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A GENERAL APPROACH TO SUBSTITUTED ITACONATE ESTERS

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Abstract: *A general approach to the synthesis of various itaconates including 3-substituted esters is presented. The complementarity of the approach is also shown.*

Although itaconic acid esters (**1**) are useful for the preparation of more complex intermediates and products, general synthetic methods for the preparation of these compounds are limited.[1-4] Dialkyl itaconates (**1**) with R^1=R^2 are accessible by standard esterification methods starting from the commercially available itaconic acid, its anhydride or itaconyl chloride.[1] Preparation of mixed itaconate esters is more laborious. The current synthetic approach is based upon the higher reactivity of the 4-position in the itaconyl system. For example, dimethyl itaconate can be partially hydrolyzed to the 1-methyl half ester which subsequently can be converted to the 1-methyl 4-alkyl ester.[1a] Based upon the same regioselectivity principle, either itaconic acid or, preferably,

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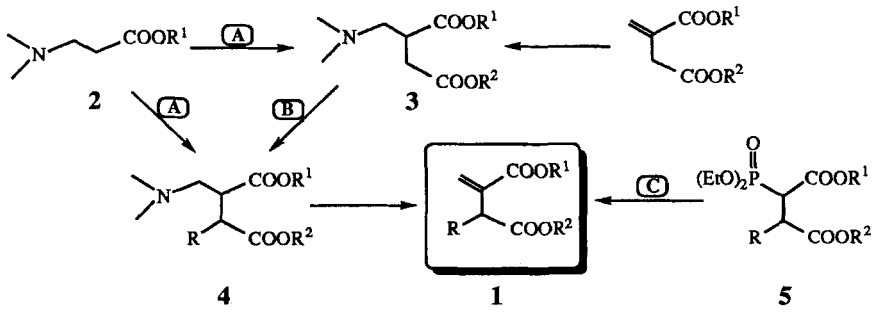
itaconic anhydride will undergo alcoholysis at the 4-position leaving the 1-position for further esterification.[1b] These approaches often require extended purification due to equilibration of the product mixture. An alternative approach is based upon the alkylation of masked anions of α-acrylates,[2] although there are only a few examples in the literature dealing with a synthesis of itaconate esters.[3] Moreover, 3-substituted itaconates that could be of synthetic importance are either difficult to prepare or the available methods are useful only for specific structures.[4] Direct alkylation of the enolate anion of dimethyl itaconate gave poor yields, even with methyl iodide as the alkylating agent.[5] The difficulties associated with undesirable condensation were overcome by generating a dianion of the 4-methyl itaconate half ester which subsequently underwent nucleophilic addition to both aldehydes and ketones.[6]

We present a general approach to the synthesis of various itaconates including 3-substituted esters. Methods A, B and C (Scheme)

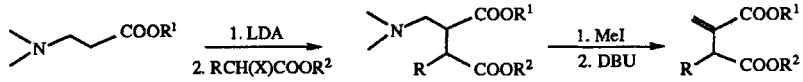
SCHEME



show approaches that are complementary and flexible depending upon the availability of the substrates and the complexity of the desired products.

Commercially available ethyl 3-dimethylaminopropionate (**2**) (R^1=Et)[7] can be alkylated with haloacetates to give **3** or with α-haloesters to give **4** (Method A). The aminoester **3** is *de facto* a pro-

TABLE 1
Method A



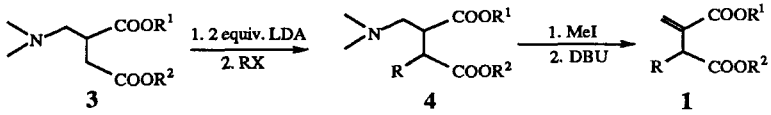
2				3 or 4		1	
R	R^1	R^2	X	3 or 4	Yield [%]	1	Yield [%]
H	Et	Et	Br	**3a**	79	**1a**	93
H	Et	*t*-Bu	Br	**3b**	55	**1b**	89
H	Et	Me	Br	**3c**	82	**1c**	86
Me	Et	Et	I	**4a**	42	**1d**	87

tected itaconate ester and can be alkylated to give **4** (Method B). Subsequent quaternization of **4** followed by elimination leads to the itaconate **1**. Method C starts with the product of alkylation of a phosphonate (*e.g.* triethyl phosphonoacetate, R^1=Et) with bromoacetate or α-haloester followed by the Horner-Wadsworth-Emmons reaction.

