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Synthesis of 3-acetonyl- and 3-(2-oxoethyl)glutarates

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Abstract—Several synthetic routes to 3-acetonyl- and 3-(2-oxoethyl)glutarates **1**–**5** have been explored. The most advantageous involves, as the key steps, the conjugate addition of an appropriately substituted vinylmagnesium bromide to an alkylidenemalonic ester, a bis-homologation of the resulting diester and, finally, the reductive ozonolysis of the carbon–carbon double bond. The synthesis can be satisfactorily conducted in good overall yield on a multigram scale.

1. Introduction

Some glutaric esters bearing a functionalized carbon chain (e.g., acetonyl, 1-cyanopropyl) at the 3-position have classically been used as building blocks for the synthesis of indolo[2,3-*a*]- and benzo[*a*]quinolizidine alkaloids.[1]

In recent work, we have reported[2] the use of prochiral or racemic 3-substituted glutarates **1**–**5** (Fig. 1) as the substrates in highly enantioselective cyclocondensation reactions with chiral aminoalcohols, leading to enantiopure bicyclic lactams. These processes involve the desymmetrization of two enantiotopic (from **1** and **3**) or diastereotopic (from **2**, **4**, and **5**) acetate chains, in the latter case with a simultaneous dynamic kinetic resolution[3] (DKR) that promotes the epimerization of the configurationally labile stereocenter α to the aldehyde or ketone carbonyl group. This methodology provides straightforward access to polysubstituted enantiopure piperidines.

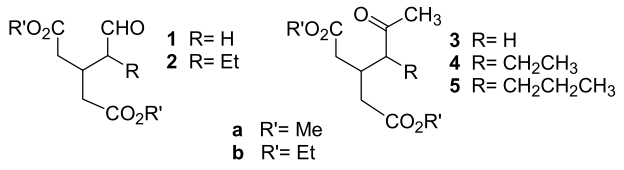

Figure 1. Target δ-oxodiesters.

With the exception of ketodiester **3b**, for which a convenient preparation has already been reported,[4] there are no precedents for the synthesis of 3-substituted glutarates **1**–**5**. We report here our synthetic efforts directed to the preparation of these δ-oxodiesters, culminating in the development of a general, high-yield synthetic route that can be conducted on a multigram scale.

2. Results

For the synthesis of aldehyde diester **1a** we initially planned to start from α,β-unsaturated ester **6**, which was prepared in 35% yield from methyl crotonate following a previously reported procedure[5] (Scheme 1).

Conjugate addition of *tert*-butyl methyl malonate to **6**, followed by treatment of the resulting triester **8** with TFA in the presence of thioanisole,[6] and subsequent heating in refluxing toluene, led to the target ester **1a** in 46% overall yield. This sequence could not be extended to the preparation of the ethyl substituted analogue **2a** since the conjugate addition of malonate esters to α,β-unsaturated ester **9**, which was prepared as in the above deethyl series from methyl-2-hexenoate, was unsuccessful.[7]

Alternatively, **1a** was prepared from **6** by conjugate addition of the lithium salt derived from methyl 1,3-dithiolane-2-carboxylate, followed by nickel boride desulfurization and chemoselective hydrolysis of the acetal function with $LiBF_4$ in wet acetonitrile.[8] The overall yield of this three-step sequence was 39%.

The main drawback of the above approaches was the

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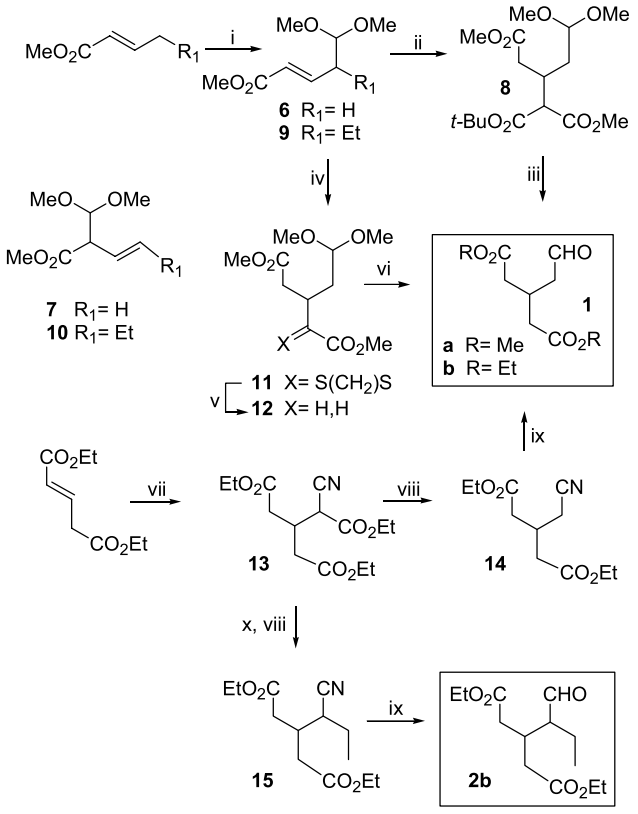


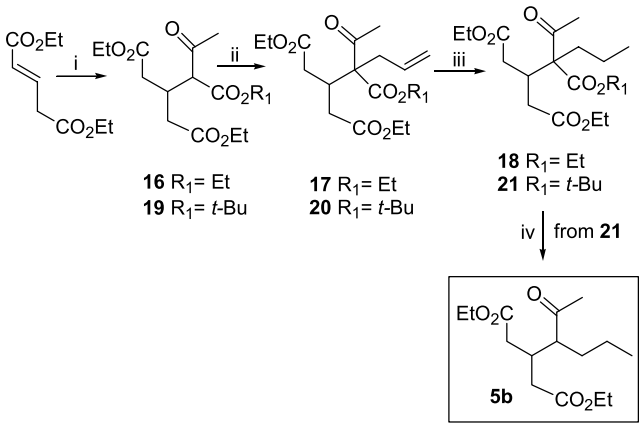
Scheme 1. Reagents: (i) **6**: see Ref. 5, 35%; **9**: LDA, HMPA, Me_3SiCl, then $ZnBr_2$, $HC(OMe)_3$; (ii) NaH, *t*-$BuO_2CCH_2CO_2Me$; (iii) TFA, C_6H_5SMe, then toluene, reflux; (iv) LDA, methyl 1,3-dithiolane-2-carboxylate; (v) $NiCl_2.6H_2O$, $NaBH_4$; (vi) $LiBF_4$, MeCN, 2% H_2O; (vii) See Refs. 1a, d, 85%; (viii) LiCl, DMSO, H_2O; (ix) Raney-Ni, NaH_2PO_2; (x) See Refs. 1a,d.

moderate yield and regioselectivity in the preparation of **6**, since the α-addition product **7** was also formed to a considerable extent.

The ethyl ester analog **1b** was prepared from the known intermediate **13**, which was easily accessible by Michael condensation of diethyl glutaconate with ethyl cyanoacetate.[1a,d] Selective hydrolysis-decarboxylation of **13** under Krapcho conditions,[9] followed by controlled Raney Ni reduction[10] of the resulting nitrile **14** gave δ-oxodiester **1b**. A similar reduction was used to obtain the ethyl substituted aldehyde diester **2b** from the known nitrile **15**, although in moderate yield. This nitrile was prepared in excellent yield by alkylation of **13** as previously reported,[1a,d] followed by hydrolysis-decarboxylation under Krapcho conditions.[9]

An important limitation of the above routes involving the controlled reduction of a cyano function is that the yield of the reduction step was somewhat erratic, leading to mixtures of the desired aldehydes **1b** and **2b** with the respective starting nitriles, which were difficult to separate.

The synthesis of the ethyl substituted ketodiester **4b** was initially attempted by a route similar to that previously employed for the preparation of **15**. The required β-ketoester **16** was obtained in 62% yield by Michael addition of ethyl acetylacetate to diethyl glutaconate[11]



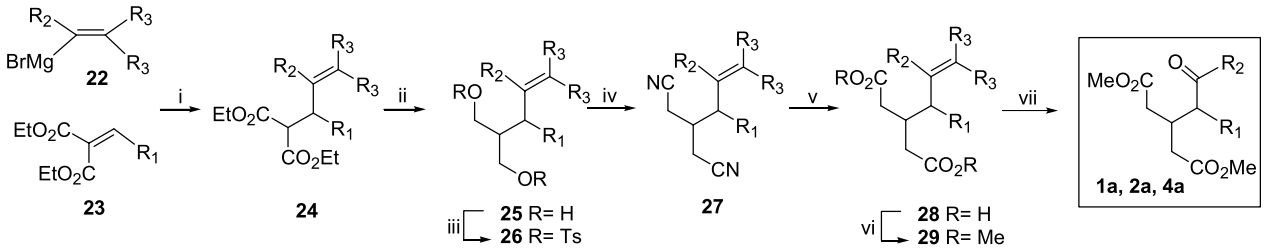
Scheme 2. Reagents: (i) NaOEt or *t*-BuOK, $CH_3COCH_2CO_2R_1$, EtOH or *t*-BuOH; (ii) DBU, $Pd(acac)_2$, Ph_3P, allyl acetate; (iii) H_2, Pd–C; (iv) TFA, C_6H_5SMe, then toluene, reflux.

