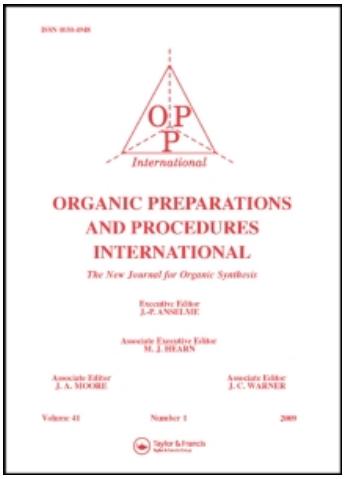

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α-VINYLATION OF TERTIARY ACTIVE HYDROGEN COMPOUNDS

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OPPI BRIEFS

α-VINYLATION OF TERTIARY ACTIVE HYDROGEN COMPOUNDS

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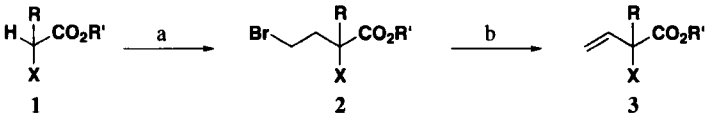
A recent synthetic project required the introduction of a vinyl group at the methine carbon of a substituted malonate ester. A search of the literature revealed that there are many procedures available to achieve this goal but most require expensive or esoteric reagents.[1-2] One method, apparently not explored, was a sequence involving alkylation with 1,2-dibromoethane followed by dehydrohalogenation. Earlier work by Salmon-Legagneur and co-workers[3] suggested that this strategy was possible, but other reports[4-6] indicated that bromination would compete with alkylation in the first step. We wish to report the successful use of an alkylation-dehydrohalogenation procedure for the α-vinylation of tertiary active hydrogen compounds.

The results of our study are summarized in the Scheme. Since our original goal was the vinylation of a tertiary malonate ester, we began by looking at ethyl methyl (±)-methylpropanedioate (**1a**).[7] The sequence was initiated by deprotonation of the diester with sodium hydride in DMF. Once anion formation was complete, the solution was cooled to 0° and 1,2-dibromoethane (1.05 eq.) was added dropwise over 30 min. The reaction was stirred at 0° for 3 h and at 25° for 1 h, then worked up to afford the alkylated diester **2a** in 72% yield; none of the bromination product was observed. The dehydrohalogenation was carried out using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[8] to avoid nucleophilic side-reactions. Optimum conditions involved heating the bromide in neat DBU (1.25 eq.) for 30-60 min at 75-80°. This gave 54% of the dehydrohalogenated product **3a**.

The alkylation with 1,2-dibromoethane was found to be highly sensitive to the steric nature of the R group at the methine carbon of the substituted malonate ester. Substrates incorporating sterically small straight-chain R groups (e.g. **1a-f**) or a ring residue (e.g. **4a**) gave the best yields. Branched R groups such as isopropyl and phenyl, on the other hand, gave less than 5% conversion (by GC) to the alkylated product. These findings reflect normal steric effects in the S_N2 reaction.

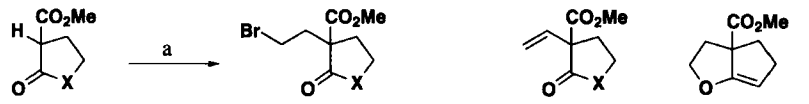
Other active methine compounds were also investigated to determine the scope of the reaction. Both ethyl (±)-2-cyanopropanoate[9] (**1g**) and methyl (±)-2-(phenylsulfonyl)propanoate[10] (**1h**)

were readily vinylated using our method. β-Keto esters, however, gave disappointing results. Ethyl (±)-2-methyl-3-oxobutanoate and methyl (±)-2-oxocyclohexanecarboxylate underwent both C- and



1 2 3

substrate	X	R	R'	% yield **2**	% yield **3**
1a	CO_2Et	Me	Me	72	54
1b	CO_2Et	Me	Et	70	52
1c	CO_2Et	$CH_2CH{=}CH_2$	Et	68	48
1d	CO_2Et	$CH_2CH_2CH{=}CH_2$	Me	65	50
1e	CO_2Et	*n*-C_6H_{13}	Et	72	52
1f	CO_2Et	(*E*)-$CH_2CH{=}CHCO_2Et$	Me	66	41
1g	CN	Me	Et	58	60
1h	SO_2Ph	Me	Me	68	70



4a (X = O) **5a** (X = O) 75% → **6a** (X = O) 48%

4b (X = CH_2) **5b** (X = CH_2) 40% → **6b** 51%

a) NaH, DMF; $BrCH_2CH_2Br$, 0→25° b) DBU, 75-80°

Scheme

O-alkylation with 1,2-dibromoethane to give complex mixtures of products. Methyl (±)-2-oxocyclopentanecarboxylate (**4b**) gave successful C-alkylation, but treatment with DBU resulted in deprotonation of the α' carbon and O-alkylation by the side chain bromide to give heterocycle **6b**. Thus, β-keto esters generally cannot be vinylated using this strategy.

