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The Preparation of 9-Substituted Δ^5-Octenolides: Synthesis of 8-Deoxy-pseudo-Ascidiatrienolide C

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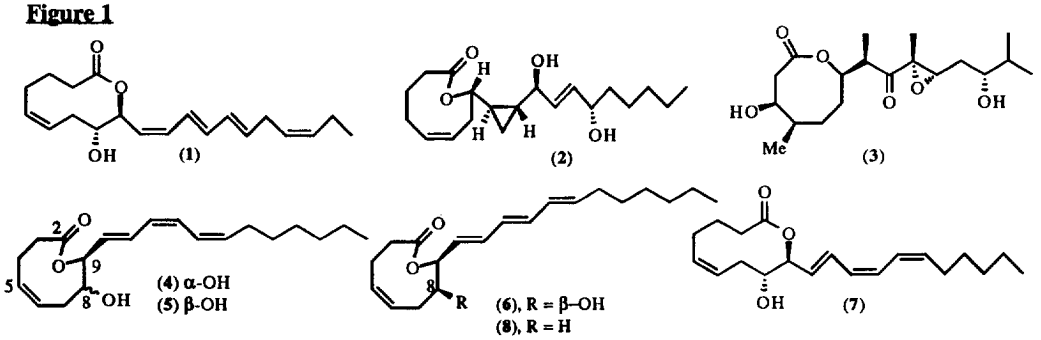
Abstract: Two routes have been explored for the preparation of the title 9 membered lactones. Lactonisation of a hydroxy acid bearing an embryonic unsaturated side chain followed by palladium-catalysed chain extension was shown to be problematic. The preferred procedure, which involved prior formation of the complete carbon skeleton followed by lactonisation using Mukaiyama conditions, was employed to prepare 8-deoxy-pseudo-Ascidiatrienolide C. The efficiency of the lactonisation process is particularly notable.

During the last decade a number of biologically active medium ring lactones have being isolated from marine organisms.[1-6] The Didemnilactone family,[2] for example, are 10 membered lactones [*e.g.* Didemnilactone A (**1**), Figure 1] isolated from the colonial tunicate *Didemnum moseleyi* and shown to exhibit weak binding affinities to leukotriene B_4 receptors. The novel 9 membered Halicholactone family [*e.g.* Neohalicholactone (**2**)] were isolated from the marine sponge *Halichondria okadai*,[3] and intriguingly contain a cyclopropane unit in their side chain. The cytotoxic Octalactins [*e.g.* Octalactin A (**3**)] were isolated from a marine microbe and shown to be based on an 8 membered lactone nucleus.[4] The Ascidiatrienolides A-C were isolated from the marine ascidian *Didemnum candidum*[5] and originally assigned as the 9 membered unsaturated lactone (Δ^5-octenolide) structures (**4**)-(**6**). Recently, however, Holmes *et al.*[6] established unambiguously that Ascidiatrienolide A possesses the 10 membered unsaturated lactone structure (**7**), *i.e.* it is closely related to the Didemnilactone structure, and presumably the other members of the Ascidiatrienolide family are also 10 membered lactones.

Figure 1



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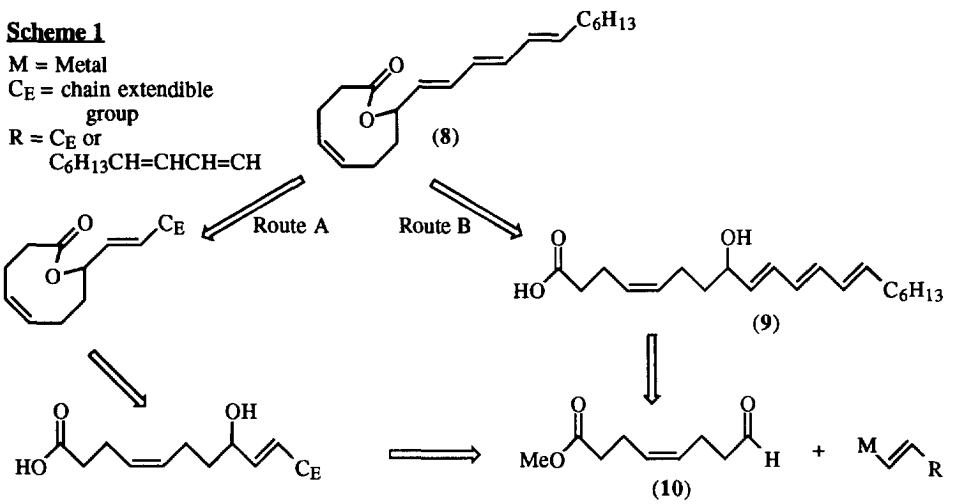
In view of the novelty of the original 9 membered lactone structures for the Ascidiatrienolides, and our interest in medium ring lactone[7] and stereoselective polyene[8] synthesis, we embarked upon synthetic studies in this area. This research, which is reported herein, produced a successful route to 8-deoxy-pseudo-Ascidiatrienolide C (**8**) and provided useful guidelines for the preparation of other unsaturated 9 membered lactones. We have recently reported[7] a route to Δ^5-octenolides based on the Claisen rearrangement but for the present study we investigated the utility of routes involving the lactonisation of unsaturated ω-hydroxy acids. Two approaches were investigated as shown in Scheme 1. Route A involves lactonisation of a substrate bearing an embryonic side chain followed by chain extension. Route B involves prior formation of the complete carbon skeleton followed by lactonisation of the acyclic tetraenoic acid (**9**). Aldehyde (**10**), readily available by the selective ozonolysis of octa-1,5-diene,[9] seemed to be the ideal starting point for both routes.