(Scheme 2). However, alkylation of **16** with ethyl iodide under a variety of conditions resulted in failure. Also unsuccessful were the attempts to directly prepare the alkylated product by Michael addition of ethyl 2-ethyl-3-oxobutanoate to diethyl glutaconate.

In contrast, satisfactorily, **16** underwent a Pd-catalyzed C-allylation by treatment with allyl acetate.[12] Catalytic hydrogenation of the resulting product **17** gave the propyl substituted derivative **18**. However, the difficulties encountered in the deethoxycarbonylation of **18** prompted us to develop a similar sequence starting from *tert*-butyl acetylacetate. Thus, triester **19** was prepared in 74% yield,[13] allylated to **20** (69%), and then hydrogenated to give **21** (73%). Removal of the *tert*-butoxycarbonyl group with TFA and thioanisole[6] led to the propyl substituted ketodiester **5b** in 86% yield.

Although racemic ketodiester **5b** was a suitable substrate to study cyclocondensation reactions involving tandem DKR-diastereoselective differentiation processes,[2] the scope of the above synthetic route is quite limited as a consequence of the need to introduce an allyl group on β-ketoester moiety of **16** or **19**. For this reason, and also taking into account the inconveniences of the synthetic routes depicted in Scheme 1, we designed a new synthetic route that could provide general access to 3-(2-oxoethyl)- and 3-acetonylglutarates. It involves the introduction of an alkene moiety as a latent form of the aldehyde or ketone carbonyl group by conjugate addition[14] of an appropriately substituted vinylmagnesium bromide **22** to an alkylidenemalonic ester **23**, a bis-homologation of the resulting diester and, finally, the reductive ozonolysis of the carbon–carbon double bond (Scheme 3).

To check the viability of this synthetic route we considered the synthesis of the ethyl substituted ketone **4a**, which had been inaccessible by the route depicted in Scheme 2. Conjugate addition of isopropenylmagnesium bromide (**22**; R_2=Me, R_3=H) to diethyl propylidenemalonate (**23**; R_1=Et) in the presence of CuCl gave the malonic ester derivative **24a** in 70% yield. $LiAlH_4$ reduction, followed by tosylation of the resulting diol **25a** and subsequent substitution of tosylate **26a** with NaCN gave dinitrile **27a**,



Scheme 3. Reagents and conditions: (i) CuCl; (ii) $LiAlH_4$; (iii) KOH, TsCl; (iv) NaCN; (v) 35% aq. NaOH, MeOH, then 6 N HCl; (vi) Me_3ClSi; (vii) O_3, Me_2S.

Table 1. Synthesis of the target δ-oxodiesters

Compound	R_1	R_2	R_3	**24** (%)	**25** (%)	**26** (%)	**27** (%)	**28** (%)	**29** (%)	**1a**, **2a**, **4a** (%)
a	Et	Me	H	70	93	87	90	90	91	65 (**4a**: R_1=Et; R_2=Me)
b	Et	H	Me	74	94	88	90	82	92	64 (**2a**: R_1=Et, R_2=H)
c	Et	H	H	92	97	88	88	95	92	75 (**2a**: R_1=Et, R_2=H)
d	H	H	H	—	71	96	91	92	88	84 (**1a**: R_1=R_2=H)

which was then converted to diester **29a** via diacid **28a**. This bis-homologation sequence from **24a** took place in 60% overall yield. Finally, reductive ozonolysis of **29a** led to the target δ-oxodiester **4a** in 65% yield.

A similar reaction sequence allowed us to prepare aldehyde diester **2a**, following two alternative routes (Table 1). Initially, we started from the malonic ester derivative **24b**, which was obtained in 74% yield by conjugate addition of 2-methyl-1-propenylmagnesium bromide (**22**; R_2=H, R_3=Me) to diethyl propylidenenalonate (**23**; R_1=Et). However, the yields of both the conjugate addition reaction and the final ozonolysis step were improved starting from vinylmagnesium bromide (**22**; R_2=R_3=H): diester **24c** was obtained in 92% yield, and the overall yield for the seven-step sequence leading to **2a** was 45%. The synthesis can be satisfactorily conducted on a 50–100 g scale and most of the steps take place in excellent yield.

Illustrating the general scope of the above route, aldehyde diester **1a** was satisfactorily obtained in 42% overall yield from the commercially available malonic ester derivative **24d**, via the known intermediates **25d**–**29d**.[15] In this series ozonolysis of the alkene moiety took place in 84% yield.

In conclusion, the synthetic sequence depicted in Scheme 3 provides a general, high yield route for the preparation of diversely substituted 3-(2-oxoethyl)- and 3-acetonylglutarates on a multigram scale.

3. Experimental

3.1. General experimental procedures

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. NMR spectra were recorded at 200, 300 or 400 MHz (^{1}H) and 50.3, 75 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography (TLC) was done on SiO_2 (silica gel 60 F_{254}), and the spots were located with aqueous potassium permanganate solution or with iodoplatinate reagent. Column chromatography was carried out using the flash chromatography technique. All non-aqueous reactions were performed under an inert atmosphere. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried following standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centre D'Investigació i Desenvolupament (CSIC), Barcelona and Unidade de Espectrometria de Masas, Santiago de Compostela.

3.1.1. Dimethyl 2-(*tert*-butoxycarbonyl)-3-(2,2-dimethoxyethyl)glutarate (8). *tert*-Butyl methyl malonate (762 mg, 4.38 mmol) and ester **6**[5] (504 mg, 2.9 mmol) were added to a cooled (0 °C) suspension of NaH (55% in oil dispersion, 23 mg, 0.58 mmol) in anhydrous THF (30 mL). The mixture was heated at reflux until disappearance of the starting compound was observed by TLC. The reaction was quenched with brine at 0 °C, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried and concentrated. Column chromatography (gradient of eluents hexane/EtOAc) of the residue afforded triester **8** (540 mg, 80%): IR (film) 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H, CCH_3), 1.79 (m, 2H, CH_2CHO), 2.59 (m, 2H, 2H-4), 2.72 (m, 1H, H-3), 3.30 (s, 6H, OCH_3), 3.60 (dd, J=5.7, 1.9 Hz, 1H, H-2), 3.68 (s, 3H, CO_2CH_3), 3.72 (s, 3H, CO_2CH_3), 4.46 (t, J=5.4 Hz, 1H, $CHOCH_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 27.8 (CH_3), 31.2 (CH), 34.2 (CH_2), 35.8 (CH_2), 51.5 (CH_3), 52.1 (CH_3), 52.5 (CH_3), 52.9 (CH_3), 54.8 (CH), 82.1 (C), 103.0 (CH), 167.3 (C), 169.1 (C), 172.6 (C).

3.1.2. Methyl 4-(dimethoxymethyl)-2-hexenoate (9). A solution of methyl 2-hexenoate[5] (1 g, 7.8 mmol) in anhydrous THF (2 mL) was slowly added to a cooled (−78 °C) solution of LDA (1.5 M in THF, 7.8 mmol) and HMPA (1.6 mL, 9.36 mmol) in anhydrous THF (6 mL), and the resulting mixture was stirred for 30 min at this temperature. Then, a solution of Me_3SiCl (1.55 mL, 12.2 mmol) in anhydrous THF (2 mL) was slowly added, and the stirring was continued at room temperature for 2 h.

The mixture was diluted with pentane, washed with brine, dried, filtered, and concentrated. The ketene acetal obtained was dissolved in anhydrous CH_2Cl_2 (10 mL) and stirred in presence of anhydrous $ZnBr_2$ (1.75 g, 7.8 mmol) and anhydrous methyl ortoformate (2.6 mL, 23.4 mmol) at room temperature for 16 h. The crude mixture was poured into brine and extracted with EtOAc. The organic extracts were dried, filtered, and concentrated. Flash chromatography (hexane) of the residue afforded compounds **9** (230 mg, 15%) and **10** (460 mg, 30%). **9**: IR (film) 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J=7.5 Hz, 3H, H-6), 1.37 (ddd, J=15.0, 9.6, 7.5 Hz, 1H, H-5), 1.67 (tdd, J=15.0, 7.5, 3.9 Hz, 1H, H-5), 2.41 (ddd, J=9.6, 6.3, 2.4 Hz, 1H, H-4), 3.34 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.73 (s, 3H, CO_2CH_3), 4.25 (d, J=6.3 Hz, 1H, C*H*OCH_3), 5.88 (dd, J=15.6, 0.6 Hz, 1H, H-2), 6.81 (dd, J=15.6, 9.6 Hz, 1H, H-3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 11.4 (CH_3), 22.3 (CH_2), 47.5 (CH), 51.4 (CH_3), 54.0 (CH_3), 54.3 (CH_3), 106.1 (CH), 122.6 (CH), 147.8 (CH), 166.6 (C). HRMS calcd for $C_{10}H_{18}O_4$ 202.1202, found 202.1205. **10**: IR (film) 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J=7.5 Hz, 3H, H-6), 2.12 (ddd, J=15.0, 7.5, 1.5 Hz, 1H, H-5), 3.31 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.69 (s, 3H, CO_2CH_3), 3.70 (masked, 1H, H-2), 4.68 (d, J=7.8 Hz, 1H, C*H*OCH_3), 5.37 (dd, J=11.4, 1.5 Hz, 1H, H-4), 5.64 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.7 (CH_3), 20.9 (CH_2), 48.0 (CH), 51.8 (CH_3), 52.8 (CH_3), 54.7 (CH_3), 104.2 (CH), 121.4 (CH), 136.3 (CH), 171.4 (C). HRMS calcd for $C_{10}H_{18}O_4$ 202.1202, found 202.1205.

