Tetrahedron 65 (2009) 8418–8427

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of isomeric polyacetylenes based on natural hydroxy matricaria esters

Solange Garrais, Jennifer Turkington, William P.D. Goldring *

School of Chemistry and Chemical Engineering, Queen's University Belfast, David Keir Building, Stranmillis Road, Belfast, Northern Ireland BT9 5AG, United Kingdom

ARTICLE INFO

Article history:
Received 6 May 2009
Received in revised form 9 July 2009
Accepted 28 July 2009
Available online 6 August 2009

Keywords:
Polyacetylenes
Matricaria esters
Cross-coupling
Tuberculosis

ABSTRACT

The construction of a library of natural and related polyacetylenes using a convergent synthetic strategy based on a palladium mediated cross-coupling reaction is described. The systematic synthetic study led to all possible alkene isomers of the hydroxy matricaria esters **29**–**32**, and the corresponding tiglates **1**–**4**. The synthesis of many of these compounds is described for the first time.

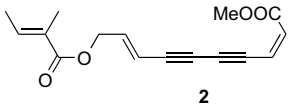
1. Introduction

A wide variety of polyacetylenes have been isolated from natural sources for decades,[1] and have been pursued in target synthesis for over 50 years.[2] Among this class of natural products are the matricaria esters, which are structurally characterised by a conjugated ene–diyne–ene system. This core structure is commonly substituted with alkyl groups, allylic alcohols and esters, in all possible alkene isomer combinations.

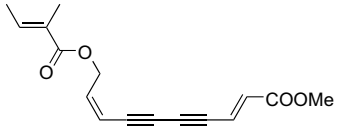
Natural matricaria-type esters, such as the tiglate **4** and the hydroxy ester **29**, possess insecticidal activity,[3] together with activity against *Mycobacterium tuberculosis*, the cause of the bacterial disease tuberculosis (TB), and *Mycobacterium avium*, a bacteria which targets patients with immune deficiency, such as AIDS.[4] Furthermore, other structurally related matricaria esters isolated in Nature possess antibacterial and antitumour activity.[5]

The polyacetylenes continue to be pursued as targets for synthesis, and a number of recent examples highlight the importance of, and interest in these natural compounds.[6] In this article we describe the syntheses of all possible alkene isomers of the hydroxy matricaria esters **29**–**32**, and the corresponding tiglates **1**–**4**, using a convergent strategy based on palladium mediated cross-coupling methodology. We also describe the construction of related metabolites, such as the isomeric dimethyl esters **21**–**23**, and the diols **24**–**26**.

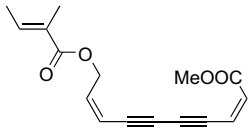
1



2



3



4

2. Results and discussion

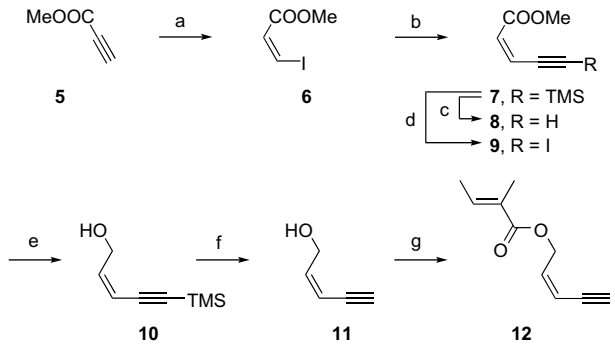
Our plan for the construction of a library of matricaria-type esters relied on the Sonogashira coupling reaction as the key step in the assembly of the core diene–diyne structure. Therefore, a number of enyne subunits, readily accessible in both alkene isomers and with the appropriate substitution, were required for this alkyne–alkyne cross-coupling strategy. This includes, for example,

* Corresponding author. Tel.: +44 (0)28 9097 4414; fax: +44 (0)28 9097 6524.
E-mail address: w.goldring@qub.ac.uk (W.P.D. Goldring).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.07.082

a number of isomeric enyne alcohol (cf. **11**) and iodoalkyne ester (cf. **9**) subunits, which in turn could be derived from the corresponding vinyl iodide and acetylene.

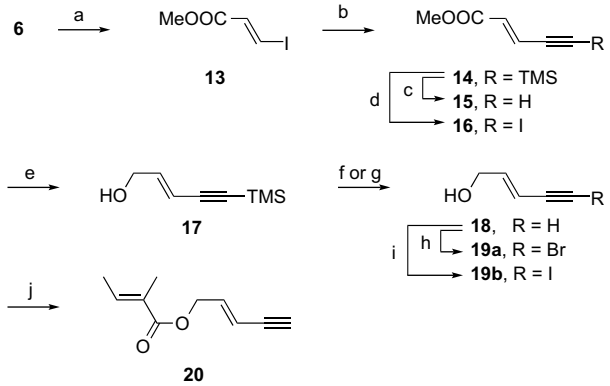
Construction of the (*Z*)-enyne subunits started from commercially available methyl propiolate (**5**). Treatment of the alkyne **5** with sodium iodide in acetic acid led exclusively to the (*Z*)-vinyl iodide **6** in quantitative yield (Scheme 1).[7] Under Sonogashira coupling conditions the vinyl iodide **6** was coupled with ethynyltrimethylsilane to give the enyne ester (*Z*)-**7** in quantitative yield.[8] The enyne **7** was used to access a number of important coupling partners required for our synthesis. For example, deprotection of the TMS-protected alkyne **7**, using TBAF, gave the enyne (*Z*)-**8** in 73% yield.[8] Alternatively, deprotection of **7** with silver nitrate in a mixture of ethanol and water, followed by treatment of the resulting alkynyl silver salt with iodine gave the iodoalkyne (*Z*)-**9** in 68% yield.[9]



Scheme 1. Reagents and conditions: (a) NaI, AcOH, 70 °C, 99%; (b) TMSC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 99% (**7**); (c) TBAF, THF, 0 °C to rt, 73%; (d) $AgNO_3$, EtOH/H_2O (1:1); then I_2, CH_2Cl_2, 68%; (e) DIBALH, CH_2Cl_2, −78 °C, 96%; (f) TBAF, THF, 0 °C to rt, 95%; (g) tiglic acid, DCC, DMAP, CH_2Cl_2, 90%.

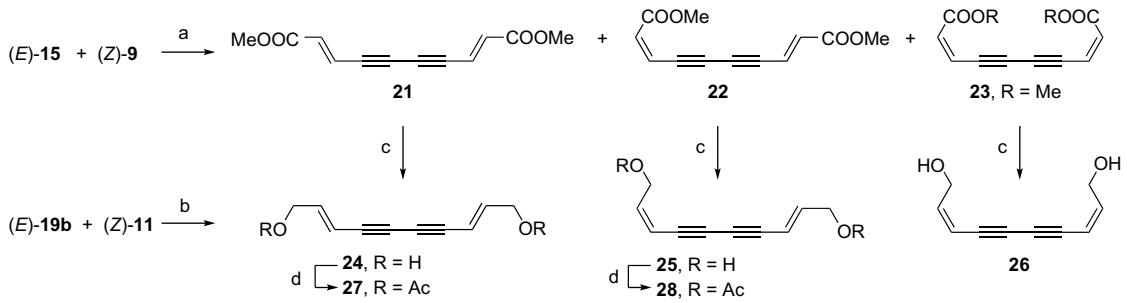
The corresponding (*Z*)-enyne alcohol coupling partners were elaborated from the enyne ester (*Z*)-**7**. During our synthetic studies towards these subunits we examined the order of steps for the conversion of **6** into **10**. For example, we were disappointed to discover the reduction of the ester **6**, using DIBALH, followed by Sonogashira coupling of the resulting vinyl iodide with ethynyltrimethylsilane gave the enyne **10** in 10% yield over two steps. The overall yield of this two-step process was significantly improved when the vinyl iodide **6** was coupled with TMS–acetylene, as described earlier, followed by reduction of the resulting ester **7** with DIBALH to give the allylic alcohol **10** in 96% yield over two steps. Deprotection of the TMS-protected alkyne **10**, using TBAF, gave the enyne (*Z*)-**11** in 95% yield.[10] Finally, esterification of the alcohol **11** with tiglic acid under standard DCC coupling conditions gave an inseparable 13:1 mixture of the isomeric tiglates (*Z*)-**12** and (*E*)-**20** in 90% combined yield.

The isomeric (*E*)-series of coupling partners were synthesised in a similar manner from the vinyl iodide (*E*)-**13**, which was previously prepared from (*Z*)-iodoacrylic acid via an isomerisation–methylation sequence.[11] We, however, employed a direct approach and were pleased to observe the smooth isomerisation of (*Z*)-**6**, in the presence of HI, into the vinyl iodide (*E*)-**13** (Scheme 2).[12] The vinyl iodide (*E*)-**13** was then coupled with ethynyltrimethylsilane to give the enyne ester (*E*)-**14** in quantitative yield over two steps. Deprotection of the TMS-protected alkyne **14**, using TBAF, gave the enyne (*E*)-**15** in 74% yield. Treatment of the alkyne **14** with silver nitrate, and then iodine, led directly to the iodoalkyne (*E*)-**16** in 86% yield. Using a reduction–deprotection sequence the enyne alcohol (*E*)-**18** was elaborated from the ester **14**, via the TMS-protected alkyne **17**, in 82% yield over two steps. The enyne **18** was converted into either the bromoalkyne **19a**, using silver nitrate and *N*-bromosuccinimide,[6a,c,13] or the iodoalkyne **19b**, using iodine and potassium hydroxide. The TMS-protected acetylene **17** could be converted directly into the bromoalkyne **19a** under the conditions described above (viz. **18**→**19a**). Finally, esterification of the alcohol **18** with tiglic acid under standard DCC coupling conditions gave an inseparable 32:1 mixture of the isomeric tiglates (*E*)-**20** and (*Z*)-**12** in 93% combined yield.



Scheme 2. Reagents and conditions: (a) HI, benzene, 80 °C, 99%; (b) TMSC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 99% (**14**); (c) TBAF, THF, 0 °C to rt, 74%; (d) $AgNO_3$, EtOH/H_2O (1:1); then I_2, CH_2Cl_2, 86%; (e) DIBALH, CH_2Cl_2, −78 °C, 85%; (f) NaOH, MeOH, −10 °C, 97% (**18**); (g) NBS, $AgNO_3$, acetone, 0 °C, 84% (**19a**); (h) NBS, $AgNO_3$, acetone, 0 °C, 84%; (i) KOH, I_2, MeOH, H_2O, 64%; (j) tiglic acid, DCC, DMAP, CH_2Cl_2, 93%.

