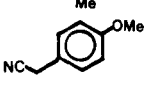
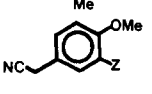
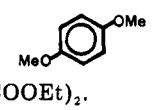
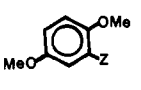




when the para position is occupied.[13] Thus, DEOM behaves as a sterically demanding electrophile.

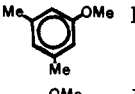
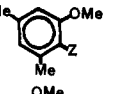
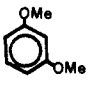
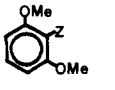
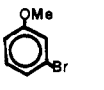
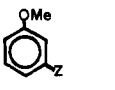
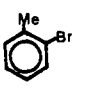
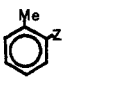
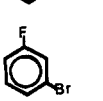
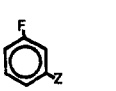
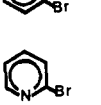
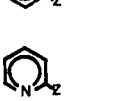
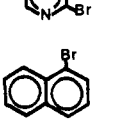
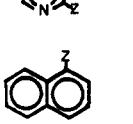
We further explored the scope and selectivity of the $SnCl_4$-catalyzed reaction of DEOM with alkyl- and methoxybenzenes (Table I). All reactions were performed with 1.25 equiv of $SnCl_4$ in CH_2Cl_2 at room temperature for 3 h. Yields of diethyl aryltartronates **3e–g** from isobutyl-

Table I. $SnCl_4$-Catalyzed Reactions of DEOM with Arenes

entry	arene 1	diethyl aryltartronate 3	yield, %
e			94
f			54
g			5
h			71
i			87
j			77
k			82
l			100

[a] Z = C(OH)(COOEt)$_2$.

Table II. Synthesis of Diethyl Aryltartronates from Aryl Organometallics

entry	aryl halide or arene 1	activating agent	diethyl aryltartronate 3	yield, %
c		BuLi		52
j		BuLi		13
m		BuLi		41
n		Mg		74
o		Mg		87 (30)[15]
p		Mg		48
q		BuLi		27
r		Mg		(40)[15]

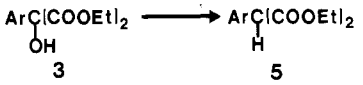
[a] Z = C(OH)(COOEt)$_2$.

(9) Guyot, A.; Gry, A. *C. R. Hebd. Seances Acad. Sci.* **1909**, *148*, 929.
(10) Guyot, A.; Martinet, J. *C. R. Hebd. Seances Acad. Sci.* **1913**, *156*, 1625.
(11) Achmatowicz, O., Jr.; Zmojsk, A. *Rocz. Chem.* **1968**, *42*, 453–8.
(12) (a) Ando, T. *Nippon Kagaku Kaishi* **1935**, *56*, 745–56. (b) Riebsomer, J. L.; Irvine, J.; Andrews, R. *J. Am. Chem. Soc.* **1938**, *60*, 1015–6. (c) Riebsomer, J. L.; Baldwin, R.; Buchanan, J.; Burkett, H. *Ibid.* **1938**, *60*, 2974–6. (d) Riebsomer, J. L.; Staufer, D.; Glick, F.; Lambert, F. *Ibid.* **1942**, *64*, 2080–1.
(13) Riebsomer, J. L.; Irvine, J. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 326.

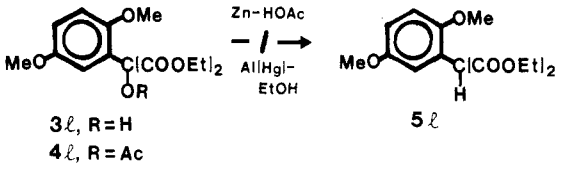
benzene, (β-acetoxyethyl)benzene and ethyl phenylacetate, respectively, decreased sharply as a result of relatively small decreases in nucleophilicity. Substitution para to a methoxy group is usually favored over ortho substitution. The isomerically pure products **3g–i** were isolated, in the yields indicated, by a single fractional crystallization from the crude reaction product. For **1j** in which the para position is flanked by two methyl groups, substitution occurs ortho to the less sterically demanding methoxy group to give **3j**. This regioselectivity was confirmed by an alternative synthesis of **3j** (see Table II below). Substitution ortho to a methoxy group occurs in high yields (Table I, entries k and l) if the para position is occupied.

(B) Reaction of Arylmagnesium Halides and Aryllithiums with DEOM. Though often useful, the high and predictable positional selectivity of electrophilic aromatic substitution with DEOM precludes application of this reaction for preparation of certain diethyl aryltartronates, i.e., meta and sometimes ortho isomers. However, many substituents can direct an alternative regiospecific enhancement of nucleophilicity. Thus, many substituents promote ortho proton abstraction ("ortho metalation") by coordination with the metal counterion of strong bases.[14] The resulting aryl organometallic can react with electrophiles, resulting in net electrophilic aromatic substitution at the ortho position. Organometallic reagents not available by ortho metalation of arenes often can be prepared from aryl halides. In fact, DEOM was reported to afford diethyl aryltartronates in low yields by reaction with aryl Grignard reagents.[15] Not surprisingly, we found that yields can be dramatically improved by slow inverse addition of an organometallic to an ether solution of DEOM cooled to −78 °C (Table II).

Synthesis of Diethyl Arylmalonates. The α-carbonyl group of DEOM imparts the required electrophilicity to the central carbon of this malonyl synthon allowing C–C bond formation with nucleophilic aryl synthons. Completion of a synthesis of arylmalonates **5** depends on removal of the vestigial α-hydroxyl group of the intermediate aryltartronates **3**.



Reductive α-deoxygenation of α-hydroxy or α-acetoxy *ketones* can be accomplished by various dissolving-metal reactions. However, both α-hydroxymalonate **3l** and α-

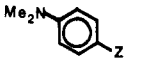
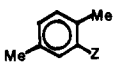
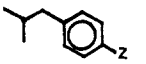
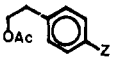
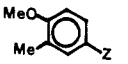
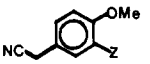
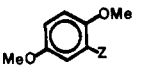
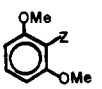
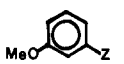


3ℓ, R = H
4ℓ, R = Ac

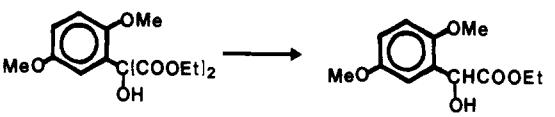
5ℓ

acetoxymalonate **4l** were recovered unreduced after treatment with zinc in acetic acid[18] or with aluminum amalgam in aqueous ethanol.[19] Lithium plus ammonium chloride in liquid ammonia is effective for deoxygenation of simple benzylic alcohols.[16] However, the method fails with tartronates **3** because the carboethoxy groups are not stable under the reaction conditions. Thus **3l** was consumed by the reagent, but the desired arylmalonate **5l** was not obtained. The major product isolated (16% yield), mandelate **8**, arises by decarboethoxylation of **3l** and not by reductive deoxygenation. Attempted reductive deoxygenation of **3l** with sodium α-(dimethylamino)-naphthalenide (NaDMANp) in hexamethylphosphoramide (HMPA) was similarly unrewarding.

Table III. Synthesis of Diethyl Arylmalonates from Diethyl Aryltartronates

entry	aryltartronate 3[a]	% yield 4	% yield 5
b		100	53
c		90	81
d		100	70
e		85	95
f		84	80
h		89	78
k		85	95
l		63	95
m		66	50
n		86	78
o		74	95
q		41	80

[a] Z = C(OH)(COOEt)$_2$.

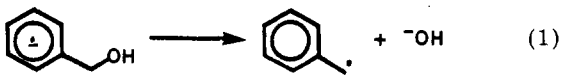


Benzylic acetates are reductively cleaved by lithium in liquid ammonia in the presence of *tert*-butyl alcohol.[20a,b] Similar reduction of α-acetoxy-α-arylmalonic esters would be favored by the generation of acetate, a more stable anion than hydroxide. Moreover, generation of hydroxide, which might cause decarbethoxylation, would be avoided. Perhaps most significantly, if such reductions could be preformed under aprotic conditions, alkylation of the intermediate α-arylalkanoic ester carbanions would be possible. The requisite acetylation of the hindered tertiary alcohols **3** was readily achieved with acetic anhydride and triethylamine in the presence of the acylation catalyst, *p*-(dimethylamino)pyridine (DMAP).[17]

(14) For a review see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–360.
(15) Lapkin, I.; Golovkova, A. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1948**, *18*, 494–5; *Chem. Abstr.* **1948**, *42*, 7273h.
(16) Hall, S. S.; Lipsky, S. D. *J. Org. Chem.* **1973**, *38*, 1735–8 and references cited therein.
(17) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(18) (a) Dutcher, J. D.; Johnson, J. R.; Bruce, W. F. *J. Am. Chem. Soc.* **1945**, *67*, 1736–46. (b) Rosenfeld, R. S. *Ibid* **1950**, *72*, 4077–80.

(A) Reductive Deoxygenation of α-Acetoxymalonates (4). Although reductive deoxygenation with lithium in liquid ammonia failed with α-hydroxymalonate **3l**, α-acetoxymalonate **4l** is deacetoxylated in excellent yield with this reagent.[20] We also discovered that malonates **5** are produced in good to excellent yields by adding a solution of sodium α-(dimethylamino)naphthalenide[21] in hexamethylphosphoramide[22] to a benzene solution of the acetate **4** (Table III). The dark green color of the naphthalenide anion is discharged rapidly, and the reduction can be done as a titration. Nearly pure diethyl arylmalonates are obtained after extractive removal of the aminonaphthalene with aqueous HCl. We prefer the later method for small scale reductions. However, considering the health hazard and cost of HMPA, we recommend the liquid ammonia procedure for larger scale preparations.

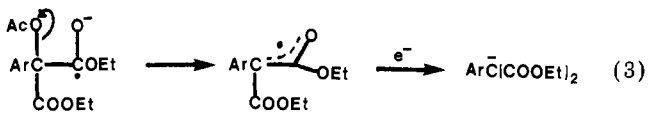
These reductive deacetoxylations are probably *not* related mechanistically to deoxygenations of benzylic alcohols with lithium and ammonium chloride in liquid ammonia.[16] The latter reactions almost certainly involve key aryl anion–radical intermediates which eliminate benzylic hydroxide (eq 1). Such a mechanism would be particularly



(1)

unfavorable for electron rich aryltartronate derivatives such as **4l** or **4m**. Rather, the reductive deacetoxylations may be related mechanistically to reductive deoxygenation of benzylic acetates with Li and *t*-BuOH in liquid NH_3[20a] or of alkyl acetates with Na and *t*-BuOH in HMPA[23a] or Li in $EtNH_2$[23b] which probably involve acetate–carbonyl anion radicals (eq 2). Or an anion–radical of the ethyl ester–carbonyl group may be involved (eq 3).