3.1.3. Methyl 2-[1-(methoxycarbonylmethyl)-3,3-dimethoxypropyl]-1,3-dithiolane-2-carboxylate (11). Methyl 1,3-dithiolane-2-carboxylate (625 mg, 3.5 mmol) was added to a cooled (−78 °C) solution of LDA (1.5 M in ciclohexane, 7.19 mmol) in anhydrous THF (30 mL), and the mixture was stirred for 15 min at this temperature. Then, a solution of acetal **6** (1.2 g, 7.56 mmol) in anhydrous THF (1 mL) was slowly added, and the mixture was stirred at room temperature for 4 h. The mixture was poured into brine, the aqueous layer was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography of the resulting yellow oil (8:2 hexane/EtOAc) afforded pure compound **11** (1.1 g, 95%): IR(film) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (ddd, J=14.1, 10.1, 6.0 Hz, 1H, H-4), 1.84 (ddd, J=14.1, 5.4, 2.9 Hz, 1H, H-4), 2.49 (dd, J=16.5, 6.0 Hz, 1H, H-2), 2.79 (dd, J=16.5, 4.0 Hz, 1H, H-2), 3.13 (m, 1H, H-3), 3.28 (s, 6H, OCH_3), 3.30–3.41 (m, 4H, $S(CH_2)_2S$), 3.69 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 4.47 (t, J=5.4 Hz, 1H, C*H*OCH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 37.1 (CH_2), 37.3 (CH_2), 38.3 (CH), 39.8 (CH_2), 39.9 (CH_2), 51.6 (CH_3), 51.9 (CH_3), 53.3 (CH_3), 53.6 (CH_3), 75.9 (CH and C), 171.9 (C), 172.9 (C). HRMS calcd for $C_{13}H_{22}O_6S_2$ 338.0859, found 338.0857.

3.1.4. Dimethyl 3-(2,2-dimethoxyethyl)glutarate (12). Compound **11** (900 mg, 2.6 mmol) was dissolved in a mixture of MeOH/THF (2:1, 7.5 mL) at 0 °C. Then, $NiCl_2\cdot 6H_2O$ (5 g, 18.2 mmol) and $NaBH_4$ (2 g, 54.2 mmol) were added, and the resulting mixture was stirred at 0 °C for 30 min. The crude mixture was concentrated to give an oil, which was dissolved in EtOAc. The organic layer was washed with brine, dried, filtered, and concentrated to give **12** (432 mg, 67%), which was used in the next reaction without further purification: IR (film) 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68 (t, J=5.9 Hz, 2H, CH_2CHO), 2.42–2.48 (m, 5H, CH(CH_2-$CO_2)_2$), 3.30 (s, 6H, OCH_3), 3.67 (s, 6H, CO_2CH_3), 4.45 (t, J=5.9 Hz, 1H, C$H$$OCH_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 28.3 (CH), 36.2 (CH_2), 38.1 (CH_2), 51.4 (CH_3), 52.5 (CH_3), 102.7(CH), 172.5 (C).

3.1.5. Diethyl 3-(cyanomethyl)glutarate (14). Triester **13**[1a,d] (391 mg, 1.30 mmol) and LiCl (61 mg, 1.43 mmol) were dissolved in DMSO (2 mL) containing a few drops of H_2O, and the mixture was stirred at 140 °C for 4 h. Then the mixture was cooled, dissolved in EtOAc, and washed with H_2O. The combined organic solutions were dried, filtered, and concentrated to give an oil. Flash chromatography (1:9 hexane/EtOAc) afforded **14** (222 mg, 75%) as an oil: IR (film) 2246, 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J=7.4 Hz, 6H, CH_3), 2.53 (d, J=5.2 Hz, 4H, CH_2CO_2), 2.66 (masked, 1H, CH), 2.68 (d, J=2.2 Hz, 2H, CH_2CN), 4.17 (q, J=7.4 Hz, 4H, OCH_2); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.0 (CH_3), 21.3 (CH_2), 28.7 (CH), 36.9 (CH_2), 60.7 (CH_2), 117.6 (C), 170.8 (C).

3.1.6. Diethyl 3-(1-cyanopropyl)glutarate (15). Compound **13** was ethylated following a previously reported procedure.[1a,d] The product (219 mg, 0.73 mmol), was treated with LiCl (34 mg, 0.80 mmol) in DMSO (2 mL) containing a few drops of H_2O, as in the above deethyl series, to give pure **15** (85 mg, 74%) after flash chromatography (EtOAc): IR (film) 2978, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, J=7.2 Hz, 3H, CH_3), 1.27 (t, J=7.0 Hz, 6H, CH_3), 1.66 (qd, J=7.2, 2.3 Hz, 2H, CH_2), 2.40–2.58 (m, 4H, H-2 and H-4), 2.60 (m, 1H, CHCN), 2.88 (ddd, J=8.4, 6.3, 4.2 Hz, 1H, H-3), 4.16 (qd, J=7.0, 2.1 Hz, 4H, OCH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.0 (CH_3), 14.0 (CH_3), 23.3 (CH_2), 33.0 (CH), 35.1 (CH_2), 36.5 (CH_2), 36.9 (CH), 60.7 (CH_2), 60.8 (CH_2), 120.0 (C), 171.2 (C), 171.3 (C).

3.1.7. Diethyl 2-acetyl-3-(ethoxycarbonylmethyl)glutarate (16). Ethyl acetylacetate (22 g, 0.16 mmol) and a 0.57 M solution of NaOEt in EtOH (5 mL) were added to a solution of diethyl glutaconate (10 mL, 0.05 mmol) in absolute EtOH (20 mL), and the mixture was heated at reflux for 4 h. Then, 0.57 M NaOEt (5 mL) was added at intervals of 14, 8 and 14 h. After 6 h of additional reflux, concentrated AcOH (2 mL) was added, and the mixture was evaporated. The brown residue was dissolved in Et_2O, and the organic solution was exhaustively washed with $NaHCO_3$ and brine, dried, and evaporated to give an oil. Purification by fractional distillation (150 °C, 1 mmHg) gave triester **16** (11 g, 62%): IR (film) 1736, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J=7.2 Hz, 6H, CH_3), 1.26 (t, J=7.2 Hz, 3H, CH_3), 2.27 (s, 3H, $COCH_3$), 2.47 (dd, J=16.5, 7.5 Hz, 1H, CH_2CO), 2.49 (dd, J=16.5, 4.5 Hz, 1H, CH_2CO), 2.54 (dd, J=4.5, 6.3 Hz, 1H, CH_2CO), 2.59 (dd, J=16.5, 1.8 Hz, 1H, CH_2CO), 3.05 (ddt, J=13.0, 6.9, 1.8 Hz, 1H, H-3), 3.93 (d, J=6.9 Hz, 1H, H-2), 4.11 (q, J=7.2 Hz, 4H, OCH_2), 4.16 (q, J=7.2 Hz, 2H, OCH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.8 (CH_3), 13.9 (CH_3), 29.9 (CH_3), 30.7 (CH), 35.2 (CH_2), 35.5 (CH_2), 60.4 (CH_2), 60.5

(CH_2), 61.3 (CH_2), 61.5 (CH), 168.3 (C), 171.7 (C), 202.2 (C). HRMS calcd for $C_{15}H_{24}O_7$ 316.1526, found 316.1522.

