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A Michael Initiated - Condensation - Elimination Sequence For The Stereoselective Synthesis of Maleate Derivatives.

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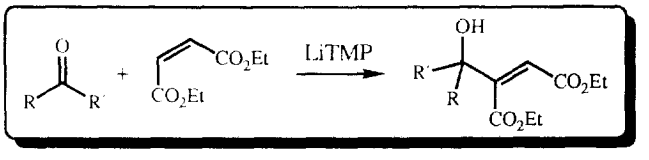
Abstract: *The paper describes a convenient method for the diastereoselective synthesis of trisubstituted alkenes through the lithium amide mediated union of ketones and diethyl maleate. The reaction has been shown to proceed via a Michael Initiated - Condensation - Elimination (MICE) sequence.*

The challenge of constructing trisubstituted alkenes in a diastereoselective manner has inspired numerous elegant methods to tackle this problem. Classical approaches have been complimented in recent years by advances in transition metal mediated sp^2-sp^n coupling reactions,[1] alkyne carbometallation reactions[2] and heteroatom assisted metallation reactions.[3] Thus, when we had cause to access a synthon for the maleate anion we perceived the possibility of generating diethyl lithiomaleate by simple deprotonation of diethyl maleate.[4] The sequence described in Scheme 1 was soon established.



Scheme 1

Lithium tetramethylpiperidide (LiTMP) was found to give superior yields to LDA or LiHMDS. Hindered and enolisable ketones all gave adducts in good yields, with α,β-unsaturated ketones giving the products of 1,2-addition exclusively. In each of the cases studied the product was furnished as a single diastereoisomer. These results are summarised in Table 1. Aldehydes were less satisfactory substrates, due in part to a competitive reduction pathway. This side reaction was most pronounced with LDA but also occurred with LiTMP (presumably by a mechanism akin to the Cannizzaro reaction).[5]

Table 1: The Lithium Tetramethylpiperidide Mediated Coupling of Diethyl Maleate with Ketones.

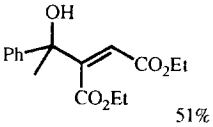
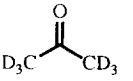
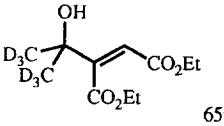
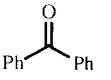
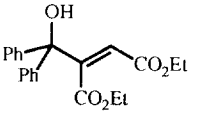
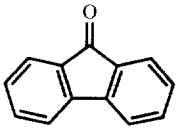
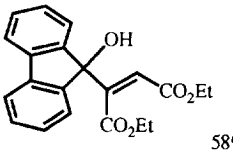
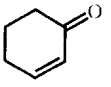
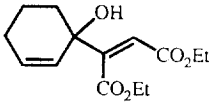
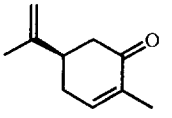
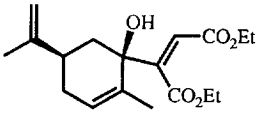
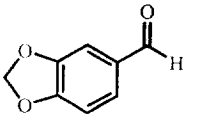
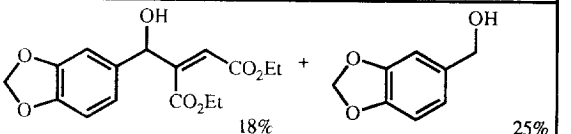
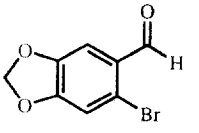
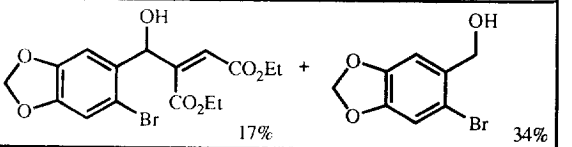
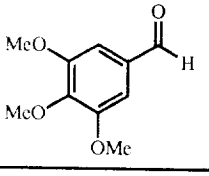
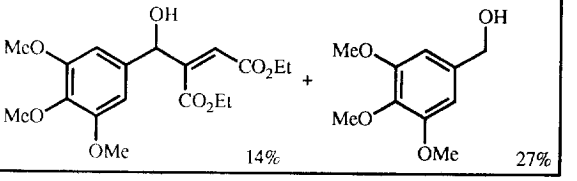
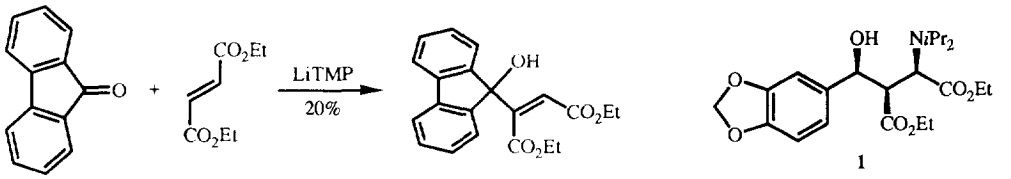
Entry	Ketone	Adduct (yield)	Entry	Ketone	Adduct (yield)
A		 51%	B		 65%
C		 54%	D		 58%
E		 63%	F		 68%

Table 2: The Lithium Tetramethylpiperidide Mediated Coupling of Diethyl Maleate with Aldehydes.