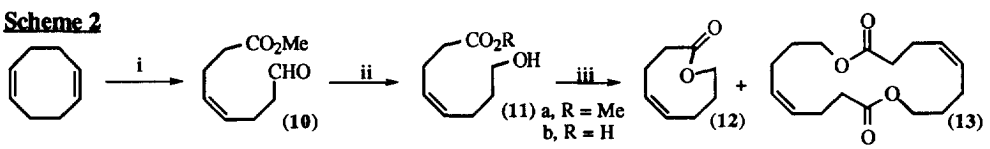
Scheme 1

M = Metal
C_E = chain extendible group
R = C_E or $C_6H_{13}CH{=}CHCH{=}CH$



Prior to the commencement of a comparison of Routes A and B the key lactonisation process was investigated on primary alcohol (**11b**) as shown in Scheme 2. This was thought to be necessary in view of the well-known difficulties associated with lactonisation to give 9 membered rings.[10] We hoped that the positioning of the alkene and its *cis* geometry would aid monolide formation[11] and this proved to be the case.

Scheme 2



Reagents
(i) O_3 (ref. 9)
(ii) a. $NaBH_4$, MeOH (72%)
b. LiOH, aq. THF (86%)
(iii) see Table 1

Table 1 Lactonisation of (**11b**)

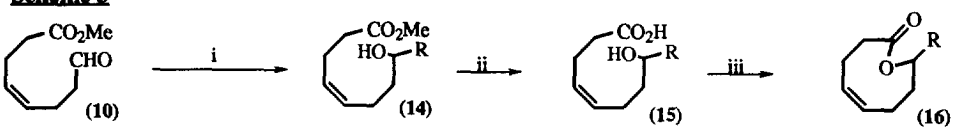
Lactonisation Method	Addition/ Reaction Time (h)	% Monolide (12)	% Diolide (13)
Corey-Nicolaou	8/11	0	0
Yamaguchi	8/18	0	23
Mukaiyama	34/40	27	<1

No cyclisation was observed using the Corey-Nicolaou procedure (2,2'-dipyridyl disulfide/$Ph_3P/AgClO_4$)[12] and the Yamaguchi method (2,4,6-trichlorobenzoyl chloride/DMAP)[13] gave only diolide (**13**). The Mukaiyama procedure (2-chloro-1-methylpyridinium iodide),[14] using a long addition time (34h), produced the required lactone (**12**) with only a trace of the diolide (identified by CI or FAB MS). Although the yield of the Δ^5-lactone (**12**) was only 27% this was unoptimised and yet still compares well with other cyclisations to give unsubstituted nine membered lactones (the only higher yield was reported by Funk *et al.*[11] who employed the Mukaiyama procedure to prepare the isomeric Δ^7-lactone in 41% yield). With this successful result we moved on to investigate the synthetic approaches to 8-deoxy-pseudo-Ascidiatrienolide C (**8**) outlined in Scheme 1.

(a) Lactonisation followed by Homologation (Scheme 1, Route A)

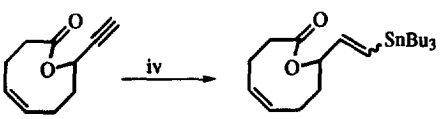
Suitable ω–hydroxy acids (**15a-c**), bearing a two carbon side chain capable of later elaboration, were readily prepared from aldehyde (**10**) by organometallic addition followed by saponification as shown in Scheme 3. The only difficulties were associated with the preparation of the pivotal intermediate, vinylstannane (**15c**). Generation of $LiCH{=}CHSnBu_3$ from bis-1,2-(tributylstannyl)ethene using the butyllithium procedure developed by Corey *et al.*[15] gave the required adduct (**14c**) in poor yield (19%). The use of methyllithium as the transmetallating reagent[16] gave a small increase in the yield of the product but it was eventually found that the diethylaluminium derivative[17] gave the most reproducible and acceptable result (48%). Saponification of the resulting methyl ester (**14c**) surprisingly gave a mixture of two ω–hydroxy acids, namely the desired (**15c**) and the product of destannylation (**15a**) in a ratio of 4:1.[18] Lactonisation of (**15a-c**) under the Mukaiyama conditions, using long addition times, was again successful[19] with excellent yields of (**16a-c**) being obtained. The 78% yield of the 9-ethynyl octenolide (**16b**) is particularly noteworthy (being the highest reported yield for any 9 membered lactone prepared by lactonisation). We therefore attempted to prepare (**16c**) *via* the hydrostannylation of alkyne (**16b**). Unfortunately this resulted in an inseparable 85:15 mixture of (**16c**) and its *cis*-vinylstannane isomer.[20]

Scheme 3



a, R = CH_2=CH- b, R = TMSC≡C- (**14**) or HC≡C- (**15**, **16**) c, R = *E*-$Bu_3SnCH{=}CH$-

Reagents
(i) RM [CH_2=CHMgBr (72%); TMSC≡CLi (66%); *E*-$Bu_3SnCH{=}CHAlEt_2$ (48%)]
(ii) LiOH, aq. THF (68-99%); (**14b**) required prior desilylation using K_2CO_3/MeOH
(iii) Mukaiyama cyclisation [(**16a**), 58%; (**16b**), 78%; (**16c**), 40%]
(iv) Bu_3SnH, AIBN, 80°C [94%; 85:15 mixture of (**16c**) and Z-vinylstannane isomer]



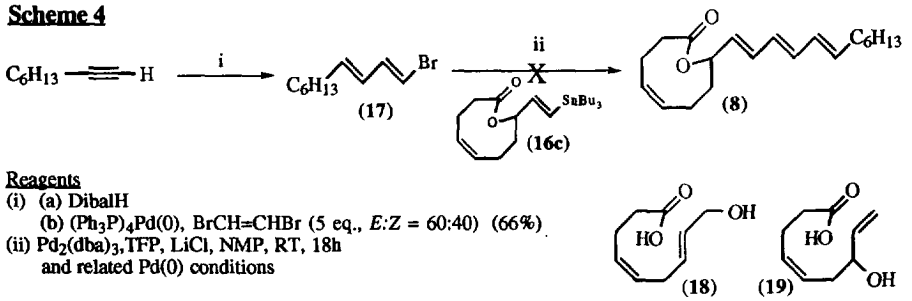
(**16b**) (**16c**) + Z-isomer

We next turned our attention to the elaboration of the polyene side chain (Scheme 4). The palladium catalysed coupling[21] of vinylstannane (**16c**) with a suitable halo diene was explored first. Following the procedure developed by Ratovelomanana and Linstrumelle,[22] dienyl bromide (**17**) was prepared from octyne *via* hydroalumination followed by selective palladium-catalysed cross-coupling with 1,2-dibromoethene. As