In summary, a simple alkylation-dehydrohalogenation procedure has been developed for the introduction of vinyl substitution to active methine compounds. The method has predictable limitations associated with the alkylation step but requires no special reagents or techniques. Though overall yields are modest in comparison to some of the established procedures, the simplicity of the scheme makes this a useful vinylation protocol for a broad range of substrates.

EXPERIMENTAL SECTION

DMF was vacuum distilled from BaO and stored over 4 Å molecular sieves under N_2. Other commercial reagents were used as received. All reactions were run under dry N_2 in oven-dried glassware. The NH_4Cl (saturated), HCl (0.5 M), $NaHCO_3$ (saturated), and NaCl (saturated) used in workup procedures refer to aqueous solutions. Reactions were monitored by capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) programmed between 50-300°. Preparative separations were performed using one of the following methods: (1) vacuum distillation, (2) flash chro-

matography[11] on silica gel (Grace, grade 62, 60-200 mesh) mixed with Sylvania no. 2282 UV-active phosphor, or (3) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015). Chromatographic band elution was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$. High resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

Diethyl (±)-(*E*)-5-methoxycarbonyl-2-hexenedioate (**1f**) was prepared on a 52.4 mmol scale by the literature method.[12] The overall yield was 6.76 g (26.2 mmol, 50%), bp. 115-116° (0.5 mm Hg).
IR: 1751, 1736, 1657, 1376, 982 cm^{-1}; ^{1}H NMR: δ 6.88 (dt, 1 H, *J* = 15.7, 7.1 Hz), 5.90 (dt, 1 H, *J* = 15.7, 1.6 Hz), 4.21 (q, 2 H, *J* = 7.1 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.76 (s, 3 H), 3.51 (t, 1 H, *J* = 7.5 Hz), 2.80 (td, 2 H, *J* = 7.3, 1.6 Hz), 1.28 (t, 3 H, *J* = 7.1 Hz) 1.27 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 169.0, 168.4, 166.1, 143.7, 124.0, 61.7, 60.3, 52.6, 50.4, 31.0, 14.1, 13.9; HRMS *m/z:* Calcd for $C_{12}H_{18}O_6$: 258.1103. Found: 258.1101.
Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 6.98. Found: C, 55.69; H, 6.95

Representative Procedure for Alkylation with 1,2-Dibromoethane: Ethyl Methyl (±)-(2-Bromoethyl)methylpropanedioate (2a).- To a stirred suspension of 1.39 g (58.0 mmol) of oil-free NaH in 30 mL of dry DMF was added a solution of 9.12 g (57.0 mmol) of ethyl methyl (±)-methylpropanedioate (**1a**)[7] in 15 mL of dry DMF. The mixture was stirred for 10-15 min, then cooled to 0° (ice-water bath), and 11.3 g (5.17 mL, 60.0 mmol) of 1,2-dibromoethane was added dropwise. The reaction was stirred at 0° for 3 h and at 25° for 1 h. The reaction was quenched with 100 mL of saturated NH_4Cl and the mixture was extracted with ether (3x). The combined ethereal layers were washed with NaCl, then dried ($MgSO_4$), and concentrated under vacuum. The crude product was distilled under vacuum to give 11.0 g (41.0 mmol, 72%) of bromo diester **2a** as a colorless oil, bp. 77-79° (0.5 mm Hg).
IR: 1740, 1387 cm^{-1}; ^{1}H NMR: δ 4.20 (q, 2 H, *J* = 7.1 Hz), 3.74 (s, 3 H), 3.39 (m, 2 H), 2.45 (m, 2 H), 1.45 (s, 3 H), 1.26 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 171.9, 171.2, 61.6, 53.6, 52.5, 38.9, 27.0, 20.0, 13.8; HRMS *m/z:* Calcd for $C_9H_{15}{}^{79}BrO_4$: 266.0153. Found: 266.0148.
Anal. Calcd for $C_9H_{15}BrO_4$: C, 40.45; H. 5.62. Found: C, 40.62; H, 5.66

The following compounds were prepared, on varying scales, using the same procedure. Purification was effected by vacuum distillation or flash chromatography as indicated.