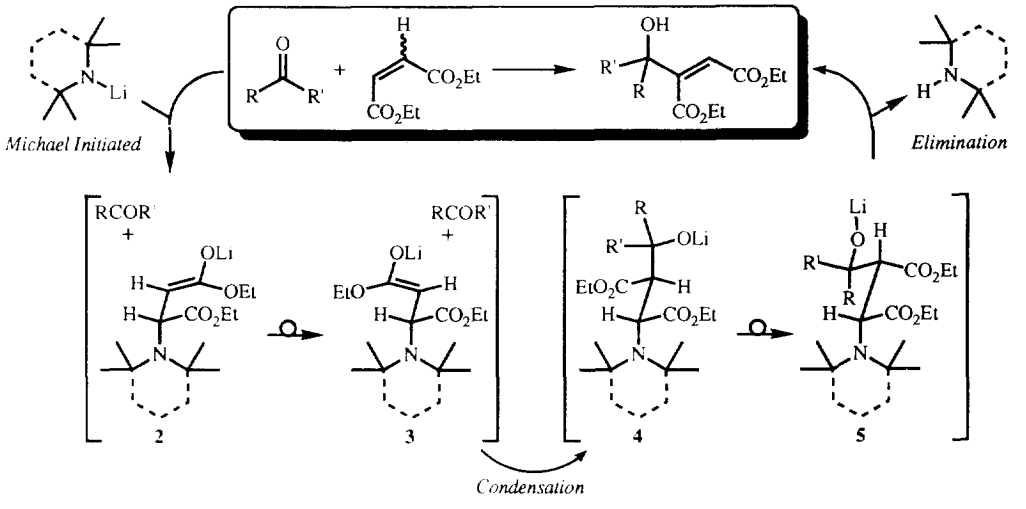
Entry	Aldehyde	Major Products (yields)
A		 18% 25%
B		 17% 34%
C		 14% 27%

Attempts to effect the analogous reaction with diethyl fumarate were disappointing. Typically, the adducts were formed in <20% yield and were identical to those obtained from experiments conducted with diethyl maleate (*e.g.* Scheme 2). Interestingly, exposing a mixture of piperonal and diethyl fumarate to a solution of LDA that had been purchased commercially, gave the amine **1** as the major product (23%, as a single diastereoisomer and assumed to be as depicted).



Scheme 2

These results, when viewed in conjunction with our observation that yields are improved when the electrophile and diethyl maleate are simultaneously added to a solution of the lithium amide, suggest that this reaction proceeds by a Michael Initiated - Condensation - Elimination (MICE) sequence.[6,7] Thus, addition of the lithium amide to the alkene first provides the ester enolate **2** which rapidly adopts the more favourable conformation **3**.[8] Condensation to **4** then proceeds in a highly diastereoselective fashion; the steric bulk of the tetramethylpiperidine (or diisopropylamine) moiety effectively blocking one face of the enolate. An *anti*-elimination of the amine, *via* conformer **5**, then re-establishes the alkene to complete the sequence (Scheme 3).



Scheme 3

We are currently seeking to optimise this reaction for intermediates akin to **1** and are exploring the possibility of performing this transformation enantioselectively through the use of homochiral lithium amide[8] and maleate derivatives.[9] The results from these studies will be reported in due course.

Acknowledgements The authors wish to thank The University of Southampton, The University of Wales, Bangor and the Nuffield Foundation for their financial support. We also extend our gratitude to Mrs. Joan Street for the n.O.e. and 2D N.M.R. studies and Dr. John Langley and The EPSRC Mass Spectrometry Unit for their provision of high resolution mass spectrometry data.

EXPERIMENTAL

General Remarks.

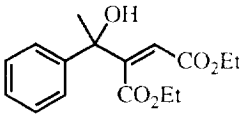
Melting points were obtained using a Mel-Temp (II) apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP800 spectrometer. Maxima and inflections (inf) are reported as λ_{max} followed in parentheses by the extinction coefficient ε ($dm^3mol^{-1}cm^{-1}$). IR spectra were recorded on a Perkin Elmer 1600 series Fourier transform infrared spectrometer using NaCl cells. Maxima are reported as ν_{max} followed by the signal intensity (described using the abbreviations s, strong; m, medium; w, weak; v, very; br, broad). ^1H n.m.r. spectra were recorded on a Bruker AC250 (250MHz), a Bruker AC300 (300MHz) or a Bruker AM360 (360MHz) spectrometer. Chemical shifts (δ_H) are reported as values in parts per million relative to tetramethylsilane (δ 0.00) or residual $CHCl_3$ (δ 7.27). Multiplicities are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app., apparent. ^{13}C spectra were recorded on a Brucker AC250 (63MHz), a Brucker AC300 (75MHz) or a Brucker AM360 (90MHz) spectrometer. Chemical shifts (δ_C) are reported as values in parts per million relative to tetramethylsilane (δ 0.00) or residual $CHCl_3$ (δ 77.2). Multiplicities refer to the signals in the off-resonance spectra, as determined by DEPT 135° and DEPT 90° experiments, and are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet. Two dimensional and n.O.e. experiments were recorded on a Bruker AC300 (300MHz) or a Bruker AM360 (360MHz) spectrometer. Optical rotation was measured on an Optical Activity Ltd. AA-100 polarimeter. Mass spectra were recorded under the supervision of Dr. J.A. Ballantine at the EPSRC Mass Spectrometry Service Centre, University of Wales, Swansea or Dr. G.J. Langley at The University of Southampton using a variety of instruments. Signals are reported as values in atomic mass units and are followed in parentheses by the peak intensity relative to the base peak (100%). NBA refers to *m*-nitrobenzyl alcohol.