iodoalkenes are generally preferred to their bromo counterparts in Stille type cross-coupling reactions[21] we attempted to prepare the iodo analogue of (**17**) by the substitution of 1,2-diiodoethene for the corresponding dibromide. Unexpectedly, however, 1,2-diiodoethene proved inert to the cross-coupling conditions, even when tri-(2-furyl)phosphine (TFP) was used as the palladium ligand with 1-methyl-2-pyrrolidinone (NMP) as solvent.[23]

With lactone (**16c**) and bromide (**17**) in hand, Stille coupling to give the target molecule (**8**) was explored (Scheme 4). Unfortunately, using a range of conditions,[21] including the optimised cross-coupling procedure developed in Route B (see later),[23] no trace of (**8**) was obtained. The starting lactone (**16c**) was consumed but a mixture of polar compounds was isolated. ^{1}H NMR and MS analysis of this crude product indicated the likely production of two isomeric ω–hydroxy acids, possibly (**18**) and (**19**). Presumably the initial η^2-palladium complex rearranges to a more favoured π-allyl system with concomitant lactone ring opening, and hydrolysis of this complex on work-up generates the observed products. The apparent ease with which the 9 membered lactone underwent ring opening indicated that route A was not a viable method for the production of target molecule (**8**) and related compounds. Attention was therefore switched to Scheme 1, Route B in which polyene elaboration was completed prior to lactonisation.

Scheme 4



(b) Homologation followed by lactonisation (Scheme 1, Route B)

The requisite precursors, vinylstannane (**14c**) and dienyl bromide (**17**) were available, and so their coupling was explored (Scheme 5). Several different solvents, catalysts and reaction temperatures were investigated for the production of the conjugated triene (**20**), and the results are collected in Table 2. Using bis(acetonitrile)palladium(II) chloride or tetrakis(triphenylphosphine)palladium(0) as catalysts gave a maximum yield of 38%. There was significant increase in yield, and reduction in reaction time, when tris(dibenzylideneacetone)dipalladium(0) and TFP were employed,[23] however. A further improvement in yield was obtained when the coupling was carried out in the presence of ultra-pure lithium chloride.[23] Under these conditions conjugated triene (**20**) was obtained in 67% yield and was shown by high field ^{1}H and ^{13}C NMR spectroscopy to be stereochemically pure. Using similar conditions (1*Z*)-1-iododecen-3-yne and (1*Z*, 3*Z*)-1-chlorodecadiene were sucessfully coupled with (**14c**) giving the stereochemically pure adducts (**21**) and (**22**) in 60% and 23% yield, respectively. Conjugated triene (**20**) was also formed from alkyne (**23**) as shown in Scheme 5. Hydroboration followed by Suzuki-type[24] coupling of the resulting vinylborane and then desilylation gave (**20**) in 32% overall yield. The Stille approach was therefore preferred in terms of efficiency and ease of operation.

Scheme 5

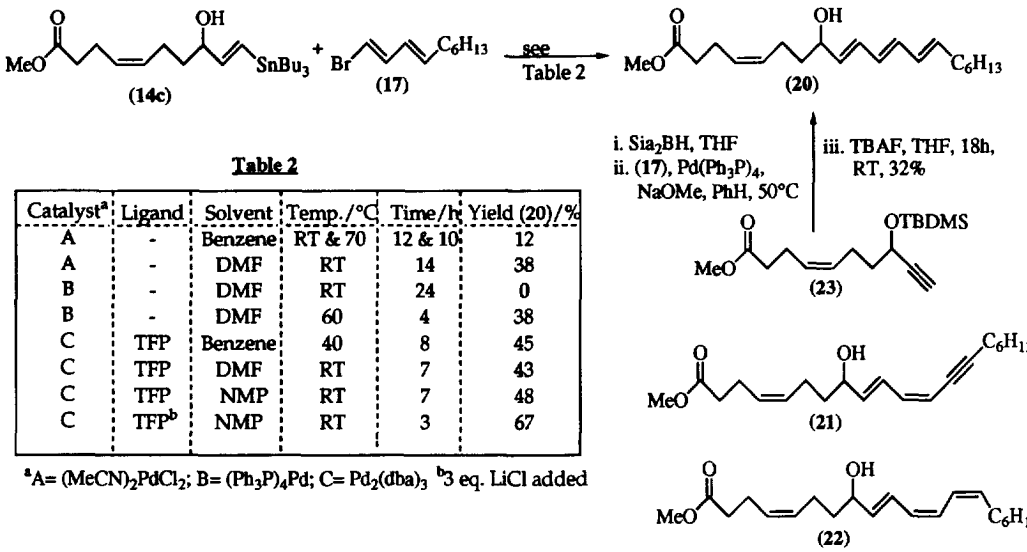


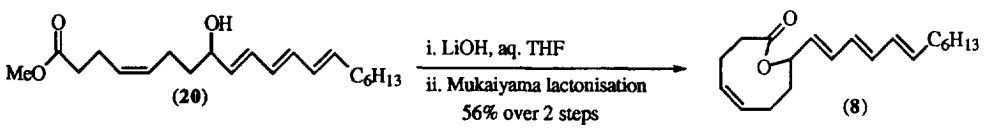
Table 2

Catalyst[a]	Ligand	Solvent	Temp./°C	Time/h	Yield (20)/%
A	-	Benzene	RT & 70	12 & 10	12
A	-	DMF	RT	14	38
B	-	DMF	RT	24	0
B	-	DMF	60	4	38
C	TFP	Benzene	40	8	45
C	TFP	DMF	RT	7	43
C	TFP	NMP	RT	7	48
C	TFP[b]	NMP	RT	3	67

[a]A= $(MeCN)_2PdCl_2$; B= $(Ph_3P)_4Pd$; C= $Pd_2(dba)_3$ [b]3 eq. LiCl added

The saponification and Mukaiyama lactonisation of hydroxy ester (**20**) was attempted next (Scheme 6). We were delighted to find that lactonisation of the crude saponification product, using the normal slow addition conditions (18 h), proceded in 56% overall yield. High field NMR analysis confirmed that (**8**) was formed as a single isomer with the required *E,E,E*-side chain (all three *J* values were discernible at ca. 15Hz; $J_{5,6}$ = 10.5 Hz). The structure was also confirmed by high resolution CI mass spectrometry.