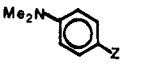
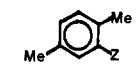
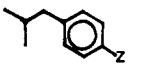
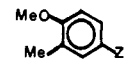
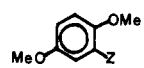
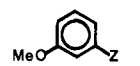
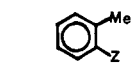
(2)



(3)

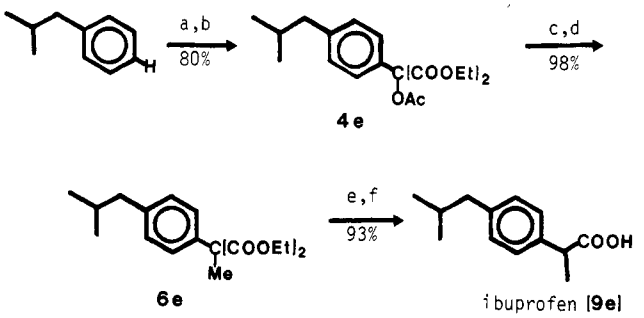
(B) Reductive Alkylation of α-Acetoxymalonates (4). Application of arylmalonic acid esters to the synthesis of drugs such as nonsteroidal antiinflammatory agents often requires α alkylation. The naphthalenide reductive deoxygenation of α-acetoxymalonates **4** is especially convenient for such applications since the intermediate malonate carbanions can be alkylated in situ. For example, 2-arylpropionic acids **9** are readily prepared from acetates **4** by reductive methylation with subsequent hydrolysis and decarboxylation of the resulting diethyl arylmethylmalonate **6** (Table IV). A wide variety of 2-arylpropionic acids show medicinally useful biological activities which are considered to stem from their ability to inhibit the cyclooxygenase enzyme of prostaglandin biosynthesis.[24] Since bioconversion of arachidonic acid into the prostaglandin endoperoxides is blocked, thromboxane and prostacyclin biosynthesis is also prevented. Our new approach to synthesis of 2-arylpropionic acids readily accommodates structural variations which are of interest for fine tuning of biological activities. The 2-arylpropionic acids **9d,h,l,o** are all new compounds. Furthermore, the commercially important antiinflammatory agent ibuprofen (**9e**) is obtained from isobutylbenzene in 73% overall yield (Scheme II).

Table IV. Synthesis of 2-Arylpropionic Acids from Aryltartronates via Reductive Alkylation

entry	diethyl acetoxyaryl-malonate 4 [a]	% yield: arylmethyl-malonate 6	% yield: 2-aryl-propionic acid 9
b		64	85
d		94	74
e		98	93
h		94	81
l		60	89
n		81	89
o		72	83

[a] Z = C(OAc)(COOEt)$_2$.

Scheme II [a]



[a] (a) DEOM/$SnCl_4$; (b) Ac_2O/Et_3N/DMAP; (c) Na^+Me_2-NNp^-/HMPA; (d) MeI; (e) $(HOCH_2)_2$/KOH; (f) H_3O^+/Δ.

Recently, isopropylidene malonate and its α-alkyl derivatives (e.g., **11**) were found to provide α-arylated products (e.g., **12**) by reaction with aryllead triacetates (e.g., **10**).[25] Hydrolysis and decarboxylation of **12** also affords ibuprofen. Since the aryllead compounds are obtained by direct plumbylation of arenes, the process provides a route

(19) Rosenfeld, R. S.; Gallagher, T. F. *J. Am. Chem. Soc.* **1955**, *77*, 4367–70.

(20) (a) Markgfraf, J. H.; Basta, S. J.; Wege, P. M. *J. Org. Chem.* **1972**, *37*, 2361. (b) Markgraf, J. H.; Hensley, W. M.; Shoer, L. I. *Ibid.* **1974**, *39*, 3168. (c) This reagent is effective for generating ketone enolates from α-hydroxy and α-acetoxy ketones: Weiss, M. J.; Schaub, R. E.; Allen, G. R., Jr.; Poletto, J. F.; Pidacks, C.; Conrow, R. B.; Coscio, C. J. *Tetrahedron* **1964**, *20*, 357–72.

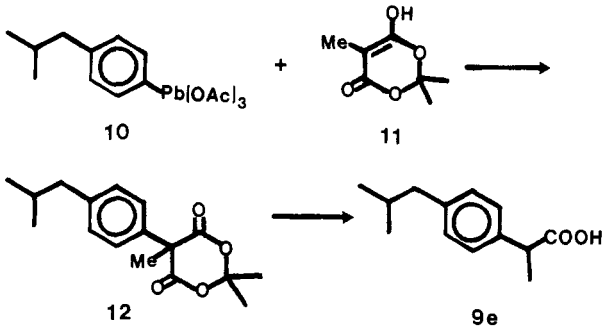
(21) (a) Argelo, B. *Bull. Soc. Chim. Fr.* **1968**, 3855–7. (b) Bank, S.; Platz, M. *Tetrahedron Lett.* **1973**, 2097–100.

(22) For examples of reductions with sodium naphthalenide in HMPA see: Marshall, J. A.; Karas, L. J.; Royce, R. D., Jr. *J. Org. Chem.* **1979**, *44*, 2994–9 and references cited therein.

(23) (a) Dehayes, H.; Pete, J.-P. *J. Chem. Soc., Chem. Commun.* **1978**, 567. (b) Boar, R. B.; Joukhadar, L.; McGuire, J. F.; Misra, S. C.; Barrett, A. G. M.; Barton, D. H. R.; Prokopiou, P. A. *Ibid.* **1978**, 68.

(24) (a) Piper, P. J.; Vane, J. R. *Nature (London)* **1969**, *223*, 29–35. (b) Fitzpatric, F. A.; Wynalda, M. A. *Prostaglandins* **1976**, *12*, 1037–51.

(25) Pinhey, J. T.; Rowe, B. A. *Tetrahedron Lett.* **1980**, 965–8.

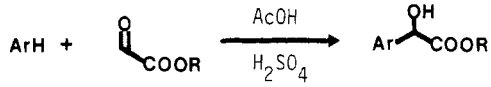


to arylmalonic acid derivatives via initial electrophilic aromatic substitution. But unlike our new method for synthesis of arylmalonic acid derivatives from arenes and DEOM, the aryllead methodology involves nucleophilic malonyl synthons. Furthermore, the yield for plumbylation of isobutylbenzene is only 61%.[25]

(C) Reduction and Reductive Alkylation of α-Acetoxy-α-arylalkanoic Esters. A related alternative synthetic route from aryl nucleophiles to 2-arylpropionic esters involves chemoselective reaction with ethyl pyruvate (13). An example of this approach is provided in Scheme III by reaction of 13 with *p*-tolylmagnesium bromide to afford α-hydroxy ester 14. Addition of the organometallic in ether to a solution of the keto ester at −78 °C gave double the yield obtained previously by addition of the keto ester to the organometallic without cooling.[15] The corresponding acetate 15 is smoothly reduced with lithium in ammonia. Excess lithium must be avoided in reduction of α-acetoxy-α-aryl monoesters since the α-aryl monoester products are reduced further. Thus, alcohol 17 is produced from 15 presumably by Bouvelout–Blanc reduction of 16. This contrasts with most reductions of α-acetoxy malonates which are presumably protected against further reduction by formation of stable enolates.

Chemoselective reaction of methyl phenylglyoxylate (18) with alkyl nucleophiles provides an alternative route for synthesis of α-aryl-α-hydroxy monoesters. For example, this provides novel methodology for synthesis of 1,2-diarylpropionic acids which are of considerable interest as medicinals.[25] Examples of this approach are provided in Scheme IV.

With mild acid catalysis nucleophilic aromatic hydrocarbons react with alkyl glyoxylates[26] or glyoxylic acid[27] to afford mandelates.

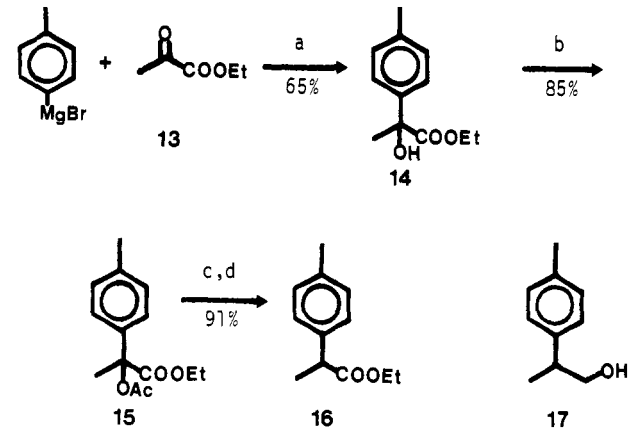


The corresponding acetates can be reductively alkylated. Thus, 20 is obtained in 97% yield in a single step by treatment of 19 in benzene with a slight excess of sodium α-(dimethylamino)naphthalenide in HMPA followed by excess ethyl iodide.

(26) (a) Werber, G.; Buccheri, F. *Gazz. Chim. Ital.* **1966**, *96*, 465–74. (b) Werber, G.; Buccheri, F.; Cusmono, S. *Chem. Abstr.* **1966**, *64*, 12587*h*–12588*f*.

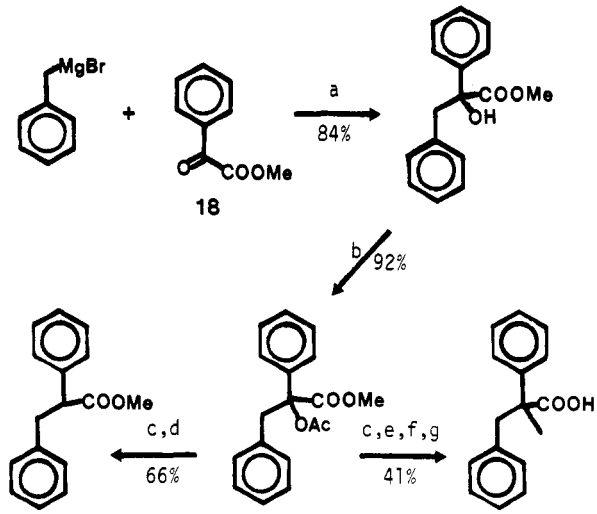
(27) Umemura, S.; Takamitsu, N.; Enomiya, T.; Shiraishi, Y.; Nakamura, T. *Chem. Abstr.* **1979**, *91*, 193005.

Scheme III [a]



[a] (a) −78 °C/Et_2O; (b) Ac_2O/Et_3N/DMAP; (c) Li/NH_3; (d) NH_4Cl.

Scheme IV [a]



[a] (a) −78 °C/Et_2O; (b) Ac_2O/Et_3N/DMAP; (c) $Na^+Me_2NNp^-$/HMPA; (d) H_3O^+; (e) MeI; (f) $(HOCH_2)_2$/KOH; (g) HCl.