All reactions were magnetically stirred and conducted under a nitrogen atmosphere using flame dried glassware. Thin layer chromatography, using Macherey-Nagel Alugram Sil G/UV_{254} precoated aluminium foil plates of layer thickness 0.25mm, was used to monitor reactions. Compounds were visualised firstly by UV irradiation then by heating plates exposed to solutions of either phosphomolybdic acid in ethanol or potassium permanganate in aq. sodium carbonate. Column chromatography was performed on Sorbsil 60 silica (230-400 mesh), slurry packed and run under low pressure. THF was dried and degassed by refluxing over sodium wire using benzophenone ketyl as indicator. All reagents used were purchased from Lancaster Synthesis Ltd. or The Aldrich Chemical Company Ltd. and used as supplied.

General Procedure

A hexane solution of n-butyllithium (1.6M, 3.1ml, 5mmol) was added dropwise over 5min to a THF solution of tetramethylpiperidine (0.2M, 25ml, 5mmol) maintained at -78°C. The resulting solution was stirred at -78°C for 5 min, warmed to 5°C over 25min then cooled to -78°C. Diethyl maleate (5mmol) and the electrophile (2mmol), as a solution in THF (10ml), were then added *via* syringe over 1min. The whole was stirred at -78°C for 10min, warmed to room temperature over 30min, then partitioned between ether (100ml) and water (100ml). The organic phase was separated, dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica; gradient elution, 10% to 50% ether in petroleum ether).

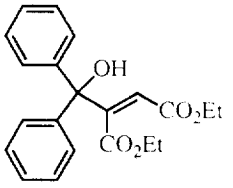
(Z)-2-(1-Hydroxy-1-phenylethyl)-but-2-enedioic acid diethyl ester



tetramethylpiperidine	2.33g, 16.6mmol.
n-butyllithium	1.6M, 10.4ml, 16.6mmol.
diethyl maleate	2.85g, 16.6mmol.
acetophenone	1.00g, 8.33mmol.
yield	1.23g, 4.20mmol, 51%.

white solid; **m.p.** 53-55°C; **FT-IR** ($CHCl_3$) υ_{max} 3495brm, 3060w, 2985m, 2940m, 1955w, 1890w, 1730s, 1645m, 1500m, 1450m, 1375s, 1255s, 1035s, 885m, 765m and 700m cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 317 (440), 270inf (3500), 263 (5300) and 251 (7500) nm; **^{1}H NMR** (360MHz, $CDCl_3$) δ_H 7.39 (2H, m, 2xAr*H*), 7.24 (3H, m, 3xAr*H*), 6.10 (1H, s, =C*H*), 4.10 (2H, q, *J* 7.2Hz, OCH_2), 4.03 (2H, q, *J* 7.2Hz, OCH_2), 3.67 (1H, s, O*H*), 1.73 (3H, s, CCH_3), 1.20 (3H, t, *J* 7.2 Hz, OCH_2CH_3) and 1.02 (3H, t, *J* 7.2Hz, OCH_2CH_3) ppm; **n.O.e.** (360MHz, $CDCl_3$) irradiation of the signal at δ_H 6.10 (=C*H*) caused an n.O.e. enhancement at δ_H 7.39 (2x*o*-Ar*H*), 3.67 (O*H*) and 1.73 (CCH_3); irradiation of the signal at δ_H 3.67 (O*H*) caused an n.O.e. enhancement at δ_H 7.39 (2x*o*-Ar*H*), 6.10 (=C*H*) and 1.73 (CCH_3); irradiation of the signal at δ_H 1.73 (CCH_3) caused an n.O.e. enhancement at δ_H 7.39 (2x*o*-Ar*H*), 6.10 (=C*H*) and 3.67 (O*H*); **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 167.7 (s, *C*=O), 165.0 (s, *C*=O), 153.5 (s, =*C*), 143.7 (s, Ar*C*), 128.3 (d, 2xAr*C*H), 127.7 (d, Ar*C*H), 125.6 (d, 2xAr*C*H), 119.9 (d, =*C*H), 75.5 (d, *C*HOH), 61.4 (t, O*C*H_2), 61.0 (t, O*C*H_2), 28.2 (q, C*C*H_3), 14.0 (q, CH_2CH_3) and 13.6 (q, CH_2CH_3) ppm; **$^m/_z$** (EI) 277 (8%, $[M\text{-}CH_3]^+$), 250 (12), 232 (14), 206 (60), 177 (46), 147 (23), 129 (87), 109 (100) and 80 (32); **$^m/_z$** (CI, NH_3) Found: $[MH]^+$ 293.1391; $C_{16}H_{21}O_5$ requires 293.1389.