Method A. Alkyl 3-dimethylaminopropionate (**2**) has been developed as a synthetic equivalent of the α-acrylate anion.[2a] It can be deprotonated with LDA and alkylated with bromoacetates yielding **3**, or alkylated with α-iodoesters to give **4**. After purification, quantitative quaternization is achieved with methyl iodide. Elimination with DBU, in dichloromethane or acetonitrile, proceeds within 10-15 minutes at room temperature. The final product **1** obtained by this method is often sufficiently pure for subsequent use, but can be easily purified further, if necessary, by passing the crude product through silica gel.

Method B. Treatment of the amino-itaconate **3** with 2 moles of LDA generates the dienolate, which may be inductively stabilized by

TABLE 2
Method B



3 4 1

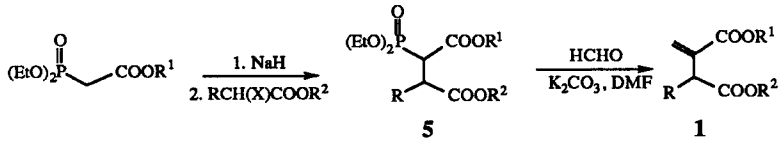
R	R^1	R^2	X	4	Yield [%]	1	Yield [%]
Me	Et	Et	I	**4a**	17	**1d**	a
Et	Me	Me	Br	**4b**	53	**1e**	87
b	Et	*t*-Bu	I	**4c**	46	**1f**	79

[a] See Method A. [b] The alkylating agent is **6**.

the nitrogen atom.[2a] The dienolate can be alkylated in the 3-position with a variety of alkylating agents to give **4**. The advantage of this method is that the aminosuccinate **3** can be constructed from **2** or quantitatively from commercially available itaconate esters, by addition of dimethylamine. Finally, quaternization of **4** followed by elimination yields 3-substituted itaconates, **1**.

Method C. This method provides what may be the best approach to the itaconates **1** where R^1=R^2 and R=H, because the appropriate substrate **5** can be conveniently prepared from diethyl phosphite and dialkyl maleates or fumarates.[8] Alkylation of phosphonate esters is well-known.[2c,9] Therefore, α-haloesters can form dialkyl diethoxyphosphonosuccinates (**5**) which undergo the Horner-Wadsworth-Emmons reaction with formaldehyde.[2c,8a,10] We have simplified and improved this transformation by using 37% formaldehyde solution in combination with solid potassium carbonate and dimethylformamide.[11] In this short, clean reaction, further purification is usually not necessary.

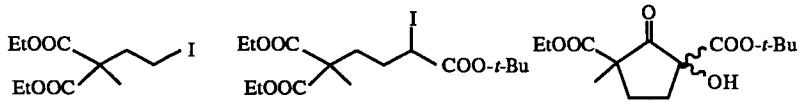
TABLE 3
Method C



5 1

R	R^1	R^2	X	5	Yield [%]	1	Yield [%]
H	Et	*t*-Bu	Br	**5a**	51	**1b**	79
H	Et	Me	Br	**5b**	69	**1c**	55
Ph	Et	Et	Br	**5c**	74	**1g**	93

The following examples illustrate the complementary nature of the methods. Attempted alkylation of **2** (R^1=Et) with ethyl 2-bromophenylacetate yielded diethyl 2,3-diphenylsuccinate (97%) as a *dl*/*meso* mixture[12] instead of the expected product **4** (R=Ph, R^1=R^2=Et). However, alkylation of triethyl phosphonoacetate with ethyl 2-bromophenylacetate, according to Method C, gives the desired product **5c** in 74% yield. The preparation of **1f** can be accomplished either with iodide **6** (Method B) or iodide **7** (Method A). Iodide **6** is relatively easy



6 **7** **8**

to prepare,[13] but conditions for the preparation of the α-iodoester **7** by the Rathke method[14] resulted, in our hands, in cyclization to **8**.[15] Thus, Method B was the method of choice for this synthesis. Finally, the symmetrical itaconates **1** (R^1=R^2 and R=H) can be prepared by the

classic acidic esterification of itaconic acid (or its derivatives) and by Method C under acid-free conditions.