Scheme 6



The efficiency of the Mukaiyama cyclisation process, together with the versatilty of the palladium-catalysed coupling reactions, indicates that the approach shown in Scheme 1, Route B is a potentially valuable method for preparing a range of substituted 9 membered lactones. We are currently applying the strategies and chemistry reported above to the synthesis of a number of complex 9 membered ring targets.

Experimental section

General: ^1H and ^{13}C NMR spectra were recorded on JNM EX-270 and JNM GX-400 in $CDCl_3$ with tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 1720X FT-IR spectrometer as neat liquid films or nujol mulls for solid material. Low resolution EI mass spectra were recorded on a Kratos MS Spectrometer and CI, FAB and high resolution EI mass spectra were recorded on a V.G. Analytical ZAB-IF spectrometer. All solvents were dried by standard methods and organolithium reagents were regularly standardised using the double titration method.[25] Commercially obtained reagents were used without further purification. All reactions were monitored by TLC on aluminium backed Merck 5554 silica gel coated plates. Visualisation of the reaction components was obtained by UV or by

development using potassium permanganate of phosphomolybdic acid solutions. Column chromatography was carried out using Merck 7734 silica gel at ambient pressure or May and Baker Sorbsil™ C60 silica gel for flash column chromatography at increased pressure. Preparative centrifugal chromatography was preformed on a Chromatatron model 7924 using Merck 7749 silica gel.

Methyl 8-hydroxy-4Z-octenoate (11a)

Sodium borohydride (0.548 g, 0.014 mol) was added in small portions to a stirried solution of methyl 8-oxo-4Z-octenoate (**10**) (2.204 g, 13.0 mmol) in methanol (30 ml) at -70 °C. After 2 h the reaction mixture was allowed to warm to RT, ether (100 ml) followed by saturated ammonium chloride solution (30 ml) was added and the organics were washed with brine (2 x 30 ml) and water (20 ml) before drying ($MgSO_4$). Solvent removal under reduced pressure followed by column chromatography (petrol-ethyl acetate, 1:1) gave the *title compound* (**11a**) (1.61 g, 72%) as a colourless oil, (Found: C, 62.75; H, 9.4. $C_9H_{16}O_3$ requires C, 62.77; H, 9.36%); R_f 0.46 (ethyl acetate-methanol, 99.5:0.5); υ_{max} / cm^{-1} 3416, 3009, 2936, 1740 and 1437; δ_H (90 MHz; $CDCl_3$) 1.4-1.9 (2 H, m), 2.0-2.60 (6 H, m), 3.20 (1 H, s, OH), 3.6 (2 H, t, *J* 6.5 Hz), 3.7 (3 H, s,) and 5.3-5.5 (2 H, m); δ_C (22.5 MHz; $CDCl_3$) 22.7, 23.1, 33.9, 36.7, 51.5, 72.4, 128.1, 130.6 and 173.2; *m/z* 172 (M^+, 0.9%).

Representative procedure for ester hydrolysis: 8-Hydroxy-4Z-octenoic acid (11b)

Lithium hydroxide monohydrate (0.74 g, 17.6 mmol) was added to a stirred solution of (**11a**) (0.762 g, 4.4 mmol) in a mixture of THF (60ml), methanol (10 ml) and water (10 ml). After 2 h acidic amberlyst 15 resin (ca. 2 g) was added until pH 4 was attained whereupon the mixture was filtered. The crude product was purified by extraction into aqueous sodium hydroxide solution (40 ml, 1 *M*) followed by acidification using aqueous hydrochloric acid (40 ml, 1 *M*) and re-extraction into ether (2 x 50 ml). Drying ($MgSO_4$) and solvent removal under reduced pressure gave the title compound (**11b**) (0.594 g, 86%) as a viscous, pale yellow oil, R_f 0.05 (ethyl acetate/ methanol, 97:3); υ_{max} / cm^{-1} 3500 and 1711; δ_H (400 MHz; $CDCl_3$) 1.62 (2 H, m), 2.15 (2 H, dt appears as q, *J* 7.5 Hz), 2.34-2.40 (4 H, m), 2.48 (1 H, br s, exchangeable), 3.63 (2 H, t, *J* 6.5 Hz), 5.34-5.47 (2 H, m) and 7.56 (1 H, br s, exchangable); δ_C (22.5 MHz; $CDCl_3$) 22.5, 23.3, 32.0, 34.0, 61.8, 128.0 130.6 and 178.0; *m/z* 158 (M^+, 1%); HRMS (Found: $M+NH_4^+$, 176.1287. $C_8H_{14}O_3$ requires $M+NH_4^+$, 176.128668).