Conclusions

Widely applicable new methods for synthesis of α-aryl esters are founded on our recent discovery of reagents which generate ester enolates by reductive α-deacetoxylation of the corresponding acetoxy esters.[2] For example, regiospecific replacement of aryl hydrogen with a malonyl group by direct electrophilic aromatic substitution (usually para) or indirectly after metalation (ortho) is possible with DEOM. Conversion of the intermediate α-hydroxymalonates into malonates or α-methylmalonates is achieved by reductive α-deoxygenation of the derived acetates. These reactions also provide a new method for replacement of aryl halogen by a malonyl group since aryl halides are readily converted to the corresponding organometallic nucleophiles. Generation of ester enolates by reductive α-deacetoxylation is also effective with α-acetoxy-α-aryl carboxylic esters which are readily available from aryl nucleophiles and α-keto esters or glyoxalate esters. It is likely that other important applications of this novel route to ester enolates will be reported in the future.

Experimental Section

General Methods. All melting points are uncorrected and were measured with a Thomas-Hoover capillary melting point

apparatus. Nuclear magnetic resonance spectra were recorded with a Varian A-60A or XL-100FT spectrometer with tetramethylsilane as an internal standard and $CDCl_3$ as the solvent unless otherwise specified. Mass spectra were recorded with a Kratos MS-30 dual-beam mass spectrometer with a Katos DS-50S data system, an ionizing voltage of 70 eV, an acceteration potential of 4000 V, a source temperature of 200 °C, and sample introduction by a direct-inlet probe. Preparative thin-layer chromatography was performed by using precoated 0.5-mm or 2.0-mm silica gel plates (20 × 20 cm, Merck F254). All reactions were conducted under an atmosphere of dry nitrogen.

Materials. Benzene and THF were freshly distilled from potassium benzophenone ketyl. Diethyl ether was freshly distilled from lithium aluminum hydride. Hexamethylphosphoramide (Aldrich) and *N,N*-dimethyl-1-naphthylamine (Eastman) were used without further purification as received. Diethyl oxomalonate was prepared from diethyl malonate by a modification[28] of the Faust–Mayer procedure.[29]

Synthesis of Aryl Tartronates from Arenes. The general method for preparing aryl tartronates from arenes is illustrated with the preparation of **diethyl (4-methoxy-3-methylphenyl)tartronate (3h)**. To an ice-cooled and magnetically stirred solution of *o*-methylanisole (**1h**; 1.46 g, 12 mmol) and diethyl oxomalonate (DEOM; 1.74 g, 10 mmol) in CH_2Cl_2 (5 mL) was added dropwise through a syringe $SnCl_4$ (3.25 g, 12.5 mmol) over 5 min. After the mixture was stirred 10 min in the cold, the ice bath was removed and stirring continued for an additional 3 h at 20 °C during which the reaction mixture turned to a solid mass. The solid mass was combined with a crushed ice–HCl mixture and extracted with ether (3 × 50 mL). The ether extract was washed with water (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to afford crystalline **3h** (2.11 g, 71%). Recrystallization from ether–pentane afforded analytically pure **3h**: mp 60–61 °C; ^1H NMR ($CDCl_3$) δ 1.28 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.21 (s, 3 H, Ar CH_3), 3.80 (s, 3 H, Ar OCH_3), 4.27 (q, 5 H, J = 7 Hz, OH and $CO_2CH_2CH_3$), 6.92 (d, 1 H, J = 9 Hz, Ar H), 7.42 (m, 2 H, Ar H); mass spectrum, m/e (relative intensity) 296.1234 (1.0; calcd for $C_{15}H_{20}O_6$ m/e 296.1260), 262 (0.7), 224 (1.6), 223 (16), 149 (100), 91 (12.4).

Diethyl (4-Isobutylphenyl)tartronate (3e). Reaction of isobutylbenzene (**1e**; 1.34 g, 10 mmol) in CH_2Cl_2 (5 mL) with DEOM (1.74 g, 10 mmol) in the presence of $SnCl_4$ (3.25 g, 12.5 mmol) afforded white crystalline **3e** (2.9 g, 94%). Recrystallization from ether–pentane afforded analytically pure **3e**: mp 116–117 °C; ^1H NMR δ ($CDCl_3$) 0.89 [d, 6 H, J = 6.5 Hz, $CH(CH_3)_2$], 1.28 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.80 (br s, 1 H, OH), 2.48 (d, 2 H, J = 6.5 Hz, $ArCH_2$), 4.34 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.06–7.68 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 308.1659 (0.7; calcd for $C_{17}H_{24}O_5$ m/e 308.1624), 236 (3.9), 235 (13.4), 163 (21.3), 162 (16.6), 161 (100), 118 (7.6), 91 (15.7).

Diethyl [4-(2-Acetoxyethyl)phenyl]tartronate (3f). A mixture of (2-acetoxyethyl)benzene (**1f**; 0.95 mL, 5 mmol) in CH_2Cl_2 (3 mL), DEOM (0.75 mL, 5 mmol), and $SnCl_4$ (0.7 mL, 6.25 mmol) was stirred at 20 °C for 3 days. The usual workup followed by distillation afforded **3f** as a pale yellow liquid: 0.92 g (54%); bp 180–182 °C (0.05 mm); ^1H NMR δ ($CDCl_3$) 1.28 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.02 (s, 3 H, $OCOCH_3$), 2.94 (t, 2 H, J = 7 Hz, $ArCH_2$), 4.29 (t, 2 H, J = 7 Hz, CH_2OAc), 4.3 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$ and a signal for OH masked in this pattern), 7.14–7.66 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) no M^+ detected, 278.1220 (5.8, M^+ – AcOH), 265 (23.2), 205 (39.9), 191 (59.2), 131 (100), 104 (13.6), 91 (5.9), 90 (9.3).

Diethyl [4-(Carbethoxymethyl)phenyl]tartronate (3g). Reaction of ethyl phenylacetate (**1g**; 0.82 g, 5 mmol) in CH_2Cl_2 (3 mL) with DEOM (0.75 mL, 5 mmol) in the presence of $SnCl_4$ (0.7 mL, 6.25 mmol) afforded a liquid after the usual workup. Unreacted oxomalonate was removed by distillation under reduced pressure [70–80 °C (0.1 mm)], and the nonvolatile residue was purified by preparative TLC on silica gel (30% ethyl acetate–hexane; R_f ~0.27) to afford **3g**: 90 mg (5%); ^1H NMR δ ($CDCl_3$) 1.23 (t, 3 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.28 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.63 (s, 2 H, $ArCH_2$), 3.96–4.48 (two partly merged, q, J = 7 Hz, 7 H, $CO_2CH_2CH_3$ and OH), 7.23–7.73 (partly resolved q, 4 H, J_{ortho} = 7 Hz, Ar H); mass spectrum, m/e (relative intensity) 338.1338 (0.3; calcd for $C_{17}H_{22}O_7$ m/e 338.1365), 265 (18.8), 192 (13.1), 191 (100), 118 (15.5), 91 (5.0), 90 (10.6).

Diethyl (3,4-Dimethoxyphenyl)tartronate (3i). Reaction of 1,2-dimethoxybenzene (**1i**; 0.69 g, 5 mmol) in CH_2Cl_2 (5 mL) with DEOM (0.75 mL, 5 mmol) in the presence of $SnCl_4$ at 20 °C for 5 h afforded **3i** as a viscous liquid (1.37 g, 87%) very pure by NMR: ^1H NMR ($CDCl_3$) δ 1.28 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.86 (s, 6 H, Ar OCH_3), 4.21 (q, 5 H, J = 7 Hz, $CO_2CH_2CH_3$ and OH), 6.78–7.28 (m, 3 H, Ar H); mass spectrum, m/e (relative intensity) 312.1190 (34.8; calcd for $C_{15}H_{20}O_7$ m/e 312.1208), 295 (2.6), 239 (18.1), 165 (100).

Diethyl (2,4-Dimethyl-6-methoxyphenyl)tartronate (3j). Reaction of 3,5-dimethylanisole (**1j**; 0.68 g, 5 mmol) in CH_2Cl_2 (3 mL) with DEOM (0.75 mL, 5 mmol) in the presence of $SnCl_4$ (0.7 mL, 6.25 mmol) for 3 h afforded, after the usual workup, a viscous liquid which on trituration with ether–pentane provided **3j** as a crystalline solid (1.2 g, 77%). Recrystallization from ether–pentane afforded a pure sample of **3j**: mp 62–63 °C; ^1H NMR ($CDCl_3$) δ 1.27 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.28 (s, 6 H, Ar CH_3), 3.73 (s, 3 H, Ar OCH_3), 4.03–4.57 (m, 5 H, $CO_2CH_2CH_3$ and OH), 6.65 (br d, 2 H, J = 3 Hz, Ar H); mass spectrum, m/e (relative intensity) 310.1311 (2.2; calcd for $C_{16}H_{22}O_6$ m/e 310.1416), 238 (1), 237 (9.7), 164 (12), 163 (100), 137 (3.9), 31 (5.6).

Diethyl [2-Methoxy-5-(cyanomethyl)phenyl]tartronate (3k). Reaction of 4-methoxy-1-(cyanomethyl)benzene (**1k**; 0.735 g, 5 mmol) in CH_2Cl_2 (5 mL) with DEOM (0.75 mL, 5 mmol) in the presence of $SnCl_4$ (0.7 mL, 6.25 mmol) for 5 h afforded **3k** after the usual workup as a viscous liquid (very pure by NMR): 1H NMR ($CDCl_3$) δ 1.27 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.66 (s, 2 H, $ArCH_2$), 3.80 (s, 3 H, Ar OCH_3), 4.30 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.79–7.36 (m, 3 H, Ar H); mass spectrum, m/e (relative intensity) 321.1190 (1.0; calcd for $C_{16}H_{19}O_6N$ m/e 321.1212), 248 (24), 175 (18), 174 (100), 131 (5.5), 116 (9.5), 91 (2.2), 90 (3.3).

Diethyl (2,4-Dimethoxyphenyl)tartronate (3l). Reaction of 1,4-dimethoxybenzene (**1l**; 1.38 g, 10 mmol) in CH_2Cl_2 (5 mL) with DEOM (1.5 mL, 10 mmol) in the presence of $SnCl_4$ (1.4 mL, 12.5 mmol) at 20 °C for 19 h afforded, after the usual workup, **3l** as a very viscous liquid (3.13 g, 100%), very pure by NMR: ^1H NMR ($CDCl_3$) δ 1.28 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.75 (s, 6 H, Ar OCH_3), 4.31 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 4.88 (br s, 1 H, OH), 6.87 (m, 3 H, Ar H); mass spectrum, m/e (relative intensity) 312.1190 (5.3; calcd for $C_{15}H_{20}O_7$ m/e 312.1209), 250 (0.9), 239 (1.8), 166 (3.2), 165 (100), 92 (3.4), 77 (5.0).

