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ScienceDirect
Tetrahedron 63 (2007) 10528–10533
Tetrahedron

Diol desymmetrization as an approach to the synthesis of unsymmetrical dienyl diesters

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Received 31 May 2007; revised 9 July 2007; accepted 20 July 2007
Available online 31 July 2007

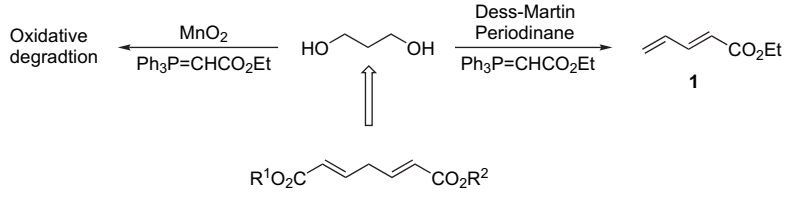
Abstract—The tandem oxidation/Wittig olefination of unactivated diols utilizing manganese dioxide produces α,β-unsaturated hydroxy esters in high yields in a highly effective desymmetrization process. The formation of small quantities of the corresponding lactones suggests that the reaction may proceed through a lactol intermediate in some cases. The α,β-unsaturated hydroxy esters are transformed into symmetrical or unsymmetrical dienyl diesters using a second oxidation/Wittig olefination sequence mediated by PCC.

1. Introduction

The development of tandem preparative procedures, where a number of transformations are carried out in a one-pot process, offers significant advantages such as a reduction in the number of synthetic steps realizing a significant improvement in efficiency.[1] A number of groups have reported the development of such tandem sequences, in particular for the direct transformation of alcohols to olefins using Wittig chemistry. The Wittig reaction remains one of the most effective synthetic methods for the introduction of a double bond,[2,3] however, its utility is limited when applied to carbonyl compounds, particularly aldehydes, that are difficult to isolate due to their instability, toxicity or volatility. The application of tandem oxidation/olefination processes circumvents these shortcomings and a range of oxidizing reagents have been employed including manganese dioxide,[4] barium permanganate,[5] Dess–Martin periodinane,[6] tetrapropylammonium perruthenate (TPAP),[7] and *ortho*-iodobenzoic acid.[8]

The range of alcohols investigated admirably demonstrates the generality of this synthetic approach, however, the application of tandem reaction sequences to the homologation of unactivated diols has proved to be highly problematic.[9] Barrett demonstrated that while 1,2-ethanediol undergoes a double oxidation/homologation sequence using the Dess–Martin periodinane as oxidant, the corresponding dienyl diester is not produced from 1,3-propanediol.[4] In this case, ethyl (*E*)-2,4-pentadienoate **1** is formed by a competing elimination from 3-hydroxypropanal (Scheme 1). Similarly, Taylor has reported that 1,2-diols undergo oxidative cleavage in the presence of manganese dioxide,[10] and also that the attempted tandem oxidation/Wittig reaction of 1,3-propanediol with manganese dioxide in refluxing toluene produces only products derived from oxidative degradation.[11]

We required an efficient route for the synthesis of a series of dienyl diesters, and were attracted to the potential simplicity and flexibility of this approach provided that undesirable elimination and degradation reactions could be avoided. In this paper we disclose the realization of this goal, in addition to the development of a highly effective desymmetrization protocol for unactivated diols leading to an efficient method for the synthesis of α,β-unsaturated hydroxy esters.



Scheme 1. Tandem oxidation/Wittig reactions of 1,3-propanediol.