Construction of the enyne structures set the stage for a synthesis of all possible hydroxy matricaria ester isomers, and the corresponding tiglates, via cross-coupling of the appropriate terminal alkyne and iodoalkyne subunits. We first set out to construct all possible diene–diyne dimethyl ester isomers from the enyne ester (*E*)-**15** and the iodoalkyne ester (*Z*)-**9**. The coupling of **15** and **9**, under Sonogashira conditions ($PdCl_2(PPh_3)_2$, CuI and diisopropylamine), gave a mixture of the dimethyl esters (*E*,*E*)-**21**, (*E*,*Z*)-**22** and (*Z*,*Z*)-**23** in 45%, 25% and 19% yield, respectively (Scheme 3). In comparison, treatment of the enyne ester (*Z*)-**8**, under the same conditions, gave the dimethyl ester (*Z*,*Z*)-**23** in 80% yield. We did not



Scheme 3. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, 45% (**21**), 25% (**22**) and 19% (**23**); (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 27% (**24**), 12% (**25**) and 23% (**26**); (c) DIBALH, CH_2Cl_2, 80% (**24**), or 99% (**25**), or 58% (**26**); (d) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 66% (**27**), or 80% (1:2, **27**/**28**).

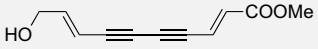
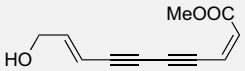
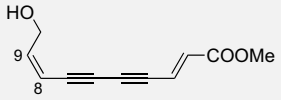
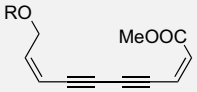
observe alkene isomerisation during the synthesis or purification of this material.

The NMR spectral data recorded for **21** were identical to the data reported for this compound previously synthesised[14] and isolated in Nature.[15] The NMR spectral data recorded for **22** were identical to the data reported for this compound previously synthesised,[14c,15b] but not yet isolated in Nature. To the best of our knowledge, this is the first synthesis to be reported for the dimethyl ester (*Z*,*Z*)-**23**, which has not yet been found in Nature.

We then set out to synthesise all possible diene–diyne diol isomers. Coupling of the iodoalkyne (*E*)-**19b** with the terminal alkyne (*Z*)-**11** led to an inseparable mixture of the diols (*E*,*E*)-**24**, (*E*,*Z*)-**25** and (*Z*,*Z*)-**26** in 27%, 12% and 23% yield, respectively (see Scheme 3).[16] In comparison, the diol (*Z*,*Z*)-**26** was synthesised from Nature, employed a direct cross-coupling approach between the appropriate terminal enyne alcohol and iodoalkyne ester subunits. For example, the coupling reaction between the enyne alcohol (*E*)-**18** and the iodoalkyne ester (*E*)-**16**, under Sonogashira conditions, gave the hydroxy ester (*E*,*E*)-**29** in 37% yield (Table 1). Together with the desired product, the dimethyl ester (*E*,*E*)-**21** and the diol (*E*,*E*)-**24** were isolated in 61% and 45% yield, respectively, which accounted for the remainder of the mass balance. The best result was achieved for the coupling reaction between (*E*)-**18** and (*Z*)-**9**, which gave the hydroxy ester (*Z*,*E*)-**30** in 55% yield, together with the corresponding dimethyl ester (*Z*,*Z*)-**23** and the diol (*E*,*E*)-**24** in 40% and 27% yield, respectively, which accounted for the remainder of the mass balance.

The hydroxy matricaria esters (*E*,*Z*)-**31** and (*Z*,*Z*)-**32** were separately synthesised in 18% and 13% yield from the coupling

Table 1
Synthesis of the matricaria esters **29**–**32**, via Sonogashira coupling[a]

Coupling partners		Hydroxy matricaria ester	Yield %	Dimethyl ester (yield %)	Diol (yield %)
Terminal alkyne	Iodoalkyne ester				
(*E*)-**18**	(*E*)-**16**	 **29**	37	(*E*,*E*)-**21** (61)	(*E*,*E*)-**24** (45)
(*E*)-**18**	(*Z*)-**9**	 **30**	55	(*Z*,*Z*)-**23** (40)	(*E*,*E*)-**24** (27)
(*Z*)-**11**	(*E*)-**16**	 **31**	18[c]	(*E*,*E*)-**21** (49)	(*Z*,*Z*)-**26** (41)
(*Z*)-**11**	(*Z*)-**9**	 b → **32**, R = H; **33**, R = Ac	13[d]	(*Z*,*Z*)-**23** (86)	(*Z*,*Z*)-**26** (40)

[a] $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, THF, rt.
[b] Ac_2O, DMAP, Et_3N, CH_2Cl_2, 70%.
[c] Isolated as a 19:1 mixture with the minor isomer (*E*,*E*)-**29**.
[d] Isolated as an 8:1 mixture with the minor isomer (*E*,*E*)-**30**.

the enyne alcohol (*Z*)-**11** in 99% yield. The diol isomers were independently synthesised directly from the corresponding dimethyl esters **21**–**23**. For example, reduction of the dimethyl ester (*E*,*E*)-**21**, using DIBALH, gave the corresponding diene–diyne diol (*E*,*E*)-**24** in 80% yield. The diols (*E*,*Z*)-**25** and (*Z*,*Z*)-**26** were obtained by reduction of the corresponding dimethyl esters **22** and **23**, respectively.

The ^{1}H NMR spectral data recorded for the isomeric diols **24** and **26** were identical to the data reported for the compounds previously synthesised[6d,14b,17] and isolated in Nature.[15a,18] To the best of our knowledge, a synthesis of the diol (*E*,*Z*)-**25** has not yet been reported, however the corresponding bis-acetate **28** was isolated in Nature from *Felicia filifolia* and *Centaurea ruthenica*.[18a,b]

The bis-acetates (*E*,*E*)-**27** and (*E*,*Z*)-**28** were prepared from the corresponding diols **24** and **25**, using acetic anhydride with DMAP and triethylamine, in 66% and 80% yield, respectively. Under these conditions the reaction of (*E*,*Z*)-**25** led to an inseparable 1:2 mixture of the bis-acetates (*E*,*E*)-**27** and (*E*,*Z*)-**28**, thus indicating some *Z* to *E* isomerisation had occurred. The ^{1}H NMR spectral data recorded for **27** and **28** were identical to the data reported for the compounds isolated from natural sources.[18a,b]

Our synthesis of the natural hydroxy matricaria esters **29**, **31** and **32**, and the isomer (*Z*,*E*)-**30**, which has not yet been isolated in partners (*Z*)-**11** and (*E*)-**16**, or (*Z*)-**11** and (*Z*)-**9**, respectively. Isolation of the corresponding dimethyl ester by-products, **21** or **23**, accounted for the remainder of the mass balance based on the iodoalkyne coupling partner (see Table 1). However, it is interesting to note the isolation of the corresponding diol by-product **26** did not account for the remainder of the mass balance based on the enyne alcohol (*Z*)-**11** used in both reactions. The hydroxy esters **31** and **32** were isolated with a minor amount of the C8–C9 double-bond isomers **29** and **30**, respectively. The *Z* to *E* isomerisation of related compounds has been reported in the literature.[15b,19]

The ^{1}H NMR spectral data recorded for the hydroxy matricaria ester (*E*,*E*)-**29** were identical to the data reported for this compound previously synthesised and isolated from natural sources.[15a,20] The ^{1}H NMR spectral data recorded for the isomer (*E*,*Z*)-**31** were identical to the data reported for this compound isolated from natural sources.[15a,21]

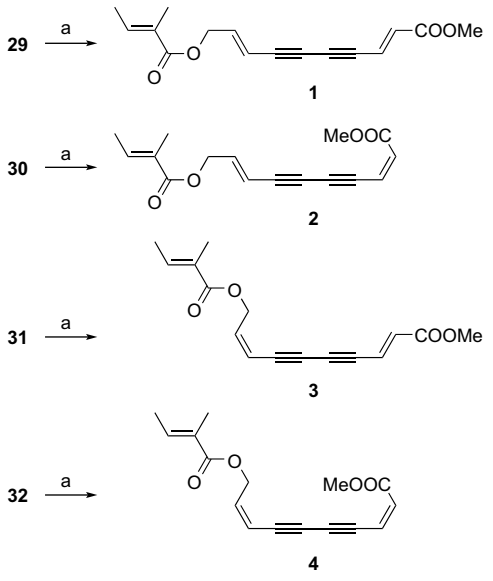
The acetoxy matricarica ester **33** was prepared from the hydroxy ester (*Z*,*Z*)-**32**, using acetic anhydride with DMAP and triethylamine, in 70% yield. The NMR spectral data recorded for (*Z*,*Z*)-**32** and the acetate **33** were identical to the data reported for the natural products isolated from *Chrysothamnus nauseosus* and *Chrysothamnus parryi*.[3,21]

To the best of our knowledge, this is the first reported synthesis of the matricaria esters **30**–**33**. Furthermore, the hydroxy ester (*Z*,*E*)-**30** has not yet been found in Nature.

Based on the cross-coupling approach employed in our synthesis of the hydroxy matricaria esters **29**–**32** we then set out to synthesise the corresponding family of matricaria-type tiglates **1**–**4**, of which **4** is the only natural member.[22] We were disappointed to discover our coupling experiments were characterised by a low yield of the desired tiglate esters, together with the formation of the dimethyl ester and bis-tiglate by-products. For example, the coupling reaction between the enyne tiglate (*E*)-**20** and the iodoalkyne ester (*E*)-**16** gave an inseparable mixture of the tiglate (*E*,*E*)-**1**, the dimethyl ester (*E*,*E*)-**21** and a product tentatively assigned as the (*E*,*E*)-bis-tiglate dimer of (*E*)-**20**. The coupling reaction between (*Z*)-**12** and (*E*)-**16** gave an inseparable mixture of the tiglates (*E*,*Z*)-**3** and (*E*,*E*)-**1**, together with the dimethyl ester **21** and the (*Z*,*Z*)-bis-tiglate dimer.

Our synthetic effort towards the tiglates **1**–**4**, using a cross-coupling approach, was complicated by alkene isomerisation and the formation of the dimethyl ester and bis-tiglate by-products. This prompted us to consider a simple and direct approach to their synthesis using the hydroxy esters **29**–**32**. For example, DCC coupling of the hydroxy ester (*E*,*E*)-**29** with tiglic acid in the presence of DMAP gave the tiglate **1** in 79% yield (Table 2). Accordingly, the tiglates **2**–**4** were synthesised from the hydroxy esters **30**–**32**, respectively. The tiglates **3** and **4** were isolated with a minor amount of the C8–C9 double-bond isomers **1** and **2**, respectively. The ^{1}H NMR spectral data recorded for the tiglate **4** were identical to the data reported for this compound previously synthesised[9] and isolated in Nature from the roots of *Solidago canadensis*.[22] The tiglates **1**–**3** have not yet been found in Nature, and to the best of our knowledge this is the first report of their synthesis.