Representative lactonisation procedure : 5Z-Octenolide (12)

Triethylamine (1.24 ml, 8.89 mmol) was slowly added to a stirred solution of freshly prepared (**11b**) (0.234 g, 1.48 mmol) in acetonitrile (25 ml) under an inert atmosphere. After stirring for 1 h, the resulting yellow solution was added with the aid of a mechanically driven syringe pump over a period of 32 h to a solution of 2-chloro-1-methylpyridinium iodide (1.70 g, 6.66 mmol) n acetonitrile (200 ml) heated at reflux. After a further 8 h at reflux the red solution was cooled to RT and the quantity of the solvent was reduced to ca. 5 ml by careful rotary evaporation (ca. 25 mm Hg). Filtration of the resulting thick red mixture through a short silica column (ether-hexane, 1:1) followed by solvent removal and column chromatography (petrol-ether, 9:1)

gave the *title product* (**12**) (0.055 g, 27%) as a colourless liquid, (Found: C, 68.3; H, 8.6. $C_8H_{12}O_2$ requires C, 68.55; H, 8.63%); R_f 0.19 (petrol-ether, 9:1); υ_{max} / cm^{-1} 1747, 1462, 1333, 1242 and 1095; δ_H (270 MHz; $CDCl_3$) 1.76 (1 H, dq, *J* 6 and 6.5 Hz), 1.78 (1 H, dq, *J* 4.5 and 6.5), 2.05 (1 H, t, *J* 8.5 Hz), 2.07 (1 H, dd, *J* 6 and 8.5 Hz), 2.22 (2 H, dd, *J* 4.5 and 7.5 Hz), 2.37 (1 H, t, *J* 8 Hz), 2.38 (1 H, m), 4.24 (2 H, t, *J* 6.5 Hz), 5.41 (1 H, dt, *J* 11 and 8 Hz) and 5.55 (1 H, dt, *J* 11 and 8.5 Hz); δ_C (67.9 MHz; $CDCl_3$) 22.1, 24.4, 27.8, 33.7, 63.1, 126.2, 134.0 and 174.8; *m/z* 141 (M^++H, 9%), 140 (M^+, 100%). Also obtained was *diolide* (**13**) as a colourless liquid (0.002 g, 0.4%), R_f 0.20 (petrol-ether, 9:1); δ_H (270 MHz; $CDCl_3$) spectrum identical to monolide except for C-9 protons [δ 4.24 (2 H, t, *J* 7 Hz) in place of δ 4.16 (2 H, t, *J*7 Hz)]; *m/z* 281 (MH^+, 0.6%), 280 (M^+, 4%); HRMS (Found: M^+, 280.1675. $C_{16}H_{24}O_4$ requires 280.167459).

Methyl 8-hydroxy-4*Z*,9-decadienoate (14a)

Vinylmagnesium bromide in THF (1.35 ml, 1 *M*, 1.35 mmol) was added dropwise to a stirring solution of (**10**) (0.142 g, 0.72 mmol) in ether (30 ml) at -70 °C under an inert atmosphere. After 2 h the reaction was quenched with saturated aqueous ammonium chloride (10 ml), washed with brine (2 x 20 ml) and water (40 ml) before being dried ($MgSO_4$). Solvent removal under reduced pressure followed by column chromatography (petrol-ethyl acetate, 2:1) gave (**14a**) (0.118 g, 72%) as a colourless oil, R_f 0.54 (petrol-ether, 1:1); υ_{max} / cm^{-1} 1723; δ_H (90 MHz; $CDCl_3$) 1.63-1.77 (2 H, m), 1.85 (1 H, br s exchangable), 2.06-2.39 (6 H, m), 3.78 (3 H, s), 4.01-4.21 (1 H, m), 5.11 (1 H, ddd, *J* 1, 2 and 10 Hz), 5.23 (1 H, ddd, *J* 1.5, 2 and 17 Hz), 5.29-5.48 (2 H, m) and 5.90 (1 H, ddd, *J* 6, 10 and 17 Hz); δ_C (22.5 MHz; $CDCl_3$) 22.5, 23.0, 33.9, 36.5, 51.5, 72.5, 114.7, 127.9, 130.6, 140.7 and 178.1.

Methyl 8-hydroxy-10-(trimethylsilyl)-4*Z*-deca-9-ynoate (14b)

Butyllithium in hexane (7.27 ml, 1.47 *M*, 10.69 mmol) was added dropwise to a stirring solution of trimethylsilylacetylene (1.00 g, 10.18 mmol) in THF (20 ml) at -78 °C under an inert atmosphere. The solution was allowed to warm to -30 °C before being re-cooled to -78 °C and added dropwise *via* a cannula to a solution of (**10**) (1.73 g, 10.02 mmol) in THF (10 ml) also at -78 °C. The resulting solution was stirred at this temperature for 1 h before being allowed to warm to RT. Work-up as for (**14a**) and column chromatography (petrol-ether, 3:1) gave the *title compound* (**14b**) as a colourless oil (1.77 g, 66%), (Found: C, 62.4; H, 9.1. $C_{14}H_{24}O_3Si$ requires C, 62.64; H, 9.01%); R_f 0.44 (petrol/ether, 3:1); υ_{max} / cm^{-1} 3442, 2170, 1741 and 844; δ_H (400 MHz; $CDCl_3$) 0.00 (9 H, s), 1.51-1.65 (2 H, m), 2.04-2.10 (2 H, m), 2.19-2.24 (4 H, m), 3.11 (1 H, d, *J* 3 Hz, OH), 3.51 (3 H, s), 4.16-4.21 (1 H, m) and 5.19-5.29 (2 H, m); δ_C (100 MHz; $CDCl_3$) -0.4, 22.4, 22.7, 33.7, 37.1, 51.3, 61.0, 88.0, 106.1, 128.2, 129.9 and 173.4; *m/z* 268 (M^+, 0.2%).