Keywords: α,β-Unsaturated hydroxy esters; Tandem oxidation/olefination; Manganese dioxide; Diol desymmetrization.
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doi:10.1016/j.tet.2007.07.089

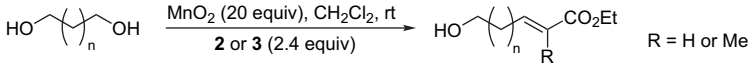
2. Results and discussion

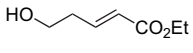
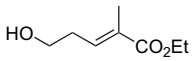
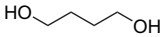
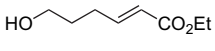
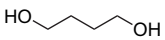
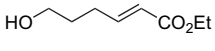
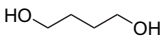
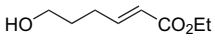
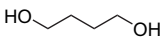
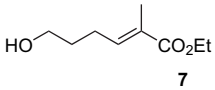
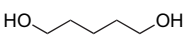
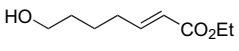
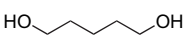
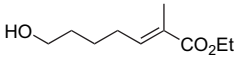
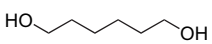
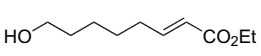
Our initial goal was to limit the extent of the competing oxidative degradation and elimination reactions, which we envisaged may be achieved by moderating the oxidizing ability of the oxidant. It has been demonstrated that there is considerable variation in the oxidizing capacity of manganese dioxide and that this property is related to the morphology of the crystallites.[12] With this in mind we investigated a range of commercially available grades of manganese dioxide to determine the variability in their oxidizing ability, and were gratified to observe that reaction of 1,2-ethanediol with Wittig reagents **2** ($Ph_3P{=}CHCO_2Et$) and **3** ($Ph_3P{=}C(CH_3)CO_2Et$) with manganese dioxide (Aldrich, 10 μm, 90%) at room temperature produced the corresponding dienyl diesters in good yields.[13] Surprisingly, reactions involving longer chain diols furnished only small quantities of dienyl diester and instead produced α,β-unsaturated hydroxy esters as the major product.[14] The yield of α,β-unsaturated hydroxy ester was highly dependent on the grade of manganese dioxide employed with 1,3-propanediol, 1,4-butanediol, and 1,5-pentanediol giving only trace amounts of products when alternate grades were used. The oxidation proceeds with impressive selectivity to give the mono-oxidized material as the major product regardless of the quantity of oxidant used (Table 1).[15]

We noted during these studies that in the case of 1,4- and 1,5-diols, the yields of the α,β-unsaturated hydroxy product were reduced by a competing oxidative cyclization, which produced the corresponding lactone products. These reactions provided small quantities of these materials as by-products in a highly capricious reaction suggesting that, in these cases, the desymmetrization process may proceed through a lactol intermediate.[16] We therefore investigated the manganese dioxide-mediated oxidative cyclization reaction of 1,5-pentanediol as a model substrate to understand further the desymmetrization reaction (Table 2). Reactions at room temperature produced high conversions of the diol to lactol and lactone products, and significant quantities of the lactone were produced on carrying out the reaction in chloroform under reflux conditions.

The desymmetrization of symmetrical diols has attracted considerable attention due to the lack of convenient methods by which the transformation can be carried out.[17] Furthermore, the oxidative cyclization of diols to lactones typically involves co-reagents, harsh reaction conditions or utilizes

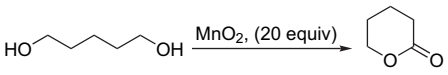
Table 1. Synthesis of α,β-unsaturated hydroxy esters



Entry	Diol	Time (h)	Product[a]	Yield (%)[b,c]
1		24	 **4**	79
2		24	 **5**	66
3		24	 **6**	71
4		48	 **6**	91
5		8	 **6**	70[d]
6		24	 **7**	66
7		24	 **8**	52
8		24	 **9**	52
9		24	 **10**	56

[a] Reactions in CH_2Cl_2 using Aldrich 10 μm MnO_2.
[b] Reactions produced ~5% *Z*-isomer.
[c] Reactions produced <5% diester.
[d] At reflux in CH_2Cl_2 with 10 equiv of manganese dioxide.

Table 2. Manganese dioxide-mediated oxidative cyclization of 1,5-pentanediol



Entry	Conditions[a]	Conversion[b] (%)
1	CH_2Cl_2, 20 h, rt	30[c]
2	CH_3Cl, 20 h, rt	57[c]
3	CH_3Cl, 4 h, reflux	29[c]
4	CH_3Cl, 24 h, reflux	91

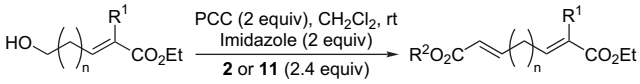
[a] Diol was used as supplied (Aldrich).
[b] Determined from ^{1}H NMR spectrum of the crude reaction mixture.
[c] Contains ~40% lactol.