Table 2
Synthesis of the tiglates **1**–**4** from the hydroxy esters **29**–**32**[a]



Hydroxy ester	Tiglate	Yield %
(*E*,*E*)-**29**	**1**	79
(*Z*,*E*)-**30**	**2**	60
(*E*,*Z*)-**31**	**3**	54[b]
(*Z*,*Z*)-**32**	**4**	36[c]

[a] Tiglic acid, DCC, DMAP, CH_2Cl_2.
[b] Isolated as a 10:1 mixture with the minor isomer (*E*,*E*)-**1**.
[c] Isolated as a 6:1 mixture with the minor isomer (*Z*,*E*)-**2**.

3. Conclusions

In conclusion, a library of natural and related isomeric matricaria-type esters, based on the polyacetylenic structure, were synthesised in a convergent manner from enyne coupling partners. This includes the dimethyl esters **21**–**23**, the diols **24**–**26**, the hydroxy matricaria esters **29**–**32** and the tiglates **1**–**4**. Most notably, we completed the first syntheses of the dimethyl ester (*Z*,*Z*)-**23**, the diol (*E*,*Z*)-**25**, the matricaria esters **30**–**33** and the tiglates **1**–**3**. Our synthetic approach to polyacetylenes exposed some issues with the palladium mediated alkyne–alkyne cross-coupling reaction, which included the formation of dimeric self-coupled products. However, the convergent nature of our synthetic approach could be employed in the future for the construction of other diene–diyne structures, thus expanding our library of polyacetylenes for biological evaluation.

4. Experimental

4.1. General details

Melting points were determined on a Stuart SMP10 electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer RX I FT-IR spectrometer as liquid films or as dilute solutions in spectroscopic grade chloroform or deuterochloroform between two sodium chloride plates. IR spectra of solids were recorded as KBr discs. Proton NMR spectra were recorded on either a Bruker AVX300 (300 MHz), Bruker DPX300 (300 MHz), or a Bruker DRX500 (500 MHz) spectrometer as dilute solutions in deuterochloroform. Chemical shifts are referenced to residual protonated solvent (δ_H=7.26 for $CDCl_3$) and are quoted in parts per million (ppm). The multiplicity of a signal is designated by one of the following abbreviations: s=singlet; d=doublet; t=triplet; q=quartet; br=broad; m=multiplet; app.=apparent; obsd=obscured. All coupling constants, *J*, are reported in Hertz and quoted to the nearest 0.1 Hz. Carbon-13 NMR spectra were recorded on either a Bruker AVX300 (75 MHz), a Bruker DPX300 (75 MHz) or a Bruker DRX500 (125 MHz) spectrometer as dilute solutions in deuterochloroform on a broad band decoupled mode. Chemical shifts are referenced to residual protonated solvent (δ_C=77.0 for $CDCl_3$) and are quoted in parts per million (ppm). Mass spectra were recorded on either a Micromass GCT Premier or a Waters Micromass LCT Premier spectrometer using electron ionisation (EI) at 70 eV or electrospray (ES) techniques, respectively. Microanalytical data were obtained on a Perkin Elmer series II CHNS/O 2400 analyser by the Analytical Services and Environmental Projects unit (ASEP) operating within the School of Chemistry and Chemical Engineering at Queen's University Belfast.

All reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated aluminium plates, which were visualised with ultraviolet light and then developed with basic potassium permanganate. Flash chromatography was performed on either Fluorochem silica gel 60 or Davisil silica gel 60 as the stationary phase and the solvents employed were of analytical grade. Radial chromatography was performed using a Chromatotron 7924T using a glass plate prepared with a 4 mm layer of Merck 7749 grade silica gel with binder and fluorescent indicator.

Unless stated otherwise, all commercially available reagents were used as received. When necessary, commonly used organic solvents were dried prior to use. Tetrahydrofuran (THF), diethyl ether, toluene and benzene were distilled from sodium benzophenone ketyl or dried by passing through towers of activated alumina. Dichloromethane was distilled from calcium hydride. Acetone was distilled from potassium carbonate. Triethylamine and

diisopropylamine were distilled from potassium hydroxide. Solvents were removed on a Büchi rotary evaporator using water aspirator pressure. Brine refers to a saturated aqueous solution of sodium chloride. Petroleum ether refers to light petroleum ether boiling in the range 40–60 °C. Where necessary, reactions requiring anhydrous conditions were performed under an atmosphere of argon in oven dried apparatus.

*4.1.1. (Z)-3-Iodoacrylic acid methyl ester (**6**).*[7] Methyl propiolate (**5**) (4.9 mL, 59.0 mmol, 1 equiv) was added to a solution of sodium iodide (13.27 g, 88.5 mmol, 1.5 equiv) in acetic acid (35 mL, 1.7 M) at room temperature and then stirred at 70 °C for 16 h. The mixture was cooled to room temperature, diluted with water (60 mL) and diethyl ether (60 mL), and then the separated aqueous phase was extracted with diethyl ether (2×30 mL). The combined organic extracts were neutralised with a 3 M aqueous solution of potassium hydroxide, washed with brine (40 mL), and then dried over $MgSO_4$, filtered and concentrated in vacuo to leave the vinyl iodide **6** (12.50 g, quantitative) as a yellow oil; (Found: C, 22.5; H, 2.4. $C_4H_5O_2I$ requires C, 22.6; H, 2.4%); ν_{max} (film)/cm^{-1} 3064, 2950, 2841, 1729, 1598 and 808; δ_H (300 MHz, $CDCl_3$) 7.47 (1H, d, *J* 8.8, I*H*C=CH), 6.92 (1H, d, *J* 8.8, IHC=C*H*), 3.78 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.0, 129.5, 95.1, 51.6.

*4.1.2. (Z)-5-Trimethylsilanylpent-2-en-4-ynoic acid methyl ester (**7**).*[8] A solution of the vinyl iodide **6** (12.0 g, 57 mmol, 1 equiv) in THF (140 mL, 0.4 M) was sparged with argon over 20 min and then $PdCl_2(PPh_3)_2$ (0.39 g, 0.56 mmol, 0.01 equiv), CuI (0.10 g, 0.56 mmol, 0.01 equiv) and triethylamine (15.5 mL, 0.11 mol, 2 equiv) were sequentially added at 0 °C, followed immediately by trimethylsilylacetylene (7.8 mL, 56 mmol, 1 equiv). The stirred reaction mixture was allowed to warm to room temperature over 16 h and then filtered through silica and washed with diethyl ether. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica using 10% ethyl acetate in petroleum ether as eluent to give the enyne ester (*Z*)-**7** (10.31 g, quantitative) as a yellow oil; (Found: C, 59.2; H, 8.0. $C_9H_{14}O_2Si$ requires C, 59.3; H, 7.7); R_f (10% ethyl acetate/petroleum ether) 0.63; ν_{max} (film)/cm^{-1} 2959, 2901, 2150, 1718 and 1608; δ_H (300 MHz, $CDCl_3$) 6.16 (1H, d, *J* 11.6, MeOOCCH=C*H*), 6.10 (1H, d, *J* 11.6, MeOOCC*H*=CH), 3.77 (3H, s, OCH_3), 0.24 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 165.0, 129.1, 122.8, 108.3, 100.7, 51.4, −0.4.

*4.1.3. (Z)-5-Pent-2-en-4-ynoic acid methyl ester (**8**).*[8] Tetrabutylammonium fluoride trihydrate (3.44 g, 13.0 mmol, 1.5 equiv) was added to a stirred solution of the TMS-protected alkyne **7** (1.60 g, 8.8 mmol, 1 equiv) in THF (60 mL, 0.15 M) at 0 °C. The reaction mixture was allowed to warm to room temperature over 3 h, and then diluted with a saturated aqueous solution of ammonium chloride (30 mL) and diethyl ether (30 mL). The separated aqueous phase was extracted with diethyl ether (3×30 mL) and the combined organic extracts were washed with brine (50 mL), and then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 50% diethyl ether in pentane as eluent to give the enyne ester **8** (0.70 g, 73%) as a yellow oil; R_f (50% diethyl ether/petroleum ether) 0.45; ν_{max} (film)/cm^{-1} 2954, 2098, 1729 and 1615; δ_H (300 MHz, $CDCl_3$) 6.20 (1H, dd, *J* 11.6 and 0.8, CH=C*H*COOCH$_3$), 6.12 (1H, dd, *J* 11.6 and 2.5, C*H*=CHCOOCH$_3$), 3.76 (3H, s, COOCH_3), 3.61 (1H, dd, *J* 2.5 and 0.8, *H*C≡C); δ_C (75 MHz, $CDCl_3$) 164.7, 130.3, 122.1, 89.2, 79.4, 51.5.

*4.1.4. (Z)-5-Iodopent-2-en-4-ynoic acid ethyl ester (**9**).* A solution of silver nitrate (2.05 g, 12 mmol, 1.1 equiv) in a 1:1 mixture of ethanol and water (40 mL, 0.3 M) was added slowly to a stirred solution of the TMS-protected alkyne **7** (2.00 g, 11 mmol, 1 equiv) in ethanol (55 mL, 0.2 M). The reaction mixture was stirred for 30 min, and then filtered and washed with water. The solid residue was dissolved in dichloromethane (55 mL, 0.2 M), and a saturated solution of iodine in dichloromethane (100 mL) was added and the mixture was stirred for 5 min. The resulting pink coloured mixture was filtered, successively washed with a saturated aqueous solution of sodium thiosulfate (40 mL) and water (40 mL), and then dried over $MgSO_4$, filtered, and concentrated in vacuo to leave the *iodoalkyne* **9** (1.60 g, 68%) as a brown solid; mp 70–72 °C (petroleum ether); ν_{max} (film)/cm^{-1} 2952, 2152, 1715, 1601 and 979; δ_H (300 MHz, $CDCl_3$) 6.31 (1H, d, *J* 11.4, C*H*=CHCOOMe), 6.10 (1H, d, *J* 11.4, CH=C*H*COOMe), 3.77 (3H, s, COOCH_3); δ_C (75 MHz, $CDCl_3$) 164.7, 130.4, 122.9, 90.7, 51.6, 20.9; *m*/*z* (EI) 235.9352 (M^+, 100%, $C_6H_5O_2I$ requires 235.9334).

*4.1.5. (Z)-5-Trimethylsilanylpent-2-en-4-yn-1-ol (**10**).*[10a] A solution of diisobutylaluminium hydride (1.0 M) in hexanes (77 mL, 77 mmol, 2 equiv) was added dropwise to a solution of the ester **7** (7.00 g, 38 mmol, 1 equiv) in dichloromethane (190 mL, 0.2 M) at −78 °C and stirred for 4 h. The reaction mixture was quenched with a 1 M aqueous solution of hydrochloric acid (22 mL) and then allowed to warm to room temperature. The separated aqueous phase was extracted with dichloromethane (3×40 mL), and the combined organic extracts were then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 10% ethyl acetate in petroleum ether as eluent to give the alcohol **10** (5.60 g, 96%) as a yellow oil; R_f (10% ethyl acetate/petroleum ether) 0.17; ν_{max} (film)/cm^{-1} 3337, 2961, 2900, 2148 and 1612; δ_H (300 MHz, $CDCl_3$) 6.09 (1H, dt, *J* 11.0 and 6.3, CH=C*H*CH$_2$), 5.58 (1H, dt, *J* 11.0 and 1.5, C*H*=CHCH$_2$), 4.40 (2H, dd, *J* 6.3 and 1.5, CH$_2$OH), 1.97 (1H, br s, O*H*), 0.18 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 142.7, 110.4, 100.8, 100.5, 60.9, −0.1.