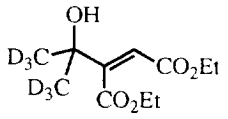
(Z)-2-(Hydroxydiphenylmethyl)-but-2-enedioic acid diethyl ester



tetramethylpiperidine	1.55g, 11.0mmol.
n-butyllithium	1.6M, 6.9ml, 11.0mmol.
diethyl maleate	1.89g, 11.0mmol.
benzophenone	1.00g, 5.5mmol.
yield	1.10g, 2.9mmol, 54%.

pale yellow solid; **m.p.** 79-81°C; **FT-IR** ($CHCl_3$) υ_{max} 3450 brs, 2980w, 1725s, 1640m, 1440m, 1375m, 1250s, 1040s, 900s and 730s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 253 (4100) and 237inf (2100) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 7.43 (4H, m, 4xAr*H*), 7.33 (6H, m, 6xAr*H*), 5.71 (1H, s, =C*H*), 4.52 (1H, s, O*H*), 4.19 (2H, q, *J* 7.2Hz, OCH_2), 4.14 (2H, q, *J* 7.2Hz, OCH_2), 1.28 (3H, t, *J* 7.2Hz, OCH_2CH_3) and 1.13 (3H, t, *J* 7.2Hz, OCH_2CH_3) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 168.2 (s, *C*=O), 165.5 (s, *C*=O), 149.6 (s, =*C*), 143.0 (s, 2xAr*C*), 128.3 (d, 4xAr*C*H), 128.1 (d, 2xAr*C*H), 127.6 (d, 4xAr*C*H), 126.7 (d, =*C*H), 81.3 (s, *C*OH), 62.0 (t, O*C*H_2), 61.4 (t, O*C*H_2), 14.2 (q, CH_2CH_3) and 13.8 (q, CH_2CH_3) ppm; **$^m/_z$** (CI, NH_3) Found: $[M+NH_4]^+$, 372.1811 (14%); $C_{21}H_{26}O_5N$ requires 372.1811; 354 (8, $[M]^+$ or $[M+NH_4\text{-}H_2O]^+$), 337 (19, $[M\text{-}OH]^+$), 308 (100, $[M\text{-}OEt]^+$), 291 (88), 200 (23) and 183 (26).

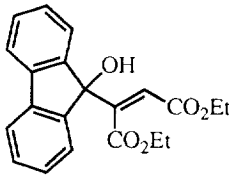
(Z)-2-(1-Hydroxy-1-[$^2H_3$]-methyl-[$^2H_3$]-ethyl)-but-2-enedioic acid diethyl ester



tetramethylpiperidine	5.64g, 40.0mmol.
n-butyllithium	1.6M, 25.0ml, 40.0mmol.
diethyl maleate	6.88g, 40.0mmol.
d_6-acetone	1.00g, 15.6mmol.
yield	2.42g, 10.3mmol, 65%.

pale yellow oil; **FT-IR** (neat) υ_{max} 3500brm, 2985s, 2910m, 2235m, 1710s, 1645s, 1465m, 1370s, 1340s, 1245s, 1025s, 945w, 890m and 820w cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 298inf (300), 249 (2100) and 237inf (1100) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 6.04 (1H, s, =C*H*), 4.26 (2H, q, *J* 7.2Hz, OCH_2), 4.12 (2H, q, *J* 7.2Hz, OCH_2), 2.91 (1H, s, O*H*), 1.28 (3H, t, *J* 7.2Hz, OCH_2CH_3) and 1.22 (3H, t, *J* 7.2Hz, OCH_2CH_3) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 168.0 (s, *C*=O), 165.1 (s, *C*=O), 157.5 (s, =*C*), 117.1 (d, =C*H*), 71.4 (s, *C*OH), 61.4 (t, O*C*H_2), 60.8 (t, O*C*H_2), 28.1 (1:2:3:2:1 quintet, 2x*C*D_3), 14.0 (q, CH_2CH_3) and 13.9 (q, CH_2CH_3) ppm; **m/z** (EI) 218 (15%, $[M-H_2O]^+$), 191 (14, $[M-OEt]^+$), 172 (53), 144 (100), 116 (25), 100 (10), 65 (14) and 46 (22); **m/z** (FAB, NBA) 237 (42%, $[MH]^+$), 219 (26, $[MH-H_2O]^+$), 191 (35, $[M-OEt]^+$), 172 (100), 144 (38) and 116 (18); **m/z** (CI, NH_3) Found: $[MH]^+$ 237.1612; $C_{11}H_{13}D_6O_5$ requires 237.1612.