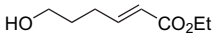
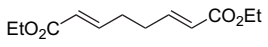
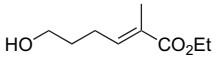
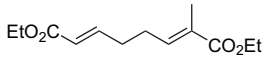
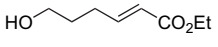
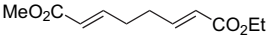
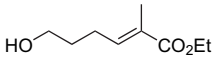
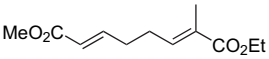
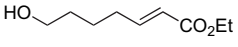
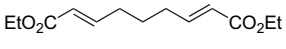
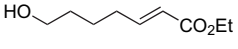
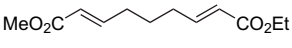
expensive metal catalysts.[18] Thus, manganese dioxide provides a potentially mild and inexpensive alternative to current methodologies and our recent results in this area will be the subject of a subsequent publication.[19] The α,β-unsaturated hydroxy esters produced in this process are highly versatile intermediates that have found widespread use in numerous synthetic pathways and in natural product synthesis.[20] Our protocol, in which desymmetrization is achieved in a one-pot tandem procedure directly from the diol, avoids the requirement for protection/deprotection strategies or the use of air sensitive reagents and results in a significant improvement in efficiency.

While the α,β-unsaturated hydroxy esters **4**–**10** were produced efficiently, the yields of dienyl diesters were poor and could not be improved using this one-pot approach. Indeed, when the α,β-unsaturated hydroxy esters were isolated and subjected to a second oxidation/Wittig protocol, only traces of the dienyl diesters were isolated. Additional experiments utilizing activated manganese dioxide, extended reaction times or elevated temperatures furnished only moderate (20–25%) yields with the balance of material being unreacted alcohol. The desired dienyl diesters, however, were obtained by oxidation of the α,β-unsaturated hydroxy esters using silica supported pyridinium chlorochromate (PCC)[21] followed by trapping of the intermediate aldehydes with Wittig reagents **2** or **11** ($Ph_3P{=}CHCO_2Me$) in a sequential one-pot procedure.

Initial one-pot reactions involving the addition of silica supported PCC at the start of the reaction followed after 2 h by the Wittig reagent resulted in efficient generation of the intermediate aldehyde, however, this was not converted to significant yields of the diester even after protracted reaction times (up to 48 h). This is presumably due to the reprotonation of the Wittig reagent due to the acidic nature of the oxidant. We therefore sought to control the acidity of the reaction conditions by the addition of a buffering agent, such as imidazole, which would suppress the reprotonation of the Wittig reagent.[22] Our initial studies showed that oxidation over a 2 h period followed by simultaneous addition of 2 equiv of imidazole and Wittig reagent produced reasonable yields of diester. Further improvements in yields were obtained by leaving the oxidation step for 4 h and introducing the imidazole 1 h before the Wittig reagent followed by an additional 19 h stirring. Under these conditions, the desired diester products were produced in good yields (Table 3).[23]

Table 3. PCC-mediated synthesis of dienyl diesers



Entry	Ester	Product	Yield (%)[a]
1	 **6**	 **12**	83
2	 **7**	 **13**	73
3	 **6**	 **14**	65
4	 **7**	 **15**	69
5	 **8**	 **16**	74
6	 **8**	 **17**	70

[a] Reactions produced ~5% *E*,*Z*-isomer.