*4.1.6. (Z)-2-Penten-4-yn-1-ol (**11**).*[10b] Tetrabutylammonium fluoride trihydrate (10.19 g, 39 mmol, 3 equiv) was added to a stirred solution of the TMS-protected alkyne **10** (2.00 g, 13 mmol, 1 equiv) in THF (86 mL, 0.15 M) at 0 °C. The reaction mixture was allowed to warm to room temperature over 3 h, and then diluted with a saturated aqueous solution of ammonium chloride (50 mL) and diethyl ether (50 mL). The separated organic layer was washed with brine (40 mL), and then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 35% diethyl ether in pentane as eluent to give the enyne alcohol **11** (1.00 g, 95%) as a yellow oil; R_f (50% diethyl ether/petroleum ether) 0.30; ν_{max}(film)/cm^{-1} 3294, 3035, 2930, 2872, 2095 and 1653; δ_H (300 MHz, $CDCl_3$) 6.17 (1H, dt, *J* 11.0 and 6.3, CH=C*H*CH$_2$), 5.57 (1H, dt, *J* 11.0 and 1.0, C*H*=CHCH$_2$), 4.41 (2H, dd, *J* 6.3 and 1.0, CH$_2$OH), 3.17 (1H, s, C≡C*H*), 1.82 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 143.5, 109.5, 83.2, 79.2, 60.8.

*4.1.7. (Z)-((E)-2-Methylbut-2-enoyloxy)pent-2-en-4-ynyl ester (**12**).* Dicyclohexylcarbodiimide (0.55 g, 2.7 mmol, 1.1 equiv) and *N*,*N*-dimethylaminopyridine (59 mg, 0.50 mmol, 0.2 equiv) were added to a stirred solution of tiglic acid (0.29 g, 2.7 mmol, 1.1 equiv) in dichloromethane (11 mL, 0.15 M) at 0 °C. The reaction mixture was stirred for 30 min and then a solution of the alcohol **11** (0.20 g, 2.4 mmol, 1 equiv) in dichloromethane (10 mL, 0.25 M) was added dropwise. The mixture was allowed to warm to room temperature over 16 h, diluted with diethyl ether (20 mL), and then sequentially washed with a saturated aqueous solution of NH_4Cl (10 mL), a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to leave an inseparable 13:1 mixture of the *tiglate esters* (*Z*)-**12** and (*E*)-**20** (0.40 g, 90%) as a yellow oil; ν_{max} (film)/cm^{-1} 2931, 2857, 2119, 1713 and 1652; data corresponding to the major isomer (*Z*)-**12**:

δ_H (300 MHz, $CDCl_3$) 6.87 (1H, qq, *J* 7.1 and 1.4, C(CH_3)=C*H*(CH_3)), 6.10 (1H, ddt, *J* 11.0, 0.8 and 6.5, CH=C*H*CH_2), 5.64 (1H, ddt, *J* 11.0, 2.3 and 1.5, C*H*=CHCH_2), 4.89 (2H, dd, *J* 6.5 and 1.4, CH_2O), 3.20 (1H, dd, *J* 2.3 and 0.3, *H*C≡C), 1.82 (3H, q, *J* 1.2, C(CH_3)=CH(CH_3)), 1.78 (3H, dq, *J* 7.1 and 1.1, (CH_3)=CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 167.7, 138.7, 137.6, 128.3, 111.4, 83.9, 78.7, 62.1, 14.3, 11.9; *m*/*z* (EI) 164.0834 (M^+, 80%, $C_{10}H_{12}O_2$ requires 164.0837).

*4.1.8. (E)-3-Iodoacrylic acid methyl ester (**13**).*[12] A solution of hydriodic acid in water (57% v/v, 2 mL, 0.15 equiv) was added to a solution of the vinyl iodide (*Z*)-**6** (25.00 g, 0.12 mol, 1 equiv) in benzene (65 mL, 1.8 M) and the reaction mixture was stirred at 80 °C for 3 days. The mixture was cooled to room temperature, and then diluted with diethyl ether (60 mL) and a saturated aqueous solution of sodium thiosulfate (20 mL). The separated aqueous phase was extracted with diethyl ether (3×30 mL) and the combined organic extracts were then dried over $MgSO_4$, filtered and concentrated in vacuo to leave the vinyl iodide (*E*)-**13** (25.0 g, quantitative) as a colourless solid; mp 48–50 °C (lit.[11a] 41–44 °C) (hexane); ν_{max} (film)/cm^{-1} 3155, 2954, 1722, 1593 and 742; δ_H (300 MHz, $CDCl_3$) 7.89 (1H, d, *J* 14.8, I*H*C=C), 6.88 (1H, d, *J* 14.8, IHC=C*H*), 3.75 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 164.6, 136.1, 99.6, 51.9.

*4.1.9. (E)-5-Trimethylsilanylpent-2-en-4-ynoic acid methyl ester (**14**).* A solution of the vinyl iodide **13** (10.0 g, 47 mmol, 1 equiv) in THF (120 mL, 0.4 M) was sparged with argon over 20 min and then $PdCl_2(PPh_3)_2$ (0.32 g, 0.47 mmol, 0.01 equiv), CuI (89 mg, 0.47 mmol, 0.01 equiv) and triethylamine (13 mL, 94 mmol, 2 equiv) were sequentially added at 0 °C, followed immediately by trimethylsilylacetylene (6.6 mL, 47 mmol, 1 equiv). The stirred reaction mixture was allowed to warm to room temperature over 16 h and then filtered through silica and washed with diethyl ether. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica using 5% ethyl acetate in petroleum ether as eluent to give the *enyne ester* (*Z*)-**14** (8.50 g, quantitative) as a yellow oil; R_f (5% ethyl acetate/petroleum ether) 0.43; ν_{max} (film)/cm^{-1} 2957, 2255, 1721 and 1619; δ_H (300 MHz, $CDCl_3$) 6.74 (1H, d, *J* 15.9, MeOOCCH=C*H*), 6.24 (1H, d, *J* 15.9, MeOOCC*H*=CH), 3.73 (3H, s, OCH_3), 0.21 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 166.2, 130.7, 125.1, 105.7, 101.2, 51.9, 0.3; *m*/*z* (EI) 182.0760 (M^+, 20%, $C_9H_{14}O_2Si$ requires 182.0763).

*4.1.10. (E)-5-Pent-2-en-4-ynoic acid methyl ester (**15**).* Tetrabutylammonium fluoride trihydrate (1.29 g, 4.9 mmol, 1.5 equiv) was added to a stirred solution of the TMS-protected alkyne **14** (0.60 g, 3.3 mmol, 1 equiv) in THF (22 mL, 0.15 M) at 0 °C. The reaction mixture was allowed to warm to room temperature over 3 h, and then diluted with a saturated aqueous solution of ammonium chloride (15 mL) and diethyl ether (15 mL). The separated aqueous phase was extracted with diethyl ether (3×15 mL) and the combined organic extracts were washed with brine (25 mL), and then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 30% diethyl ether in pentane as eluent to give the *enyne ester* **15** (0.27 g, 74%) as a yellow oil; R_f (50% diethyl ether/petroleum ether) 0.55; ν_{max} (film)/cm^{-1} 2954, 2856, 2106, 1727 and 1621; δ_H (300 MHz, $CDCl_3$) 6.73 (1H, dd, *J* 16.0 and 2.4, C*H*=CHCOOCH_3), 6.32 (1H, d, *J* 16.0, CH=C*H*COOCH_3), 3.77 (3H, s, COOCH_3), 3.35 (1H, d, *J* 2.4, *H*C≡C); δ_C (75 MHz, $CDCl_3$) 165.9, 132.0, 124.2, 85.9, 80.1, 51.9; *m*/*z* (EI) 110.0371 (M^+, 90%, $C_6H_6O_2$ requires 110.0368).

*4.1.11. (E)-5-Iodopent-2-en-4-ynoic acid ethyl ester (**16**).* A solution of silver nitrate (9.73 g, 57.0 mmol, 1 equiv) in a 1:1 mixture of ethanol and water (190 mL, 0.3 M) was added slowly to a stirred solution of the TMS-protected alkyne **14** (9.50 g, 52.0 mmol, 1 equiv) in ethanol (250 mL, 0.2 M). The reaction mixture was stirred for 30 min, and then filtered and washed with water. The solid residue was dissolved in dichloromethane (250 mL, 0.2 M), and a saturated solution of iodine in dichloromethane (500 mL) was added and the mixture was stirred for 5 min. The resulting pink coloured mixture was filtered, successively washed with a saturated aqueous solution of sodium thiosulfate (200 mL) and water (200 mL), and then dried over $MgSO_4$, filtered and concentrated in vacuo to leave the *iodoalkyne* **16** (10.5 g, 86%) as a brown solid; mp 62–64 °C (petroleum ether); ν_{max} (film)/cm^{-1} 2951, 2175, 1719, 1617 and 1081; δ_H (300 MHz, $CDCl_3$) 6.87 (1H, d, *J* 15.8, C*H*=CHCOOMe), 6.25 (1H, d, *J* 15.8, CH=C*H*COOMe), 3.78 (3H, s, COOCH_3); δ_C (75 MHz, $CDCl_3$) 165.9, 132.0, 125.1, 91.0, 51.9, 17.7; *m*/*z* (EI) 235.9353 (M^+, 40%, $C_6H_5O_2I$ requires 235.9334).

*4.1.12. (E)-5-Trimethylsilanylpent-2-en-4-yn-1-ol (**17**).*[12] A solution of diisobutylaluminium hydride (1.0 M) in hexanes (11 mL, 11 mmol, 2 equiv) was added dropwise to a solution of the ester **14** (1.00 g, 5.5 mmol, 1 equiv) in dichloromethane (28 mL, 0.2 M) at −78 °C and stirred for 4 h. The reaction mixture was quenched with a 1 M aqueous solution of hydrochloric acid (15 mL) and then allowed to warm to room temperature. The separated aqueous phase was extracted with dichloromethane (3×10 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 10% ethyl acetate in petroleum ether as eluent to give the alcohol **17** (0.72 g, 85%) as a yellow oil; R_f (10% ethyl acetate/petroleum ether) 0.13; ν_{max} (film)/cm^{-1} 3338, 2960, 2900, 2178 and 1631; δ_H (300 MHz, $CDCl_3$) 6.28 (1H, dt, *J* 16.0 and 5.1, CH=C*H*CH_2), 5.74 (1H, dt, *J* 16.0 and 1.9, C*H*=CHCH_2), 4.17 (2H, dd, *J* 5.1 and 1.9, CH_2OH), 2.02 (1H, br s, O*H*), 0.18 (9H, s, Si(CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 142.9, 110.2, 103.0, 95.3, 62.8, 0.0.