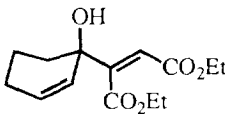
(Z)-2-(9-Hydroxy-9*H*-fluoren-9-yl)-but-2-enedioic acid diethyl ester



tetramethylpiperidine	1.55g, 11.1mmol.
n-butyllithium	1.6M, 7.0ml, 11.2mmol.
diethyl maleate	1.91g, 11.1mmol.
9-fluorenone	1.00g, 5.6mmol.
yield	1.13g, 3.22mmol, 58%.

white solid; **m.p.** 87-88°C; **FT-IR** ($CHCl_3$) υ_{max} 3430brm, 2980s, 2935w, 1730s, 1645m, 1450s, 1375s, 1340s, 1255s, 1185s, 1095s, 1035s and 910s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 308inf (1900), 300inf (3800), 287inf (7200), 279 (8600), 265 (8300) and 247 (7000) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* 7.3Hz, 2xAr*H*), 7.53 (2H, d, *J* 7.3Hz, 2xAr*H*), 7.40 (4H, m, 4xAr*H*), 6.43 (1H, s, =C*H*), 4.15 (2H, q, *J* 7.2Hz, OCH_2), 3.94 (2H, q, *J* 7.2Hz, OCH_2), 2.91 (1H, s, O*H*), 1.26 (3H, t, *J* 7.2Hz, OCH_2CH_3) and 0.91 (3H, t, *J* 7.2Hz, OCH_2CH_3) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 166.1 (s, *C*=O), 164.9 (s, *C*=O), 151.9 (s, =*C*), 146.4 (s, 2xAr*C*), 139.8 (s, 2xAr*C*), 129.8 (d, 2xAr*C*H), 128.3 (d, 2xArCH), 124.9 (d, 2xAr*C*H), 120.1 (d, 2xAr*C*H), 119.3 (d, =*C*H), 82.3 (s, *C*OH), 61.0 (t, O*C*H_2), 60.9 (t, O*C*H_2), 14.0 (q, CH_2CH_3) and 13.5 (q, CH_2CH_3) ppm; **m/z** (EI) 352 (20%, $[M]^+$), 290 (8), 260 (13), 233 (90), 205 (20), 189 (50), 181 (100), 165 (15) and 152 (48); **m/z** (CI, NH_3) Found: $[M+NH_4-H_2O]^+$ 352.1549; $C_{21}H_{22}O_4N$ requires 352.1549.

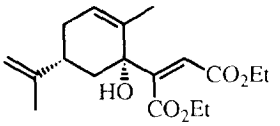
(*Z*)-2-(1-Hydroxycyclohex-2-en-1-yl)-but-2-enedioic acid diethyl ester



tetramethylpiperidine	2.82g, 20.0mmol.
n-butyllithium	1.6M, 12.5ml, 20.0mmol.
diethyl maleate	3.44g, 20.0mmol.
2-cyclohexen-1-one	1.00g, 10.0mmol.
yield	1.69g, 6.30mmol, 63%.

yellow oil; **FT-IR** (neat) υ_{max} 3490brm, 2980m, 2940m, 2870m, 1725s, 1650m, 1370m, 1250m, 1180s and 1030m cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 243 (1000) and 234inf (600) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 6.00 (1H, s, =C*H*), 5.99 (1H, dt, *J* 10.1 & 7.8Hz, =C*H*CH_2), 5.63 (1H, d, *J* 10.1Hz, HC=C*H*), 4.30 (2H, q, *J* 7.1Hz, OCH_2), 4.18 (2H, q, *J* 7.1Hz, OCH_2), 2.90 (1H, s, O*H*), 2.07 (3H, m), 1.75 (3H, m), 1.32 (3H, t, *J* 7.1Hz, OCH_2CH_3) and 1.27 (3H, t, *J* 7.1Hz, OCH_2CH_3) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 172.3 (s, *C*=O), 167.5 (s, *C*=O), 155.7 (s, =*C*), 132.2 (d, =*C*H), 129.0 (d, =*C*H), 119.2 (d, =*C*H), 71.8 (s, *C*OH), 61.3 (t, OCH_2), 60.7 (t, OCH_2), 35.2 (t, CH_2), 24.6 (t, CH_2), 18.3 (t, CH_2), 14.0 (q, CH_2CH_3) and 13.9 (q, CH_2CH_3) ppm; **m/z** (EI) 268 (2%, $[M]^+$), 250 (1, $[M-H_2O]^+$], 240 (10, $[M-C_2H_4]^+$), 222 (30), 205 (32), 194 (61), 176 (77), 166 (94), 149 (100), 138 (62), 121 (77), 110 (19), 103 (31), 97 (92), 93 (50), 79 (74), 67 (35), 53 (61) and 41 (46); **m/z** (CI, NH_3) Found: $[MH]^+$ 269.1369; $C_{14}H_{21}O_5$ requires 269.1389.