Synthesis of Diethyl Aryltartronates from Aryl Organometallics. Diethyl (2,4-Dimethyl-6-methoxyphenyl)tartronate (3j). Preparation of **3j** by metalation of the arene **1j** with BuLi provided only a 13% yield in contrast with the 77% yield obtained by $SnCl_4$-catalyzed reaction of DEOM with the arene vide supra.

To a refluxing solution of 3,5-dimethylanisole (1.36 g, 10 mmol) in anhydrous ether (15 mL) under N_2 was added dropwise *n*-BuLi (1.3 M, 8.36 mL, 11 mmol) in hexane. Refluxing was continued for 22 h, during which a white precipitate appeared and the mixture turned to yellow. The mixture was cooled to 20 °C, and 2 mL of anhydrous THF was added to dissolve the salt. The resulting clear solution was then siphoned into a cooled (−78 °C) and stirred solution of DEOM (1.5 mL, 10 mmol) in THF (10 mL). The bath temperature was then slowly increased in 20 °C (~2 h) and the mixture stirred at 20 °C for 1 h. The reaction mixture was poured into cold 10% HCl. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 40 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Removal of solvent afforded a brown liquid which was distilled. The first fracction [1.0 g; bp 70–125 °C (0.2 mm)] was mostly recovered DEOM and 3,5-dimethylanisole. The second fraction [865 mg; bp 160–170 °C (0.1 mm)], a highly viscous liquid, was further purified by preparative TLC (30% ethyl acetate–hexane) to afford a white solid (403 mg, 13%), identical by TLC and ^1H NMR with a sample obtained by the $SnCl_4$-catalyzed reaction of DEOM with **1j** described above.

(2,6-Dimethoxyphenyl)tartronate (3m). Lithiation of *m*-dimethoxybenzene was carried out according to the method of Shirley[30] by refluxing a solution of *m*-dimethoxybenzene (1.96

(28) Pardo, S. N.; Salomon, R. G. *J. Org. Chem.* **1981**, *46*, 2598.
(29) Faust, J.; Mayer, R. *Synthesis* **1976**, 411–2.

mL, 15 mmol) in ether (20 mL) with a solution of *n*-BuLi (11.5 mL, 15 mmol) in hexane for 22 h. The powdered solid suspended in the solution was siphoned into a well-stirred cooled (−78 °C) solution of DEOM (2.25 mL, 15 mmol) in THF (15 mL). The bath temperature was allowed to increase slowly to 20 °C, and stirring was continued at 20 °C for an additional 2 h. The reaction mixture was poured into crushed ice–HCl. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extract was washed with brine (30 mL), dried ($CaCl_2$), and concentrated in vacuo. The semisolid residue was repeatedly washed with ether, leaving a white solid which was recrystallized from CH_2Cl_2–ether to afford **3m**: 1.914 g (41%); mp 124–128 °C; ^1H NMR ($CDCl_3$) δ 1.30 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.83 (s, 6 H, Ar OCH_3), 4.38 (m, 5 H, $CO_2CH_2CH_3$ and OH), 6.71 (d, 2 H, J = 8 Hz, Ar H), 7.5 (d, 1 H, J = 8 Hz, Ar H); mass spectrum, m/e (relative intensity) 312.11 (0.3; calcd for $C_{15}H_{20}O_7$ m/e 312.1209), 295 (0.7); ^{13}C NMR ($CDCl_3$ at 25.16 M Hz) δ 171.1 (s), 158.4 (s), 130.8 (d), 116.1 (s), 105.6 (d), 76.9 (s), 62.7 (t), 56.5 (q), 14.3 (q).

Diethyl (3-Methoxyphenyl)tartronate (3n). To a magnetically stirred, cooled (−78 °C) solution of DEOM (3.0 mL, 20 mmol) in ether (20 mL) was added dropwise a solution of (3-methoxyphenyl)magnesium bromide in THF [20 mL, 20 mmol; prepared from *m*-bromoanisole (7.48 g, 40 mmol) and Mg (1.056 g, 44 mmol) in THF (40 mL)]. After complete addition, the bath temperature was slowly increased to 20 °C (~2 h) and the mixture stirred at 20 °C for an additional 1.5 h. The reaction mixture was poured into a crushed ice–HCl mixture and extracted with ether (3 × 50 mL). The ether extract was washed with brine (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The yellow viscous liquid thus obtained was distilled to afford **3n**: 4.2 g (74%); bp 152–158 °C (0.6 mm); ^1H NMR ($CDCl_3$) δ 1.27 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.79 (s, 3 H, Ar OCH_3), 4.28 (q, 5 H, J = 7 Hz, $CO_2CH_2CH_3$ and OH), 6.75–7.29 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 282.1139 (10; calcd for $C_{14}H_{18}O_6$ m/e 282.1103), 209 (22.5), 136 (18.7), 135 (100), 107 (21), 92 (11), 77 (16.5).

Diethyl (2-Methylphenyl)tartronate (3o). To a magnetically stirred, cooled (−78 °C) solution of DEOM (1.5 mL, 10 mmol) in ether (10 mL) was added dropwise a solution of (2-methylphenyl)magnesium bromide in THF [10 mL, 10 mmol; prepared from Mg (0.408 g, 17 mmol) and 2-bromotoluene (2.56 g, 15 mmol) in ether (15 mL)]. After complete addition, the bath temperature was slowly increased to 20 °C and the mixture stirred at 20 °C for 1.5 h. Quenching of the reaction mixture with crushed ice–HCl followed by the usual workup and distillation afforded **3o**: 2.32 g (87%); bp 125–135 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 1.30 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.35 (s, 3 H, Ar CH_3), 4.36 (q, 5 H, J = 7 Hz, $CO_2CH_2CH_3$ and OH), 7.23 (s, 4 H, Ar H).

Diethyl (3-Fluorophenyl)tartronate (3p). Reaction of DEOM (1.5 mL, 10 mmol) in ether (10 mL) with a solution of (3-fluorophenyl)magnesium bromide in THF (10 mL, 10 mmol; prepared from Mg (0.528 g, 22 mmol) and *m*-bromofluorobenzene (3.5 g, 20 mmol) in ether (20 mL)] afforded **3p**: 1.3 g (48%); bp 105–110 °C (0.2 mm); ^1H NMR ($CDCl_3$) δ 1.29 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.49 (q, 5 H, J = 7 Hz, $CO_2CH_2CH_3$ and OH), 6.99–7.57 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 270.0916 (1.3; calcd for $C_{13}H_{15}O_5F$ m/e 270.0903), 224 (2.5), 198 (9), 197 (33.3), 124 (23.2), 123 (100), 95 (50.5).

Diethyl (2-Pyridyl)tartronate (3q). To a magnetically stirred, cooled (−20 °C) solution of 2-bromopyridine (1.26 g, 8 mmol) in ether (4 mL) was added dropwise *n*-BuLi in hexane (5 mL, 1.6 M). The mixture was stirred at −20 °C for 15 min. The dark brown solution thus obtained was siphoned into a magnetically stirred, cooled (−78 °C) solution of DEOM (1.2 mL, 8 mmol) in ether (2 mL). The bath temperature was then allowed to increase slowly to 20 °C, and stirring was continued at 20 °C for 1.5 h. The reaction mixture was poured into a crushed ice–HCl mixture and then made alkaline (pH 8.5) by adding powdered $NaHCO_3$. The alkaline mixture was extracted with ether (3 × 20 mL). The ether extract was dried (Na_2SO_4) and concentrated. The dark brown liquid obtained was vacuum transferred [bath temperature 115–120 °C (0.01 mm)] to afford **3q**: 0.54 g (27%); ^1H NMR ($CDCl_3$) δ 1.31 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 4.34 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 5.53 (br s, 1 H, OH), 7.44–8.25 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) no M^+ detected, 251 (0.3), 235 (0.1), 226 (0.8), 185 (6.9), 180 (39.3), 156 (16.5), 78 (100).

Acetylation of Diethyl Aryltartronates. A general procedure for acetylation of diethyl aryltartronates is illustrated with the synthesis of **diethyl acetoxy(2-methylphenyl)propanedioate (4o).** A solution of (2-methylphenyl)tartronate (**3o**; 1.97 g, 7.39 mmol) in CH_2Cl_2 (10 mL) was stirred with acetic anhydride (10 mL, 106 mmol), triethylamine (5 mL, 36 mmol), and 4-(dimethylamino)pyridine (0.5 g, 4 mmol) for 2 days at 20 °C. The dark brown reaction mixture was poured into cold water (70 mL). The acetic acid generated was then neutralized by adding powdered $NaHCO_3$ until no effervescence of CO_2 was observed. The organic material was extracted with ether (5 × 40 mL). The ether extract was washed successively with water (3 × 30 mL), 10% HCl (5 × 30 mL), and brine (40 mL) and dried ($MgSO_4$). Evaporation of ether at reduced pressure afforded a brown liquid which was distilled to furnish **4o**: 1.699 g (74%); bp 150–156 °C (0.5 mm); ^1H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.21 (s, 3 H, $OCOCH_3$), 2.38 (s, 3 H, Ar CH_3), 4.21 (q, 4 H, $CO_2CH_2CH_3$), 7.20 (s, 4 H, Ar H).

Diethyl acetoxy[4-(dimethylamino)phenyl]propanedioate (4b): 100% yield; ^1H NMR (crude product, $CDCl_3$) δ 1.23 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.25 (s, 3 H, $OCOCH_3$), 2.95 (s, 6 H, NMe_2), 4.22 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.64 (d, 2 H, J = 9 Hz, Ar H), 7.40 (d, 2 H, J = 9 Hz, Ar H). This unpurified product was very pure by ^1H NMR and used directly for the next step: mass spectrum, m/e (relative intensity) 337.1527 (12.5; calcd for $C_{17}H_{23}O_6N$ m/e 337.1525), 236 (35.2), 222 (46.5), 162 (67.8).

Diethyl acetoxy(2-furyl)propanedioate (4c) was obtained in quantitative yield. The crude product [^1H NMR ($CDCl_3$) δ 1.30 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.21 (s, 3 H, $OCOCH_3$), 4.28 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.40–6.76 (m, 2 H, ring H), 7.47 (m, 1 H, ring H)] was about 90% pure and directly used for the next step. This product was characterized further by conversion into **5c** (vide infra).

Diethyl acetoxy(2,5-dimethylphenyl)propanedioate (4d) was obtained in 100% yield after vacuum transfer [bath temperature 145–150 °C (0.1 mm)] of the crude material: ^1H NMR ($CDCl_3$) δ 1.21 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.13 (s, 3 H, $OCOCH_3$), 2.26 (s, 3 H, Ar CH_3), 2.30 (s, 3 H, Ar CH_3), 4.25 (q, 4 H, $CO_2CH_2CH_3$), 7.00 (s, 3 H, Ar H). This product was characterized further by conversion into **3d** and **8d** (vide infra).