Diethyl (2-Bromoethyl)methylpropanedioate (2b): 11.2 g (39.9 mmol, 70%); bp. 84-85° (0.5 mm Hg); lit.[3] bp. 150° (10 mm Hg); IR: 1735, 1387 cm^{-1}; ^{1}H NMR: δ 4.20 (q, 4 H, *J* = 7.1 Hz), 3.39 (m, 2 H), 2.45 (m, 2 H), 1.45 (s, 3 H), 1.26 (t, 6 H, *J* = 7.1 Hz); ^{13}C NMR: δ 171.4 (2), 61.5 (2), 53.7, 38.9, 27.1, 20.0, 13.8 (2); HRMS *m/z:* Calcd for $C_{10}H_{17}{}^{79}BrO_4$: 280.0309. Found: 280.0305.
Anal. Calcd for $C_{10}H_{17}BrO_4$: C, 42.70; H, 6.05. Found: C, 42.81; H, 6.09

Diethyl (2-Bromoethyl)(2-propenyl)propanedioate (2c): 12.0 g (39.0 mmol, 68%), bp. 94-96° (0.3 mm Hg); IR: 3084, 1742, 1652, 1376, 998, 923 cm^{-1}; ^{1}H NMR: δ 5.66 (ddt, 1 H, *J* = 17.1, 10.4, 7.4 Hz), 5.15 (d, 1 H, *J* = 17.1 Hz), 5.14 (d, 1 H, *J* = 10.4 Hz), 4.21 (q, 4 H, *J* = 7.1 Hz), 3.36 (m, 2 H),

2.66 (dt, 2 H, J = 7.4, 1.2 Hz), 2.44 (m, 2 H), 1.27 (t, 6 H, J = 7.1 Hz); ^{13}C NMR: δ 170.4 (2), 131.9, 119.7, 61.6 (2), 57.4, 37.6, 36.1, 27.0, 13.9 (2); HRMS *m/z:* Calcd for $C_{12}H_{19}{}^{79}BrO_4$: 306.0466. Found: 306.0464.

Anal. Calcd for $C_{12}H_{19}BrO_4$: C, 47.06; H, 6.21. Found: C, 47.28; H, 6.26

Ethyl Methyl (±)-(2-Bromoethyl)(3-butenyl)propanedioate (2d): 11.4 g (37.1 mmol, 65%); bp. 97-99° (0.3 mm Hg); IR: 3084, 1742, 1645, 1370, 995, 914 cm^{-1}; ^{1}H NMR: δ 5.76 (m, 1 H), 5.04 (d, 1 H, J = 17.1 Hz), 4.99 (d, 1 H, J = 10.2 Hz), 4.21 (q, 2 H, J = 7.1 Hz), 3.74 (s, 3 H), 3.34 (m, 2 H), 2.48 (m, 2 H), 1.99 (m, 4 H), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR: δ 171.3, 170.6, 137.1, 115.5, 61.6, 57.4, 52.5, 36.2, 32.3, 28.3, 27.0, 13.9; HRMS *m/z:* Calcd for $C_{12}H_{19}{}^{79}BrO_4$: 306.0466. Found: 306.0461.

Anal. Calcd for $C_{12}H_{19}BrO_4$: C, 46.91; H, 6.19. Found: C, 47.14; H, 6.25

Diethyl (2-Bromoethyl)hexylpropanedioate (2e): 5.62 g (13.3 mmol, 72%); bp. 120-122° (0.5 mm Hg); IR: 1737, 1374 cm^{-1}; ^{1}H NMR: δ 4.20 (q, 4 H, J = 7.1 Hz), 3.33 (m, 2 H), 2.46 (m, 2 H), 1.88 (m, 2 H), 1.29-1.18 (complex, 8 H), 1.25 (t, 6 H, J = 7.1 Hz), 0.88 (t, 3 H, J = 6.7 Hz); ^{13}C NMR: δ 171.0 (2), 61.4 (2), 57.7, 36.1, 33.0, 31.4, 29.3, 27.3, 23.9, 22.4, 13.9 (3); HRMS *m/z:* Calcd for $C_{15}H_{27}{}^{79}BrO_4$: 350.1092. Found: 350.1087.