EXPERIMENTAL

General Methods. ^1H NMR spectra were determined in $CDCl_3$ on a Bruker IBM AF-300 (300.13 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.26 ppm). Coupling constants (J) are reported in cycles per second (Hz). ^{13}C NMR spectra were recorded in $CDCl_3$ at 75.46 MHz on a Bruker IBM AF-300. Carbon chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (77.09). Coupling constants (J) are reported as cycles per second (Hz) and were determined by the use of a ^{13}CWNOE microprogram. Infrared spectra (IR) were obtained as thin films between sodium chloride plates on an IBM IR/132 FT-IR spectrophotometer recorded in wavenumbers (cm^{-1}) and are uncalibrated. Low-resolution mass spectra (MS) were recorded on an LKB-9000 mass spectrometer or a VG 70-SE double focusing magnetic sector mass spectrometer via direct probe with peaks as units of mass charge (m/e). High-resolution mass spectra (HRMS) were recorded on a Varian Mat CH-5DH spectrometer and were calibrated by peak matching. Flash chromatography was carried out on Merck 230-400 mesh silica gel. Gas chromatography-mass spectroscopy (GC-MS) was performed on a Hewlett Packard 5890 using a 12 m x 0.2 mm I. D. x 0.33 μm film thickness fused silica capillary column with 100% dimethyl polysiloxane (HP-1, Hewlett-Packard). The GC-MS conditions were: initial temp. 70 °C, final temp. 300 °C, temp. rate 25 °C/min, inj. temp. 250 °C, det. temp. 280 °C. All reactions were carried out in flame-dried flasks under an argon atmosphere with positive pressure maintained throughout unless otherwise noted.

Materials. Distilled reagent grade solvents were used for all chromatographic separations. Solvents (CH_2Cl_2, CH_3CN, DMF) were used as received. THF was obtained by distillation from sodium ben-

zophenone ketyl prior to use. HMPA (Aldrich) was distilled from CaH_2 and stored over molecular sieves. Methyl, ethyl, *tert*-butyl bromoacetates and ethyl 2-bromopropionate (Aldrich) as well as ethyl 2-bromophenyl acetate (Lancaster) were distilled before use. Dimethyl itaconate (Aldrich) was distilled. Diethyl itaconate was prepared according to a literature procedure.[16] All other reagents were purchased from Aldrich except ethyl 2-dimethylaminopropionate which was purchased from Lancaster and anhydrous potassium carbonate which was purchased from J. T. Baker. Lithium diisopropylamide was freshly prepared from diisopropylamine (distilled from NaH) and BuLi in hexanes (Aldrich).

METHOD A

TYPICAL PROCEDURE 2 —> 3 or 4 (3a).

A solution of 2-dimethylaminopropionate **2** (0.22 g, 1.53 mmol), HMPA (0.31 g, 1.73 mmol) and THF (2 mL) was added dropwise to a solution of lithium diisopropylamide (1.78 mmol) in THF (3 mL) at -78 °C. After 45 min, ethyl bromoacetate (0.20 mL, 1.80 mmol) was added dropwise. After 5 min the bath was removed and stirring was continued for 1 hr. The reaction was then quenched by the addition of saturated aqueous ammonium chloride (10 mL) and partitioned between ether (30 mL) and water. The ether extract was washed with water (4x5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated on a rotary evaporator. Chromatography of the residue (10 g of silica gel, hexane/ethyl acetate 4:1 v/v) afforded 0.28 g (79%) of the product **3a**.

3a: ^{1}H-NMR 4.15 (q, J=7.1, 2H), 4.11 (q, J=7.1, 2H), 3.05-2.95 (m, 1H), 2.70-2.52 (m, 3H), 2.38-2.31 (m, 1H), 2.21 (s, 6H), 1.25 (t, J=7.1, 3H), 1.24 (t, J=7.1, 3H). ^{13}C-NMR 173.6 (s), 171.6 (s), 60.4 (t, J=134), 60.2 (t, J=148), 60.1 (t, J=148), 45.2 (q, J=132), 40.1 (d, J=132), 34.1 (t, J=130), 13.8 (q, J=127). IR 2953, 2824, 2772, 1738, 1458, 1437, 1372, 1341, 1265, 1165, 1101.

MS (70 ev) 231 (3, M^+), 186 (6, M^+-OEt), 84 (8), 58 (100, $Me_2N^+=CH_2$). HRMS calc'd for $C_{11}H_{21}NO_4$ 231.1471; found 231.1476.

3b: Yield 55%. ^{1}H-NMR 4.17 (q, J=7.1, 2H), 3.08-2.94 (m, 1H), 2.73-2.51 (m, 3H), 2.32 (br s, 7H), 1.42 (s, 9H), 1.25 (t, J=7.1, 3H). ^{13}C-NMR 174.0 (s), 171.1 (s), 80.6 (s), 60.7 (t, J=129), 60.6 (t, J=147), 45.5 (q, J=134), 40.5 (d, J=132), 35.9 (t, J=131), 28.0 (q, J=127), 14.2 (q, J=127). IR 2978, 2940, 2865, 2822, 2770, 1732, 1462, 1393, 1368, 1339, 1259, 1217, 1154, 1101, 1036. MS 259 (1, M^+), 202 (1, M^+-CMe_3), 186 (6, M^+-$OCMe_3$), 158 (4, M^+-COO*t*Bu), 84 (3), 58 (100, $Me_2N^+=CH_2$). HRMS calc'd for $C_{13}H_{25}NO_4$ 259.1783; found 259.1782.