*4.1.13. (E)-2-Penten-4-yn-1-ol (**18**).*[23] A 2.5 M aqueous solution of NaOH (3.2 mL, 8.1 mmol, 2.5 equiv) was added to a stirred solution of the TMS-protected alkyne **17** (0.50 g, 3.2 mmol, 1 equiv) in methanol (13 mL, 0.25 M) at −10 °C and stirred for 2 h. The solution was allowed to warm to room temperature and then concentrated in vacuo. The residue was diluted with diethyl ether (10 mL) and washed with brine (3×5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo, and the residue was purified by flash column chromatography on silica using 30% diethyl ether in pentane as eluent to give the enyne alcohol **18** (0.26 g, 97%) as a yellow oil; R_f (50% diethyl ether/petroleum ether) 0.30; ν_{max} (film)/cm^{-1} 3292, 3033, 2919, 2867, 2104 and 1632; δ_H (300 MHz, $CDCl_3$) 6.35 (1H, dt, *J* 16.0 and 4.9, CH=C*H*CH_2), 5.74 (1H, ddt, *J* 16.0, 2.1 and 1.9, C*H*=CHCH_2), 4.18 (2H, dd, *J* 4.8 and 1.6, CH_2OH), 2.90 (1H, ddd, *J* 2.2, 1.5 and 0.6, C≡C*H*), 1.66 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 143.7, 109.1, 81.5, 77.9, 62.6.

*4.1.14. (E)-5-Bromo-2-penten-4-yne-1-ol (**19a**).*[6c] *N*-Bromosuccinimide (0.17 g, 0.98 mmol, 1.2 equiv) and silver nitrate (22 mg, 0.13 mmol, 0.02 equiv) were added to a solution of the alkyne **18** (0.10 g, 0.65 mmol, 1 equiv) in acetone (4.3 mL, 0.15 M) at 0 °C and stirred in the dark for 2 h. The reaction mixture was diluted with cold water (16 mL) and ethyl acetate (10 mL), and then the separated aqueous phase was extracted with ethyl acetate (5×10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo, and then the residue was purified by flash column chromatography on silica using 5% diethyl ether in dichloromethane to give the bromoalkyne **19a** (0.10 g, 84%) as a brown oil; R_f (20% ethyl acetate/petroleum ether) 0.32; ν_{max} (film)/cm^{-1} 3359, 2924, 2868, 2212, 1709 and 806; δ_H (300 MHz, $CDCl_3$) 6.31 (1H, dt, *J* 15.9 and 5.0, CH=C*H*CH_2OH), 5.72 (1H, dt, *J* 15.9 and 1.9, C*H*=CHCH_2OH), 4.20 (2H, dd, *J* 4.9 and 1.8, CH_2OH),

1.65 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 143.5, 109.7, 78.0, 62.5, 49.9.

*4.1.15. (E)-5-Iodo-2-penten-4-yne-1-ol (**19b**).*[6c] The alkyne **18** (0.24 g, 2.9 mmol, 1 equiv) was added to a solution of potassium hydroxide (0.41 g, 7.3 mmol, 2.5 equiv) and iodine (0.81 g, 3.2 mmol, 1.1 equiv) in a 1:1 mixture of methanol and water (7.0 mL, 0.4 M) at room temperature and stirred for 25 h. The reaction mixture was concentrated in vacuo, and the residue was diluted with water (10 mL) and diethyl ether (20 mL). The separated aqueous phase was extracted with diethyl ether (2×20 mL) and the combined organic extracts were then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 40% ethyl acetate in petroleum ether as eluent to give the iodoalkyne **19b** (0.39 g, 64%) as a white solid; mp 62–63 °C (lit.[6c] 61–63 °C) (petroleum ether); R_f (20% ethyl acetate/petroleum ether) 0.31; ν_{max} (film)/cm^{-1} 3350, 2919, 2863, 1548 and 1091; δ_H (300 MHz, $CDCl_3$) 6.29 (1H, dt, *J* 15.9 and 5.0, CH=C*H*CH_2OH), 5.87 (1H, dt, *J* 15.9 and 1.9, C*H*=CHCH_2OH), 4.23 (2H, dd, *J* 5.0 and 1.9, CH_2OH), 1.65 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 144.1, 110.3, 92.0, 62.5, 6.3.

*4.1.16. (E)-((E)-2-Methylbut-2-enoyloxy)pent-2-en-4-ynyl ester (**20**).* Dicyclohexylcarbodiimide (0.68 g, 3.3 mmol, 1.1 equiv) and *N*,*N*-dimethylaminopyridine (73 mg, 0.60 mmol, 0.2 equiv) were added to a stirred solution of tiglic acid (0.33 g, 3.3 mmol, 1.1 equiv) in dichloromethane (22 mL, 0.15 M) at 0 °C. The reaction mixture was stirred for 30 min and then a solution of the alcohol **18** (0.25 g, 3.0 mmol, 1 equiv) in dichloromethane (12 mL, 0.25 M) was added dropwise. The mixture was allowed to warm to room temperature over 16 h, diluted with diethyl ether (30 mL), and then sequentially washed with a saturated aqueous solution of NH_4Cl (15 mL), a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to leave an inseparable 32:1 mixture of the *tiglate esters* (*E*)-**20** and (*Z*)-**12** (0.50 g, 93%) as a yellow oil; ν_{max} (film)/cm^{-1} 2932, 2857, 2119, 1713 and 1652; data corresponding to the major isomer (*E*)-**20**: δ_H (300 MHz, $CDCl_3$) 6.87 (1H, qq, *J* 7.1 and 1.4, C(CH_3)=C*H*(CH_3)), 6.28 (1H, ddt, *J* 16.0, 0.5 and 5.6, CH=C*H*CH_2), 5.72 (1H, ddt, *J* 16.0, 2.2 and 1.8, C*H*=CHCH_2), 4.65 (2H, dd, *J* 5.6 and 1.3, CH_2O), 2.90 (1H, dd, *J* 2.2 and 0.5, *H*C≡C), 1.82 (3H, q, *J* 1.2, C(CH_3)=CH(CH_3)), 1.78 (3H, dq, *J* 7.1 and 1.1, C(CH_3)=CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 167.3, 138.8, 137.8, 128.2, 111.5, 81.0, 78.5, 63.4, 14.3, 11.9; *m*/*z* (EI) 164.0840 (M^+, 70%, $C_{10}H_{12}O_2$ requires 164.0837).

4.2. General procedure for the coupling reaction between terminal alkynes and iodoalkynes

A solution of the iodoalkyne (1 equiv) in THF (0.4 M) was sparged with argon over 20 min and then $PdCl_2(PPh_3)_2$ (0.01 equiv), CuI (0.01 equiv) and either diisopropylamine (2 equiv) or triethylamine (2 equiv) were added sequentially at room temperature, followed immediately by the terminal alkyne (1.1 equiv). The reaction mixture was stirred at room temperature for 16 h and then filtered through silica, washed with diethyl ether, and then concentrated in vacuo.

*4.2.1. (2E,8E)-, (2E,8Z)- and (2Z,8Z)-Deca-2,8-diene-4,6-diyndioic acid dimethyl esters (**21**, **22** and **23**).* Following the general procedure using the iodoalkyne ester (*Z*)-**9** (0.58 g, 2.5 mmol), the enyne ester (*E*)-**15** (0.27 g, 2.5 mmol), $PdCl_2(PPh_3)_2$ (17 mg, 0.02 mmol), CuI (5 mg, 0.02 mmol), diisopropylamine (0.68 mL, 4.9 mmol) and THF (6 mL), the resulting residue was purified by flash column chromatography on silica using 5% ethyl acetate in petroleum ether as eluent to give: (i) the dimethyl ester (*E*,*E*)-**21** (0.12 g, 45%) (eluted first) as a colourless solid; mp 105–107 °C (lit.[14a] 104.5–107.5 °C) (petroleum ether); R_f (20% ethyl acetate/petroleum ether) 0.25; ν_{max} (film/cm^{-1}) 2954, 2254, 1716 and 1609; δ_H (300 MHz, $CDCl_3$) 6.82 (2H, d, *J* 16.1, C*H*=CHCOOMe), 6.38 (2H, d, *J* 16.1, CH=C*H*COOMe), 3.78 (6H, s, COOCH_3); δ_C (75 MHz, $CDCl_3$) 165.6, 133.5, 123.3, 81.2, 81.1, 52.1; *m*/*z* (EI) 218.0564 (M^+, 100%, $C_{12}H_{10}O_4$ requires 218.0579); (ii) the dimethyl ester (*E*,*Z*)-**22** (0.13 g, 25%) (eluted second) as a colourless solid; mp 77–79 °C (lit.[15b] 76–78 °C) (petroleum ether); R_f (20% ethyl acetate/petroleum ether) 0.20; ν_{max} (film/cm^{-1}) 2952, 2130, 1734, 1716 and 1610; δ_H (300 MHz, $CDCl_3$) 6.84 (1H, dd, *J* 15.8 and 0.9, C*H*=CHCOOMe), 6.37 (1H, d, *J* 15.8, CH=C*H*COOMe), 6.31 (1H, d, *J* 11.4, C*H*=CHCOOMe), 6.24 (1H, dd, *J* 11.4 and 0.9, CH=C*H*COOMe), 3.79 (3H, s, COOCH_3), 3.78 (3H, s, COOCH_3); δ_C (75 MHz, $CDCl_3$) 165.7, 164.5, 133.1, 132.3, 123.6, 121.3, 84.2, 82.1, 81.7, 80.7, 52.1, 51.8; *m*/*z* (EI) 218.0569 (M^+, 70%, $C_{12}H_{10}O_4$ requires 218.0579); and (iii) the *dimethyl ester* (*Z*,*Z*)-**23** (50 mg, 19%) (eluted third) as a colourless solid; mp 104–106 °C (petroleum ether); R_f (20% ethyl acetate/petroleum ether) 0.18; ν_{max} (film/cm^{-1}) 3092, 2948, 2121, 1718 and 1599; δ_H (300 MHz, $CDCl_3$) 6.27 (4H, s, C*H*=C*H*$COOCH_3$), 3.78 (6H, s, COOCH_3); δ_C (75 MHz, $CDCl_3$) 164.4, 131.7, 121.4, 84.5, 81.7, 51.7; *m*/*z* (ES) 241.0488 (M^++Na, 70%, $C_{12}H_{10}O_4Na$ requires 241.0477).