Anal. Calcd for $C_{15}H_{27}BrO_4$: C, 51.28; H, 7.69. Found: C, 51.49; H, 7.74

Diethyl (±)-(*E*)-5-(2-Bromoethyl)-5-methoxycarbonyl-2-hexenedioate (2f): 3.62 g (9.92 mmol, 66%); purified by flash chromatography; IR: 1729, 1656, 1368, 984 cm^{-1}; ^{1}H NMR: δ 6.76 (dt, 1 H, J = 15.5, 7.6 Hz), 5.90 (dt, 1 H, J = 15.5, 1.4 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 4.20 (q, 2 H, J = 7.1 Hz), 3.77 (s, 3 H), 3.36 (m, 2 H), 2.80 (dq, 2 H, J = 7.6, 0.8 Hz), 2.46 (m, 2 H), 1.29 (t, 3 H, J = 7.1 Hz), 1.27 (t, 3 H, J = 7.1 Hz); ^{13}C NMR: δ 170.3, 169.6, 165.7, 141.6, 125.6, 61.9, 60.4, 57.2, 52.7, 36.4, 36.1, 26.5, 14.0, 13.8; HRMS *m/z:* Calcd for $C_{14}H_{21}{}^{79}BrO_6$: 364.0520. Found: 364.0517.

Anal. Calcd for $C_{14}H_{21}{}^{79}BrO_6$: C, 46.02; H, 5.75. Found: C, 46.29; H, 5.82

Ethyl (±)-4-Bromo-2-cyano-2-methylbutanoate (2g): 7.42 g (31.8 mmol, 58%); bp. 84-86° (0.5 mm Hg); IR: 2248, 1744, 1383 cm^{-1}; ^{1}H NMR: δ 4.30 (q, 2 H, J = 7.1 Hz), 3.46 (m, 2 H), 2.55 (ddd, 1 H, J = 14.0, 10.5, 6.0 Hz), 2.34 (ddd, 1 H, J = 14.0, 10.5, 5.2 Hz), 1.65 (s, 3 H), 1.35 (t, 3 H, J = 7.1 Hz); ^{13}C NMR: δ 168.4, 118.8, 63.2, 43.6, 40.4, 25.5, 23.5, 13.8; HRMS *m/z:* Calcd for $C_8H_{12}{}^{79}BrNO_2$: 233.0051. Found: 233.0050.

Anal. Calcd for $C_8H_{12}BrNO_2$: C, 41.03; H, 5.13. Found: C, 41.31; H, 5.16

Methyl (±)-4-Bromo-2-(phenylsulfonyl)-2-methylbutanoate (2h): 3.02 g (9.01 mmol, 68%); purified by flash chromatography; IR: 3070, 3012, 1736, 1584, 1383, 1325, 1145, 763, 727, 691 cm^{-1}; ^{1}H NMR: δ 7.83 (d, 2 H, J = 7.2 Hz), 7.71 (t, 1 H, J = 7.5 Hz), 7.58 (t, 2 H, J = 7.5 Hz), 3.70 (s, 3 H), 3.46 (td, 1 H, J = 10.2, 5.1 Hz), 3.31 (td, 1 H, J = 10.0, 6.5 Hz), 2.77 (ddd, 1 H, J = 14.0, 10.2, 6.5 Hz), 2.52 (ddd, 1 H, J = 14.0, 10.2, 5.1 Hz), 1.62 (s, 3 H); ^{13}C NMR: δ 168.1, 135.3, 134.6, 130.5, 129.0, 72.4, 53.2, 35.9, 25.9, 16.4; HRMS *m/z:* Calcd for $C_{12}H_{15}{}^{79}BrO_4{}^{32}S$: 333.9874. Found: 333.9871.

Anal. Calcd for $C_{12}H_{15}BrO_4S$: C, 43.11; H, 4.49. Found: C, 43.34; H, 4.52

Methyl (±)-3-(2-Bromoethyl)tetrahydro-2-oxo-3-furancarboxylate (5a):[13] 10.7 g (42.8 mmol, 75%); purified by flash chromatography; IR: 1779, 1742, 1384 cm^{-1}; ^{1}H NMR: δ 4.38 (m, 2 H), 3.81

(s, 3 H), 3.54 (td, 1 H, J = 10.0, 5.8 Hz), 3.40 (td, 1 H, J = 10.0, 5.8 Hz), 2.80 (ddd, 1 H, J = 13.1, 6.0, 4.1 Hz), 2.68 (ddd, 1 H, J = 14.4, 9.9, 5.8 Hz), 2.36 (complex, 2 H); ^{13}C NMR: δ 173.8, 169.3, 66.2, 53.8, 53.3, 37.0, 32.2, 26.4; HRMS *m/z:* Calcd for $C_8H_{11}{}^{79}BrO_4$: 249.9840. Found: 249.9841.