Methyl 8-hydroxy-10-(tributylstannyl)-4*Z*,9*E*-decadienoate (14c)

Methyllithium in ether (0.53 ml, 1.98 *M*, 1.05 mmol) was added dropwise to a stirred solution of bis(tributylstannyl)ethene[15,16] (0.61 g, 1.00 mmol) in THF (10 ml) at -78 °C under an inert atmosphere. After 1 h the solution was warmed to 0 °C for 30 min before being re-cooled to -70 °C. A solution of diethylaluminium chloride in hexane (0.95 ml, 1.00 *M*, 0.95 mmol) was added to the reaction mixture at -70

°C, decolourising the pale yellow solution. After 1 h the organoaluminium solution was added dropwise to a solution of aldehyde (**10**) (0.145 g, 0.85 mmol) in THF (5 ml), again at -78 °C. After a further 1 h the reaction mixture was allowed to warm to RT and quenched sequentially with ice-cold water (3 ml), potassium fluoride (0.3 g, 5.16 mmol) and celite (0.2 g). The mixture was stirred vigorously until the slurry became granular. Extraction of the organics with ether (3 x 15ml), drying ($MgSO_4$) and solvent removal under reduced pressure gave a pale yellow oil, column chromatography of which gave the *title compound* (**14c**) (0.198 g, 48%) as a colourless oil, (Found: C, 56.7; H, 9.4. $C_{23}H_{44}O_3Sn$ requires C, 56.69; H, 9.10%); R_f 0.61 (petrol-ether, 9:2); b.p. (Kugelrohr) 200° C at 1.0 mm Hg; υ_{max} / cm^{-1} 3452, 1743, 1610, 990 and 734; δ_H (400 MHz; $CDCl_3$) 0.89 (9 H, t, *J* 7.5 Hz), 0.87-0.91 (6 H, m), 1.26-1.36 (6 H, m), 1.44-1.52 (6 H, m), 1.58 (2 H, q, *J* 7.5 Hz), 1.80 (1 H, d, *J* 4.5 Hz, OH), 2.13-2.20 (2 H, m), 2.35-2.40 (4 H, m), 3.67 (3 H, s), 4.07 (1 H, m), 5.32-5.40 (1 H, m), 5.44 (1 H, dt, *J* 10.5 and 7 Hz), 6.01 (1 H, dd *J* 5.5 and 19 Hz) and 6.15 (1 H, dd, *J* 1 and 19 Hz); δ_C (22.5 MHz; $CDCl_3$) 9.4, 13.6, 22.7, 23.2, 27.2, 29.0, 34.0, 36.7, 51.5 , 74.7, 127.5, 128.4, 131.0, 150.9 and 173.5; *m/z* 457 (M^+-OMe, 5%), 431 (M^+-Bu, 100%).

8-Hydroxy-4Z-9-decadienoic acid (15a)

Ester (**14a**) (0.997 g, 5.04 mmol) was saponified using the representative procedure for ester hydrolysis to give the (**15a**) (0.63 g, 68%) as a pale yellow viscous oil, R_f 0.05 (ethyl acetate); υ_{max} / cm^{-1} 3396, 1714 and 1656; δ_H (90 MHz; $CDCl_3$) 1.42-1.67 (2 H, m), 2.04-2.37 (6 H, m), 4.10 (1 H, m), 5.11 (1 H, ddd, *J* 1, 2 and 10 Hz), 5.23 (1 H, ddd, *J* 1, 2 and 17 Hz), 5.29-5.48 (2 H, m), 5.90 (1 H, ddd, *J* 6, 10 and 17 Hz) and 6.20-6.50 (2 H, br s); δ_C (22.5 MHz; $CDCl_3$) 22.5, 23.0, 33.9, 36.5, 72.5, 114.7, 127.9, 130.6, 140.7 and 178.1; *m/z* 184 (M^+, 0.3%), 166 (M^+-H_20, 10.6%); HRMS (Found: M+NH_4^+, 202.1443. $C_{10}H_{16}O_3$ requires M+NH_4^+, 202.144319).

8-Hydroxy-4Z-decen-9-ynoic acid (15b)

(a) Potassium carbonate (0.15 g, 1.1 mmol) was added to a stirred solution of silane (**14b**) (2.0 g, 7.45 mmol) in dry methanol (20 ml) at RT. After stirring for 18 h the solvent was removed under reduced pressure and the crude product dissolved in ether. This solution was washed sequentially with aq. sodium hydrogencarbonate (10 ml), brine (10 ml), and water (10 ml) and then dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography (petrol-ether, 3:1) gave *methyl 8-hydroxy-4Z-decen-9-ynoate* (1.23 g, 84%) as a fully characterised colourless oil.

(b) The ester from (a) (0.874 g, 4.46 mmol) was saponified using the representative procedure for ester hydrolysis. Bulb to bulb distillation of the crude product (230 °C at 0.8mmHg) gave the *title compound* (**15b**) (0.810 g, 99%) as a colourless, viscous oil, (Found: C, 66.1; H, 7.9. $C_{10}H_{14}O_3$ requires C, 65.92; H, 7.74%); R_f 0.05 (ethyl acetate); υ_{max} / cm^{-1} 3458, 3293, 2100 and 1711; δ_H (270 MHz; $CDCl_3$) 1.61-1.80 (2 H, m), 2.13-2.21 (2 H, m), 2.31-2.37 (4 H, m), 2.44 (1 H, d, *J* 2 Hz), 4.32 (1 H, dt, *J* 2 and 6.5 Hz), 5.27-5.41 (2 H, m) and 6.71-8.52 (2 H, br s); δ_C (67.9 MHz; $CDCl_3$) 22.9, 23.2, 34.4, 37.4, 61.8, 73.6, 84.9, 128.8, 130.4 and 179.2; *m/z* 195 (M^+-H, 0.2%).

8-Hydroxy-10-(tributylstannyl)-4*Z*,9*E*-decadienoic acid (15c)

Ester (**14c**) (0.473 g, 1.00 mmol) was saponified using the representative procedure for ester hydrolysis to give an inseparable mixture (*ca.* 4:1) of the title compound (**15c**) and (**15a**) (combined weight 0.413 g) as a yellow oil, R_f 0.05 (petrol-ether, 9:2); υ_{max} / cm^{-1} 3377, 1713 and 1645; δ_H (60 MHz; $CDCl_3$) 0.8-1.1 (15 H, m), 1.1-1.9 (12 H, m), 1.9-2.5 (8 H, m), 4.0-4.3 (1 H, m), 5.3-5.6 (2 H, m), 6.0-6.2 (2 H, m) and 8.7 (2 H, br s); *m/z* 473 (M^+, 2%), 455 (M^+-H_2O, 13%); HRMS (Found: M^+, 474.2156. $C_{22}H_{42}O_3Sn$ requires 474.215594).