3. Conclusions

In summary, the tandem oxidation/Wittig homologation protocol leads to the highly effective desymmetrization of unactivated diols, and serves as a highly efficient protocol for the synthesis of α,β-unsaturated hydroxy esters without the requirement for prior protecting group manipulation. The competing oxidative degradation and elimination reactions previously observed are avoided by moderation of the oxidative capacity of the oxidant, which is achieved by judicious choice of the grade of manganese dioxide employed. It is assumed that in the case of 1,4- and 1,5-diols, the desymmetrization process proceeds through the initial formation of the lactol intermediate, which undergoes subsequent reaction in the presence of the ylide to produce the corresponding α,β-unsaturated hydroxy esters. Reactions of 1,5-pentanediol under reflux temperatures in the absence of Wittig reagents produced good conversions to the corresponding lactone products. The intermediate α,β-unsaturated hydroxy esters are remarkably resistant to further oxidation reactions but are converted to dienyl diesters in good yields by oxidation with silica supported pyridinium chlorochromate. Subsequent trapping of the intermediate aldehydes provides access to both symmetrical and unsymmetrical dienyl diesters.

4. Experimental

4.1. General methods

Commercially available reagents were used without further purification. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminum-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualized under UV light (at 254 and/or 360 nm) or using potassium permanganate solution (1% in water) followed by charring. Infra-red (IR) spectra were recorded in the range 4000–600 cm^{-1} as neat oils or solids and are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ at 25 °C unless stated otherwise and are reported in parts per million; *J* values are recorded in hertz and multiplicities are expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using the ionization technique stated. ES refers to electrospray ionization, CI refers to chemical ionization (ammonia) and EI refers to electron impact ionization. High-resolution mass spectra (HRMS) were obtained courtesy of the EPSRC Mass Spectrometry Service University of Wales Swansea, UK using the ionization method specified. Removal of solvent refers to evaporation at reduced pressure using a rotary evaporator followed by the removal of trace volatiles using a vacuum pump.

4.2. General procedure for the desymmetrization of unactivated diols

4.2.1. *E*-5-Hydroxy-pent-2-enoic acid ethyl ester (4). A mixture of 1,3-propanediol (762 mg, 10 mmol), (ethoxycarbonylmethylene)triphenylphosphorane **2** (2.4 equiv, 8.37 g, 24 mmol), and manganese dioxide (20 equiv, 17.44 g, 200 mmol) in dichloromethane (80 ml) was stirred for 24 h at room temperature. At this time the manganese dioxide was removed by filtration through a Celite pad, which was then washed with additional dichloromethane (2×10 ml). The solvent was then removed in vacuo to give an orange oil, which was purified by column chromatography (hexane → 20% ethyl acetate–hexane) to give the title compound **4** (1.14 g, 79%) as a yellow oil. IR ν_{max} (film)/cm^{-1} (neat) 3422, 1714, 1653, 1267, 1162, 1038; ^1H NMR (400 MHz; $CDCl_3$) δ=1.25 (3H, t, *J*=7 Hz), 2.20 (1H, br s, OH), 2.46 (2H, dq, *J*=7, 1 Hz), 3.76 (2H, t, *J*=7 Hz), 4.20 (2H, q, *J*=7 Hz), 5.91 (1H, dt, *J*=16, 1 Hz), 6.95 (1H, dt, *J*=16, 7 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=166.9, 145.8, 123.9, 61.3, 60.8, 35.8, 14.6; MS (ES, NH_3) *m/z* 162 $(M+NH_4)^+$, 145 $(M+H)^+$; HRMS (ES, NH_3) calculated for $C_7H_{16}O_3N$ $(M+NH_4)^+$ 162.1125; found $(M+NH_4)^+$ 162.1124.

4.2.2. *E*-5-Hydroxy-2-methyl-pent-2-enoic acid ethyl ester (5). The title compound (150 mg, 66%) was obtained as a yellow oil. IR ν_{max} (film)/cm^{-1} (neat) 3417, 2936, 1706, 1650, 1272, 1194, 1038; ^1H NMR (400 MHz; $CDCl_3$) δ=1.30 (3H, t, *J*=7 Hz), 1.87 (3H, d, *J*=1 Hz), 2.05 (1H, br s, OH), 2.46 (2H, dq, *J*=7, 1 Hz), 3.76 (2H, t, *J*=7 Hz), 4.19 (2H, q, *J*=7 Hz), 6.95 (1H, dt, *J*=7, 1 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=168.1, 138.0, 130.1, 61.4, 60.6, 32.1, 14.3, 12.6; MS (CI, NH_3) *m/z* 176 $(M+NH_4)^+$, 159 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_8H_{18}O_3N$ $(M+NH_4)^+$ 176.1281; found $(M+NH_4)^+$ 176.1282.