Diethyl acetoxy(4-isobutylphenyl)propanedioate (4e): 80% yield; bp 135–140 °C (0.15 mm); ^1H NMR ($CDCl_3$) δ 0.89 (d, 6 H, J = 6 Hz, $CHMe_2$), 1.23 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.65–2.05 (m, 1 H, $CHMe_2$), 2.28 (s, 3 H, $OCOCH_3$), 2.49 (d, 2 H, J = 6 Hz, Ar CH_3), 4.26 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.09–7.60 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 350.1816 (2.1; calcd for $C_{19}H_{26}O_6$ m/e 350.1729), 246 (3.3), 236 (11), 235 (39.8), 162 (12.9), 161 (100), 118 (7.7), 91 (5.9).

Diethyl acetoxy[4-(2-acetoxyethyl)phenyl]propanedioate (4f) was obtained in 84% yield after purification of the crude product through preparative TLC (30% ethyl acetate in hexane): ^1H NMR ($CDCl_3$) δ 1.21 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.03 (s, 3 H, $OCOCH_3$), 2.28 (s, 3 H, $OCOCH_3$), 2.95 (t, 2 H, J = 7 Hz, $ArCH_2$), 4.25 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 4.29 (t, 2 H, J = 7 Hz, CH_2OAc), 7.23 (d, 2 H, J = 8.5 Hz, Ar H), 7.57 (d, 2 H, J = 8.5 Hz, Ar H); mass spectrum, m/e (relative intensity) no M^+ detected, 321 (32), 320 (21.8), 265 (17.8), 262 (24.1), 261 (83.8), 205 (27.7), 202 (20.7), 191 (100).

Diethyl acetoxy(4-methoxy-3-methylphenyl)propanedioate (4h) was obtained in 89% yield. The crude product [^1H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.23 and 2.28 (2 partly resolved s, $OCOCH_3$), 3.90 (s, 3 H, Ar OCH_3), 4.27 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.75–7.57 (m, 3 H, Ar H)] was used directly for the next step: mass spectrum, m/e (relative intensity) 338.1375 (4.4; calcd for $C_{17}H_{22}O_7$ m/e 338.1365), 223 (42.6), 208 (15.1), 151 (16.3), 150 (10.1), 149 (100).

Diethyl acetoxy[2-methoxy-5-(cyanomethyl)phenyl]propanedioate (4k) was obtained in quantative yield. The crude product [^1H NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 2.17 (s, 3 H, $OCOCH_3$), 3.70 (s, 2 H, Ar CH_2CN), 3.80 (s, 3 H, Ar OCH_3), 4.28 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.85–7.43 (m, 3 H,

(30) Shirley, D. A.; Johnson, J. R., Jr.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209.

Ar H)] which is ~85% pure by ^{1}H NMR was directly used for the next step: mass spectrum, *m/e* (relative intensity) 363.1304 (6.1; calcd for $C_{18}H_{21}O_7N$ *m/e* 363.1318), 304 (25.8), 248 (15.6), 174 (100).

Diethyl acetoxy(2,5-dimethoxyphenyl)propanedioate (4l), mp 66–67 °C, was prepared in 63% yield after purification of the crude acetate through preparative TLC (30% ethylacetate in hexane) followed by crystallization from ether–pentane: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.20 (s, 3 H, $OCOCH_3$), 3.79 (s, 6 H, Ar OCH_3), 4.30 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 6.90–7.14 (m, 3 H, Ar H); mass spectrum, *m/e* (relative intensity) 354.1306 (20; calcd for $C_{17}H_{22}O_8$ *m/e* 354.1314), 239 (16.8), 166 (11.8), 165 (100).

Diethyl acetoxy(2,6-dimethoxyphenyl)propanedioate (4m) was obtained in 66% yield as a very viscous liquid purified by preparative TLC (50% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.13 (s, 3 H, $COCH_3$), 3.78 (s, 6 H, Ar $OCcH_3$), 4.28 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 6.60 (d, 2 H, *J* = 8 Hz, Ar H), 7.31 (q, 1 H, *J* = 8 Hz, Ar H); mass spectrum, *m/e* (relative intensity) 354.1327 (6.1; calcd for $C_{17}H_{22}O_8$ *m/e* 354.1315), 296 (9.5), 295 (52.6), 239 (27.3), 166 (12.3), 165 (100).

Diethyl acetoxy(3-methoxyphenyl)propanedioate (4n) was obtained in 86% yield after purification of the crude product through preparative TLC (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.28 (s, 3 H, $OCOCH_3$), 3.83 (s, 3 H, Ar OCH_3), 4.20 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 6.83–7.37 (m, 4 H, Ar H); mass spectrum, *m/e* (relative intensity) 324.1215 (10; calcd for $C_{16}H_{20}O_7$ *m/e* 324.1209), 238 (1.4), 220 (2.1), 210 (9.2), 209 (24.4), 136 (12.8), 135 (100), 92 (5.9).

Diethyl Acetoxy(2-pyridyl)propanedioate (4q) was obtained in 41% yield after purification of the crude product through preparative TLC (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.26 (s, 3 H, $OCOCH_3$), 4.31 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 7.17–7.81 (m, 4 H, Ar H). This product was characterized further by conversion into **3g** (vide infra).

Li–NH_3 Reduction of Diethyl (2,5-Dimethoxyphenyl)-tartaronate (3l). To a magnetically stirred solution of Li (24 mg, 3.4 mmol) in liquid NH_3 (~15 mL) was added a solution of the tartronate (**3l**) in anhydrous ether until the blue color just disappeared [247 mg (0.79 mmol) of the tartronate in 2.5 mL of ether was required]. The reaction mixture was then quenched with powdered NH_4Cl. NH_3 was then evaporated completely, and the residue, after acidification with cold 10% HCl, was extracted with ether (3 × 20 mL). The ether extract was washed with brine (20 mL), dried ($MgSO_4$), and concentrated, leaving a residue of 140 mg. Purification of the crude product through preparative TLC afforded ethyl hydroxy(2,5-dimethoxyphenyl)acetate (**8**) in 16% yield as the major product: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3 H, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 3.81 (s, 3 H, Ar OCH_3), 3.85 (s, 3 H, Ar OCH_3), 4.28 (q, 2 H, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 5.35 (s, 1 H, $CH(OH)CO_2Et$), 6.95 (m, 3 H, Ar H).

Reductive Deacetoxylation of Diethyl Acetoxyaryl-propanedioates 4 with Naphthalenide Anion Radicals. A general procedure for synthesis of diethyl arylpropanedioates by reduction of acetates **4** with sodium α-(dimethylamino)-naphthalenide or sodium naphalenide is illustrated by the preparation of **diethyl (2-methylphenyl)propanedioate (5o)**. A reducing reagent solution was prepared under dry nitrogen by stirring a mixture of sodium (24 mmol), α-(dimethylamino)-naphthalene (20 mmol), and hexamethylphosphoramide (20 mL) for 15 h at 20 °C. This solution was added dropwise with a syringe under dry nitrogen to a solution of acetate **4o** (0.58 mmol) in dry benzene (2 mL) until the green color persisted for 20–30 s. Usually only slightly more than 1 equiv of the reducing reagent solution was required. The reaction mixture was quenched by pouring it into cold 10% HCl and was extracted with ether (3 × 20 mL). The ether extract was washed successively with 10% HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine (2 × 10 mL) and dried ($MgSO_4$). Evaporation of ether under reduced pressure afforded **5o**: 140 mg (95%); very pure by ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.35 (s, 3 H, Ar CH_3), 4.24 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.88 (s, 1 H, $CH(CO_2Et)_2$), 7.25 (m, 4 H, Ar H); mass spectrum, *m/e* (relative intensity) 250.1212 (9; calcd for $C_{14}H_{18}O_4$ *m/e* 250.1205), 230 (2.3), 227 (4), 223 (9.3), 222 (4.0), 221 (8.9).

Diethyl [4-(dimethylamino)phenyl]propanedioate (5b) was prepared in 53% yield by the procedure used for **5q** (vide infra): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.92 (s, 6 H, $N(CH_3)_2$), 4.12 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.50 (s, 1 H, $CH(COOEt)_2$), 6.68 (q, 2 H, J_{ortho} = 7 Hz, J_{meta} = 2 Hz, Ar H), 7.25 (q, 2 H, J_{ortho} = 7 Hz, J_{meta} = 2 Hz); mass spectrum, *m/e* (relative intensity) 279.1460 (36.6; calcd for $C_{15}H_{21}O_4N$ *m/e* 179.1470), 207 (14.1), 206 (100), 178 (167), 134 (24.8), 132 (11.5).

Diethyl (2-furyl)propanedioate (5c) was prepared in 81% yield and was purified by preparative TLC on silica gel (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.24 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.76 (s, 1 H, $CH(COOEt)_2$), 6.41 (m, 2 H, ring H), 7.40 (br s, 1 H, ring H); mass spectrum, *m/e* (relative intensity) 226.0838 (17.6; calcd for $C_{11}H_{14}O_5$ *m/e* 226.0841), 197 (5.9), 169 (11.7), 154 (26.5), 153 (75.6), 126 (29.8), 125 (23.9).

Diethyl (2,5-dimethylphenyl)propanedioate (5d) was prepared in 70% yield after purification of the crude product through preparative TLC on silica gel (25% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 6 H, *J* = Hz, $CO_2CH_2CH_3$), 2.27 (s, 6 H, Ar CH_3), 4.20 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.80 (s, 1 H, $CH(COOEt)_2$), 6.98–7.20 (m, 3 H, Ar H); mass spectrum, *m/e* (relative intensity) 264.1388 (47.2; calcd for $C_{15}H_{20}O_4$ *m/e* 264.1361), 218 (45.9), 192 (19.3), 191 (76), 190 (27), 172 (54.5), 163 (76.6), 162 (37.4), 144 (67.1).

Diethyl (4-isobutylphenyl)propanedioate (5e) was prepared in 95% yield and was very pure by ^{1}H NMR ($CDCl_3$) δ: 0.90 (d, 6 H, *J* = 6 Hz, $CHCH_3)_2$), 1.25 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 1.67–1.99 (m, 1 H, $CH(CH_3)_3$), 2.47 (d, 2 H, *J* = 6 Hz, $ArCH_2$), 4.21 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 4.57 (s, 1 H, $CH(CO_2Et)_2$), 7.04–7.39 (m, 4 H, Ar H). **5e** is a known compound.[31]

Diethyl [(2-acetoxyethyl)phenyl]propanedioate (5f): 80% yield; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.03 (s, 3 H, $OCOCH_3$), 2.93 (t, 2 H, $ArCH_2$), 4.22 (q, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$ and CH_2OAc), 4.59 (s, 1 H, $CH(COOEt)_2$), 7.13–7.45 (m, 4 H, Ar H); mass spectrum, *m/e* (relative intensity) no M^+ detected, 263 (12.2), 262 (66.0), 250 (14.6), 190 (50.2), 189 (100).