3c: Yield 82%. ^{1}H-NMR 4.15 (q, J=7.1, 2H), 3.66 (s, 3H), 3.03-2.95 (m, 1H), 2.71-2.51 (m, 3H), 2.38-2.29 (m, 1H), 2.21 (s, 6H), 1.25 (t, J=7.1, 3H). ^{13}C-NMR 173.8 (s), 172.5 (s), 60.7 (t, J=144), 60.6 (t, J=144), 51.6 (q, J=147), 45.5 (q, J=134), 40.4 (d, J=132), 34.1 (t, J=129), 14.1 (q, J=127). IR 2959, 2880, 1738, 1653, 1634,1507, 1456, 1437, 1248, 1202, 1148, 1094. MS 217 (5, M^+), 186 (5, M^+-OMe), 172 (1, M^+-OEt), 158 (1, M^+-COOMe), 84 (18), 58 (100, $Me_2N^+=CH_2$). HRMS calc'd for $C_{10}H_{19}NO_4$ 217.1314; found 217.1324.

Compound **4a** was obtained in 42% yield as a 1.4:1 mixture (by GC-MS) of the diastereoisomers **4a'** and **4a"** which were separated by flash chromatography.

4a': ^{1}H-NMR 4.20-4.07 (m, 4H), 3.00-2.93 (m, 1H), 2.71-2.59 (m, 2H), 2.27-2.23 (m, 1H), 2.20 (s, 6H), 1.26 (t, J=7.1, 3H), 1.24 (t, J=7.1, 3H), 1.12 (d, J=7.1, 3H). ^{13}C-NMR 174.7 (s), 173.2 (s), 60.5 (t, J=148), 59.7 (t, J=136), 46.9 (d, J=132), 45.5 (q, J=135), 40.3 (d, J=132), 14.5 (q, J=129), 14.1 (q, J=127).

4a": ^{1}H-NMR 4.16-4.08 (m, 4H), 2.97-2.83 (m, 2H), 2.71-2.64 (m, 1H), 2.37-2.24 (m, 1H), 2.20 (s, 6H), 1.24 (t, J=7.1, 6H), 1.17 (d, J=7.1, 3H). ^{13}C-NMR 174.6 (s), 173.7 (s), 60.6 (t, J=146), 60.5 (t, J=146), 58.4 (t, J=136), 46.2 (d, J=130), 45.8 (q, J=132), 39.9 (d, J=131), 14.2 (q, J=127), 13.8 (q, J=128). IR 2980, 2824, 2770, 1734, 1699, 1684, 1653, 1559, 1539, 1456, 1373, 1263, 1202. CI 246 (100, M^++H), 200 (5, M^+-OEt), 173 (2, M^++H-COOEt), 144 (2, M^+-MeCHCOOEt), 98 (4, M^++H-MeCHCOOEt-OEt).

TYPICAL PROCEDURE 3 or 4 —> 1 (1a).

The aminosuccinate **3a** (0.23 g, 1.00 mmol) was dissolved in methylene chloride (1 mL). Iodomethane (1 mL, 16 mmol) was added to this solution at room temperature. After 2 min a white precipitate formed. The reaction mixture was stirred for 1 hr, evaporated, and pumped to dryness under vacuum, affording 0.37 g of a white solid that was used directly in the next step.

The quaternary ammonium salt (0.36 g, 0.96 mmol) was dissolved in acetonitrile (10 mL) and stirred with DBU (1 mL) for 15 min. The solution was then extracted with ether (60 mL) and water (20 mL). The ether extract was washed with water (10 mL), 1M HCl (10 mL) and water (2x10 mL), then dried over $MgSO_4$, filtered and evaporated. The product **1a** (0.16 g, 93%) had spectroscopic properties identical with those of an authentic sample.[16]

1b: Yield 89%. ^{1}H-NMR 6.27 (s, 1H), 5.63 (s, 1H), 4.20 (q, J=7.1, 2H), 3.23 (s, 2H), 1.42 (s, 9H), 1.28 (t, J=7.1, 3H). ^{13}C-NMR 170.0 (s), 166.3 (s), 134.6 (s), 127.6 (t, J=160), 80.9 (s), 60.9 (t, J=149), 39.0 (t, J=128), 27.9 (q, J=125), 14.1 (q, J=126). IR 2986, 1744 (br), 1642, 1437, 1372, 1319, 1262, 1202, 1148. MS 158 (3, M^+-$Me_2C{=}CH_2$), 141 (20, M^+-$OCMe_3$), 113 (23, M^+-COO*t*Bu), 57 (100, Me_3C^+). HRMS calc'd for $C_7H_{10}O_4$ 158.0579; found 158.0576.