Anal. Calcd for $C_8H_{11}BrO_4$: C, 38.40; H, 4.40. Found: C, 38.58; H, 4.51

Methyl (±)-1-(2-Bromoethyl)-2-oxocyclopentanecarboxylate (5b): 5.68 g (22.8 mmol, 40%); bp. 100-101° (0.5 mm Hg); IR: 1758, 1729 cm^{-1}; ^{1}H NMR: δ 3.73 (s, 3 H), 3.50 (m, 1 H), 3.37 (m, 1 H), 2.59-1.90 (complex, 8 H); ^{13}C NMR: δ 213.7, 170.9, 60.1, 52.7, 37.5, 36.9, 33.2, 27.4, 19.5; HRMS *m/z:* Calcd for $C_9H_{13}{}^{79}BrO_3$: 248.0047. Found: 248.0043.

Anal. Calcd for $C_9H_{13}BrO_3$: C, 43.55; H, 5.24. Found: C, 43.78; H, 5.26

Representative Procedure for the Dehydrohalogenation: Ethyl Methyl (±)-Ethenylmethylpropanedioate (3a).- A solution of 2.66 g (10.0 mmol) of ethyl methyl (±)-(2-bromoethyl)methylpropanedioate (**2a**) and 1.90 g (12.5 mmol) of DBU was heated at 75-80° until GC indicated complete consumption of the bromo diester (30-60 min). The reaction was cooled to rt, 50 mL of saturated NH_4Cl was added, and the mixture was agitated until the viscous (or solid) residue dissolved. The solution was extracted with ether (2x) and the combined organic layers were washed with 0.5 M HCl, $NaHCO_3$, and NaCl, then dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by vacuum distillation to give 1.04 g (5.41 mmol, 54%) of olefin **3a** as a colorless oil, bp. 57-59° (2.5 mm Hg).

IR: 1737, 1644, 1374, 997, 926 cm^{-1}; ^{1}H NMR: δ 6.30 (dd, 1 H, J = 17.6, 10.8 Hz), 5.27 (d, 1 H, J = 10.8 Hz), 5.20 (d, 1 H, J = 17.6 Hz), 4.20 (q, 2 H, J = 7.1 Hz), 3.75 (s, 3 H), 1.56 (s, 3 H), 1.26 (t, 3 H, J = 7.1 Hz); ^{13}C NMR: δ 171.7, 171.0, 136.0, 116.1, 61.6, 56.1, 52.6, 19.5, 13.8; HRMS *m/z:* Calcd for $C_9H_{14}O_4$: 186.0892. Found: 186.0889.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.52. Found: C, 58.29; H, 7.57

The following compounds were prepared, on varying scales, using the same procedure. Purification was effected by vacuum distillation or PTLC as indicated.

Diethyl Ethenylmethylpropanedioate (3b): 1.87 g (9.35 mmol, 52%); bp. 61-63° (2.5 mm Hg); IR: 1744, 1643, 1376, 993, 927 cm^{-1}; ^{1}H NMR: δ 6.31 (dd, 1 H, J = 17.6, 10.7 Hz), 5.27 (d, 1 H, J = 10.7 Hz), 5.21 (d, 1 H, J = 17.6 Hz), 4.21 (q, 4 H, J = 7.1 Hz), 1.56 (s, 3 H), 1.26 (t, 6 H, J = 7.1 Hz); ^{13}C NMR: δ 171.1 (2), 136.1, 115.9, 61.4 (2), 56.0, 19.4, 13.8 (2); HRMS *m/z:* Calcd for $C_{10}H_{16}O_4$: 200.1048. Found: 200.1044.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00. Found: C, 59.87; H, 7.98

Diethyl Ethenyl(2-propenyl)propanedioate (3c): 1.78 g (7.87 mmol, 48%); bp. 79-81° (2 mm Hg); IR: 3086, 1737, 1644, 1367, 997, 924 cm^{-1}; ^{1}H NMR: δ 6.30 (dd, 1 H, J = 17.9, 10.9 Hz), 5.70 (ddt, 1 H, J = 17.2, 10.2, 7.3 Hz), 5.32 (d, 1 H, J = 10.9 Hz), 5.21 (d, 1 H, J = 17.9 Hz), 5.09 (m, 2 H), 4.20 (q, 4 H, J = 7.1 Hz), 2.81 (d, 2 H, J = 7.3 Hz), 1.25 (t, 6 H, J = 7.1 Hz); ^{13}C NMR: δ 170.1 (2), 134.7, 132.5, 118.9, 116.9, 61.4 (2), 59.9, 39.2, 13.9 (2); HRMS *m/z:* Calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1202.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.71; H, 7.96. Found: C, 63.92; H, 7.99