*4.2.2. (2E,8E)-, (2E,8Z)- and (2Z,8Z)-Deca-2,8-diene-4,6-diyne-1,10-diols (**24**, **25** and **26**).* Following the general procedure using the iodoalkyne alcohol (*E*)-**19b** (0.50 g, 2.4 mmol), the terminal alkyne (*Z*)-**11** (0.24 g, 2.9 mmol), $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol), CuI (14 mg, 0.07 mmol), triethylamine (0.70 mL, 4.8 mmol) and THF (8 mL), the resulting residue was purified by flash column chromatography on silica using 40% ethyl acetate in petroleum ether as eluent to give an inseparable 2:1:2 mixture of the diols (*E*,*E*)-**24**, (*E*,*Z*)-**25** and (*Z*,*Z*)-**26** (150 mg) in 27%, 12% and 23% yield, respectively, as determined by proton NMR.

*4.2.3. (2E,8E)-10-Hydroxydeca-2,8-diene-4,6-diynoic acid methyl ester (**29**).* Following the general procedure using the iodoalkyne ester (*E*)-**16** (0.70 g, 3.0 mmol), the enyne alcohol (*E*)-**18** (0.24 g, 3.0 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (6 mg, 0.03 mmol), diisopropylamine (0.83 mL, 6.0 mmol) and THF (7.5 mL), the resulting residue was purified by repeated flash column chromatography on silica using 20–50% ethyl acetate in petroleum ether as eluent to give: (i) the dimethyl ester (*E*,*E*)-**21** (0.20 g, 61%) (eluted first); (ii) the hydroxy ester (*E*,*E*)-**29** (0.21 g, 37%) (eluted second) as a colourless solid; mp 78–80 °C (lit.[20] 80–81 °C) (petroleum ether); R_f (30% ethyl acetate/petroleum ether) 0.20; ν_{max} (film/cm^{-1}) 3274, 2919, 2193, 1720 and 1613; δ_H (300 MHz, $CDCl_3$) 6.81 (1H, dd, *J* 15.9 and 0.6, C*H*=C$HCOOCH_3$), 6.48 (1H, dt, *J* 15.9 and 4.6, CH=C*H*CH_2OH), 6.32 (1H, d, *J* 15.9, CH=C*H*$COOCH_3$), 5.90 (1H, dt, *J* 15.9 and 0.8, C*H*=CHCH_2OH), 4.29 (2H, m, CH_2OH), 3.77 (3H, s, COOCH_3), 1.60 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 165.9, 146.8, 132.3, 124.1, 108.3, 83.5, 82.4, 77.6, 73.8, 62.6, 52.0; *m*/*z* (EI) 190.0620 (M^+, 100%, $C_{11}H_{10}O_3$ requires 190.0630); and (iii) the diol (*E*,*E*)-**24** (0.11 g, 45%) (eluted third).

*4.2.4. (2Z,8E)-10-Hydroxydeca-2,8-diene-4,6-diynoic acid methyl ester (**30**).* Following the general procedure using the iodoalkyne ester (*Z*)-**9** (0.44 g, 1.9 mmol), the enyne alcohol (*E*)-**18** (0.15 g, 1.90 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol), diisopropylamine (0.52 mL, 3.8 mmol) and THF (5 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give: (i) the dimethyl ester (*Z*,*Z*)-**23** (83 mg, 40%) (eluted first); (ii) the *hydroxy ester* (*Z*,*E*)-**30** (0.20 g, 55%) (eluted second) as a colourless solid; mp 73–74 °C (petroleum ether); R_f (30% ethyl acetate/petroleum ether) 0.20; ν_{max} (film/cm^{-1}) 3368, 2952, 2195, 1723, 1653 and 1597; δ_H (300 MHz, $CDCl_3$) 6.46 (1H, dt, *J* 15.9 and 4.7, CH=C*H*CH_2OH), 6.23 (2H, s, C*H*=C*H*$COOCH_3$), 5.90 (1H, dt, *J* 15.9

and 2.0, C*H*=CHCH$_2$OH), 4.28 (2H, br s, CH_2OH), 3.79 (3H, s, COOCH_3), 1.68 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 164.8, 146.5, 130.9, 122.1, 108.5, 85.6, 84.6, 77.3, 74.1, 62.6, 51.7; *m*/*z* (EI) 190.0619 (M^+, 50%, $C_{11}H_{10}O_3$ requires 190.0630); and the diol (*E*,*E*)-**24** (42 mg, 27%) (eluted third).

*4.2.5. (2E,8Z)-10-Hydroxydeca-2,8-diene-4,6-diynoic acid methyl ester (**31**).* Following the general procedure using the iodoalkyne ester (*E*)-**16** (0.70 g, 3.0 mmol), the enyne alcohol (*Z*)-**11** (0.24 g, 3.0 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (6 mg, 0.03 mmol), diisopropylamine (0.83 mL, 6.0 mmol) and THF (7.5 mL), the resulting residue was purified by repeated flash column chromatography on silica using 20–30% ethyl acetate in petroleum ether as eluent to give: (i) the dimethyl ester (*E*,*E*)-**21** (0.16 g, 49%) (eluted first); (ii) a 19:1 mixture of the hydroxy esters (*E*,*Z*)-**31** and (*E*,*E*)-**29** (0.10 g, 18%) (eluted second) as a colourless solid; mp 37–38 °C (lit.[21] 38 °C) (petroleum ether); R_f (30% ethyl acetate/petroleum ether) 0.20; ν_{max} (film/cm^{-1}) 3416, 2952, 2201, 1721 and 1613; data corresponding to the major isomer (*E*,*Z*)-**31**: δ_H (300 MHz, $CDCl_3$) 6.81 (1H, dd, *J* 16.0 and 1.1, C*H*=CHCOOCH$_3$), 6.33 (1H, d, *J* 15.8, CH=C*H*COOCH$_3$), 6.31 (1H, dt, *J* 11.1 and 6.4, CH=C*H*CH$_2$OH), 5.68 (1H, ddt, *J* 11.0, 1.3 and 1.1, C*H*=CHCH$_2$OH), 4.42 (2H, dd, *J* 6.4 and 1.1, CH_2OH), 3.76 (3H, s, COOCH_3), 1.95 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 165.8, 146.9, 132.5, 123.9, 108.8, 81.9, 80.9, 79.1, 78.6, 61.1, 52.0; *m*/*z* (EI) 190.0625 (M^+, 100%, $C_{11}H_{10}O_3$ requires 190.0630); and (iii) the diol (*Z*,*Z*)-**26** (0.10 g, 41%) (eluted third).

*4.2.6. (2Z,8Z)-10-Hydroxydeca-2,8-diene-4,6-diynoic acid methyl ester (**32**).* Following the general procedure using the iodoalkyne ester (*Z*)-**9** (1.18 g, 5.0 mmol), the enyne alcohol (*Z*)-**11** (0.41 g, 5.0 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), CuI (9 mg, 0.05 mmol), diisopropylamine (1.39 mL, 10 mmol) and THF (12.5 mL), the resulting residue was purified by flash column chromatography on silica using 40% ethyl acetate in petroleum ether as eluent to give: (i) the dimethyl ester (*Z*,*Z*)-**23** (0.47 g, 86%) (eluted first); (ii) an 8:1 mixture of the hydroxy esters (*Z*,*Z*)-**32** and (*Z*,*E*)-**30** (0.12 g, 13%) (eluted second) as a colourless solid; mp 47–48 °C (lit.[21] 48 °C) (petroleum ether); R_f (30% ethyl acetate/petroleum ether) 0.20; ν_{max} (film/cm^{-1}) 3422, 2951, 2198, 1718 and 1606; data corresponding to the major isomer (*Z*,*Z*)-**32**: δ_H (300 MHz, $CDCl_3$) 6.28 (1H, dt, *J* 11.0 and 6.4, CH=C*H*CH$_2$OH), 6.23 (2H, s, C*H*=C*H*COOCH$_3$), 5.68 (1H, dt, *J* 11.0 and 1.3, C*H*=CHCH$_2$OH), 4.41 (2H, dd, *J* 6.3 and 0.9, CH_2OH), 3.70 (3H, s, COOCH_3), 2.20 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 164.7, 146.5, 131.1, 121.9, 108.9, 85.0, 81.9, 78.8, 78.6, 61.1, 51.7; *m*/*z* (EI) 190.0626 (M^+, 100%, $C_{11}H_{10}O_3$ requires 190.0630); and (iii) the diol (*Z*,*Z*)-**26** (0.16 g, 40%) (eluted third).

4.3. General procedure for the reduction of the dimethyl esters 21–23

A solution of diisobutylaluminium hydride (1.0 M) in hexanes (4 equiv) was added dropwise to a solution of the dimethyl ester (1 equiv) in dichloromethane (0.2 M) at −78 °C and stirred for 4 h. The reaction mixture was quenched with a 1 M aqueous solution of hydrochloric acid and then allowed to warm to room temperature. The separated aqueous phase was extracted with dichloromethane (3×), and the combined organic extracts were then dried over $MgSO_4$, filtered and concentrated in vacuo.

*4.3.1. (2E,8E)-Deca-2,8-diene-4,6-diyne-1,10-diol (**24**).* Following the general procedure using a solution of diisobutylaluminium hydride (1.0 M) in hexanes (3.70 mL, 3.70 mmol), the dimethyl ester (*E*,*E*)-**21** (0.20 g, 0.92 mmol) and dichloromethane (4.6 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give the diol (*E*,*E*)-**24** (0.12 g, 80%) as a colourless solid; mp 157–158 °C (lit.[15a] 157–158 °C) (petroleum ether); R_f (30% ethyl acetate/petroleum ether) 0.13; ν_{max} (film/cm^{-1}) 3189, 2932, 2908, 2871 and 1631; δ_H (300 MHz, $CDCl_3$) 6.41 (2H, dt, *J* 15.7 and 4.8, CH=C*H*CH$_2$OH), 5.85 (2H, dt, *J* 15.6 and 1.6, C*H*=CHCH$_2$OH), 4.26 (4H, dd, *J* 4.8 and 1.2, CH_2OH), 1.56 (2H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 145.3, 109.0, 79.5, 74.5, 62.8; *m*/*z* (EI) 162.0677 (M^+, 100%, $C_{10}H_{10}O_2$ requires 162.0681).

*4.3.2. (2E,8Z)-Deca-2,8-diene-4,6-diyne-1,10-diol (**25**).* Following the general procedure using a solution of diisobutylaluminium hydride (1.0 M) in hexanes (2.75 mL, 2.75 mmol), the dimethyl ester (*E*,*Z*)-**22** (0.15 g, 0.68 mmol) and dichloromethane (3.5 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give the *diol* (*E*,*Z*)-**25** (0.11 g, quantitative) as a colourless solid; mp 50–52 °C (petroleum ether); R_f (30% ethyl acetate/petroleum ether) 0.08; ν_{max} (film/cm^{-1}) 3367, 3306, 2920, 2903, 2839, 2202 and 1627; δ_H (300 MHz, $CDCl_3$) 6.42 (1H, dt, *J* 15.8 and 5.0, CH=C*H*CH$_2$OH), 6.23 (1H, dt, *J* 11.1 and 6.4, CH=C*H*CH$_2$OH), 5.86 (1H, ddt, *J* 16.1, 2.0 and 0.9, C*H*=CHCH$_2$OH), 5.66 (1H, ddt, *J* 11.1, 1.5 and 0.9, C*H*=CHCH$_2$OH), 4.41 (2H, dd, *J* 6.4 and 1.5, CH_2OH), 4.25 (2H, dd, *J* 5.0 and 2.0, CH_2OH), 2.08 (2H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 145.7, 145.2, 109.5, 108.7, 81.1, 79.5, 79.4, 74.0, 62.6, 61.1; *m*/*z* (EI) 162.0671 (M^+, 100%, $C_{10}H_{10}O_2$ requires 162.0681).