Diethyl (4-methoxy-3-methylphenyl)propanedioate (5h) was prepared in 78% yield and purified by preparative TLC on silica gel (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.20 (s, 3 H, Ar CH_3), 3.80 (s, 3 H, Ar OCH_3), 4.11 (q, 4 H, *J* = Hz, $CO_2CH_2CH_3$), 4.50 (s, 1 H, $CH(COOEt)_2$), 6.70–7.14 (m, 3 H, Ar H); mass spectrum, *m/e* (relative intensity) 280.1315 (21.6; calcd for $C_{15}H_{20}O_5$ 280.1311), 208 (18.1), 207 (56), 180 (1.9), 179 (14.1), 151 (16.2), 149 (16.0), 135 (100).

Diethyl [1-methoxy-5-(cyanomethyl)phenyl]propanedioate (5k): 95% yield; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 3.68 (s, 2 H, $ArCH_2$), 3.85 (s, 3 H, Ar OCH_3), 4.23 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 5.08 (s, 1 H, $CH(COOEt)_2$), 6.80–7.38 (m, 3 H, Ar H).

Diethyl (2,5-dimethoxyphenyl)propanedioate (5l): 95% yield; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 6 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 3.80 (s, 6 H, Ar OCH_3), 4.27 (q, 4 H, *J* = 7 Hz, $CO_2CH_2CH_3$), 5.15 (s, 1 H, $CH(COOEt)_2$), 6.86–7.05 (m, 3 H, Ar H); mass spectrum, *m/e* (relative intensity) 296.1284 (43.5; calcd for $C_{15}H_{20}O_6$ *m/e* 296.1259), 225 (12.7), 224 (95.3), 223 (13.6), 199 (13.8), 178 (8.8), 165 (10.8).

Diethyl (2,6-dimethoxyphenyl)propanedioate (5m) was obtained in 50% yield as a white solid (mp 79–80 °C) after purification through preparative TLC on silica gel (30% ethyl acetate in hexane) followed by crystallization from ether–hexane: ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 6 H, *J* = 7.5 Hz, $CO_2CH_2CH_3$), 3.90 (s, 6 H, Ar OCH_3), 4.36 (q, 4 H, *J* = 7.5 Hz, $COOCH_2CH_3$), 5.27 (s, 1 H, $CH(COOEt)_2$), 6.80 (d, 2 H, *J* = 8.5 Hz, Ar H), 7.51 (q, 1 H, *J* = 8.5 Hz, Ar H); mass spectrum, *m/e* (relative intensity) 296.1253 (9; calcd for $C_{15}H_{20}O_6$ *m/e* 296.1259), 250 (4.7), 224 (3.6), 223 (17.2), 180 (14.2), 168 (14.2), 167 (8.9), 163 (6.2).

Diethyl (3-methoxyphenyl)propanedioate (5n) was obtained in 78% yield after purification of the crude product through

(31) Cavalleri, B.; Bellasio, E.; Vigevani, A.; Testa, E. *Farmaco, Ed. Sci.* **1969**, *24*, 451. Cf.: *Chem. Abstr.* **1969**, *71*, 112570.

preparative TLC (20% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.80 (s, 3 H, Ar OCH_3), 4.22 (q, 4 H, J = 7 Hz, $COOCH_2CH_3$), 4.58 (s, 1 H, $CH(COOEt)_2$), 6.75–7.28 (m, 4 H, Ar H). **5n** is a known compound.[32]

Diethyl (2-Pyridyl)propanedioate (5q). A solution of sodium naphthalenide in HMPA was prepared by the same procedure by using naphthalene instead of α-(dimethylamino)naphthalene. This solution was added dropwise with a syringe to a solution of the acetate (70 mg, 0.23 mmol) in benzene (2 mL) until the green color presisted for 20–30 s. The reaction mixture was quenched with cold water (7 mL) and extracted with ether (3 × 15 mL). The extract was dried ($MgSO_4$) and concentrated. The crude product (contaminated with naphthalene) was chromatographed through a short column (1 ft) of SiO_2 (60–300 mesh). Naphthalene was eluted first with hexane. The reduced product was eluted with 10% and 20% ether in hexane (250 mL) to afford **3q**: 45 mg (80%); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 4.25 (q, 4 H, J = 7 Hz, $COOCH_2CH_3$), 4.94 (s, 1 H, $CH(COOEt)_2$), 7.11–7.85 (m, 4 H, ring H). **5q** is a known compound.[33]

Reductive Deacetoxylation of Diethyl Acetoxy(2,5-dimethoxyphenyl)propanedioate (4l) with Lithium in Ammonia. A solution of the acetate **4l** (68 mg, 0.19 mmol) in ether (2 mL) was added dropwise to a stirred solution of Li (14 mg, 2 mmol) in liquid NH_3 (10 mL). After being stirred for 3 h, the reaction mixture was quenched with excess powdered NH_4Cl. NH_3 was evaporated completely, and the residue was acidified with 10% HCl. The acidic mixture was extracted with ether (3 × 20 mL). The ether extract was washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated to afford diethyl (2,5-dimethoxyphenyl)propanedioate (**5l**) as a colorless oil (50 mg, 89%), identical by ^{1}H NMR with the sample obtained by napthalenide method (vide supra).

Reductive Methylation of Diethyl Acetoxyarylpropanedioates 4. A general procedure for synthesis of diethyl arylmethylpropanedioates **6** by reduction of acetates **4** with sodium α-(dimethylamino)napthalenide or sodium naphthalenide and methylation of the resulting carbanion is illustrated by the preparation of **diethyl (4-isobutylphenyl)methylpropanedioate (6e)**. To a magnetically stirred solution of the acetate (99 mg, 0.28 mmol) in benzene (2 mL) was added dropwise a solution of sodium α-(dimethylamino)naphthalenide in HMPA (prepared as described above) until the green color of the reagent persisted for 20–30 s. MeI (150 μL, 2.4 mmol) was then added dropwise to the reaction mixture and stirred for 30 min. The reaction mixture was quenched by pouring it into cold 10% HCl and was extracted with ether (3 × 15 mL). The ether extract was washed with 10% HCl (3 × 10 mL) and brine (20 mL) and dried ($MgSO_4$). Evaporation of solvent afforded **6e** as a pale yellow liquid: 85 mg (98%); ^{1}H NMR ($CDCl_3$) δ (0.90 (d, 6 H, J = 6.5 Hz, $CH(CH_3)_2$), 1.25 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.85 (s, 3 H, CH_3), 2.48 (d, 2 H, J = 6.5 Hz, $ArCH_2$), 4.26 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.05–7.40 (m, 4 H, Ar H). This compound was characterized further by conversion into **9e** (vide infra).

Diethyl [4-(dimethylamino)phenyl]methylpropanedioate (6b) was obtained in 64% yield by a modification of the general procedure by using sodium naphthalenide in HMPA instead of sodium α-(dimethylamino)naphthalenide. After quenching the reaction mixture with 10% HCl, naphthalene was extracted with ether (3 × 20 mL). The aqueous acidic phase was made basic by addition of powdered $NaHCO_3$ and then was extracted with ether (3 × 20 mL). The ether extract on washing with water (2 × 10 mL), drying ($MgSO_4$), and concentration in vacuo furnished the pure **6b**: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.83 (s, 3 H, CH_3), 4.20 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.67 (q, 2 H, J_{ortho} = 9 Hz, J_{meta} = 2 Hz), 7.24 (q, 2 H, J_{ortho} = 9 Hz, J_{meta} = 2 Hz, Ar H); mass spectrum, m/e (relative intensity) 293.1633 (21.3; calcd for $C_{16}H_{23}O_4N$ m/e 293.1627), 279 (5.4), 250 (4.7), 246 (8.6), 235 (8), 234 (15.7), 220 (100), 206 (43.4).

Diethyl (2,5-dimethylphenyl)methylpropanedioate (6d) was obtained in 94% yield and was quite pure by ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.95 (s, 3 H, CH_3), 2.35 (s, 3 H, Ar CH_3), 2.42 (s, 3 H, $ArCH_3$), 4.50 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.29–7.43 (m, 3 H, Ar H); mass spectrum, m/e (relative intensity) 278.1534 (4.3; calcd for $C_{16}H_{22}O_4$ m/e 278.1518), 232 (15.1), 205 (34.2), 204 (35.8), 177 (16.8), 175 (316), 159 (46.4), 158 (44.7), 131 (80.6).

Diethyl (4-methoxy-3-methylphenyl)methylpropanedioate (6h) was obtained in 94% yield and was quite pure by ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.93 (s, 3 H, CH_3), 2.33 (s, 3 H, Ar CH_3), 4.03 (s, 3 H, Ar CH_3), 4.46 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.06–7.66 (m, 3 H, Ar H); mass spectrum, m/e (relative intensity) 294.1472 (24.1; calcd for $C_{16}H_{22}O_5$ m/e 294.1467), 221 (96.5), 148 (18), 147 (100).

Diethyl (2,5-dimethoxyphenyl)methylpropanedioate (6l) was obtained in 60% yield after purification through preparative TLC (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 3.60 (s, 6 H, Ar OCH_3), 4.26 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.76–6.92 (m, 3 H, Ar H). **6l** is a known compound.[34]

Diethyl (3-methoxyphenyl)methylpropanedioate (6n) was obtained in 81% yield after purification by preparative TLC on silica gel (30% ethyl acetate in hexane: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7 Hz, $COCH_2CH_3$), 1.86 (s, 3 H, CH_3), 3.83 (s, 3 H, Ar OCH_3), 4.19 (q, 4 H, J = 4 Hz, $CO_2CH_2CH_3$), 6.83–7.49 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 280.1313 (71.4; calcd for $C_{15}H_{20}O_5$ m/e 280.1313), 208 (21.4), 207 (75), 179 (47.4), 162 (83.8).

Diethyl (2-methylphenyl)methylpropanedioate (6o) was obtained in 72% yield after purification by preparative TLC on silica gel (20% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.86 (s, 3 H, CH_3), 2.26 (s, 3 H, Ar CH_3), 4.16 (q, 4 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.15 (m, 4 H, Ar H); mass spectrum, m/e (relative intensity) 264.1319 (1.1; calcd for $C_{15}H_{20}O_4$ m/e 264.1362), 218 (11.6), 191 (29), 190 (32.9), 176 (10.7), 163 (21.2), 162 (13.3), 161 (17.9), 146 (22.5).