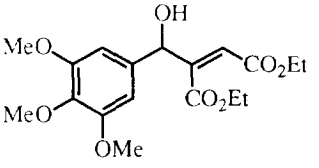
(*Z*)-2-(1*R*-Hydroxy-5*R*-propen-2-yl-2-methylcyclohex-2-en-1-yl)-but-2-enedioic acid diethyl ester



tetramethylpiperidine	1.87g, 13.3mmol.
n-butyllithium	1.6M, 8.3ml, 13.3mmol.
diethyl maleate	2.29g, 13.3mmol.
(*R*)-carvone	1.00g, 6.8mmol.
yield	1.46g, 4.5mmol, 68%.

pale yellow oil; **FT-IR** (neat) υ_{max} 3500brs, 3020s, 2940m, 2800w, 1725s, 1645m, 1445m, 1375m, 1340m, 1215s, 1180s, 1030s and 910m cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 253 (5800) nm; $[\alpha]_D^{25}$ = -37; **^{1}H NMR** (360MHz, $CDCl_3$) δ_H 5.76 (1H, s, =C*H*), 5.68 (1H, brm, =C*H*CH_2), 4.68 (1H, app. quintet, *J* 1.5Hz, =C*H*H), 4.63 (1H, brm, =CH*H*), 4.30 (1H, dq, *J* 10.7 & 7.1Hz, OC*H*H), 4.23 (1H, dq, *J* 10.7 & 7.1Hz, OCH*H*), 4.13 (2H, q, *J* 7.1Hz, OCH_2), 2.75 (1H, s, O*H*), 2.36 (1H, app. dt, *J* 12.7 & 2.0Hz, HOCC*H*H), 2.15 (2H, m, =CHC*H*H & CH_2CHCH_2), 1.90 (1H, m, =CHCH*H*), 1.67 (3H, brs, CH_2=CCH_3), 1.66 (1H, obscured, HOCCH*H*), 1.65 (3H, brs, CH=CCH_3), 1.28 (3H, t, *J* 7.1Hz, OCH_2CH_3) and 1.23 (3H, t, *J* 7.1Hz, OCH_2CH_3) ppm (these assignments were confirmed by a ^{1}H-^{1}H COSY experiment); **n.O.e.** (360MHz, $CDCl_3$) irradiation of the signal at δ_H 2.75 (O*H*) caused an n.O.e. enhancement at δ_H 5.76 (=C*H*); **^{13}C NMR** (63MHz, $CDCl_3$) δ_C 167.5 (s, *C*=O), 164.6 (s, *C*=O), 156.3 (s, =*C*), 147.8 (s, =*C*), 133.9 (s, =*C*), 127.6 (d, =*C*H), 120.5 (d, =*C*H), 109.4 (t, =CH_2), 76.6 (s, *C*OH), 61.6 (t, OCH_2), 61.1 (t, OCH_2), 40.2 (t, CH_2), 37.4 (d, *C*H), 30.6 (t, CH_2), 20.7 (q, CH_3), 17.3 (q, CH_3), 14.0 (q, CH_2CH_3) and 13.9 (q, CH_2CH_3); **m/z** (FAB, NBA) 305 (45%, $[MH-H_2O]^+$), 259 (100), 231 (28), 189 (34) and 157 (42); **m/z** (EI) Found: $[M]^+$ 322.1770; $C_{18}H_{26}O_5$ requires 322.1780.

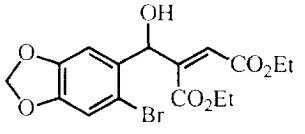
(*Z*)-2-(Hydroxy-[3,4,5-trimethoxyphenyl]-methyl)-but-2-enedioic acid diethyl ester



tetramethylpiperidine	1.51g, 10.7mmol.
n-butyllithium	1.6M, 6.7ml, 10.7mmol.
diethyl maleate	1.84g, 5.4mmol.
3,4,5-trimethoxybenzaldehyde	1.00g, 5.4mmol.
yield	0.27g, 0.7mmol, 14%.