*4.3.3. (2Z,8Z)-Deca-2,8-diene-4,6-diyne-1,10-diol (**26**).* A solution of diisobutylaluminium hydride (1.0 M) in hexanes (5.1 mL, 51 mmol, 4 equiv) was added dropwise to a solution of the dimethyl ester (*Z*,*Z*)-**23** (0.28 g, 1.3 mmol, 1 equiv) in dichloromethane (6.5 mL, 0.2 M) at −78 °C and stirred for 4 h. The reaction mixture was quenched with a 1 M aqueous solution of hydrochloric acid (6 mL) and then allowed to warm to room temperature. The separated aqueous phase was extracted with dichloromethane (3×3 mL), and the combined organic extracts were then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give the diol (*Z*,*Z*)-**26** (0.12 g, 58%) as a colourless solid; mp 62–63 °C (lit.[17d] 62–63 °C) (petroleum ether); R_f (40% ethyl acetate/petroleum ether) 0.25; ν_{max} (film/cm^{-1}) 3304, 2012 and 1608; δ_H (300 MHz, $CDCl_3$) 6.26 (2H, dt, *J* 10.8 and 6.4, CH=C*H*CH$_2$OH), 5.67 (2H, dt, *J* 10.8 and 0.9, C*H*=CHCH$_2$OH), 4.43 (4H, dd, *J* 6.4 and 1.5, CH_2OH), 1.65 (2H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 145.6, 109.1, 78.9, 78.5, 60.8; *m*/*z* (EI) 162.0685 (M^+, 30%, $C_{10}H_{10}O_2$ requires 162.0681).

4.4. General acetylation procedure

Triethylamine (2 equiv) was added to a stirred solution of the diol (1 equiv), acetic anhydride (4 equiv) and *N*,*N*-dimethylaminopyridine (0.2 equiv) in dichloromethane (0.2 M) at room temperature. The reaction mixture was stirred for 3 h and then sequentially washed with water, brine and a saturated aqueous solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo.

*4.4.1. Acetic acid (2E,8E)-10-acetoxydeca-2,8-diene-4,6-diynyl ester (**27**).* Following the general procedure using triethylamine (85 μL, 0.60 mmol), the diol (*E*,*E*)-**24** (50 mg, 0.31 mmol), acetic anhydride (110 μL, 1.2 mmol), *N*,*N*-dimethylaminopyridine (7 mg, 0.1 mmol) and dichloromethane (1.5 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give the bis-acetate (*E*,*E*)-**27** (50 mg, 66%) as a yellow oil; R_f (20% ethyl acetate/petroleum ether) 0.21; ν_{max} (film/cm^{-1}) 2930, 2206, 1737 and 1658; δ_H (300 MHz,

$CDCl_3$) 6.31 (2H, dt, *J* 15.8 and 5.7, CH=C*H*CH_2OAc), 5.82 (2H, dt, *J* 15.6 and 1.5, C*H*=$CHCH_2OAc$), 4.63 (4H, dd, *J* 5.8 and 1.5, CH_2OAc), 2.09 (6H, s, $COCH_3$); δ_C (75 MHz, $CDCl_3$) 170.4, 140.0, 111.8, 79.2, 75.0, 63.6, 20.8; *m*/*z* (EI) 246.0884 (M^+, 100%, $C_{14}H_{14}O_4$ requires 246.0892).

*4.4.2. Acetic acid (2E,8Z)-10-acetoxydeca-2,8-diene-4,6-diynyl ester (**28**).* Following the general procedure using triethylamine (85 μL, 0.60 mmol), the diol (*E*,*Z*)-**25** (50 mg, 0.31 mmol), acetic anhydride (110 μL, 1.2 mmol), *N*,*N*-dimethylaminopyridine (7 mg, 0.1 mmol) and dichloromethane (1.5 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give an inseparable 1:2 mixture of the bis-acetates (*E*,*E*)-**27** and (*E*,*Z*)-**28** (60 mg, 80%) as a yellow oil; R_f (20% ethyl acetate/petroleum ether) 0.21; ν_{max} (film/cm^{-1}) 2935, 2210 and 1741; data corresponding to the major isomer (*E*,*Z*)-**28**: δ_H (300 MHz, $CDCl_3$) 6.31 (1H, dt, *J* 15.8 and 5.8, CH=C*H*CH_2OAc), 6.15 (1H, dt, *J* 11.0 and 6.6, CH=C*H*CH_2OAc), 5.81 (1H, dt, *J* 15.6 and 2.2, C*H*=$CHCH_2OAc$), 5.73 (1H, dt, *J* 11.0 and 1.5, C*H*=$CHCH_2OAc$), 4.82 (2H, dd, *J* 6.6 and 1.5, CH_2OAc), 4.62 (2H, dd, *J* 5.7 and 2.1, CH_2OAc), 2.09 (3H, s, $COCH_3$), 2.07 (3H, s, $COCH_3$); δ_C (75 MHz, $CDCl_3$) 170.9, 170.6, 140.4, 140.2, 111.8, 111.7, 80.8, 80.2, 79.4, 75.2, 63.8, 62.6, 21.0, 21.0; *m*/*z* (EI) 246.0883 (M^+, 20%, $C_{14}H_{14}O_4$ requires 246.0892).

*4.4.3. (2Z,8Z)-10-Acetoxydeca-2,8-diene-4,6-diynoic acid methyl ester (**33**).* Following the general procedure using triethylamine (73 μL, 0.52 mmol), the alcohol **32** (0.10 g, 0.52 mmol), acetic anhydride (100 μL, 1.05 mmol), *N*,*N*-dimethylaminopyridine (13 mg, 0.10 mmol) and dichloromethane (2.6 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give the acetoxy matricaria ester (*Z*,*Z*)-**33** (80 mg, 70%) as a yellow oil; R_f (20% ethyl acetate/petroleum ether) 0.17; ν_{max} (film/cm^{-1}) 2951, 2199, 1740 and 1605; δ_H (300 MHz, $CDCl_3$) 6.23 (2H, s, C*H*=C*H*$COOCH_3$), 6.18 (1H, dt, *J* 11.0 and 6.5, CH=C*H*CH_2OAc), 5.77 (1H, dt, *J* 11.0 and 1.5, C*H*=$CHCH_2OAc$), 4.81 (2H, dd, *J* 6.5 and 1.5, CH_2OAc), 3.77 (3H, s, $COOCH_3$), 2.07 (3H, s, $COCH_3$); δ_C (75 MHz, $CDCl_3$) 170.6, 164.6, 140.8, 131.4, 121.7, 111.2, 84.7, 81.1, 79.6, 78.9, 62.2, 51.7, 20.7; *m*/*z* (EI) 232.0738 (M^+, 100%, $C_{13}H_{12}O_4$ requires 232.0736).

4.5. General procedure for the DCC coupling reaction between the hydroxy matricaria esters and tiglic acid

Dicyclohexylcarbodiimide (1.5 equiv) and *N*,*N*-dimethylaminopyridine (0.4 equiv) were added to a stirred solution of tiglic acid (1.5 equiv) in dichloromethane (0.15 M) at 0 °C. The reaction mixture was stirred for 30 min and then a solution of the alcohol (1 equiv) in dichloromethane (0.25 M) was added dropwise. The mixture was allowed to warm to room temperature over 16 h, diluted with diethyl ether, and then sequentially washed with a saturated aqueous solution of NH_4Cl, a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo.

*4.5.1. (2E,8E)-10-((E)-2-Methylbut-2-enoyloxy)deca-2,8-diene-4,6-diynoic acid methyl ester (**1**).* Following the general procedure using dicyclohexylcarbodiimide (0.16 g, 0.79 mmol, 1.5 equiv), *N*,*N*-dimethylaminopyridine (25 mg, 0.21 mmol, 0.4 equiv), tiglic acid (79 mg, 0.79 mmol, 1.5 equiv), the alcohol (*E*,*E*)-**29** (0.10 g, 0.53 mmol, 1 equiv) and dichloromethane (6.5 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give the *tiglate* (*E*,*E*)-**1** (0.12 g, 79%) as yellow oil; R_f (10% ethyl acetate/petroleum ether) 0.35; ν_{max} (film/cm^{-1}) 2952, 2205, 1722, 1717, 1653 and 1615; δ_H (300 MHz, $CDCl_3$) 6.88 (1H, dq, *J* 7.0 and 1.2, CH_3CH=CCH_3), 6.79 (1H, dd, *J* 15.8 and 0.9, C*H*=$CHCOOCH_3$), 6.40 (1H, dt, *J* 16.0 and 5.3, CH=C*H*CH_2O), 6.32 (1H, d, *J* 15.8, CH=C*H*$COOCH_3$), 5.84 (1H, ddt, *J* 16.0, 1.7 and 0.9, C*H*=$CHCH_2O$), 4.70 (2H, dd, *J* 5.3 and 1.7, CH_2O), 3.76 (3H, s, $COOCH_3$), 1.83 (3H, t, *J* 1.2, CH_3CH=CCH_3), 1.79 (3H, dq, *J* 7.0 and 1.2, CH_3CH=CCH_3); δ_C (75 MHz, $CDCl_3$) 167.2, 165.7, 141.8, 138.2, 132.5, 128.1, 123.9, 110.6, 82.9, 82.2, 77.9, 74.3, 63.3, 52.0, 14.4, 12.0; *m*/*z* (EI) 272.1035 (M^+, 100%, $C_{16}H_{16}O_4$ requires 272.1049).