3.1.8. Diethyl 2-acetyl-2-allyl-3-(ethoxycarbonylmethyl) glutarate (17). DBU (1.3 mL, 8.7 mmol), $Pd(acac)_2$ (132 mg, 0.4 mmol), Ph_3P (457 mg, 1.7 mmol), and allyl acetate (1.4 mL, 13.5 mmol) were added to a solution of triester **16** (2.6 g, 8.7 mmol) in anhydrous toluene (43 mL), and the resulting mixture was heated at reflux for 6 h. The solvent was eliminated under reduced pressure, and the residue was dissolved in EtOAc. The organic extract was washed with aqueous 2 N HCl, dried, filtered, and concentrated to give a brown oil (3.7 g). Flash chromatography (hexane) afforded **17** (1.89 g, 64%) as a transparent oil: IR (film) 1639, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, $J=7.2$ Hz, 6H, CH_3), 1.27 (t, $J=7.2$ Hz, 3H, CH_3), 2.18 (s, 3H, $COCH_3$), 2.30 (dd, $J=16.0$, 8.4 Hz, 1H, CH_2CO), 2.41 (dd, $J=16.0$, 8.4 Hz, 1H, CH_2CO), 2.55 (dd, $J=16.0$, 3.9 Hz, 1H, CH_2CO), 2.58 (dd, $J=16.0$, 3.9 Hz, 1H, CH_2CO), 2.63 (d, $J=10.2$ Hz, 2H, CH_2CH=), 3.20 (dt, $J=6.9$, 3.9 Hz, 1H, H-3), 4.12 (ddd, $J=14.4$, 7.2, 3.0 Hz, 4H, OCH_2), 4.24 (ddd, $J=14.4$, 7.2, 0.6 Hz, 2H, OCH_2), 55.07–5.15 (m, 2H, CH_2=), 5.74 (dd, $J=17.1$, 10.2 Hz, 1H, CH=); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.0 (CH_3), 14.1 (CH_3), 28.2 (CH_3), 34.5 (CH), 35.8 (CH_2), 36.7 (CH_2), 36.9 (CH_2), 60.5 (CH_2), 60.6 (CH_2), 61.5 (CH_2), 66.3 (C), 119.1 (CH_2=), 132.3 (CH=), 170.7 (C), 171.8 (C), 172.1 (C), 204.0 (C).

3.1.9. Diethyl 2-acetyl-3-(ethoxycarbonylmethyl)-2-propylglutarate (18). Pd–C (10%, 125 mg) was added to a solution of **17** (500 mg, 1.4 mmol) in MeOH (28 mL), and the resulting suspension was hydrogenated at atmospheric pressure for 4 h. The catalyst was removed by filtration, and the solution was concentrated to give **18** as an oil (430 mg, 85%), which was used in the next reaction without further purification: IR (film) 1709, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, $J=7.2$ Hz, 3H, CH_3), 1.16 (m, 2H, CH_2), 1.25 (t, $J=7.2$ Hz, 6H, CH_3), 1.29 (t, $J=7.2$ Hz, 3H, CH_3), 1.31 (t, $J=7.2$ Hz, 2H, CH_2), 2.18 (s, 3H, CH_3CO), 2.27 (dd, $J=15.6$, 8.4 Hz, 1H, CH_2CO), 2.33 (dd, $J=16.5$, 8.4 Hz, 1H, CH_2CO), 2.53 (dd, $J=15.6$, 3.5 Hz, 1H, CH_2CO), 2.62 (dd, $J=16.5$, 3.5 Hz, 1H, CH_2CO), 3.18 (dt, $J=7.2$, 3.5 Hz, 1H, H-3), 4.12 (ddd, $J=14.4$, 7.2, 1.8 Hz, 4H, OCH_2), 4.23 (ddd, $J=14.4$, 7.2, 1.8 Hz, 2H, OCH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.0 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 14.5 (CH_3), 17.5 (CH_2), 28.1 (CH_3), 34.1 (CH), 34.6 (CH_2), 35.9 (CH_2), 36.8 (CH_2), 60.5 (CH_2), 60.6 (CH_2), 61.3 (CH_2), 66.1 (C), 171.2 (C), 171.9 (C), 172.2 (C), 204.6 (C).

3.1.10. Ethyl *tert*-butyl 2-acetyl-3-(ethoxycarbonylmethyl)glutarate (19). Operating as described for the preparation of **16**, compound **19** was prepared from diethyl glutaconate (9.5 mL, 0.053 mmol), *tert*-butyl acetylacetate (9.2 g, 0.058 mmol), and 1 M *t*-BuOK in *t*-BuOH (5 mL) in anhydrous *t*-BuOH (11 mL). After fractionated distillation (150 °C, 1 mmHg), a mixture (16 g) of ketotriester **19** and starting material was obtained. Flash chromatography (hexane) afforded **19** (13.7 mg, 74%) as a transparent oil: IR (film) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, $J=7.5$ Hz, 6H, CH_3), 1.95 (s, 9H, CH_3), 2.25 (s, 3H, CH_3CO), 2.39–2.61 (m, 4H, CH_2CO), 3.0 (m, 1H, H-3), 3.80 (d, $J=7.0$ Hz, 1H, H-2), 4.13 (q, $J=7.5$ Hz, 4H, OCH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.0 (CH_3), 27.9 (CH_3), 29.9 (CH_3), 30.7 (CH), 35.2 (CH_2), 35.5 (CH_2), 60.3 (CH_2), 61.5 (CH), 82.3 (C), 167.4 (C), 171.6 (C), 171.7 (C), 202.3 (C). HRMS calcd for $C_{17}H_{28}O_7$ 344.1463, found 344.1460.

3.1.11. Ethyl *tert*-butyl 2-acetyl-2-allyl-3-(ethoxycarbonylmethyl)glutarate (20). Operating as described for the preparation of **17**, pure compound **20** (470 mg, 69%) was obtained from ketotriester **19** (610 mg, 1.77 mmol) after flash chromatography (hexane): IR (film) 1709, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, $J=7.2$ Hz, 6H, CH_3), 1.49 (s, 9H, CH_3), 2.18 (s, 3H, CH_3CO), 2.25 (dd, $J=15.6$, 8.4 Hz, 1H, CH_2CO), 2.32 (dd, $J=16.5$, 9.3 Hz, 1H, CH_2CO), 2.53 (dd, $J=15.6$, 3.6 Hz, 1H, CH_2CO), 2.59 (d, $J=1.8$ Hz, 2H, CH_2CH=), 2.63 (dd, $J=16.5$, 2.4 Hz, 1H, CH_2CO), 3.19 (m, 1H, H-3), 4.12 (qd, $J=7.2$, 2.4 Hz, 4H, OCH_2), 5.06–5.14 (m, 2H, CH_2=), 5.75 (dd, $J=17.1$, 10.2 Hz, 1H, CH=); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.0 (CH_3), 14.1 (CH_3), 27.9 (CH_3), 28.3 (CH_3), 34.5 (CH), 36.3 (CH_2), 36.9 (CH_2), 37.1 (CH_2), 60.5 (CH_2), 60.6 (CH_2), 66.8 (C), 82.8 (C), 118.8 (CH_2=), 132.6 (CH=), 169.7 (C), 171.9 (C), 172.1 (C), 204.2 (C).

3.1.12. Ethyl *tert*-butyl 2-acetyl-3-(ethoxycarbonylmethyl)-2-propylglutarate (21). Operating as described for the preparation of **18**, ketotriester **21** (800 mg, 73%) was obtained from **20** (1.2 g, 3.1 mmol) after flash chromatography (hexane): IR (film) 1708, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, $J=6.0$ Hz, 3H, CH_3), 1.24 (masked, 2H, CH_2), 1.25 (t, $J=7.2$ Hz, 6H, CH_3), 1.49 (s, 9H, CH_3), 1.77 (td, $J=11.7$, 5.4 Hz, 2H, CH_2), 2.18 (s, 3H, CH_3CO), 2.20 (dd, $J=15.9$, 7.8 Hz, 1H, CH_2CO), 2.26 (dd, $J=16.5$, 9.3 Hz, 1H, CH_2CO), 2.52 (dd, $J=15.9$, 4.2 Hz, 1H, CH_2CO), 2.62 (dd, $J=16.5$, 3.0 Hz, 1H, CH_2CO), 3.16 (m, 1H, H-3), 4.09 (qd, $J=7.2$, 2.4 Hz, 4H, OCH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.0 (CH_3), 14.0 (CH_3), 14.5 (CH_3), 17.3 (CH_2), 27.8 (CH_3), 28.0 (CH_3), 33.9 (CH), 34.5 (CH_2), 36.2 (CH_2), 37.1 (CH_2), 60.3 (CH_2), 60.5 (CH_2), 66.5 (C), 82.4 (C), 170.1 (C), 171.9 (C), 172.1 (C), 204.6 (C). HRMS calcd for $C_{20}H_{34}O_7$ 386.2618, found 386.2609.