5*Z*, 10-Decadien-9-olide (16a)

Hydroxy acid (**15a**) (0.463 g, 2.52 mmol) was cyclised using the representative lactonisation procedure to give, after chromatography, the *title compound* (**16a**) (0.243 g, 58%) as a colourless oil, (Found: C, 72.0; H, 8.7. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%); R_f 0.70 (petrol-ether, 9:2); υ_{max} / cm^{-1} 1743, 1650 and 1022; δ_H (270 MHz; $CDCl_3$) 1.67-1.83 (1 H, m), 1.87-2.02 (2 H, m), 2.18-2.44 (4 H, m), 2.55-2.67 (1 H, m), 5.12 (1 H, dt, *J* 10.5 and 1.5 Hz), 5.25 (1 H, dt, *J* 17.5 and 1.5 Hz), 5.32-5.39 (1 H, m), 5.46-5.53 (1 H, m), 5.56 (1 H, dt, *J* 11 and 8 Hz), 5.86 (1 H, ddd, *J* 6, 10.5 and 17.5 Hz); δ_C (67.9 MHz; $CDCl_3$) 21.6, 24.0, 33.0, 33.6, 74.0, 115.0, 126.1, 133.4, 136.6 and 173.8; *m/z* 184 ($M+NH_4^+$, 46%), 167 (MH^+, 100%).

5*Z*-Decen-10-yne-9-olide (16b)

Hydroxy acid (**15b**) (0.928 g, 5.10 mmol) was cyclised using the representative lactonisation procedure to give, after chromatography, the *title compound* (**16b**) (0.653 g, 78%) as a colourless liquid; R_f 0.54 (petrol-ether, 9:2); υ_{max} / cm^{-1} 3291, 2123, 1739 and 1027; δ_H (270 MHz; $CDCl_3$) 1.86-1.97 (1 H, m), 1.99-2.10 (2 H, m), 2.12-2.28 (2 H, m), 2.30-2.45 (2 H, m), 2.47 (1 H, d, *J* 2.5 Hz), 2.52-2.61 (1 H, m), 5.44-5.54 (1 H, m), 5.51 (1 H, dt, *J* 2.5 and 6.5 Hz) and 5.56 (1 H, dt, *J* 11 and 8 Hz); δ_C (67.9 MHz; $CDCl_3$) 21.8, 24.2, 33.6, 34.7, 63.3, 73.6, 81.7, 126.8, 133.2 and 173.6; *m/z* 165 (M^++H, 100%), 164 (M^+, 62%); HRMS (Found: M^+, 164.0837. $C_{10}H_{12}O_2$ requires 164.083729).

11-(Tributylstannyl)-5*Z*,10*E*-decadien-9-olide (16c)

(a) A mixture of hydroxy acid (**15c**) and (**15a**) (4:1, 0.544 g) was cyclised using the representative lactonisation procedure to give, after chromatography, the *title compound* (**16c**) (0.166 g, 40%) as a colourless oil, (Found: C, 58.15; H, 9.0. $C_{22}H_{42}O_2Sn$ requires C, 58.04; H, 8.86%); R_f 0.75 (petrol/ether, 9:2); υ_{max} / cm^{-1} 1742, 1603; δ_H (400 MHz; $CDCl_3$) 0.81 (9 H, t, *J* 7.5 Hz,), 0.79-0.83 (6 H, m), 1.18-1.27 (6 H, m), 1.37-1.45 (6 H, m), 1.69-1.76 (1 H, m), 1.83-1.95 (2 H, m), 2.16-2.23 (3 H, m), 2.29-2.34 (1 H, m), 2.48-2.54 (1 H, m), 5.28 (1 H, dt, *J* 4.9 and 8.5 Hz), 5.42-5.49 (1 H, m), 5.55 (1 H, dt, *J* 11 and 8.5 Hz), 5.92 (1 H, dd, *J* 5 and 19 Hz) and 6.12 (1 H, dd, *J* 1.5 and 19 Hz); δ_C (100 MHz; $CDCl_3$) 9.4, 13.7, 22.1, 24.4, 27.3, 29.0, 33.65, 34.1, 75.6, 126.3, 129.5, 134.2, 146.0 and 174.7; *m/z* 455 (M^+, 6%). The vinyl lactone (**16a**) (0.014 g) was also isolated from this reaction as a colourless oil with data was identical to previous sample.

(b) A neat solution of alkyne (**16b**) (0.534 g, 3.26 mmol), tributyltin hydride (0.948 g, 3.12 mmol) and AIBN (0.046 g, 0.326 mmol) was heated at 90 °C for 8 h under an inert atmosphere. Column chromatography (petrol) gave an inseparable mixture of the title compound (**16c**) and its 10*Z*-isomer (1.392 g, 94%) in a ratio 85:15 in favour of the *E*-isomer. No separation could be achieved by chromatography or distillation.