Synthesis of 2-Arylpropionic Acids by Hydrolysis–Decarboxylation of Diethyl Propanedioates 6. A general procedure for hydrolysis of the diethyl propanedioates **6** and decarboxylation of the resulting propanedioic acids is illustrated with the synthesis of **2-(4-isobutylphenyl)propionic acid (9e)**. The diester **6e** (180 mg, 0.58 mmol) was hydrolyzed by refluxing with a solution of KOH (324 mg, 5.8 mmol) in water (1.3 mL) for 4 h. The cooled reaction mixture was extracted with ether (2 × 5 mL) to remove unhydrolyzed material. The aqueous phase was then acidified with concentrated HCl (0.7 mL) and heated under reflux for 2 h. The reaction mixture was then cooled to 20 °C and extracted with ether (3 × 25 mL). The ether extract on drying ($MgSO_4$) and concentration afforded a light brown liquid which solidified after trituration with pentane. The solid was recrystallized from pentane to afford **9e**: 112 mg (93%); mp 70–72 °C; ^{1}H NMR ($CDCl_2$) δ 0.89 (d, 6 H, J = 6.5 Hz, $CH(CH_3)_2$), 1.50 (d, 3 H, J = 7.5 Hz, $CHCH_3$), 1.78–2.10 (m, 1 H, $CH(CH_3)_2$), 2.48 (d, 2 H, J = 7.5 Hz, $ArCH_2$), 3.75 (q, 1 H, J = 7.5 Hz, $CHCH_3$), 7.13–7.41 (m, 4 H, Ar H), 11.01 (br s, 1 H, COOH). **9e** is a known compound[35] also known as ibuprofen.

2-[4-(Dimethylamino)phenyl]propionic acid (9b) was obtained in 85% yield by the general procedure except that the workup was modified. Thus, the aqueous acidic reaction product mixture was made basic (litmus) by dropwise addition of 30% aqueous NH_4OH. Excess NH_3 was evaporated under reduced pressure [50 °C (20 mm)] for 30 min. The partially aqueous mixture was then extracted with ether (4 × 25 mL). The ether extract was dried ($MgSO_4$) and concentrated by rotary evaporation to afford a light brown crystalline solid: mp 124–127 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.93 (s, 6 H, $N(CH_3)_2$), 3.51 (q, 1 H, J = 7 Hz, $CHCH_3$), 6.66–7.33 (m, 4 H, Ar H), 9.57 (br s, 1 H, COOH). **9b** is a known compound.[36]

(32) Guyot, M.; Molho, D. *Tetrahedron Lett.* **1973**, 3433.
(33) (a) Carlson, L. A.; Hedbom, C.; Misiorny, A.; Sjoberg, B.; Stjernstrom, N. E.; Westin, G. *Acta Pharm. Suec.* **1972**, *9*, 405. (b) Newkome, G. R.; Robinson, J. M.; Bhacca, N. S. *J. Org. Chem.* **1973**, *38*, 2234.
(34) Takada, T.; Kunugi, S.; Ohki, S. *Chem. Pharm. Bull.* **1971**, *19*, 782.
(35) French Patent 1 545 270, 1968. Cf.: *Chem. Abstr.* **1970**, *72*, 21492.
(36) Carney, R. W. J.; DeStevens, G. German Patent 1 913 742, 1964. Cf.: *Chem. Abstr.* **1970**, *72*, 55024.

2-(2,5-Dimethylphenyl)propionic acid (9d) was obtained in 74% yield as white needles: mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.65 (s, 6 H, Ar CH_3), 3.91 (q, 1 H, J = 7 Hz, $CHCH_3$), 6.96 (m, 3 H, Ar H), 9.15 (br s, 1 H, COOH); mass spectrum (as the methyl ester), m/e (relative intensity) 192.1159 (16.7; calcd for $C_{12}H_{16}O_2$ m/e 192.1150) 180 (27.3), 179 (3.6), 178 (8.2), 177 (14.5), 176 (13.2), 168 (28.8).

2-(4-Methoxy-3-methylphenyl)propionic acid (9h) was obtained in 73% yield as a colorless liquid which was quite pure by ^{1}H NMR ($CDCl_3$) δ: 1.52 (d, 3 H, J = 7.5 Hz, $CHCH_3$), 2.30 (s, 3 H, Ar CH_3), 3.81 (q, 1 H, J = 7.5 Hz, $CHCH_3$), 3.95 (s, 3 H, Ar OCH_3), 6.97–7.54 (m, 3 H, Ar H), 9.73 (br s, 1 H, COOH); mass spectrum (as the methyl ester), m/e (relative intensity) 310.1394 (45.0; calcd for $C_{12}H_{16}O_3$ m/e 310.1416), 237 (14.2), 192 (17.7), 191 (28.9), 181 (19.5), 177 (33.4), 164 (11.2), 163 (100).

2-(2,5-Dimethoxyphenyl)propionic acid (9l) was obtained in 89% yield: mp 95–96 °C (ether–pentane); ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 7.5 Hz, $CHCH_3$), 3.75 (s, 6 H, Ar OCH_3), 4.05 (q, 1 H, $CHCH_3$), 6.78 (m, 3 H, Ar H), 9.53 (br s, 1 H, COOH); mass spectrum (as methyl ester), m/e (relative intensity) 224.1054 (46.3; calcd for $C_{12}H_{16}O_4$ m/e 224.1048), 180 (44.2), 168 (38.4), 166 (11), 165 (100).

2-(3-Methoxyphenyl)propionic acid (9n) was obtained in 60% yield as a colorless liquid which was purified by preparative TLC on silica gel (30% ethyl acetate in hexane) and characterized as methyl ester (CH_2N_2): ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.73 (s, 3 H, $COOCH_3$), 3.87 (s, 3 H, Ar OCH_3), 6.82–7.41 (m, 4 H, Ar H). **9n** is a known compound.[37]

2-(2-Methylphenyl)propionic acid (9o) was obtained in 83% yield: mp 91–92 °C (crystallized from ether–pentane); ^{1}H NMR ($CDCl_3$) δ 1.47 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.36 (s, 3 H, Ar CH_3), 3.98 (q, 1 H, J = 7 Hz, $CHCH_3$), 7.11 (m, 4 H, Ar H), 10.16 (br s, 1 H, COOH; mass spectrum (as methyl ester) m/e (relative intensity) 178.0975 (6.5; calcd for $C_{11}H_{14}O_2$ m/e 178.0993), 164 (7.5), 132 (3.3), 130 (29.1), 120 (3.1), 119 (100).

Ethyl 2-Hydroxy-2-*p*-tolylpropionate (14). To a magneticall stirred cooled (–75 °C) solution of ethyl pyruvate (1.74 g, 15 mmol) in ether (15 mL) was added dropwise *p*-tolylmagnesium bromide in ether [prepared from Mg (396 mg, 16.5 mmol) and *p*-bromotoluene in ether (15 mL)]. After completion of the addition, the reaction temperature was allowed to increase slowly to 20 °C and the mixture left overnight. The reaction mixture was then quenched by pouring it into ice–HCl and was extracted with ether (3 × 40 mL). The ether extract was washed with brine (30 mL) and dried ($MgSO_4$). Evaporation of ether followed by distillation afforded **14** as a pale yellow oil: 2.02 g (65%); bp 92–93 °C (0.07 mm); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.76 (s, 3 H, CH_3), 2.35 (s, 3 H, Ar CH_3), 3.7 (br s, 1 H, OH), 4.21 (q, 2 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.06–7.45 (m, 4 H, Ar H). The previous synthesis of **14** by the same method but without cooling to –78 °C gave less than half the yield.[15]

Ethyl 2-Acetoxy-2-*p*-tolylpropionate (15). The alcohol **14** was converted into the acetate **15** in 88% yield by the usual acetic anhydride–pyridine–4-(dimethylamino)pyridine method (vide supra): bp 105–110 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.93 (s, 3 H, CH_3), 2.16 (s, 3 H, $OCOCH_3$), 2.33 (s, 3 H, Ar CH_3), 4.12 (q, 2 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.05–7.46 (m, 4 H, Ar H). **15** was characterized further by conversion into **16**.

Reduction of Ethyl 2-Acetoxy-2-*p*-tolylpropionate with Sodium α-(Dimethylamino)naphthalenide. Synthesis of Ethyl 2-*p*-Tolylpropionate (16). Acetate **15** was reduced by the general procedure described earlier for the **4** → **5** conversion. Preparative TLC (20% ethyl acetate in hexane) of the crude reaction mixture led to the isolation of the starting hydroxy compound **14** in 15% yield and the reduced product **16**: 26% yield; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz, $CO_2CH_2CH_3$), 1.45 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.33 (s, 3 H, Ar CH_3), 3.65 (q, 1 H, J = 7 Hz, $CHCH_3$), 4.10 (q, 2 H, J = 7 Hz, $CO_2CH_2CH_3$), 7.15 (s, 4 H, Ar H); mass spectrum, m/e (relative intensity) 192.1163 (12.9; calcd for $C_{12}H_{16}O_2$ m/e 192.1150), 168 (11), 140 (8.4).

Li–NH_3 Reduction of Ethyl 2-Acetoxy-2-*p*-tolylpropionate. Synthesis of Ethyl 2-*p*-Tolylpropionate (16). To a magnetically stirred solution of Li (14 mg, 2 mmol) in liquid NH_3 (~15 mL) was added dropwise a solution of the acetate **15** in anhydrous ether until the blue color just disappeared [180 mg (0.72 mmol) of the acetate dissolved in 1.5 mL of ether was required]. Powdered NH_4Cl was then added to quench the reaction mixture, the NH_3 was evaporated completely, and the residue was acidified with cold 10% HCl and extracted with ether (3 × 20 mL). The ether extract was washed with brine (20 mL), dried ($MgSO_4$), and concentrated to afford 125 mg (91%) of **16** as the only isoluble product, nearly pure by ^{1}H NMR comparison with a sample prepared as described above. Preparative TLC on silica gel (20% ethyl acetate in hexane) of the crude product afforded 67 mg (49%) of pure **16**.

With excess Li, **16** is reduced further, and the primary alcohol **17** can become the major product. Thus, a solution of the acetate (500 mg, 2 mmol) in anhydrous ether (4 mL) was added dropwise to a stirred solution of Li (70 mg, 10 mmol) in liquid NH_3 (30 mL). After being stirred for 3 h, the reaction mixture was quenched with excess powdered NH_4Cl. Evaporation of the NH_3 and acidification with 10% HCl followed by extraction with ether (3 × 40 mL), washing the ether extract with brine (20 mL), drying ($MgSO_4$), and concentration in vacuo afforded a light brown oil. The oil after preparative TLC on silica gel (20% ethyl acetate in hexane) furnished the reduced product **16** in 14% yield and **17** in 38% yield: ^{1}H NMR ($CDCl_3$) δ 1.22 (d, 3 H, J = 7 Hz, $CHCH_3$), 1.98 (br s, 1 H, OH), 2.31 (s, 3 H, Ar CH_3), 2.85 (q, 1 H, J = 7 Hz, $CHCH_3$), 3.62 (d, 2 H, J = 7 Hz, CH_2OH), 7.10 (s, 4 H,

Methyl 2-Hydroxy-2,3-diphenylpropionate. To a magnetically stirred cooled (–78 °C) solution of methyl benzoylformate (1.64 g, 10 mmol) in anhydrous ether (10 mL) was adde dropwise benzylmagnesium chloride (10 mL, 10 mmol) in ether. After the addition was complete, the bath temperature was allowed to increase slowly to 20 °C, and the reaction mixture was left overnight at 20 °C. The reaction mixture was quenched by pouring int into crushed ice–HCl and was extracted with ether (4 × 20 mL). The ether extract, on washing with brine (2 × 20 mL), drying ($MgSO_4$), and removal of the solvent by rotary evaporation, afforded the title compound as a white solid (2.16 g, 84%). Recrystallization from ether–pentane gave the pure hydroxy ester: mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 3.41 (q, 2 H, J = 14 Hz, $ArCH_2$), 3.76 (s, 3 H, $COOCH_3$), 6.90–7.91 (m, 10 H, Ar H). This compound was characterized further by conversion to methyl 2,3-diphenylpropionate via its acetate.