3.1.13. Ethyl 3-(ethoxycarbonylmethyl)-4-propyl-5-oxohexanoate (5b). Thioanisole (1.9 mL) and TFA (1.5 mL, 19.9 mmol) were added to a cooled (0 °C) solution of **21** (770 mg, 1.9 mmol) in CH_2Cl_2 (9.6 mL). The mixture was stirred at room temperature for 8 h and concentrated. The residue was dissolved in anhydrous toluene (4 mL). The resulting solution was heated at reflux for 3 h and concentrated to dryness. Flash chromatography (hexane) afforded **5b** (660 mg, 86%): IR (film) 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, $J=10.5$ Hz, 3H, CH_3), 1.25 (td, $J=10.5$, 6.0 Hz, 6H, CH_3), 1.27 (masked, 3H, CH_2CH_2), 1.61 (m, 1H, CH_2CH_2), 2.21 (s, 3H, CH_3CO), 2.26 (d, $J=11.0$ Hz, 1H, CH_2CO), 2.36 (d, $J=8.0$ Hz, 1H, CH_2CO), 2.39 (d, $J=11.0$ Hz, 1H, CH_2CO), 2.41 (masked, 1H, H-3), 2.42 (d, $J=8.0$ Hz, 1H, CH_2CO), 2.70 (m, 1H, H-4), 4.13 (q, $J=10.5$ Hz, 4H, OCH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.1 (CH_3), 14.2 (CH_3), 21.0 (CH_3), 29.0 (CH_2), 30.5 (CH_3), 32.6 (CH), 35.1 (CH_2), 36.5 (CH_2), 53.8 (CH), 60.5 (CH_2), 172.1 (C), 211.2 (C). HRMS calcd for $C_{15}H_{26}O_5$ 286.1517, found 286.1520.

3.1.14. Diethyl 2-(1-ethyl-2-methyl-2-propenyl)malonate (24a). Diethyl 2-propylidenemalonate[16] (**23**, R_1=Et; 45.5 g, 0.21 mol) in anhydrous Et_2O (500 mL) was added to a cooled (−78 °C) suspension of CuCl (0.41 g, 4.1 mmol) and isopropenylmagnesium bromide (**22**, R_2=Me, R_3=H; 0.5 M in THF, 500 mL, 0.25 mol), and the mixture was stirred until the temperature was raised to 25 °C. Then saturated aqueous NH_4Cl (200 mL) was added, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried, and filtered. Flash chromatography (gradient hexane/EtOAc) afforded pure **24a** (41.3 g, 75%): IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.82 (t, J=7.2 Hz, 3H, CH_3), 1.22 (t, J=7.2 Hz, 3H, CH_3), 1.27 (t, J=7.2 Hz, 3H, CH_3), 1.30 (m, 1H, CH_2), 1.50 (m, 1H, CH_2), 1.68 (dd, J=1.5, 0.9 Hz, 3H, CH_3), 2.77 (td, J=11.1, 3.6 Hz, 1H, CHC=), 3.42 (d, J=11.1 Hz, 1H, H-2), 4.12 (q, J=7.2 Hz, 1H, CH_2O), 4.13 (q, J=7.2 Hz, 1H, CH_2O), 4.20 (q, J=7.2 Hz, 2H, CH_2O), 4.79 (m, 1H, =CH_2), 4.85 (m, 1H, =CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.2 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 18.7 (CH_3), 23.5 (CH_2), 48.4 (CH), 56.3 (CH), 61.0 (CH_2), 61.2 (CH_2), 114.2 (CH_2), 143.2 (CH), 167.9 (C), 168.3 (C). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.37; H, 9.12.

3.1.15. Diethyl 2-(1-ethyl-3-methyl-2-butenyl)malonate (24b). Operating as above, pure **24b** (18.4 g, 74%) was obtained from 2-methyl-1-propenylmagnesium bromide (**22**, R_2=H, R_3=Me; 0.5 M in THF, 216 mL, 0.11 mol), CuCl (0.19 g, 1.8 mmol), and diethyl 2-propylidenemalonate[16] (**23**, R_1=Et; 18.0 g, 0.09 mol) after flash chromatography (hexane, 25:1 hexane/EtOAc): IR (film) 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.83 (t, J=7.2 Hz, 3H, CH_3), 1.15–1.21 (m, 1H, CH_2), 1.22 (t, J=7.2 Hz, 3H, CH_3), 1.26 (t, J=7.2 Hz, 3H, CH_3), 1.48–1.58 (m, 1H, CH_2), 1.65 (d, J=1.6 Hz, 3H, CH_3C=), 1.69 (d, J=1.6 Hz, 3H, CH_3C=), 2.96 (qd, J=9.6, 3.2 Hz, 1H, C*H*CH_2), 3.24 (d, J=9.6 Hz, 1H, H-2), 4.07–4.16 (m, 2H, CH_2O), 4.18 (q, J=7.2 Hz, 2H, CH_2O), 4.88 (m, 1H, =CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.4 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 18.2 (CH_3), 25.8 (CH_3), 26.4 (CH_2), 39.9 (CH), 57.2 (CH), 60.8 (CH_2), 61.0 (CH_2), 124.2 (CH), 134.4 (C), 168.2 (C), 168.5 (C). HRMS calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1675. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.50; H, 9.44. Found: C, 65.43; H, 9.66.

3.1.16. Diethyl 2-(1-ethyl-2-propenyl)malonate (24c). Operating as above, pure **24c** (67.9 g, 92%) was obtained from vinylmagnesium bromide (**22**, R_2=R_3=H; 0.5 M in THF, 390 mL, 0.39 mol), CuCl (0.65 g, 6.5 mmol), and diethyl 2-propylidenemalonate[16] (**23**, R_1=Et; 65 g, 0.32 mol) after flash chromatography (hexane, 95:5 hexane/EtOAc): IR (film) 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.88 (t, J=7.6 Hz, 3H, CH_3), 1.24 (t, J=7.2 Hz, 3H, CH_3), 1.27 (t, J=7.2 Hz, 3H, CH_3), 1.29 (m, 1H, CH_2), 1.53 (m, 1H, CH_2), 2.68 (qd, J=9.2, 3.6 Hz, 1H, C*H*CH_2), 3.35 (d, J=9.2 Hz, 1H, H-2), 4.15 (q, J=7.2 Hz, 2H, CH_2O), 4.19 (q, J=7.2 Hz, 2H, CH_2O), 5.07–5.12 (m, 2H, =CH_2), 5.59–5.68 (m, 1H, =CH–); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR) δ 11.4 (CH_3), 14.0 (CH_3), 25,2 (CH_2), 45.6 (CH), 56.6 (CH), 61.0 (CH_2), 61.1 (CH_2), 117.3 (CH_2), 137.7 (CH), 168.0 (C), 168.2 (C). HRMS calcd for $C_{12}H_{20}O_4$ (M^++H) m/z 228.1362, found 229.1439.

3.1.17. 2-(1-Ethyl-2-methyl-2-propenyl)-1,3-propanediol (25a). A solution of malonate **24a** (15.3 g, 0.06 mol) in Et_2O (100 mL) was slowly added to a suspension of $LiAlH_4$ (6 g, 0.16 mol) in anhydrous Et_2O (100 mL) at 0 °C. The mixture was stirred under Ar at 0 °C for 30 min, at room temperature for 30 min, and heated at reflux for 8 h. Then, the temperature was lowered to 0 °C, and EtOH was slowly added until the formation of a transparent solution. After 30 min the solvent was eliminated under reduced pressure. The residue was dissolved in 20% aqueous KOH, and the mixture was heated at reflux for 2 h. The solution was extracted with Et_2O, and the combined ethereal extracts were dried, filtered, and concentrated to give diol **25a** (9.32 g, 93%): IR (film) 3100–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.80 (t, J=7.2 Hz, 3H, CH_3), 1.21–1.30 (m, 1H, CH_2), 1.55–1.70 (m, 2H, CH_2 and CH_2C=), 1.60 (s, 3H, CH_3), 1.95 (s, 2H, OH), 2.09 (ddd, J=10.8, 10.4, 3.6 Hz, 1H, H-2), 3.69 (dd, J=10.0, 6.0 Hz, 1H, CH_2O), 3.77–3.82 (m, 2H, CH_2O), 3.96 (dd, J=10.8, 3.2 Hz, 1H, CH_2O), 4.76 (m, 1H, =CH_2), 4.85 (m, 1H, =CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.9 (CH_3), 18.2 (CH_3), 22.4 (CH_2), 43.3 (CH), 46.8 (CH), 63.7 (CH_2), 64.7 (CH_2), 113.3 (CH_2), 145.0 (C).

3.1.18. 2-(1-Ethyl-3-methyl-2-butenyl)-1,3-propanediol (25b). Operating as above, diol **25b** (20.4 g, 94%) was obtained from diester **24b** (32.3 g, 0.13 mol) after purification of the crude mixture by flash chromatography (Et_2O): IR (film) 2800–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.81 (t, J=7.6 Hz, 3H, CH_3), 1.13–1.24 (m, 1H, CH_2), 1.49–1.59 (m, 1H, CH_2), 1.61 (d, J=1.2 Hz, 3H, CH_3C=), 1.65–1.71 (m, 1H, H-2), 1.72 (d, J=1.2 Hz, 3H, CH_3C=), 2.22–2.29 (m, 1H, CHC=), 2.38 (br s, 1H, OH), 2.52 (br s, 1H, OH), 3.68–3.78 (m, 2H, CH_2O), 3.82–3.87 (m, 2H, CH_2O), 4.86 (m, 1H, =CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.7 (CH_3), 18.2 (CH_3), 25.7 (CH_3), 25.9 (CH_2), 38.3 (CH), 46.3 (CH), 64.8 (CH_2), 65.4 (CH_2), 126.7 (CH), 133.0 (C); mp 43–46 °C (hexane). HRMS calcd for $C_{14}H_{24}O_4$ (M^++H) m/z 172.1463, found 173.1541. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.67; H, 11.70.