1*E*,3*E*-1-Bromodecadiene (17)

A solution of DibalH (43 ml, 1.00 *M*, 0.043 mol) in hexane was added dropwise to a stirring solution of octyne (4.76 g, 0.043 mol) in hexane (10 ml) at room temperature under an inert atmosphere. After the addition was complete the solution was heated at 50 °C for 4 h and then left to cool to room temperature. This solution was then added dropwise at room temperature to a solution of 1,2-dibromoethene (60:40 *E*/*Z* mixture, 40.2 g, 0.216 mol) and tetrakis(triphenylphosphine)palladium(0) (0.994 g, 0.86 mmol) in ether (250 ml). The resulting orange solution was stirred for 17 h before being hydrolysed with dilute hydrochloric acid (100 ml, 1 *M*). The organic layer was separated and the aqueous layer extracted with ether (4 x 15 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Preparative centrifugal chromatography (petrol) followed by bulb-to-bulb distillation gave the title product (**17**) (6.23 g, 66%) as a pale yellow liquid, R_f 0.58 (petrol-ether, 9:2); b.p. (Kugelrohr) 105 °C at 0.5 mm Hg; υ_{max} / cm^{-1} 1700 and 1652; δ_H (400 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.5 Hz), 1.2-1.38 (8 H, m), 2.04 (2 H, m), 5.72 (1 H, dt, *J* 15.5 and 7Hz), 5.94 (1 H, ddt, *J* 10.5, 15.5 and 1 Hz), 6.16 (1 H, d, *J* 13.5 Hz) and 6.66 (1 H, dd, *J* 10.5 and 13.5 Hz); δ_C (22.5 MHz; $CDCl_3$) 14.0, 22.6, 28.9, 29.4, 31.7, 32.6, 105.0, 127.5, 136.5 and 137.7; *m/z* 218 (M^+, 21%), 216 (M^+, 21%).

Methyl 4*Z*, 9*E*, 11*E*, 13*E*-8-hydroxy-eicosatetraenoate (20)

Tris(dibenzylideneacetone)dipalladium(0) (0.029 g, 0.03 mmol) and tri-(2-furyl)phosphine (0.023 g, 0.10 mmol) were added sequentially to a solution of dienyl bromide (**17**) (0.130 g, 0.60 mmol) in NMP (2 ml) under an inert atmosphere. Ultra-pure (99.999%) lithium chloride (0.076 g, 1.80 mmol) was then added and the mixture stirred vigourously for 30 min. Finally vinylstannane (**14c**) (0.243 g, 0.499 mmol) was added and the reaction mixture stirred for a further 8 h. Hexane (5 ml) and aqueous ammonium hydroxide (2 ml, 3 *M*) were added and the bi-phasic system stirred for 20 min. Separation of the organic layer followed by drying (Na_2SO_4), extraction of the crude product with acetonitrile (6 x 5 ml) and solvent removal under reduced pressure gave a dark orange oil. Preparative centrifugal chromatography (petrol/ether, 4:1) gave the *title compound* (**20**) (0.111 g, 67%) as a yellow oil, (Found: C, 75.7; H, 10.4. $C_{21}H_{34}O_3$ requires C, 75.41; H, 10.25%); R_f 0.47 (petrol-ether, 1:2); υ_{max} / cm^{-1} 3455, 1740 and 1651; δ_H (400 MHz; $CDCl_3$) 0.84 (3 H, t, *J* 6.5 Hz), 1.22-1.42 (8 H, m), 1.53-1.67 (2 H, m), 1.89-1.93 (1 H, br s, OH), 2.09 (2 H, q, *J* 7 Hz), 2.10-2.20 (2 H, m), 2.33-2.36 (4 H, m), 3.65 (3 H, s), 4.14 (1 H, q, *J* 6.5 Hz), 5.30-5.37 (1 H, m), 5.42 (1 H, dt, *J* 10.5 and 7.0 Hz), 5.65 (1 H, dd, *J* 6.5 and 15 Hz), 5.70 (1 H, dt, *J* 15 and 7.5 Hz), 6.06 (1 H, ddd, *J* 1.5, 10.5 and 15 Hz), 6.10 (1 H, dd, *J* 10.5 and 15 Hz), 6.19 (1 H, dd, *J* 10.5 and 15 Hz) and 6.23 (1 H, dd, *J* 10.5 and 15 Hz); δ_C (100 MHz; $CDCl_3$) 14.0, 22.5, 22.6, 23.1, 28.1, 29.1, 31.6, 32.8, 33.9, 36.9, 51.5, 71.9, 128.0, 129.5, 130.0, 130.6, 130.7, 133.4, 135.0, 135.9 and 173.7; *m/z* 335 (MH^+, 6%), 334 (M^+, 20%).

5*Z*, 10*E*, 12*E*, 14*E*-eicosatetraene-9-olide (8)

Ester (**20**) (0.190 g, 0.568 mmol) was saponified using the representative procedure for ester hydrolysis and the crude product (**9**) was cyclised using the representative lactonisation procedure to give, after chromatography, the *title compound* (**11**) (0.096 g, 56%) as a yellow oil, R_f 0.48 (petrol-ether, 3:2); υ_{max} / cm^{-1} 1743, 1641, 1462, 1242, 1150, 1004 and 736; δ_H (400 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 7 Hz), 1.24-1.36 (8 H, m), 1.75 (1 H, ddt, *J* 14, 5.5 and 3 Hz), 1.93 (1 H, ddt, *J* 14, 4 and 2 Hz), 1.92-1.96 (1 H, m), 2.08 (2 H, m), 2.24 (2 H, m), 2.21-2.27 (1 H, m), 2.29-2.39 (1 H, m), 2.53-2.61 (1 H, m), 5.40 (1 H, m), 5.43-5.50 (1 H, m), 5.55 (1 H, dt, *J* 10.5 and 8 Hz), 5.60 (1 H, dd, *J* 15 and 6.5 Hz), 5.66 (1 H, ddd overlapping, *J* 14.5, 7.5 and 7 Hz), 5.99 (1 H, dd, *J* 14.5 and 10.5 Hz), 6.01 (1 H, dd, *J* 14.5 and 10.5 Hz), 6.15 (1 H, dd, *J* 14.5 and 10.5 Hz) and 6.18 (1 H, dd, *J* 15 and 10.5 Hz); δ_C (67.9 MHz; $CDCl_3$) 14.0, 22.1, 22.6, 24.3, 28.8, 29.1, 31.7, 32.8, 33.9, 34.0, 74.6, 126.4, 129.2, 130.0, 130.4, 131.8, 133.9, 134.3, 136.4 and 174.5; *m/z* 303 (MH^+, 100%); HRMS (Found: MH^+, 303.2324. $C_{20}H_{30}O_2$ requires MH^+, 303.232405).

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