yellow oil; **FT-IR** (neat) υ_{max} 3490brs, 2980m, 2940m, 2840w, 1725s, 1650w, 1595m, 1505m, 1465m, 1420m, 1375w, 1330m, 1235m, 1185m, 1130s, 1060w and 1030w cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 281inf (2400), 270inf (3100) and 238 (25000) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 6.54 (2H, s, 2xAr*H*), 6.14 (1H, d, *J* 1.6Hz, =C*H*), 5.43 (1H, dd, *J* 4.1 & 1.6Hz, C*H*OH), 4.15 (2H, q, *J* 7.1Hz, OCH_2), 4.14 (2H, q, *J* 7.1Hz, OCH_2), 3.82 (6H, s, 2xOCH_3), 3.80 (3H, s, OCH_3), 3.23 (1H, d, *J* 4.1Hz, O*H*), 1.26 (3H, t, *J* 7.1Hz, OCH_2CH_3) and 1.14 (3H, t, *J* 7.1Hz, OCH_2CH_3) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_c 167.0 (s, *C*=O), 165.2 (s, *C*=O), 153.2 (s, 2xAr*C*), 149.6 (s, =*C*), 137.8 (s, Ar*C*), 135.1 (s, Ar*C*), 120.6 (d, =*C*H), 104.0 (d, 2xAr*C*H), 74.0 (d, *C*HOH), 61.4 (t, OCH_2), 61.0 (t, OCH_2), 60.7 (q, OCH_3), 56.0 (q, 2xOCH_3), 14.0 (q, CH_2CH_3) and 13.7 (q, CH_2CH_3) ppm; **$^m/_z$** (FAB, NOVA) 391 (15%, $[M+Na]^+$), 368 (77, $[M]^+$), 351 (13, $[M\text{-}OH]^+$), 305 (12, $[M\text{-}OEt]^+$), 277 (100), 249 (17), 195 (31); **$^m/_z$** (CI, NH_3) Found: $[M]^+$, 368.1470; $C_{18}H_{24}O_8$ requires 368.1471.

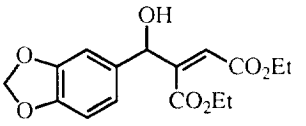
(*Z*)-2-[(6-bromobenzo[1,3]dioxol-5-yl)-hydroxymethyl]-but-2-enedioic acid diethyl ester



tetramethylpiperidine	1.23g, 8.7mmol.
n-butyllithium	1.6M, 5.5ml, 8.8mmol.
diethyl maleate	1.50g, 8.7mmol.
6-bromopiperonal	1.00g, 4.4mmol.
yield	0.30g, 0.7mmol, 17%.

yellow oil; **FT-IR** (neat) υ_{max} 3490brm, 2985w, 2925w, 1725s, 1650w, 1480s, 1235m, 1185m, 930w and 865w cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 293 (4300) and 247 (4970) nm; **^{1}H NMR** (250MHz, $CDCl_3$) δ_H 6.98 (2H, s, 2xAr*H*), 6.11 (1H, d, *J* 1.6Hz, =C*H*), 5.99 (2H, abq, OCH_2O), 5.87 (1H, d, *J* 1.6Hz, CHO*H*), 4.22 (2H, q, *J* 7.2Hz, OCH_2), 4.19 (2H, q, *J* 7.2Hz, OCH_2), 2.97 (1H, brs, O*H*), 1.28 (3H, t, *J* 7.2Hz, OCH_2CH_3) and 1.23 (3H, t, *J* 7.2Hz, OCH_2CH_3) ppm; **^{13}C NMR** (63MHz, $CDCl_3$) δ_c 166.6 (s, *C*=O), 165.1 (s, *C*=O), 148.5 (s, =*C*), 147.9 (s, Ar*C*), 147.8 (s, Ar*C*), 131.8 (s, Ar*C*), 121.7 (d, =*C*H), 113.8 (s, Ar*C*), 112.5 (d, Ar*C*H), 108.5 (d, Ar*C*H), 102.0 (t, OCH_2O), 72.5 (d, *C*HOH), 61.7 (t, OCH_2), 61.1 (t, OCH_2), 14.0 (q, CH_2CH_3) and 13.8 (q, CH_2CH_3) ppm; **$^m/_z$** (FAB, NBA) 402 (4%, $[M(^{81}Br)]^+$), 400 (4%, $[M(^{79}Br)]^+$), 385 (5, $[M(^{81}Br)H\text{-}H_2O]^+$), 383 (5, $[M(^{79}Br)H\text{-}H_2O]^+$), 337 (7), 309 (8) and 219 (13); **$^m/_z$** (EI) Found: $[M]^+$, 400.0184; $C_{16}H_{17}{}^{79}BrO_7$ requires 400.0158.

(Z)-2-[(benzo[1,3]dioxol-5-yl)-hydroxymethyl]-but-2-enedioic acid diethyl ester



tetramethylpiperidine	0.94g, 6.7mmol.
n-butyllithium	1.6M, 4.2ml, 6.7mmol.
diethyl maleate	1.15g, 6.7mmol.
piperonal	0.50g, 3.3mmol.
yield	0.19g, 0.6mmol, 18%.