Ethyl Methyl (±)-(3-Butenyl)ethenylpropanedioate (3d): 1.79 g (7.92 mmol, 50%); bp. 80-82° (2 mm Hg); IR: 3082, 1744, 1644, 1374, 997, 919 cm^{-1}; ^1H NMR: δ 6.34 (dd, 1 H, *J* = 17.9, 10.9 Hz), 5.78 (ddt, 1 H, *J* = 17.2, 10.3, 6.5 Hz), 5.33 (d, 1 H, *J* = 10.9 Hz), 5.19 (d, 1 H, *J* = 17.9 Hz), 5.00 (m, 2 H), 4.21 (q, 2 H, *J* = 7.1 Hz), 3.74 (s, 3 H), 2.14 (m, 2 H), 1.98 (m, 2 H), 1.25 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 171.0, 170.3, 137.6, 134.7, 116.9, 115.0, 61.5, 59.7, 52.5, 33.9, 28.3, 13.8; HRMS *m/z:* Calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1201.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.71; H, 7.96. Found: C, 63.86; H, 7.92

Diethyl Ethenylhexylpropanedioate (3e): 1.89 g (7.00 mmol, 52%); bp. 95-98° (0.5 mm Hg); IR: 1758, 1737, 1637, 1374, 997, 926 cm^{-1}; ^1H NMR: δ 6.33 (dd, 1 H, *J* = 17.7, 10.9 Hz), 5.29 (d, 1 H, *J* = 10.9 Hz), 5.17 (d, 1 H, *J* = 17.7 Hz), 4.20 (q, 4 H, *J* = 7.1 Hz), 2.02 (m, 2 H), 1.32-1.16 (complex, 8 H), 1.25 (t, 6 H, *J* = 7.1 Hz), 0.87 (t, 3 H, *J* = 6.7 Hz); ^{13}C NMR: δ 170.7 (2), 135.1, 116.5, 61.3 (2), 60.0, 34.8, 31.4, 29.4, 23.9, 22.4, 13.9 (3); HRMS *m/z:* Calcd for $C_{15}H_{26}O_4$: 270.1831. Found: 270.1826.

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.67; H, 9.63. Found: C, 66.89; H, 9.67

Diethyl (±)-(*E*)-5-Ethenyl-5-methoxycarbonyl-2-hexenedioate (3f): 1.14 g (4.01 mmol, 41%); purified by PTLC; IR: 1736, 1657, 1368, 986 cm^{-1}; ^1H NMR: δ 6.80 (dt, 1 H, *J* = 15.7, 7.5 Hz), 6.29 (dd, 1 H, *J* = 17.7, 10.9 Hz), 5.87 (dt, 1 H, *J* = 15.7, 1.4 Hz), 5.37 (d, 1 H, *J* = 10.9 Hz), 5.23 (d, 1 H, *J* = 17.7 Hz), 4.22 (q, 2 H, *J* = 7.1 Hz), 4.17 (q, 2 H, *J* = 7.1 Hz), 3.76 (s, 3 H), 2.94 (dd, 2 H, *J* = 7.6, 1.4 Hz), 1.27 (t, 3 H, *J* = 7.1 Hz), 1.25 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 170.1, 169.4, 165.9, 142.4, 133.9, 125.0, 117.7, 61.8, 60.2, 59.5, 52.7, 37.3, 14.0, 13.8; HRMS *m/z:* Calcd for $C_{14}H_{20}O_6$: 284.1259. Found: 284.1254.

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.04. Found: C, 59.27; H, 7.07

Ethyl (±)-2-Cyano-2-methyl-3-butenoate (3g): 1.58 g (10.3 mmol, 60%); bp. 35-37° (0.5 mm Hg); IR: 2248, 1751, 1643, 1383, 994, 936 cm^{-1}; ^1H NMR: δ 5.90 (dd, 1 H, *J* = 17.0, 10.1 Hz), 5.64 (d, 1 H, *J* = 17.0 Hz), 5.39 (d, 1 H, *J* = 10.1 Hz), 4.27 (q, 2 H, *J* = 7.1 Hz), 1.70 (s, 3 H), 1.33 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR: δ 167.9, 133.3, 118.1 (2), 63.1, 46.9, 23.8, 13.7; HRMS *m/z:* Calcd for $C_8H_{11}NO_2$: 153.0790. Found: 153.0788.