4.2.3. *E*-6-Hydroxy-hex-2-enoic acid ethyl ester (6). The title compound (615 mg, 71%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 3419, 1715, 1699, 1269, 1195, 1037; ^1H NMR (400 MHz; $CDCl_3$) 1.25 (3H, t, *J*=7 Hz), 1.65 (2H, pent, *J*=7 Hz), 2.25 (2H, dq, *J*=7, 1 Hz), 2.55 (br s, 1H, OH), 3.60 (2H, t, *J*=7 Hz), 4.15 (2H, q, *J*=7 Hz), 5.85 (1H, dt, *J*=16, 1 Hz), 6.95 (1H, dt, *J*=16, 7 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=167.2, 149.0, 122.0, 62.1, 60.7, 31.2, 28.9, 14.6; MS (CI, NH_3) *m/z* 176 $(M+NH_4)^+$, 159 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_8H_{18}O_3N$ $(M+NH_4)^+$ 176.1281; found $(M+NH_4)^+$ 176.1279.

4.2.4. *E*-6-Hydroxy-2-methyl-hex-2-enoic acid ethyl ester (7). The title compound (1.13 g, 66%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 3421, 1705, 1648, 1259, 1125, 1090; ^1H NMR (400 MHz; $CDCl_3$) 1.18 (3H, t, *J*=7 Hz), 1.45 (1H, br s, OH), 1.60–1.75 (2H, m), 1.80 (3H, s), 2.25 (2H, dq, *J*=7, 1 Hz), 3.65 (2H, t, *J*=7 Hz), 4.15 (2H, q, *J*=7 Hz), 6.70 (1H, t, *J*=7 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=168.7, 141.8, 128.7, 62.5, 60.9, 31.8, 25.4, 14.6, 12.7; MS (CI, NH_3) *m/z* 190 $(M+NH_4)^+$, 173 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_9H_{17}O_3$ $(M+H)^+$ 173.1172; found $(M+H)^+$ 173.1174.

4.2.5. *E*-7-Hydroxy-hept-2-enoic acid ethyl ester (8). The title compound (96 mg, 52%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 3410, 1716, 1652, 1266, 1186, 1096; ^1H NMR (400 MHz; $CDCl_3$) 1.20 (3H, t, *J*=7 Hz), 1.40–1.55 (4H, m), 1.60 (1H, br s, OH), 2.15–2.25 (2H, m), 3.55 (2H, t, *J*=7 Hz), 4.15 (2H, q, *J*=7 Hz), 5.80 (1H, d, *J*=16 Hz), 6.95 (1H, dt, *J*=16, 7 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=167.1, 149.3, 122.0, 62.9, 60.6,

32.5, 32.3, 24.6, 14.7; MS (CI, NH_3) *m/z* 190 $(M+NH_4)^+$, 173 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_9H_{17}O_3$ $(M+H)^+$ 173.1172; found $(M+H)^+$ 173.1172.

4.2.6. *E*-7-Hydroxy-2-methyl-hept-2-enoic acid ethyl ester (9). The title compound (163 mg, 52%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 3390, 1706, 1655, 1367, 1252, 1092; ^1H NMR (400 MHz; $CDCl_3$) 1.05 (3H, t, *J*=7 Hz), 1.20 (1H, br s, OH), 1.25–1.45 (4H, m), 1.65 (3H, s), 1.95–2.15 (2H, m), 3.45 (2H, t, *J*=7 Hz), 4.00 (2H, q, *J*=7 Hz), 6.60 (1H, t, *J*=7 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=168.7, 142.2, 128.4, 63.0, 60.9, 32.7, 28.7, 25.2, 14.7, 12.8; MS (CI, NH_3) *m/z* 204 $(M+NH_4)^+$, 187 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{10}H_{19}O_3$ $(M+H)^+$ 187.1329; found $(M+H)^+$ 187.1328.