1c: Yield 86%. ^{1}H-NMR 6.33 (s, 1H), 5.70 (s, 1H), 4.22 (q, J=7.1, 2H), 3.70 (s, 2H), 3.34 (s, 2H), 1.29 (t, J=7.1, 3H). ^{13}C-NMR 171.2 (s), 166.0 (s), 133.9 (s), 128.2 (t, J=162), 61.0 (t, J=147), 51.9 (q, J=147), 37.5 (t, J=125), 14.1 (q, J=127). IR 2986, 1744 (br), 1708, 1642, 1437, 1372, 1319, 1262, 1202, 1148. MS 172 (7, M^+), 141 (38, M^+-OMe), 127 (100, M^+-OEt), 113 (66, M^+-COOMe), 99 (83, M^+-COOEt), 85 (54), 69 (73), 59 (M^+-CH_2COOMe). HRMS calc'd for $C_8H_{12}O_4$ 172.0736; found 172.0780.

1d: Yield 87%. ^{1}H-NMR 6.32 (s, 1H), 5.68 (s, 1H), 4.21 (q, J=7.1, 2H), 4.13 (q, J=7.1, 2H), 3.58 (q, J=7.1, 1H), 1.36 (d, J=7.2, 3H), 1.29 (t, J=7.1, 3H), 1.23 (t, J=7.1, 3H). ^{13}C-NMR 173.8 (s), 166.2 (s), 125.4 (t, J=159), 60.9 (t, J=142), 60.7 (t, J=142), 41.3 (d, J=130), 16.1 (q, J=129), 14.1 (q, J=127). IR

2984, 2942, 1736, 1718, 1634, 1464, 1372, 1308, 1262, 1186, 1096, 1030. MS 200 (8, M^+), 185 (22, M^+-Me), 155 (85, M^+-OEt), 127 (53, M^+-COOEt), 99 (100, M^+-MeCHCOOEt). HMRS calc'd for $C_{10}H_{16}O_4$ 200.1049; found 200.1081.

METHOD B

The aminosuccinates **3a** and **3d** (R^1=Me, R^2=Me; Table 2) were prepared in quantitative yield by reacting either diethyl or dimethyl itaconates with an ether solution of dimethylamine according to Rouvier and co-workers.[7] The spectroscopic properties of **3a** were the same as those of the compound obtained by Method A.

3d: ^{1}H-NMR 3.70 (s, 3H), 3.66 (s, 3H), 3.08-2.99 (m, 1H), 2.73-2.56 (m, 3H), 2.40-2.28 (m, 1H), 2.23 (s, 6H). ^{13}C-NMR 173.7 (s), 171.7 (s), 60.4 (t, J=136), 51.2 (q, J=146), 51.0 (q, J=146), 45.0 (q, J=130), 39.9 (d, J=132), 33.6 (t, J=130). IR 2953, 2824, 2772, 1738, 1458, 1437, 1372, 1341, 1265, 1165, 1101, 1034. MS 203 (3, M^+), 172 (2, M^+-OMe), 84 (8), 58 (100, Me_2N^+=CH_2). HRMS calc'd for $C_9H_{17}NO_4$ 203.1158; found 203.1147.

TYPICAL PROCEDURE 3 —> 4 (4c).

A solution of the aminosuccinate **3b** (0.10 g, 0.40 mmol) in THF (0.5 mL) was added slowly to a solution of lithium diisopropylamide (0.8 mmol) in THF (1 mL) at -78 °C. After 30 min the bath was removed and stirring was continued for another 40 min The clear, yellow solution was then recooled to -78 °C. A solution of 3,3-(dicarboethoxy)-iodobutane **6** (0.24 g, 0.73 mmol), HMPA (0.29 g, 1.64 mmol), and THF (0.5 mL) was added dropwise. The bath was removed again and stirring was continued for 1.5 hr. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 mL) and partitioned between ether (30 mL) and water. The ether extract was washed with water (4x5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated on a rotary evaporator. Chromatography on

silica gel (10 g, hexane/ethyl acetate 4:1) afforded a total of 0.085 g (46%) of **4c** as a 3:2 mixture (by GC-MS) of the diastereoisomers.

4a: The product (17% yield) was identical to that obtained by Method A.