Methyl 2-Acetoxy-2,3-diphenylpropionate. The acetoxy derivative was prepared in 92% yield with acetic anhydride–pyridine and 4-(dimethylamino)pyridine as a catalyst by the general procedure described above: ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3 H, $OCOCH_3$), 3.78 (s, 3 H, CO_2CH_3), 3.85 (q, 2 H, J = 14.5 Hz, $ArCH_2$), 6.68–7.46 (m, 10 H, Ar H). This acetate was characterized further by reduction to methyl 2,3-diphenylpropionate and reductive alkylation to give methyl 2,3-diphenyl-2-methylpropionate.

Methyl 2,3-diphenylpropionate was obtained in 66% yield by reduction of methyl 2-acetoxy-2,3-diphenylpropionate with sodium α-(dimethylamino)naphthalenide by the general procedure described earlier (vide supra). The product was purified by preparative TLC on silica gel (20% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$) δ 2.84–3.24 (m, 2 H, $ArCH_2$), 3.59 (s, 3 H, $COOCH_3$), 3.76–4.01 (m, 1 H, ArCH), 7.20–7.22 (m, 10 H, Ar H); mass spectrum, m/e (relative intensity) 240.1148 (14.3; calcd for $C_{16}H_{16}O_2$ 40.1150), 181 (13.6), 180 (4.5), 179 (3.3), 178 (3.6), 149 (4), 118 (6.8), 102 (7.4).

Methyl 2,3-diphenyl-2-methylpropionate was obtained in 46% yield by the general reductive methylation procedure described earlier (vide supra) followed by preparative TLC on silica gel (20% ethyl acetate in hexane) of the crude product: ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3 H, CH_3), 3.24 (q, 2 H, J = 14 Hz, $ArCH_2$), 3.66 (s, 3 H, CO_2CH_3), 6.78–7.31 (m, 10 H, ArH); mass spectrum, m/e (relative intensity) 254.1314 (17.4; calcd for $C_{17}H_{18}O_2$ m/e 254.1306), 222 (6.6), 195 (12.2), 179 (27.2), 163 (55.4), 162 (11.6).

2,3-Diphenyl-2-methylpropionic Acid. Methyl 2,3-diphenyl-2-methylpropionate (100 mg, 0.39 mmol) was hydrolyzed by refluxing with a mixture of ethylene glycol (2 mL), KOH (100 mg, 1.78 mmol), and H_2O (100 μL) for 2 h. The reaction mixture

(37) Kugita, H.; Oine, T.; Hayashi, H. Japanese Patent 17 862(66). Cf.: *Chem. Abstr.* **1967**, *66*, 55255.

was cooled to 20 °C and extracted with ether (15 mL) to remove any unhydrolyzed material. The basic aqueous phase after acidification with iced HCl was extracted with ether (3 × 15 mL). The ether extract was washed with brine, dried ($MgSO_4$), and concentrated to afford the title compound as a white solid 85 mg (89%). Recrystallization from ether–pentane afforded a pure sample of this acid: mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 1.5 (s, 3 H, CH_3), 3.46 (q, 2 H, J = 14 Hz, Ar H), 6.8–7.36 (m, 10 H, Ar H), 9.74 (br s, 1 H, COOH).

Reductive Alkylation of Methyl 2-Acetoxy-2-phenylacetate (19). Synthesis of Methyl 2-Ethyl-2-phenylacetate (20). To a stirred solution of the acetate **19** from methyl mandelate (144 mg, 0.69 mmol) in *anhydrous* THF (3 mL) was added a solution of sodium α(dimethylamino)naphthalenide in HMPA at 20 °C until a green color persisted for 30 s. The reaction mixture was then cooled (−10 °C), and EtI (0.129 g, 0.83 mmol) was added dropwise. The reaction mixture was then stirred for 2 h at −10 °C and then quenched with 10% HCl. The organic material was extracted with ether (3 × 20 mL). The ether extract was washed with 10% HCl (5 × 10 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford a light brown oil (120 mg, 97%), which was identical with an authentic sample of **20** by GC comparison (15% FFAP on Chromosorb W 60/80, 4 ft × 0.25 in. column, at 160 °C) and by ^1H NMR.

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Registry No. **1c**, 110-00-9; **1e**, 538-93-2; **1f**, 103-45-7; **1g**, 101-97-3; **1h**, 578-58-5; **1i**, 91-16-7; **1j**, 874-63-5; **1k**, 104-47-2; **1l**, 150-78-7; **1m**, 151-10-0; **1n**, 2398-37-0; **1o**, 95-46-5; **1p**, 1073-06-9; **1q**, 109-04-6; 1r, 90-11-9; **3b**, 83026-11-3; **3c**, 19377-69-6; **3d**, 83026-12-4; **3e**, 83026-13-5; **3f**, 83026-14-6; **3g**, 83026-15-7; **3h**, 83026-16-8; **3i**, 83026-17-9; **3j**, 83026-18-0; **3k**, 83026-19-1; **3l**, 83026-20-4; **3m**, 83026-21-5; **3n**, 83026-22-6; **3o**, 83026-23-7; **3p**, 83026-24-8; **3q**, 83026-25-9; **3r**, 83026-26-0; **4b**, 83026-27-1; **4c**, 83026-28-2; **4d**, 83026-29-3; **4e**, 83026-30-6; **4f**, 83026-31-7; **4h**, 83026-32-8; **4k**, 83026-33-9; **4l**, 83026-34-0; **4m**, 83026-35-1; **4n**, 83026-36-2; **4o**, 83026-37-3; **4q**, 83026-38-4; **5b**, 83026-39-5; **5c**, 40572-09-6; **5d**, 83026-40-8; **5e**, 23197-72-0; **5f**, 83026-41-9; **5h**, 4503-92-8; **5k**, 83026-42-0; **5l**, 33254-63-6; **5m**, 83026-43-1; **5n**, 50874-07-2; **5o**, 70484-46-7; **5q**, 39541-69-0; **6b**, 83026-44-2; **6d**, 83026-45-3; **6e**, 62707-18-0; **6h**, 83026-46-4; **6l**, 83026-47-5; **6n**, 83026-48-6; **6o**, 83026-49-7; **8**, 56979-61-4; **9b**, 25899-90-5; **9d**, 18288-28-3; **9e**, 15687-27-1; **9h**, 83026-50-0; **9l**, 83026-51-1; **9n**, 3146-60-9; **9o**, 62835-95-4; **13**, 617-35-6; **14**, 78925-99-2; **15**, 78926-00-8; **16**, 78926-01-9; **17**, 4371-50-0; **18**, 15206-55-0; **19**, 947-94-4; **20**, 2294-71-5; DEOM, 609-09-6; $SnCl_4$, 7646-78-8; methyl iodide, 74-88-4; *p*-bromotoluene, 106-38-7; methyl 2-hydroxy-2,3-diphenylpropionate, 83026-52-2; benzyl chloride, 100-44-7; methyl 2-acetoxy-2,3-diphenylpropionate, 41366-89-6; methyl 2,3-diphenylpropionate, 35030-49-0; methyl 2,3-diphenyl-2-methylpropionate, 57625-75-9; 2,3-diphenyl-2-methylpropionic acid, 7511-43-5; methyl mandelate, 771-90-4; ethyl iodide, 75-03-6.

Selective Reductions. 30. Effect of Cation and Solvent on the Reactivity of Saline Borohydrides for Reduction of Carboxylic Esters. Improved Procedures for the Conversion of Esters to Alcohols by Metal Borohydrides

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A comparative study of the relative reactivity of saline borohydrides (Li, Na, Ca) for the reduction of carboxylic esters has been made in selected solvents (ether, tetrahydrofuran, diglyme, 2-propanol, and ethanol) at 25 °C. In ether solvents the reactivity follows the trend $LiBH_4 > Ca(BH_4)_2 > NaBH_4$. On the other hand, in alcohol solvents the order of reactivity is $Ca(BH_4)_2 > LiBH_4 > NaBH_4$. The reactivities of $LiBH_4$ in ethyl ether and THF, of $Ca(BH_4)_2$ in THF and 2-propanol, and of $NaBH_4$ in ethanol proved to be promising for the reduction of esters. However, alcohol solvents are not useful for reductions at elevated temperatures because the decomposition of the reagents becomes competitive with the reduction. A convenient synthetic procedure has been developed for the rapid conversion of esters to alcohols by using $LiBH_4$ in ethyl ether, $LiBH_4$ in THF, and $Ca(BH_4)_2$ in THF and utilizing essentially stoichiometric amounts of the reagents. The procedure involves adding toluene to the reaction mixture and bringing the temperature to 100 °C while allowing the solvent do distill off. Following completion of the reaction, toluene is readily removed under vacuum and the reaction product hydrolyzed. These reductions were generally complete in 0.5–2.0 h, and high yields of alcohols (73–96%) were isolated. A number of ester derivatives, including compounds containing nitro, halo, cyano, and alkoxy groups, diesters, and lactones were reduced by this procedure. The study demonstrated the high selectivity of these reagents, permitting the rapid reduction of the ester group in the presence of many substituents. However, unsaturated esters undergo simultaneous hydroboration when reduced by this procedure.

Since its original discovery,[2] sodium borohydride has proven to be a very useful reagent for the selective reduction of aldehyde and ketone groups.[3] It has not been generally applicable for the reduction of ester and similar functional groups, which are relatively difficult to reduce. However, the reducing properties of sodium borohydride could be increased (1) by varying the solvent, (2) by changing the cation, (3) by the use of catalysts, and (4) by the presence of activating substituents.[4] Thus the successful reduction of esters by potassium borohydride and lithium chloride was first reported by Paul and Joseph.[5] Later, the reduction of esters by sodium borohydride was

(1) Postdoctoral research associates on Grant ARO-DAAG-29-79-C-0027 supported by the U.S. Army Research Office.
(2) Schlesinger, H. I.; Brown, H. C.; Hoekstra, H. R.; Rapp, L. R. *J. Am. Chem. Soc.* **1953**, *75*, 199.
(3) Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122.
(4) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 572. Esters containing electron-withdrawing substituents activate the ester group for reduction by sodium borohydride: Meschino, J. A.; Bond, C. H. *J. Org. Chem.* **1963**, *28*, 3129.
(5) Paul, R.; Joseph, N. *Bull. Soc. Chim. Fr.* **1952**, 550.

0022-3263/82/1947-4702$01.25/0