4.2.7. *E*-8-Hydroxy-oct-2-enoic acid ethyl ester (10). The title compound (180 mg, 56%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 3425, 1717, 1652, 1266, 1182, 1095; ^1H NMR (400 MHz; $CDCl_3$) 1.31 (3H, t, *J*=7 Hz), 1.38–1.66 (7H, m), 2.24 (2H, m), 3.67 (2H, t, *J*=7 Hz), 4.20 (2H, q, *J*=7 Hz), 5.84 (1H, dt, *J*=16, 1.5 Hz), 6.98 (1H, dt, *J*=16, 7 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=167.2, 149.5, 121.8, 63.1, 60.6, 32.9, 32.5, 28.2, 25.7, 14.7; MS (CI, NH_3) *m/z* 204 $(M+NH_4)^+$, 187 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{10}H_{22}O_3N$ $(M+NH_4)^+$ 204.1594; found $(M+NH_4)^+$ 204.1595.

4.3. General procedure for the PCC-mediated synthesis of dienyl diesters

4.3.1. *E*,*E*-Octa-2,6-dienedioic acid diethyl ester (12). A mixture of *E*-6-hydroxy-hex-2-enoic acid ethyl ester (167 mg, 1.06 mmol) **6** and pyridinium chlorochromate (2 equiv, 0.46 g, 2.12 mmol, ground with 2 wt equiv of silica, 0.92 g) was stirred for 4 h at room temperature in dichloromethane (50 ml). Imidazole (2 equiv, 0.14 g, 2.12 mmol) was added and the reaction mixture stirred for a further 1 h. The addition of (ethoxycarbonylmethylene)triphenylphosphorane **2** (2.4 equiv, 0.88 g, 2.54 mmol) was followed by 19 h of stirring. At this time the silica supported pyridinium chlorochromate was removed by filtration through a Celite pad, which was then washed with additional dichloromethane (2×50 ml). The solvent was then removed in vacuo to give an orange/brown oil, which was purified by column chromatography (hexane → 10% ethyl acetate–hexane) to give to give the title compound **12** (199 mg, 83%) as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 2982, 1714, 1654, 1368, 1265, 1095; ^1H NMR (400 MHz; $CDCl_3$) 1.28 (6H, t, *J*=7 Hz), 2.35–2.40 (4H, m), 4.18 (4H, q, *J*=7 Hz), 5.84 (2H, d, *J*=16 Hz), 6.90–6.95 (2H, m); ^{13}C NMR δ=(100 MHz; $CDCl_3$) 166.7, 147.3, 123.0, 60.7, 30.8, 14.6; MS (CI, NH_3) *m/z* 244 $(M+NH_4)^+$, 227 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{12}H_{22}O_4N$ $(M+NH_4)^+$ 244.1543; found $(M+NH_4)^+$ 244.1542.

4.3.2. *E*,*E*-2-Methyl-octa-2,6-dienedioic acid diethyl ester (13). The title compound (351 mg, 73%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 2982, 1707, 1652, 1367, 1259, 1094; ^1H NMR (400 MHz; $CDCl_3$) 1.19 (6H, t, *J*=7 Hz), 1.75 (3H, s), 2.20–2.30 (4H, m), 4.10 (4H, q, *J*=7 Hz), 5.76 (1H, d, *J*=16 Hz), 6.60–6.65 (1H, m) 6.85–6.95 (1H, m); ^{13}C NMR δ=(100 MHz; $CDCl_3$) 168.3, 166.8, 147.8, 140.2, 129.4, 122.5, 60.9, 60.7, 31.4, 27.5, 14.6, 12.8; MS (CI, NH_3) *m/z* 258 $(M+NH_4)^+$, 241 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{13}H_{24}O_4N$ $(M+NH_4)^+$ 258.1700; found $(M+NH_4)^+$ 258.1697.