3.1.19. 2-(1-Ethyl-2-propenyl)-1,3-propanediol (25c). Operating as above, diol **25c** (12.3 g, 97%) was obtained from malonate **24c** (32.3 g, 0.13 mol): IR (film) 3000–3600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.86 (t, J=7.2 Hz, 3H, CH_3), 1.28 (m, 1H, CH_2), 1.55 (m, 1H, CH_2), 1.73 (m, 1H, H-2), 2.01 (m, 1H, CHC=), 2.70 (br s, 2H, OH), 3.71 (dd, J=10.4, 7.6 Hz, 1H, CH_2O), 3.76 (dd, J=10.4, 7.6 Hz, 1H, CH_2O), 3.85 (dd, J=10.4, 3.6 Hz, 2H, CH_2O), 5.02 (dd, J=16.8, 2.0 Hz, 1H, =CH_2 *trans*), 5.06 (dd, J=10.0, 2.0 Hz, 1H, =CH_2 *cis*), 5.55 (ddd, J=16.8, 10.0, 10.0 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR) δ 11.8 (CH_3), 24.7 (CH_2), 44.8 (CH), 45.2 (CH), 63.7 (CH_2), 64.3 (CH_2), 116.0 (CH_2), 139.8 (CH). Anal. Calcd for $C_8H_{16}O_2 \cdot 1/4$ EtOAc: C, 65.03; H, 10.91. Found: C, 65.09; H, 11.20.

3.1.20. 2-(1-Ethyl-2-methyl-2-propenyl)propane-1,3-diol ditosylate (26a). A solution of diol **25a** (8.70 g, 0.058 mol)

and tosyl chloride (66 g, 0.35 mol) in anhydrous THF (200 mL) was added to a suspension of KOH (30 g, 0.52 mol) in anhydrous THF (100 mL) at 0 °C. The crude mixture was stirred at 0 °C for 2 h and at room temperature for additional 3 days. The organic solvent was removed at reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (400 mL). The organic solution was washed with ice-water, the aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, and filtered. Removal of the solvent followed by flash chromatography (gradient hexane/EtOAc) afforded ditosylate **26a** (17.3 g, 64%): IR (film) 1178, 1364 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.67 (t, J=7.2 Hz, 3H, CH_3), 1.10 (m, 1H, CH_2), 1.32 (m, 1H, CH_2), 1.46 (d, J=0.4 Hz, 3H, CH_3), 1.90 (m, 1H, CHC=), 1.95 (qd, J=10.4, 3.6 Hz, 1H, H-2), 2.45 (s, 3H, CH_3Ar), 2.46 (s, 3H, CH_3Ar), 3.79 (dd, J=10.4, 7.6 Hz, 1H, CH_2O), 4.00 (dd, J=10.4, 5.6 Hz, 1H, CH_2O), 4.02 (dd, J=10.4, 6.8 Hz, 1H, CH_2O), 4.15 (dd, J=10.4, 3.2 Hz, 1H, CH_2O), 4.61 (m, 1H, =CH_2), 4.77 (m, 1H, =CH_2), 7.33 (d, J=8.0 Hz, 2H, ArH), 7.35 (d, J=8.0 Hz, 2H, ArH), 7.71 (d, J=8.0 Hz, 2H, ArH), 7.75 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.4 (CH_3), 17.6 (CH_3), 21.6 (CH_3), 21.7 (CH_2), 39.7 (CH), 45.7 (CH), 66.7 (CH_2), 67.9 (CH_2), 115.0 (CH_2), 127.6 (CH), 127.7 (CH), 129.7 (CH), 129.8 (CH), 132.2 (C), 132.4 (C), 142.5 (CH), 144.8 (C), 144.9 (C). Anal. Calcd for $C_{23}H_{30}O_6S_2$: C, 59.20; H, 6.48; S, 13.74. Found: C, 59.39; H, 6.56; S, 13.88.

3.1.21. 2-(1-Ethyl-3-methyl-2-butenyl)-1,3-propanediol ditosylate (26b). Operating as above (reaction conditions: 18 h at 0 °C), ditosylate **26b** (43.9 g, 88%) was obtained from diol **25b** (18.0 g, 0.10 mol) after flash chromatography (8:1 hexane/EtOAc): IR (film) 1177, 1362 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.70 (t, J=7.2 Hz, 3H, CH_3), 0.96–1.08 (m, 1H, CH_2), 1.29–1.38 (m, 1H, CH_2), 1.49 (d, J=0.8 Hz, 3H, CH_3C=), 1.63 (d, J=1.2 Hz, 3H, CH_3C=), 1.83 (m, 1H, H-2), 2.18–2.26 (m, 1H, CHC=), 2.46 (s, 6H, CH_3Ar), 3.85 (dd, J=10.0, 7.6 Hz, 1H, CH_2O), 3.96–4.06 (m, 3H, CH_2O), 4.62 (m, 1H, =CH), 7.34 (d, J=8.0 Hz, 2H, ArH), 7.35 (d, J=8.0 Hz, 2H, ArH), 7.71 (d, J=8.4 Hz, 2H, ArH), 7.74 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.3 (CH_3), 18.3 (CH_3), 21.6 (CH_3), 25.2 (CH_2), 25.8 (CH_3), 37.1 (CH), 42.2 (CH), 67.6 (CH_2), 67.8 (CH_2), 124.5 (CH), 127.8 (CH), 127.9 (CH), 129.8 (CH), 129.9 (CH), 132.5 (C), 132.6 (C), 135.2 (C), 144.8 (C), 144.9 (C). HRMS calcd for $C_{24}H_{32}O_6S_2$ (M^++H) m/z 480.1640, found 481.1719. Anal. Calcd for $C_{24}H_{32}O_6S_2$: C, 59.97; H, 6.71; S, 13.34. Found: C, 60.04; H, 6.96; S, 13.24.

3.1.22. 2-(1-Ethyl-2-propenyl)-1,3-propanediol ditosylate (26c). Operating as above, ditosylate **26c** (81.1 g, 88%) was obtained from diol **25c** (15 g, 0.10 mol) after flash chromatography (4:1 hexane/EtOAc): IR (NaCl) 1167, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.75 (t, J=7.6 Hz, 3H, CH_3), 1.14 (m, 1H, CH_2), 1.34 (m, 1H, CH_2), 1.96 (m, 2H, CHC= and H-2), 2.46 (s, 6H, CH_3Ar), 3.85 (dd, J=10.0, 7.6 Hz, 1H, CH_2O), 3.98 (dd, J=10.0, 5.2 Hz, 1H, CH_2O), 4.04 (dd, J=10.0, 4.8 Hz, 1H, CH_2O), 4.08 (dd, J=10.0, 4.0 Hz, 1H, CH_2O), 4.88 (dd, J=16.8, 1.6 Hz, 1H, =CH_2 *trans*), 5.00 (dd, J=10.0, 1.6 Hz, 1H, =CH_2 *cis*), 5.32 (ddd, J=16.8, 10.0, 10.0 Hz, 1H, =CH), 7.35 (m, 4H, ArH), 7.74 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR) δ 11.4 (CH_3), 21.6 (CH_3), 24.1 (CH_2), 41.1 (CH), 43.5 (CH), 67.3 (CH_2), 67.5 (CH_2), 118.0 (CH_2), 127.7 (CH), 127.8 (CH), 129.7 (CH), 129.8 (CH), 132.3 (C), 132.4 (C), 137.5 (CH), 144.8 (C), 144.9 (C). Anal. Calcd for $C_{22}H_{28}O_6S_2$: C, 58.39; H, 6.24; S, 14.17. Found: C, 58.58; H, 6.30; S, 13.90.

3.1.23. 3-(1-Ethyl-2-methyl-2-propenyl)pentanedinitrile (27a). Compound **26a** (3.8 g, 8.15 mmol) and NaCN (1.6 g, 33 mmol) were dissolved in anhydrous DMSO (30 mL), and the mixture was stirred under Ar at room temperature for 10 min and at 75 °C for 20 h. The crude mixture was diluted with EtOAc (100 mL) and ice-H_2O (100 mL). The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried, and concentrated to give an oil, which was chromatographed (6:1 hexane/EtOAc) to give pure **27a** (1.24 g, 86%): IR (film) 2243 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.87 (t, J=7.2 Hz, 3H, CH_3), 1.28 (m, 1H, CH_2), 1.57 (m, 1H, CH_2), 1.61 (s, 3H, CH_3), 2.05 (m, 2H, H-3 and CHC=), 2.40 (dd, J=17.2, 7.6 Hz, 1H, CH_2CN), 2.58 (dd, J=17.2, 6.4 Hz, 1H, CH_2CN), 2.64 (dd, J=17.2, 2.6 Hz, 1H, CH_2CN), 2.76 (dd, J=17.2, 3.6 Hz, 1H, CH_2CN), 4.89 (m, 1H, =CH_2), 5.00 (m, 1H, =CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.6 (CH_3), 17.8 (CH_3), 19.5 (CH_2), 20.7 (CH_2), 22.2 (CH_2), 34.8 (CH), 51.1(CH), 116.4 (CH_2), 117.0 (C), 117.4 (C), 142.2 (C). Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.01; H, 9.15; N, 15.71.