*4.5.2. (2Z,8E)-10-((E)-2-Methylbut-2-enoyloxy)deca-2,8-diene-4,6-diynoic acid methyl ester (**2**).* Following the general procedure using dicyclohexylcarbodiimide (0.16 g, 0.79 mmol, 1.5 equiv), *N*,*N*-dimethylaminopyridine (25 mg, 0.21 mmol, 0.4 equiv), tiglic acid (79 mg, 0.79 mmol, 1.5 equiv), the alcohol (*Z*,*E*)-**30** (0.10 g, 0.53 mmol, 1 equiv) and dichloromethane (6.5 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give the *tiglate* (*Z*,*E*)-**2** (0.09 g, 60%) as yellow oil; R_f (10% ethyl acetate/petroleum ether) 0.36; ν_{max} (film/cm^{-1}) 2951, 2201, 1717 and 1653; δ_H (300 MHz, $CDCl_3$) 6.89 (1H, dq, *J* 7.1 and 1.3, CH_3CH=CCH_3), 6.39 (1H, dt, *J* 16.0 and 5.5, CH=C*H*CH_2O), 6.23 (2H, s, C*H*=C*H*$COOCH_3$), 5.87 (1H, ddt, *J* 15.8, 1.7 and 0.7, C*H*=$CHCH_2O$), 4.71 (2H, dd, *J* 5.5 and 1.7, CH_2O), 3.77 (3H, s, $COOCH_3$), 1.83 (3H, dq, *J* 1.3 and 1.1, CH_3CH=CCH_3), 1.80 (3H, ddq, *J* 7.1, 1.1 and 0.9, CH_3CH=CCH_3); δ_C (75 MHz, $CDCl_3$) 167.2, 164.6, 141.3, 138.1, 131.2, 128.1, 121.9, 110.9, 85.3, 83.9, 77.5, 74.7, 63.4, 51.7, 14.4, 12.0; *m*/*z* (EI) 272.1043 (M^+, 40%, $C_{16}H_{16}O_4$ requires 272.1049).

*4.5.3. (2E,8Z)-10-((E)-2-Methylbut-2-enoyloxy)deca-2,8-diene-4,6-diynoic acid methyl ester (**3**).* Following the general procedure using dicyclohexylcarbodiimide (95 mg, 0.46 mmol, 1.1 equiv), *N*,*N*-dimethylaminopyridine (10 mg, 0.08 mmol, 0.2 equiv), tiglic acid (46 mg, 0.46 mmol, 1.1 equiv), the alcohol (*E*,*Z*)-**31** (0.08 g, 0.42 mmol, 1 equiv) and dichloromethane (5.0 mL), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give a 10:1 mixture of the *tiglates* (*E*,*Z*)-**3** and (*E*,*E*)-**1** (60 mg, 54%) as yellow oil; R_f (10% ethyl acetate/petroleum ether) 0.33; ν_{max} (film/cm^{-1}) 2952, 2928, 2205, 1714, 1651 and 1610; data corresponding to the major isomer (*E*,*Z*)-**3**: δ_H (300 MHz, $CDCl_3$) 6.88 (1H, dq, *J* 7.1 and 1.3, CH_3CH=CCH_3), 6.80 (1H, dd, *J* 16.0 and 0.9, C*H*=$CHCOOCH_3$), 6.32 (1H, d, *J* 16.0, CH=C*H*$COOCH_3$), 6.24 (1H, dt, *J* 10.9 and 6.4, CH=C*H*CH_2O), 5.75 (1H, ddt, *J* 11.1, 1.5 and 1.1, C*H*=$CHCH_2O$), 4.88 (2H, dd, *J* 6.4 and 1.5, CH_2O), 3.75 (3H, s, $COOCH_3$), 1.82 (3H, dq, *J* 1.3 and 1.1, CH_3CH=CCH_3), 1.78 (3H, ddq, *J* 7.0, 1.1 and 0.9, CH_3CH=CCH_3); δ_C (75 MHz, $CDCl_3$) 167.6, 165.7, 141.9, 138.0, 132.6, 128.1, 123.7, 110.3, 81.8, 80.4, 79.2, 79.2, 62.2, 52.0, 14.3, 12.0; *m*/*z* (EI) 272.1035 (M^+, 70%, $C_{16}H_{16}O_4$ requires 272.1049).

*4.5.4. (2Z,8Z)-10-((E)-2-Methylbut-2-enoyloxy)deca-2,8-diene-4,6-diynoic acid methyl ester (**4**).* Following the general procedure using dicyclohexylcarbodiimide (95 mg, 0.46 mmol, 1.1 equiv), *N*,*N*-dimethylaminopyridine (10 mg, 0.08 mmol, 0.2 equiv), tiglic acid (46 mg, 0.46 mmol, 1.1 equiv), the alcohol (*Z*,*Z*)-**32** (0.08 g, 0.42 mmol, 1 equiv) and dichloromethane (5.0 mL, 0.15 M), the resulting residue was purified by flash column chromatography on silica using 30% ethyl acetate in petroleum ether as eluent to give a 6:1 mixture of the tiglates (*Z*,*Z*)-**4** and (*Z*,*E*)-**2** (40 mg, 36%) as yellow oil; R_f (10% ethyl acetate/petroleum ether) 0.38; ν_{max} (film/cm^{-1}) 2951, 2199, 1712, 1651 and 1606; data corresponding to the major isomer (*Z*,*Z*)-**4**: δ_H (300 MHz, $CDCl_3$) 6.88 (1H, dq, *J* 7.1 and 1.3, CH_3CH=CCH_3), 6.23 (2H, s, C*H*=C*H*$COOCH_3$), 6.22 (1H, dt, *J* 11.0 and 6.4, CH=C*H*CH_2O), 5.77 (1H, dt, *J* 11.1 and 1.1, C*H*=$CHCH_2O$), 4.89 (2H, dd, *J* 6.4 and 1.2, CH_2O), 3.77 (3H, s, $COOCH_3$), 1.82 (3H, q, *J* 1.3, CH_3CH=CCH_3), 1.78 (3H, dq, *J* 7.1 and 1.3, CH_3CH=CCH_3); δ_C

(75 MHz, $CDCl_3$) 167.6, 164.6, 141.4, 138.1, 131.3, 128.2, 121.7, 110.9, 84.9, 81.4, 79.5, 78.8, 62.3, 51.7, 14.3, 12.0; *m*/*z* (EI) 272.1043 (M^+, 40%, $C_{16}H_{16}O_4$ requires 272.1049).

Acknowledgements

We thank the Nuffield Foundation (summer studentship to J.T.) for their support of this work.

References and notes

1. For a review see: Christensen, L. P.; Lam, J. *Phytochemistry* **1991**, *30*, 2453–2476.
2. For a recent review see: Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034–1057.
3. Rose, A. F.; Butt, B. A.; Jermy, T. *Phytochemistry* **1980**, *19*, 563–566.
4. Lu, T.; Cantrell, C. L.; Robbs, S. L.; Franzblau, S. G.; Fischer, N. H. *Planta Med.* **1998**, *64*, 665–667.
5. For some examples see: Bär, B.; Schultze, W. *Planta Med.* **1996**, *62*, 332–335.
6. For some recent examples of polyacetylenes in synthesis see: (a) Oliveira, J. M.; Zeni, G.; Malvestiti, I.; Menezes, P. H. *Tetrahedron Lett.* **2006**, *47*, 8183–8185; (b) Nakai, Y.; Sakakibara, I.; Hirakura, K.; Terabayashi, S.; Takeda, S. *Chem. Pharm. Bull.* **2005**, *53*, 1580–1581; (c) Bellina, F.; Carpita, A.; Mannocci, L.; Rossi, R. *Eur. J. Org. Chem.* **2004**, 2610–2619; (d) Antunes, L. M.; Organ, M. G. *Tetrahedron Lett.* **2003**, *44*, 6805–6808; (e) Shi Shun, A. L. K.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 6810–6813.
7. Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488–2501.
8. For a synthesis of the enynes **7** and **8** using a similar method see: (a) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1993**, *49*, 5225–5236; (b) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 2535–2538.
9. Kobayashi, A.; Kouya, S.-I.; Yamashita, K. *Agric. Biol. Chem.* **1976**, *40*, 2257–2260.
10. For a synthesis of (*Z*)-**11** using a similar sequence of steps see: (a) Waser, J.; González-Gómez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 4249–4252; (b) Hartung, I. V.; Eggert, U.; Haustedt, L. O.; Niess, B.; Schäfer, P. M.; Hoffmann, H. M. R. *Synthesis* **2003**, 1844–1850.
11. (a) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525–2532; (b) Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558–1561.
12. Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921–17937.
13. Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727–729.
14. (a) Bu'Lock, J. D.; Jones, E. R. H.; Turner, W. B. *J. Chem. Soc.* **1957**, 1607–1617; (b) Marvell, E. N.; Seubert, J.; Vogt, G.; Zimmer, G.; Moy, G.; Siegmann, J. R. *Tetrahedron* **1978**, *34*, 1323–1332; (c) Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376–9378; (d) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815–3818; For the synthesis and isolation of **21.** Also see Ref. 15b.
15. (a) Davies, D. G.; Hodge, P.; Yates, P.; Wright, M. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1602–1606; (b) Farrell, I. W.; Thaller, V.; Turner, J. L. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1886–1888; (c) Hearn, M. T. W.; Turner, J. L. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1027–1029; (d) Hearn, M. T. W.; Jones, E. R. H.; Thaller, V.; Turner, J. L. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2335–2336; (e) Thaller, V.; Turner, J. L. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2032–2034; (f) Jones, E. R. H.; Leeming, P. R.; Remers, W. A. *J. Chem. Soc.* **1960**, 2257–2263; (g) Gardner, J. N.; Jones, E. R. H.; Leeming, P. R.; Stephenson, J. S. *J. Chem. Soc.* **1960**, 691–697.
16. The coupling reaction between (*Z*)-**11** and the bromoalkyne (*E*)-**19a** gave an inseparable mixture of the diols (*E*,*E*)-**24**, (*E*,*Z*)-**25** and (*Z*,*Z*)-**26** in 9%, 8%, and 15% yield, respectively.
17. (a) Takahashi, A.; Endo, T.; Nozoe, S. *Chem. Pharm. Bull.* **1992**, *40*, 3181–3184; (b) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555–5557; (c) Cambie, R. C.; Gardner, J. N.; Jones, E. R. H.; Lowe, G.; Read, G. *J. Chem. Soc.* **1963**, 2056–2064; (d) Bell, I.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1958**, 1313–1322.
18. (a) Bohlmann, F.; Fritz, U. *Phytochemistry* **1979**, *18*, 1221–1222; (b) Jente, R.; Bohlmann, F.; Schöneweiss, S. *Phytochemistry* **1979**, *18*, 829–837; (c) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1969**, *102*, 1679–1681.
19. Hiskey, C. F.; Slates, H. L.; Wendler, N. L. *J. Org. Chem.* **1956**, *21*, 429–433.
20. Farrell, I. W.; Keeping, J. W.; Pellatt, M. G.; Thaller, V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2642–2643.
21. Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M. *Phytochemistry* **1979**, *18*, 1519–1521.
22. (a) Lu, T.; Menelaou, M. A.; Vargas, D.; Fronczek, F. R.; Fischer, N. H. *Phytochemistry* **1993**, *32*, 1483–1488; (b) Ichihara, K.-I.; Kawai, T.; Kaji, M.; Noda, M. *Agric. Biol. Chem.* **1976**, *40*, 353–358.
23. The NMR data recorded for the alcohol (*E*)-**18**, which is commercially available (Alfa Aesar GmbH), were consistent with data reported for this compound previously synthesised using a different method. For example see: (a) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826–3827; (b) Yin, N.; Wang, G.; Qian, M.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2916–2920; (c) Holland, D.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1553–1571. Also see Ref. 6a.