4b: Yield 53%. One of the isomers (t_r=7.11 min in GC-MS; temp. rate 15 °C/min) was isolated from the reaction mixture. ^{1}H-NMR 3.70 (s, 3H), 3.67 (s, 3H), 2.96-2.88 (m, 1H), 2.70-2.63 (m, 1H), 2.52 (dt, J=10.1, J=4.1, 1H), 2.22-2.12 (m, 1H), 2.19 (s, 6H), 1.64-1.51 (m, 1H), 1.49-1.40 (m, 1H), 0.86 (t, J=7.3, 3H). ^{13}C-NMR 174.3 (s), 173.8 (s), 60.4 (t, J=133), 51.6 (q, J=147), 51.4 (q, J=147), 48.2 (d, J=133), 46.8 (d, J=133), 45.5 (q, J=132), 23.7 (t, J=129), 11.5 (q, J=128). IR 2952, 2824, 2772, 1738, 1458, 1435, 1346, 1273, 1248, 1194, 1157. MS 231 (2, M^+), 200 (2, M^+-OMe), 84 (6), 58 (100, Me_2N^+=CH_2). HRMS calc'd for $C_{11}H_{21}O_4$ 231.1471; found 231.1474.

4c: ^{1}H-NMR 4.18-4.13 (m, 6H), 2.90-2.80 (m, 2H), 2.68-2.61 (m, 2H), 2.48-2.40 (m, 1H), 2.32-2.12 (br s, 7H), 1.93-1.74 (m, 2H), 1.46 (s), 1.44 (s, 9H), 1.39 (s), 1.25 (t, J=7.1), 1.24 (t, J=7.1), 1.23 (t, J=7.1, all triplets 9H). ^{13}C-NMR 173.2 (s), 172.4 (s), 172.1 (s), 172.0 (s), 81.2 (s), 61.3 (t, J=147), 60.8 (t, J=147), 58.7 (t, J=130), 53.4 (s), 47.6 (d, J=138), 46.6 (d, J=138), 45.45 (br q, J=134), 45.1 (d, J=138), 33.2 (t, J=132), 33.0 (t, J=132), 28.05 (q, J=127), 25.3 (t, J=129), 23.9 (t, J=129), 19.8 (q, J=130), 14.2 (q, J=127), 14.1 (q, J=127). IR 2980, 2940, 2822, 2770, 1730 (vs), 1460, 1368, 1248, 1152, 1113. MS 459 (1, M^+), 414 (3, M^+-OEt), 386 (7, M^+-COOEt), 358 (10, M^+-COO*t*Bu), 286 (7, M^+-MeC(COOEt)$_2$), 230 (2, M^+-MeC(COOEt)$_2$-Me_2C=CH_2), 58 (100, Me_2N^+=CH_2). HRMS calc'd for $C_{23}H_{41}NO_8$ 459.2832; found 459.2811.

The transformation **4** —> **1** was performed as described in Method A.

1e:[4b,5] Yield 87%. ^{1}H-NMR 6.36 (s, 1H), 5.74 (s, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.41 (t, J=7.5, 1H), 1.92 (m, 1H), 1.69 (m, 1H), 0.91 (t, J=7.3, 3H). ^{13}C-NMR 173.7 (s), 166.8 (s), 138.2 (s), 126.8 (t, J=163), 52.2 (q, J=147), 52.0 (q, J=147), 48.2 (d, J=129), 24.4 (t, J=130), 12.1 (q, J=127). IR 2959, 2880, 1738, 1653, 1634, 1559, 1456, 11437, 1248, 1202, 1148, 1094. MS 186 (1, M^+), 157 (48, M^+-Et), 127 (13, M^+-COOMe), 84 (68, M^+-C_3H_7COOMe).

1f: Yield 79%. ^{1}H-NMR 6.33 (s, 1H), 5.69 (s, 1H), 4.24-4.12 (overlapping q, J=7.1, 6H), 3.35 (dd, J=10.3, J=3.7, 1H), 1.90-1.75 (m, 3H), 1.65-1.50 (m, 1H), 1.42 (s, 9H), 1.41 (s, 3H), 1.30 (t, J=7.1, 3H), 1.24 (t, J=7.1, 3H), 1.23 (t, J=7.1, 3H). ^{13}C-NMR 172.2 (s), 172.1 (s), 171.9 (s), 166.3 (s), 138.6 (s), 126.3 (t, J=160), 80.9 (s), 61.3 (t, J=148), 61.0 (t, J=148), 53.5 (s), 47.9 (d, J=131), 33.4 (t, J=130), 27.9 (q, J=127), 25.7 (t, J=128), 19.8 (q, J=131), 14.2 (q, J=128), 14.1 (q, J=128). IR 2980, 2934, 1732, 1634, 1456, 1368, 1255, 1157, 1026. MS 358 (2, M^+-$Me_2C{=}CH_2$), 341 (6, M^+-O*t*Bu), 313 (12, M^+-COO*t*Bu), 295 (5, M^+-COO*t*Bu-H_2O), 57 (100, $Me_2C{=}CH_2$). HRMS calc'd for $C_{17}H_{25}O_7$ 341.1600; found 341.1596.