3.1.24. 3-(1-Ethyl-3-methyl-2-butenyl)pentanedinitrile (27b). Operating as above, dinitrile **27b** (15.5 g, 90%) was obtained from ditosylate **26b** (43.5 g, 0.09 mol) after flash chromatography (3:7 hexane/EtOAc): IR (film) 2247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.86 (t, J=7.2 Hz, 3H, CH_3), 1.20 (m, 1H, CH_2), 1.54 (m, 1H, CH_2), 1.68 (d, J=1.2 Hz, 3H, CH_3C=), 1.77 (d, J=1.2 Hz, 3H, CH_3C=), 2.02 (m, 1H, H-3), 2.34–2.42 (m, 2H, CH_2CN and CHC=), 2.52–2.65 (m, 3H, CH_2CN), 4.75 (dm, J=10.4 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.4 (CH_3), 18.5 (CH_3), 19.4 (CH_2), 19.9 (CH_2), 25.5 (CH_2), 25.9 (CH_3), 37.4 (CH), 41.6 (CH), 117.4 (C), 117.8 (C), 123.3 (CH), 137.0 (C). HRMS calcd for $C_{12}H_{20}N_2$ (M^++H) m/z 190.1470, found 191.1548. Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.94; H, 9.60; N, 14.76.

3.1.25. 3-(1-Ethyl-2-propenyl)pentanedinitrile (27c). Operating as above (reaction time 8 h), compound **27c** (24.6 g, 88%) was obtained from **26c** (78 g, 0.17 mol) after flash chromatography (4:1 hexane/EtOAc): IR (film) 2247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.91 (t, J=7.2 Hz, 3H, CH_3), 1.32 (m, 1H, CH_2), 1.54 (m, 1H, CH_2), 2.11 (m, 2H, H-3 and CHC=), 2.39 (dd, J=17.2, 8.0 Hz, 1H, CH_2CN), 2.58 (dd, J=17.2, 6.4 Hz, 1H, CH_2CN), 2.61 (dd, J=10.0, 6.0 Hz, 1H, CH_2CN), 2.65 (dd, J=10.0, 4.0 Hz, 1H, CH_2CN), 5.21 (ddd, J=16.8, 10.0, 0.4 Hz, 1H, =CH_2 *trans*), 5.27 (dd, J=10.0, 1.6 Hz, 1H, =CH_2 *cis*), 5.45 (ddd, J=16.8, 10.0, 10.0 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR) δ 11.3 (CH_3), 19.2 (CH_2), 19.7 (CH_2), 24.2 (CH_2), 35.8 (CH), 47.7 (CH), 117.1 (C), 117.3 (C), 119.4

(CH_2), 136.2 (CH). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.63; H, 8.67; N, 17.14.

3.1.26. 3-(1-Ethyl-2-methyl-2-propenyl)pentanedioic acid (28a). A mixture of dinitrile **27a** (1.05 g, 6 mmol) and 35% aqueous NaOH solution (15 g) in MeOH (20 mL) was heated at reflux for 4 h. The MeOH was eliminated under reduced pressure, and the aqueous solution was heated at reflux temperature for additional 2 h. The crude mixture was cooled at 0 °C and brought to pH 1 by careful addition of 6 N aqueous HCl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (Et_2O) gave diacid **28a** (1.1 g, 86%): IR (film) 1724, 2500–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.83 (t, $J=7.2$ Hz, 3H, CH_3), 1.31 (m, 1H, CH_2), 1.53 (m, 1H, CH_2), 1.65 (s, 3H, CH_3), 1.83 (m, 1H, CHC=), 2.16 (m, 2H, CH_2CO), 2.46 (m, 1H, H-3), 2.57 (dd, $J=16.0$, 2.0 Hz, 1H, CH_2CO), 2.63 (dd, $J=14.4$, 2.8 Hz, 1H, CH_2CO), 4.72 (m, 1H, $=CH_2$), 4.92 (m, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 12.4 (CH_3), 19.4 (CH_3), 22.4 (CH_2), 35.0 (CH), 38.1 (CH_2), 38.7 (CH_2), 53.4 (CH), 114.8 (CH_2), 144.6 (C), 180.6 (C). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.25; H, 8.58.

3.1.27. 3-(1-Ethyl-3-methyl-2-butenyl)pentanedioic acid (28b). Operating as above, pure diacid **28b** (16.7 g, 82%) was obtained from compound **27b** (17.0 g, 0.09 mol) after flash chromatography (Et_2O): IR (film) 1697, 2800–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.83 (t, $J=7.2$ Hz, 3H, CH_3), 1.20 (m, 1H, CH_2), 1.43–1.51 (m, 1H, CH_2), 1.60 (s, 3H, $CH_3C=$), 1.72 (s, 3H, $CH_3C=$), 2.18–2.31 (m, 3H, CH_2CO, CHC= and H-3), 2.40–2.53 (m, 3H, CH_2CO), 4.79 (d, $J=10.4$ Hz, 1H, =CH), 6.10 (s.a., 2H, OH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.8 (CH_3), 18.3 (CH_3), 25.7 (CH_2), 25.9 (CH_3), 35.6 (CH_2), 36.5 (CH), 37.8 (CH_2), 43.2 (CH), 125.1 (CH), 134.5 (C), 178.9 (C); mp 99–101 °C. HRMS calcd for $C_{12}H_{20}O_4$ 228.1362, found 228.1362. Anal. Calcd for $C_{10}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.34; H, 8.98.

3.1.28. 3-(1-Ethyl-2-propenyl)pentanedioic acid (28c). Operating as above, diacid **28c** (25.8 g, 95%) was obtained from **27c** (22 g, 0.14 mol): IR (film) 1721, 2500–3500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.89 (t, $J=7.2$ Hz, 3H, CH_3), 1.34 (m, 1H, CH_2), 1.48 (m, 1H, CH_2), 1.91 (m, 1H, CH), 2.16 (dd, $J=15.2$, 12.0 Hz, 1H, CH_2CO), 2.25 (dd, $J=14.0$, 11.2 Hz, 1H, CH_2CO), 2.44 (ddd, $J=14.0$, 2.0, 0.8 Hz, 1H, CH_2CO), 2.56 (m, 2H, H-3, CH_2CO), 5.04 (ddd, $J=16.8$, 2.0, 0.8 Hz, 1H, $=CH_2$ *trans*), 5.14 (dd, $J=10.4$, 2.0 Hz, 1H, $=CH_2$ *cis*), 5.50 (ddd, $J=16.8$, 10.4, 9.2 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.9 (CH_3), 24.6 (CH_2), 35.9 (CH), 36.1 (CH_2), 38.7 (CH_2), 50.4 (CH), 117.8 (CH_2), 138.1 (CH), 180.1 (C), 180.2 (C); mp 78–79 °C (hexane). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.15; H, 8.05.

3.1.29. Dimethyl 3-(1-ethyl-2-methyl-2-propenyl) pentanedioate (29a). Me_3SiCl (50 mL, 393 mol) was added to a solution of diacid **28a** (19.1 g, 89 mmol) in anhydrous MeOH (300 mL), and the mixture was stirred at room temperature for 24 h. The solvent was eliminated under reduced pressure, and the residue was dissolved in Et_2O and washed with 5% aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried, and evaporated to give pure **29a** (19.6 g, 91%): IR (film) 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.80 (t, $J=7.2$ Hz, 3H, CH_3), 1.19–1.31 (m, 1H, CH_2), 1.45–1.54 (m, 1H, CH_2), 1.62 (s, 3H, CH_3), 1.94–2.00 (m, 1H, CHC=), 2.28–2.52 (m, 5H, H-2, H-4 and H-3), 3.65 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 4.70 (m, 1H, $=CH_2$), 4.87 (m, 1H, $=CH_2$); ^{13}CNMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 12.1 (CH_3), 19.0 (CH_3), 22.0 (CH_2), 34.1 (CH), 35.8 (CH_2), 36.7 (CH_2), 51.3 (CH_3), 51.4 (CH_3), 51.7 (CH), 113.9 (CH_2), 144.6 (C), 173.1 (C). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.40; H, 9.10.