yellow oil; **FT-IR** (neat) υ_{max} 3490brs, 2985w, 2905w, 1725s, 1650w, 1445m, 1375m, 1340m, 1250s, 1185m, 1130s, 1040s and 930s cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 288 (3100) and 248 (2700) nm; **^{1}H NMR** (300MHz, $CDCl_3$) δ_H 6.86 (1H, dd, *J* 7.7 & 1.7Hz, Ar*H*), 6.82 (1H, d, *J* 1.7Hz, Ar*H*), 6.79 (1H, d, *J* 7.7Hz, Ar*H*), 6.20 (1H, d, *J* 1.5Hz, =C*H*), 5.98 (2H, s, OCH_2O), 5.45 (1H, brd, *J* 1.5Hz, C*H*OH), 4.21 (2H, q, *J* 7.2Hz, OCH_2), 4.19 (2H, q, *J* 7.2Hz, OCH_2), 2.45 (1H, brs, O*H*), 1.30 (3H, t, *J* 7.2Hz, OCH_2CH_3) and 1.19 (3H, t, *J* 7.2Hz, OCH_2CH_3) ppm; **^{13}C NMR** (75MHz, $CDCl_3$) δ_c 166.8 (s, *C*=O), 165.2 (s, *C*=O), 149.2 (s, =*C*), 148.0 (s, Ar*C*), 147.8 (s, Ar*C*), 133.3 (s, Ar*C*), 120.9 (d, =C*H*), 120.8 (d, ArCH), 108.2 (d, ArCH), 107.4 (d, ArCH), 101.2 (t, OCH_2O), 73.8 (d, *C*HOH), 61.5 (t, OCH_2), 61.0 (t, OCH_2), 14.0 (q, CH_2CH_3) and 13.8 (q, CH_2CH_3) ppm; **$^m/_z$** (FAB, NBA) 322 (33%, $[M]^+$), 305 (26, $[MH\text{-}H_2O]^+$), 259 (56), 231 (100), 187 (33) and 149 (64); **$^m/_z$** (EI) Found: $[M]^+$, 322.1059 (6%); $C_{16}H_{18}O_7$ requires 322.1053.

(Z)-2*R-[*S**-(benzo[1,3]dioxol-5-yl)-hydroxymethyl]-3*R**-[diisopropylamino]-butanedioic acid diethyl ester 1**

To a cooled (-78°C) solution of diethyl fumarate (1.72g, 10.0mmol) and piperonal (1.00g, 6.7mmol) in THF (20ml) was added, dropwise *via* syringe, a solution of lithium diisopropylamide (2M in THF, 5ml, 10.0mmol, purchased from The Aldrich Chemical Company). The resulting solution was stirred for at -78°C for 15min then allowed to warm to ambient temperature over 30min. The whole was then partitioned between ether (100ml) and water (100ml) and the organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was then purified by column chromatography (silica; gradient elution, 10% to 50% ether in petroleum ether) to give, as one of the many components, a yellow oil which crystalised from ether-petrol to a yellow solid **1** (565mg, 1.3mmol, 23%); **m.p.** 73-75°C; **FT-IR** (neat) υ_{max} 3500brm, 2970m, 2930m, 2900m, 1725s, 1520m, 1490m, 1445m, 1250s, 1185s, 1040s and 930m cm^{-1}; **UV** ($CHCl_3$) λ_{max} (ε) 325 (380), 288 (2500) and 248 (2200) nm; **^{1}H NMR** (300MHz, $CDCl_3$) δ_H 6.78 (3H, m, 3xArC*H*), 5.96 (2H, s, OCH_2O), 5.19 (1H, brd, *J*~3Hz, C*H*OH), 4.09 (2H, m, OCH_2), 4.07 (1H, d, *J* 11Hz, NC*H*CO), 3.95 (2H, m, OCH_2), 3.38 (2H, septet, *J* 7Hz, 2xNC*H*$(CH_3)_2$), 3.38 (1H, obscured, O*H*), 3.03 (1H, dd, *J* 11 & 3Hz, CHC*H*CH), 1.26 (3H, t, *J* 7Hz, OCH_2CH_3), 1.17 (6H, d, *J* 7Hz, NCH$(CH_3)_2$), 1.08 (6H, d, *J* 7Hz, NCH$(CH_3)_2$) and 1.03 (3H, t, *J* 7Hz, OCH_2CH_3) ppm (these assignments were confirmed by a ^{1}H-^{1}H COSY experiment); **^{13}C NMR** (75MHz, $CDCl_3$) δ_c 173.9 (s, *C*=O), 173.4 (s, *C*=O), 147.7 (s, Ar*C*), 146.7 (s, Ar*C*), 137.3 (s, Ar*C*), 118.4 (d, ArCH), 108.1 (d, ArCH), 106.1 (d, ArCH), 101.1 (t, OCH_2O), 70.0 (d, *C*HOH), 60.8 (t, 2xOCH_2), 57.0 (d, 2xNCHCO), 54.2 (d, CHCHCH), 46.0 (d, NCH$(CH_3)_2$), 24.1 (q, NCH$(CH_3)_2$), 21.5 (q, NCH$(CH_3)_2$) and 13.8 (q, 2xCH_2CH_3) ppm (these assignments were confirmed by a ^{13}C-^{1}H COSY experiment); **$^m/_z$** (CI, NH_3) Found: $[MH]^+$, 424.2335 (88%); $C_{22}H_{34}O_7N$ requires 424.2335; 378 (15, $[M\text{-}OEt]^+$), 274 (52), 200 (23), 168 (35), 151 (28) and 102 (100).

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