NOTE: In the elimination step, methylene chloride was used as the solvent for those quaternary salts that were soluble (**3b, 4a, 4b, 4c**) whereas acetonitrile was used for those that were not soluble in CH_2Cl_2 (**3a, 3c**).

METHOD C

TYPICAL PROCEDURE FOR THE PREPARATION OF 5 (5c).

A solution of triethyl phosphonoacetate (1.13 g, 5.00 mmol) in THF (5 mL) was added to a suspension of sodium hydride (prepared from 0.25 g of 60% NaH washed with 2x1.5 mL of hexane) in THF (5 mL). The reaction mixture turned clear after 20 min. To this mixture, a solution of ethyl 2-bromophenylacetate (1.42 g, 5.80 mmol) in THF (3 mL) was added dropwise causing an exothermic reaction. It was heated to reflux for 5 hr, cooled, diluted with ether (50 mL) and extracted with water (10 mL and 3x5 mL). After drying over $MgSO_4$, the extract was filtered and evaporated. The residue was chromatographed on silica gel (25 g) with 2% AcOH in 4:1 v/v hexane/ethyl acetate. After evaporation, 1.43 g (75%) of the product 5c was obtained as a 1.2:1 mixture (by GC-MS) of the two diastereoisomers.

5a:[17] Yield 51%. ^{1}H-NMR 4.28-4.09 (m, 6H), 3.40 (ddd, J=24.1, J=11.6, J=3.3, 1H), 3.04-2.92 (m, 1H), 2.77-2.67 (m, 1H), 1.42 (s, 9H), 1.33

(dt, J=5.8, J=6.95, 6H),.1.28 (t, J=7.1, 3H). ^{13}C-NMR 169.6 (s), 169.4 (s), 167,7 (s), 167.6 (s), 80.7 (s), 62.4 (t, J=146), 62.35 (t, J=146), 62.3 (t, J=146), 61.0 (t, J=146), 41.8 (d, J=130), 40.0 (d, J=131), 32.0 (t, J=131), 27.5 (q, J=127), 15.9 (q, J=127), 15.8 (q, J=127), 13.6 (q, J=127). IR 2978, 2940, 1732, 1462, 1393, 1368, 1339, 1259, 1217, 1154, 1101, 1036. MS 283 (30, M^++H-$Me_2C{=}CH_2$), 265 (53, M^+-O-*t*-Bu), 237 (56, M^+-COO-*t*-Bu), 209 (32, M^+-COO-*t*-Bu-C_2H_4), 57 (100, Me_3C^+).

5b: Yield 69%. ^{1}H-NMR 4.27-4.09 (m, 6H), 3.69 (s, 3H), 3.45 (ddd, J=24.0, J=11.4, J=3.4, 1H), 3.14-3.01 (m, 1H), 2.86-2.76 (m, 1H), 1.33 (dt, J=6.85, J=6.7, 6H), 1.28 (t, J=7.1, 3H). ^{13}C-NMR 171.0 (s), 170.7 (s), 167.5 (s), 167.4 (s), 62.35 (t, J=148), 62.3 (t, J=148), 61.0 (t, J=150), 51.4 (t, J=147), 41.5 (d, J=132), 39.7 (d, J=132), 30.6 (t, J=132), 15.7 (q, J=127), 15.6 (q, J=127), 13.4 (q, J=127). IR 2951, 1738 (br), 1435, 1273, 1248, 1194, 1157, 1044. MS 297 (4, M^++H), 296 (3, M^+), 265 (30, M^+-OMe), 251 (56, M^+-OEt), 237 (100, M^+-COOMe), 223 (60, M^+-COOEt). HRMS calc'd for $C_{11}H_{21}O_7P$ 296.1025; found 296.1011.

5c: Yield 74%. ^{1}H-NMR 7.39-7.23 (m, 5H), 4.40-3.61 (m, 10H), 1.37 (t, J=7.1), 1.325 (t, J=7.1), 1.31 (t, J=7.1), 1.20 (t, J=7.1), 1.12 (t, J=7.1), 1.08 (t, J=7.1), 1.07 (t, J=7.1), 0.92 (t, J=7.1), all triplets a total of 12 H. ^{31}P-NMR (121.5 MHz, external H_3PO_4, decoupled) 18.59, 18.01. ^{13}C-NMR 40 lines at 172.9, 172.3, 172.0, 171.4, 168.5, 168.4, 166.8, 166.7, 136.1, 135.9, 135.4, 128.7, 128.5, 128.3, 127.9, 63.2, 63.1, 63.0, 62.9, 62.5, 62.4, 62.3, 61.7, 61.4 (br), 61.2, 50.3, 50.1, 49.8, 49.7, 48.3, 48.0, 16.3, 16.25, 16.2, 16.05, 16.0, 15.9, 14.0, 13.8, 13.6. IR 2980, 1732, 1634, 1559, 1539, 1456, 1368, 1300, 1256, 1157, 1026. MS 386 (12, M^+), 340 (100, M^+-OEt), 313 (18, M^+-COOEt), 267 (94, M^+-EtOH-COOEt), 239 (22, M^++H-2COOEt), 203 (47). HRMS calc'd for $C_{18}H_{27}O_7P$ 386.1494; found 386.1557.