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.75; H, 7.19. Found: C, 62.77; H, 7.21

Methyl (±)-2-(Phenylsulfonyl)-2-methyl-3-butenoate (3h): 0.80 g (3.15 mmol, 70%); purified by PTLC; IR: 3070, 3005, 1744, 1635, 1585, 1376, 1325, 1152, 763, 727, 691 cm^{-1}; ^1H NMR: δ 7.83 (d, 2 H, *J* = 7.2 Hz), 7.67 (t, 1 H, *J* = 7.5 Hz), 7.54 (t, 2 H, *J* = 7.5 Hz), 6.27 (dd, 1 H, *J* = 17.5, 10.8 Hz), 5.47 (d, 1 H, *J* = 10.8 Hz), 5.35 (d, 1 H, *J* = 17.5 Hz), 3.76 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR: δ 167.8, 135.9, 134.2, 131.6, 130.8, 128.6, 121.4, 74.4, 53.2, 15.4; HRMS *m/z:* Calcd for $C_{12}H_{14}O_4{}^{32}S$: 254.0613. Found: 254.0610.

Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.69; H, 5.51. Found: C, 56.83; H, 5.57

Methyl (±)-3-Ethenyltetrahydro-2-oxo-3-furancarboxylate (6a): 1.63 g (9.59 mmol, 48%); purified by PTLC; IR: 3091, 1780, 1736, 1643, 1376, 994, 929 cm^{-1}; ^1H NMR: δ 6.20 (dd, 1 H, *J* = 17.6, 10.6 Hz), 5.41 (d, 1 H, *J* = 10.6 Hz), 5.33 (d, 1 H, *J* = 17.6 Hz), 4.36 (m, 2 H), 3.81 (s, 3 H), 2.92 (ddd, 1 H, *J* = 13.0, 7.1, 5.6 Hz), 2.47 (ddd, 1 H, *J* = 13.0, 7.5, 6.9 Hz); ^{13}C NMR: δ 173.1, 169.1,

132.7, 117.9, 66.0, 56.8, 53.4, 32.0; HRMS *m/z:* Calcd for $C_8H_{10}O_4$: 170.0579. Found: 170.0577.

Anal. Calcd for $C_8H_{10}O_4$: 56.47; H, 5.88. Found: 56.63; H, 5.91

Methyl (±)-3,3a,4,5-Tetrahydro-2*H*-cyclopenta[b]furan-3a-carboxylate (6b): 1.35 g (8.03 mmol, 51%); bp. 50-55° (0.5 mm Hg); IR: (thin film) 3082, 1730, 1680, 1374 cm^{-1}; ^1H NMR: δ 4.59 (m, 2 H), 4.55 (m, 1 H), 3.74 (s, 3 H), 2.89 (ddd, 1 H, J = 14.4, 5.9, 1.5 Hz), 2.46 (m, 3 H), 1.85 (m, 2 H); ^{13}C NMR: δ 174.8, 163.2, 93.2, 77.5, 60.7, 52.2, 36.0, 34.6, 34.0; HRMS *m/z:* Calcd for $C_9H_{12}O_3$: 168.0786. Found: 168.0785.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.29; H, 7.14. Found: C, 64.35; H, 7.17

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REFERENCES

‡ Undergraduate Research Participant, Summer 1998.

1. Some methods for α-vinylation are: a) R. Tanikaga, H. Sugihara, K. Tanaka and A. Kaji, *Synthesis*, 299 (**1977**); b) P. F. Hudrlik and A. K. Kulkarni, *J. Am. Chem. Soc.*, **103**, 6251 (1981) and references cited therein; c) T. Ohnuma, N. Hata, H. Fujiwara and Y. Ban, *J. Org. Chem.*, **47**, 4713 (1982); d) M. Bukowska and J. Prejzner, *Pol. J. Chem.*, **57**, 867 (1983); *Chem. Abstr.*, **102**, 78338k (1985); e) M. Ochiai, T. Shu, T. Nagaoka and Y. Kitagawa, *J. Org. Chem.*, **62**, 2130 (1997) and references cited therein.

2. Some α-vinylations involving organometallic reagents are: a) A. A. Millard and M. W. Rathke, *J. Am. Chem. Soc.*, **99**, 4833, (1977); b) L. S. Hegedus, R. E. Williams, M. A. McGuire and T. Hayashi, *ibid.*, **102**, 4973 (1980); c) T. C. T. Chang, M. Rosenblum and N. Simms, *Org. Synth.*, **66**, 95 (1988); d) M. G. Maloney and J. T. Pinhey, *J. Chem Soc., Perkin Trans. 1*, 2847 (**1988**).