4.3.3. *E*,*E*-Octa-2,6-dienedioic acid ethyl methyl ester (14). The title compound (167 mg, 65%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 2984, 1716, 1655, 1368, 1267, 1094; ^1H NMR (400 MHz; $CDCl_3$) 1.30 (3H, t, *J*=7 Hz), 2.35–2.40 (4H, m), 3.75 (3H, s), 4.19 (2H, q, *J*=7 Hz), 5.80–5.85 (2H, m), 6.90–7.00 (2H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ=167.2, 166.7, 147.6, 147.2, 122.8, 122.3, 60.7, 51.9, 30.9, 30.8, 14.6; MS (CI, NH_3) *m/z* 230 $(M+NH_4)^+$, 213 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{11}H_{20}O_4N$ $(M+NH_4)^+$ 230.1387; found $(M+NH_4)^+$ 230.1388.

4.3.4. *E*,*E*-2-Methyl-octa-2,6-dienedioic acid ethyl methyl ester (15). The title compound (310 mg, 69%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 2982, 1707, 1652, 1367, 1260, 1094; ^1H NMR (400 MHz; $CDCl_3$) 1.21 (3H, t, *J*=7 Hz), 1.74 (3H, d, *J*=1 Hz), 2.27 (4H, m), 3.64 (3H, s), 4.10 (2H, q, *J*=7 Hz), 5.77 (1H, dt, *J*=16, 1 Hz), 6.60–6.65 (1H, m), 6.80–6.85 (1H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ=168.3, 167.2, 148.1, 140.2, 129.4, 122.1, 60.9, 51.8, 31.4, 27.5, 14.6, 12.8; MS (CI, NH_3) *m/z* 244 $(M+NH_4)^+$, 227 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{12}H_{22}O_4N$ $(M+NH_4)^+$ 244.1543; found $(M+NH_4)^+$ 244.1453.

4.3.5. *E*,*E*-Nona-2,7-dienedioic acid diethyl ester (16). The title compound (87 mg, 74%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 2982, 1715, 1653, 1367, 1263, 1177, 1096; ^1H NMR (400 MHz; $CDCl_3$) 1.29 (6H, t, *J*=7 Hz), 1.66 (2H, pent, *J*=7 Hz), 2.24 (4H, m), 4.20 (4H, q, *J*=7 Hz), 5.83 (2H, dd, *J*=16, 1 Hz), 6.92 (2H, dt, *J*=16, 7 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ=166.5, 148.0, 122.0, 60.2, 31.4, 26.3, 14.3; MS (CI, NH_3) *m/z* 258 $(M+NH_4)^+$, 241 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{13}H_{21}O_4$ $(M+H)^+$ 241.1434; found $(M+H)^+$ 241.1431.

4.3.6. *E*,*E*-Nona-2,7-dienedioic acid ethyl methyl ester (17). The title compound (94 mg, 70%) was obtained as a colorless oil. IR ν_{max} (film)/cm^{-1} (neat) 2984, 1717, 1655, 1368, 1266, 1175, 1097; ^1H NMR (400 MHz; $CDCl_3$) 1.22 (3H, t, *J*=7 Hz), 1.57 (2H, pent, *J*=7 Hz), 2.15–2.25 (4H, m), 3.66 (3H, s), 4.12 (2H, q, *J*=7 Hz), 5.76 (2H, dt, *J*=16, 1 Hz), 6.85 (1H, dt, *J*=16, 7 Hz), 6.90 (1H, dt, *J*=16, 7 Hz); ^{13}C NMR δ=(100 MHz; $CDCl_3$) 167.3, 166.9, 148.8, 148.4, 122.4, 122.0, 60.6, 51.9, 31.8, 31.7, 26.7, 14.7; MS (CI, NH_3) *m/z* 240 $(M+NH_4)^+$, 227 $(M+H)^+$; HRMS (CI, NH_3) calculated for $C_{12}H_{22}O_4N$ $(M+NH_4)^+$ 244.1543; found $(M+NH_4)^+$ 244.1547.

Acknowledgements

These studies have enjoyed generous financial support from the Engineering and Physical Sciences Research Council (D.J.P) and Pfizer Global Research and Development, Sandwich (K.S.P). The authors thank the EPSRC National Mass Spectrometry Service, University of Wales Swansea, UK.

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