TYPICAL PROCEDURE 5 —> 1 (1g).

The phosphonosuccinate **5c** (0.21 g, 0.54 mmol) was dissolved in dimethylformamide (0.2 mL). To this solution, anhydrous potassium carbonate was added (0.16 g, 1.18 mmol) followed by a 37% solution of

formaldehyde in water (0.2 mL). The reaction mixture was stirred for 45 min Water (5 mL) was added and the stirring was continued for another 5 min The reaction mixture was diluted with an additional portion of water (10 mL) and extracted with ether (30 mL). The ether extract was washed with water (4 x 5 mL), dried over $MgSO_4$, filtered and evaporated. The crude reaction mixture was chromatographed on 10 g of silica gel using 2% ethyl acetate in hexane affording 0.13 g (93%) of **1g**.

Compounds **1b** and **1c** prepared by Method C exhibit spectroscopic properties identical with those prepared by Method A.

1g: ^{1}H-NMR 7.39-7.25 (m, 5H), 6.40 (s, 1H), 5.36 (s, 1H), 4.80 (s, 1H), 4.26-4.11 (m, 4H), 1.29 (t, J=7.1, 3H), 1.23 (t, J=7.1, 3H). ^{13}C-NMR 171.8 (s), 166.3 (s), 139.3 (s), 135.9 (s), 129.0 (d, J=161), 128.8 (d, J=161), 127.8 (d, J=161), 127.7 (t, J=152), 61.2 (t, J=148), 61.1 (t, J=148), 53.2 (d, J=132), 14.1 (q, J=127). IR 2982, 1736 (br), 1634, 1499, 1454, 1391, 1370, 1304, 1235, 1198, 1136, 1096. MS 262 (1, M^+), 216 (100, M^+-EtOH), 188 (55, M^+-HCOOEt), 117 (55), 115 (60). HRMS calc'd for $C_{13}H_{12}O_3$ 216.0786; found 216.0792.

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15. Obtained in 44% yield, after flash chromatography on silica gel with 3:2 v/v hexane/ethyl acetate, as a 1.7:1 mixture (by GC-MS) of the diastereoisomers. R_f = 0.06 (10% ethyl acetate in hexane); for comparison R_f value of the starting ester was 0.34. One of the isomers (t_r= 2.23 in GC-MS) was isolated in a pure form. ^{1}H-NMR 4.24-4.11 (m, 2H), 3.83 (s, 1H), 2.70-2.61 (m, 1H), 2.56-2.48 (m, 1H), 2.10-1.92 (m, 2H), 1.46 (s, 9H), 1.43 (s, 3H), 1.25 (t, J=7.0, 3H). ^{13}C-NMR 210.1 (s), 171.0 (s), 170.1 (s), 84.2 (s), 80.3 (s), 61.7 (t, J=151), 55.4 (s), 31.8 (t, J=135), 31.7 (t, J=135), 27.8 (q, J=127), 21.7 (q, J=131), 14.2 (q, J=128). IR 3468 (s br, OH), 2982, 2938, 1753, 1734 (br), 1458, 1395, 1372, 1304, 1275, 1155, 1107, 1024. MS (t_r=2.23) 230 (30, M^+-Me_2=CH_2), 202 (17, M^+-Me_2=CH_2 -C_2H_4), 184 (30, M^+-HCOOtBu), 185 (39, M^+-COOtBu), 156 (34, M^+-Me_2=CH_2 -HCOOEt), 139 (14, M^+-COOtBu-EtOH), 57 (100, Me_3C^+). MS of the other isomer (t_r =2.39) 257 (5, M^+-Et), 230 (30, M^+-Me_2=CH_2), 202 (16, M^+-Me_2=CH_2 -C_2H_4), 184 (28, M^+-HCOOtBu), 185 (18, M^+-COOtBu), 156 (19, M^+-Me_2=CH_2 -HCOOEt), 139 (14, M^+-COOtBu-EtOH), 57 (100, Me_3C^+). HRMS of the mixture of both isomers as calc'd for $C_{10}H_{14}O_6$: 230.0790; found 230.0776.
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