3.1.30. Dimethyl 3-(1-ethyl-3-methyl-2-butenyl)pentanedioate (29b). Operating as above, pure compound **29b** (16.4, 92%) was obtained from diacid **28b** (15.9 g, 0.07 mol) after flash chromatography (Et_2O): IR (film) 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.81 (t, $J=7.2$ Hz, 3H, CH_3), 1.10–1.22 (m, 1H, CH_2), 1.42–1.53 (m, 1H, CH_2), 1.57 (d, $J=1.6$ Hz, 3H, $CH_3C=$), 1.71 (d, $J=1.2$ Hz, 3H, $CH_3C=$), 2.18–2.46 (m, 6H, H-2, H-3, H-4, and CHC=), 3.65 (s, 6H, OCH_3), 4.78 (dm, $J=10.4$ Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, HETCOR) δ 11.9 (CH_3), 18.2 (CH_3), 25.6 (CH_2), 25.9 (CH_3), 35.3 (CH_2), 36.4 (CH), 36.7 (CH_2), 42.3 (CH), 51.3 (CH_3), 51.4 (CH_3), 125.4 (CH), 134.3 (C), 173.3 (C), 173.6 (C). HRMS calcd for $C_{14}H_{24}O_4$ 256.1675, found 256.1675. Anal. Calcd for $C_{14}H_{24}O_4 \cdot 1/4$ EtOAc: C, 64.72; H, 9.41. Found: C, 65.01; H, 9.71.

3.1.31. Dimethyl 3-(1-ethyl-2-propenyl)pentanedioate (29c). Operating as above, pure **29c** (27.1 g, 92%) was obtained from diacid **28c** (25.8 g, 0.13 mol) after flash chromatography (Et_2O): IR (film) 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.87 (t, $J=7.2$ Hz, 3H, CH_3), 1.27 (m, 1H, CH_2), 1.47 (m, 1H, CH_2), 1.98 (m, 1H, CHC=), 2.19 (dd, $J=16.8$, 10.0 Hz, 1H, H-2), 2.37 (m, 2H, H-2), 2.44 (m, 2H, H-2 and H-3), 3.65 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 5.01 (ddd, $J=17.2$, 2.0, 0.8 Hz, 1H, $=CH_2$ *trans*), 5.11 (dd, $J=10.4$, 2.0 Hz, 1H, $=CH_2$ *cis*), 5.47 (ddd, $J=16.8$, 10.4, 9.2 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR) δ 11.9 (CH_3), 24.4 (CH_2), 35.0 (CH_2), 35.4 (CH), 36.7 (CH_2), 48.6 (CH), 51.2 (CH_3), 51.3 (CH_3), 117.3 (CH_2), 138.3 (CH), 172.8 (C), 173.0 (C). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.00; H, 8.79.

3.1.32. Dimethyl and diethyl 3-(2-oxoethyl)glutarate (1). *Method A*. Operating as described for the preparation of compound **5b** (reaction time 16 h), methyl ester **1a** (70.3 mg, 57%) was obtained from triester **8** (211 mg, 0.60 mmol) after flash chromatography (hexane): IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.46 (dd, $J=6.6$, 4.2 Hz, 4H, H-2 and H-4), 2.64 (dd, $J=6.3$, 1.5 Hz, 2H, CH_2CHO), 2.88 (td, $J=13.2$, 6.3 Hz, 1H, H-3), 3.67 (s, 6H, OCH_3), 9.79 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.5 (CH), 37.6 (CH_2), 47.3 (CH_2), 51.6 (CH_3), 172.1 (C), 200.4 (C). HRMS calcd for $C_9H_{14}O_5$ 202.1723, found 202.1719.

Method B. A solution of $LiBF_4$ (132 mg, 1.3 mmol) in acetonitrile (15 mL) containing 2% of H_2O was added via cannula to a solution of acetal **12** (326 mg, 1.31 mmol) in acetonitrile (2.5 mL), and the resulting solution was stirred at room temperature for 3 h. The crude mixture was poured into brine, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. The resulting oil was chromatographed (hexane) affording compound **1a** (161 mg, 61%).

Method C. A mixture of nitrile **15** (222 mg, 0.98 mmol), NaH_2PO_2 (650 mg), and Raney Ni (108 mg) in pyridine-AcOH-H_2O (2:1:1, 8 mL) was stirred at 50 °C for 5 h. The catalyst was removed by filtration, and the solvent was evaporated. The residue was dissolved in EtOAc, and the organic layer was washed with H_2O, dried, filtered, and concentrated to give a yellow oil (169 mg), which was chromatographed (1:1 hexane/EtOAc) affording ethyl glutarate **1b** (143 mg, 64%) as a transparent oil: IR (film) 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J= 7.2 Hz, 6H, CH_3), 2.45 (dd, J=6.6, 4.2 Hz, 4H, H-2 and H-4), 2.63 (dd, J=6.6, 1.2 Hz, 2H, CH_2CHO), 2.88 (q, J= 6.6 Hz, 1H, H-3), 4.11 (q, J=7.2 Hz, 4H, CH_2), 9.75 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.2 (CH_3), 26.5 (CH), 37.9 (CH_2), 47.3 (CH_2), 60.4 (CH_2), 171.6 (C), 200.5 (C).

Method D. Malonate (**24d**) was converted to dimethyl 3-allylpentadioate (**29d**) via the intermediates **25d**–**28d** in the yields indicated in Table 1, following reported procedures.[15] A stream of ozone gas was bubbled through a cooled (−78 °C) solution of diester **29d** (2.5 g, 12.5 mmol) in CH_2Cl_2 (40 mL) until it turned pale blue. The solution was purged with Ar until disappearance of the blue color. Then SMe_2 (35 mL, 475 mmol) was added, and the temperature was raised to 25 °C. After 30 h of stirring, the crude mixture was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, and filtered to give, after column chromatography (3:1 hexane/EtOAc), pure methyl ester **1a** (2.10 g, 84%).

3.1.33. Dimethyl and diethyl 3-(1-formylpropyl)glutarate (2). *Method A*. Nitrile **15** (100 mg, 0.39 mmol) was reduced operating as described in the above Method C, with addition of NaH_2PO_2 (273 mg) and Raney Ni (65 mg) at intervals of 6 h during 24 h. After flash chromatography (1:1 hexane/EtOAc) a 4:1 mixture of **2b** and **15** (71 mg, 57%) was obtained; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J= 7.4 Hz, 3H, CH_3), 1.25 (t, J=7.6 Hz, 6H, CH_3), 1.69 (dd, J=7.6, 2.2 Hz, 2H, CH_2), 2.37–2.55 (m, 4H, H-2 and H-4), 2.61 (m, 1H, H-3), 2.83 (m, 1H, C*H*CHO), 4.07–4.21 (m, 4H, CH_2), 9.66 (d, J=2.2 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.1 (CH_3), 14.1 (CH_3), 22.2 (CH_2), 33.2 (CH), 33.6 (CH_2), 33.7 (CH_2), 49.2 (CH), 60.4 (CH_2), 60.5 (CH_2), 172.0 (C), 172.2 (C), 203.7 (C).

Method B. Diester **29b** (262 mg, 1.02 mmol) was ozonolyzed as described in the above Method D. After stirring in the presence of SMe_2 for 4 h and flash chromatography (1:1 hexane/EtOAc), ketodiester **2a** (150 mg, 64%) was obtained: IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 0.96 (t, J=7.2 Hz, 3H, CH_3), 1.67–1.82 (m, 1H, CH_2), 1.42–1.56 (m, 1H, CH_2), 2.40–2.48 (m, 5H, H-2, H-4 and C*H*CHO), 2.80 (m, 1H, H-3), 3.67 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 9.66 (d, J= 2,4 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.4 MHz, HETCOR) δ 12.0 (CH_3), 18.6 (CH_2), 31.3 (CH), 35.4 (CH_2), 35.7 (CH_2), 51.6 (CH_3), 51.7 (CH_3), 55.4 (CH), 172.2 (C), 172.3 (C), 203.5 (C).

Method C. Operating as described in the above Method D, diester **2a** (1.09 g, 75%) was obtained from **29c** (1.5 g, 6.6 mol) after flash chromatography (1:1 hexane/EtOAc).

3.1.34. Dimethyl 3-(1-ethyl-2-oxopropyl)pentadionate (4a). Diester **29a** (2.5 g, 10 mmol) was ozonolyzed as described in the above Method D. After stirring in the presence of SMe_2 for 20 h and flash chromatography (gradient hexane–EtOAc), ketodiester **4a** (1.76 g, 65%) was obtained: IR (film) 1710, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY, HETCOR) δ 0.85 (t, J= 7.2 Hz, 3H, CH_3), 1.35–1.45 (m, 1H, CH_2), 1.60–1.71 (m, 1H, CH_2), 2.21 (s, 3H, CH_3), 2.28 (dd, J=16.0, 8.0 Hz, 1H, H-2 or H-4), 2.37–2.49 (m, 3H, H-2 and H-4), 2.62–2.71 (m, 2H, H-3 and CHCO), 3.66 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz, HETCOR) δ 12.0 (CH_3), 20.0 (CH_2), 30.6 (CH_3), 32.3 (CH), 34.7 (CH_2) 36.1 (CH_2), 51.5 (CH_3), 55.5 (CH), 172.3 (C), 172.4 (C), 210.9 (C). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.73; H, 8.23.

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