3. F. Salmon-Legagneur, L. Picquet and C. Neveu, *Bull. Soc. Chem. Fr.*, 2025 (**1966**).

4. Representative brominations with 1,2-dibromoethane: a) G. M. Whitesides, C. P. Casey and J. K. Krieger, *J. Am. Chem. Soc.*, **93**, 1379 (1971); b) A. E. Greene, J.-C. Muller and G. Ourisson, *J. Org. Chem.*, **39**, 186 (1974); c) A. R. Chamberlin and S. H. Bloom, *Tetrahedron Lett.*, **27**, 551 (1986); d) A. E. Greene and M. T. Edgar, *J. Org. Chem.*, **54**, 1468 (1989); e) M. Ando, T. Wada and K. Isogai, *ibid.* **56**, 6235 (1991); f) C. Quesnelle, T. Iihama, T. Aubert, H. Perrier and V. Snieckus, *Tetrahedron Lett.* **33**, 2625 (1992); g) P. Delair, N. Kann and A. E. Greene, *J. Chem Soc., Perkin Trans. 1*, 1651 (**1994**).

5. Representative alkylations with 1,2-dibromoethane: a) H. G. Alt, W. Milius and S. J. Palackal, *J. Organometal. Chem.*, **472**, 113 (1994); b) P. Baierweck, D. Hoell and K. Müllen, *Angew. Chem. Int. Ed. Engl.*, **24**, 972 (1985); c) A. Jonczyk, B. Serafin and M. Makosza, *Rocz. Chem.*, **45**, 2097 (1971); *Chem. Abstr.*, **76**, 139990k (1972); d) A. W. Farnham, A. Ifill, N. F. Janes, T. Javed and B. P. S. Khambay, *Pesticide Sci.* **28**, 25 (1990); e) R. K. Singh and S. Danishefsky, *Org. Synth.*,

60, 66 (1981); f) R. Pardo and M. Santelli, *Tetrahedron Lett.*, **22**, 3843 (1981); g) A. Ratajczak and J. Polanski, *Pol. J. Chem.*, **65**, 1271 (1991); *Chem. Abstr.*, **116**, 173699b (1992); h) D. F. Taber, M. J. Hennessy and J. P. Louey, *J. Org. Chem.*, **57**, 436 (1992); i) D. Iwata-Reuyl, A. Basak, L. S. Silverman, C. A. Engle and C. A. Townsend, *J. Nat. Prod.*, **56**, 1373 (1993).

6. A discussion of bromination *vs* alkylation with 1,2-dibromoethane can be found in: J. Ibarzo and R. M. Ortuño, *Tetrahedron*, **50**, 9825 (1994).

7. Prepared by alkylation (MeI, MeOH) of potassium ethyl (±)-methylpropanedioate prepared according to R. E. Strube, *Org. Synth.*, Coll. Vol. IV, p. 417, Wiley, New York, NY, 1963.

8. a) H. Oediger, F. Möller and K. Eiter, *Synthesis*, 591 (1972); b) P. Wolkoff, *J. Org. Chem.*, **47**, 1944 (1982).

9. M. Atkinson and A. M. Horsington, *J. Chem Soc (C)*, 2186 (**1969**).

10. Elimination of the phenylsulfonyl group was not observed, see R. A. Bunce, E. J. Wamsley, J. D. Pierce, A. J. Shellhammer, Jr., R. E. Drumright, *J. Org. Chem.*, **52**, 464 (1987).

11. W. C. Still, M. Kahn and A. Mitra, *ibid.*, **43**, 2923 (1978).

12. R. A. Bunce and J. D. Pierce, *Org. Prep. Proced. Int.*, **19**, 67 (1987).

13. Compound **4a**, used to prepare this compound, was prepared using the method of M. L. Quesada and R. H. Schlessinger, *J. Org. Chem.*, **43**, 346 (1978).

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AN IMPROVED LARGE SCALE SYNTHESIS OF 2,3-DIHYDROXYTEREPHTHALIC ACID AND DIMETHYL 2,3-DIHYDROXYTEREPHTHALATE

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2,3-Dihydroxyterephthalic acid (**3**) and derivatives such as dimethyl 2,3-dihydroxyterephthalate (**4**) are important synthetic intermediates.[1] They are key building blocks in the synthesis of specific sequestering agents for removal of iron (III) from human transferrin[2] and in the synthesis of antidote agents for hazardous radionuclides such as Pu(IV)[3] and Ga(III).[4] They are also used in the preparation of novel synthetic siderophores[5] and molecular receptors[6] as well as in the synthesis of