A Concise, Efficient and Flexible Strategy for the Synthesis of the Pheromones of *Oryzaephilus* and *Cryptolestes* Grain Beetles

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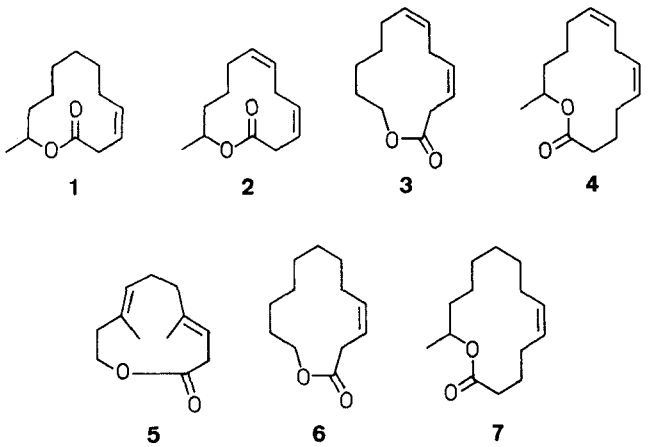
Six of the seven macrolide components of the pheromone systems of grain beetles of the genera *Oryzaephilus* and *Cryptolestes* are synthesised by new routes of greatly improved efficiency. Iterative methodology based on the Wittig olefination is employed for the construction of the (*Z,Z*)-1,4-diene subunits in three of the lactones; chlorite oxidation of (*Z*)-3-alkenals derived by this methodology is used to form the (*Z*)-3-alkenoic acid functionalities present in four of the targets. The use of recently described conditions for the cyclisation of a Combretastatin analogue gives dramatically increased yields for the macrolactonisation steps in all six cases.

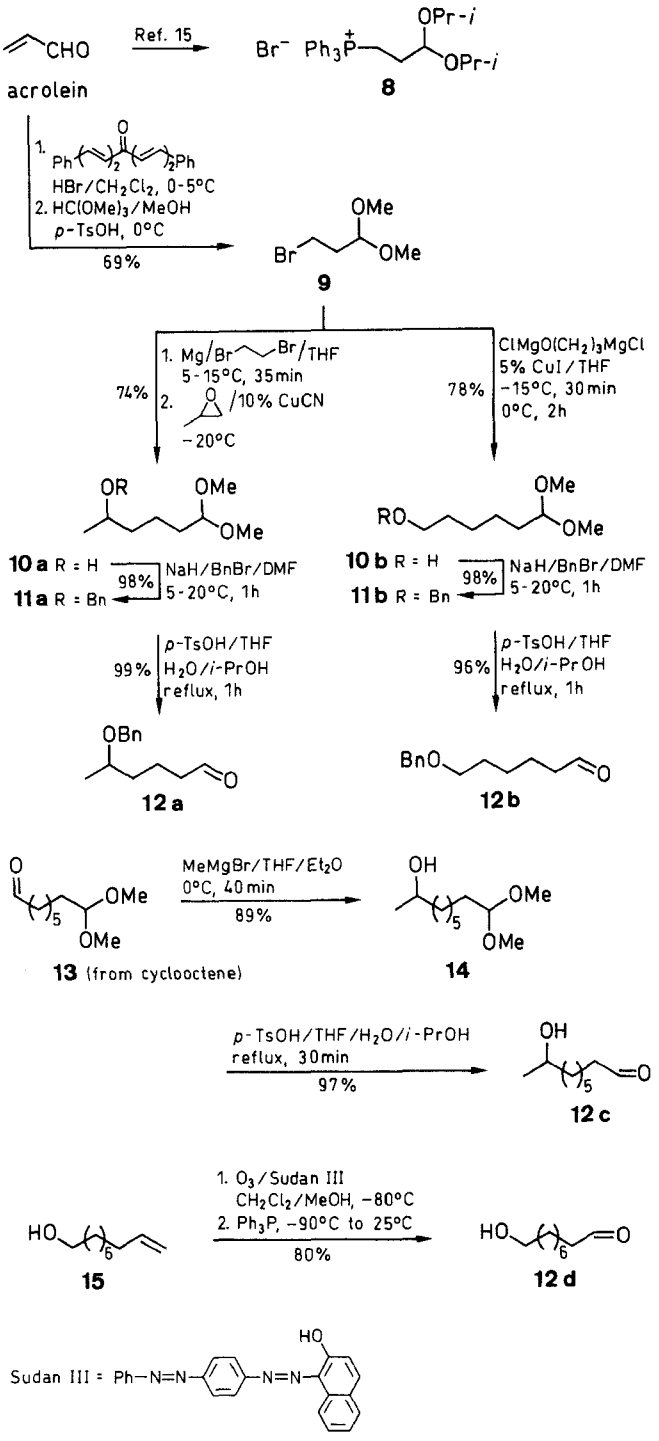
The saw-toothed grain beetle, *Oryzaephilus surinamensis*, and the related cucujid species *O. mercator, Cryptolestes ferrugineus, C. turcicus,* and *C. pusillus* are major pests of cereals and grain on a worldwide scale,[1] and a clear need exists for effective detection and control methods.[2] For some years the pheromone system of these insects (lactones **1**–**7**, Scheme 1) has been studied in pursuit of this goal and generally promising results have been obtained in laboratory and small-scale field trials.[3]



Scheme 1

The move to large scale trials and ultimately commercial use of these pheromones has however been thwarted by the inefficiency of the current syntheses[4–11] of **1**–**4**, **6**, and **7**; lactone **5** may be synthesised efficiently from geraniol[7,12] or (*E,E*)-farnesol.[8] The synthetic problems are particularly severe for **2** and **3**, where the reported syntheses[4,5] are long and give overall yields of < 3 %. The main obstacle to efficient synthesis of these lactones is the instability to heat, acid and base of the targets, resulting from the combined presences of 1,4-diene and β,γ-unsaturated ester functionalities; **2**, **3** and **4** have been reported[4] to be unstable even when stored at − 20 °C. Furthermore, for **1**, **2**, **3** and **6** lactonisation of the appropriate hydroxy acid precursor has been found to be an inefficient process; in each case yields of < 35 % were observed for this step; for **2** the yield is as low as 7 %. We wish to report a new approach which allows both facile synthesis of the hydroxy acid precursors to **1**–**4**, **6**, and **7** and also permits greatly increased efficiency in the lactonisations of these hydroxy acids.

For many years the standard preparation of (*Z,Z*)-1,4-dienes has been the method of Osbond,[13]



Scheme 2

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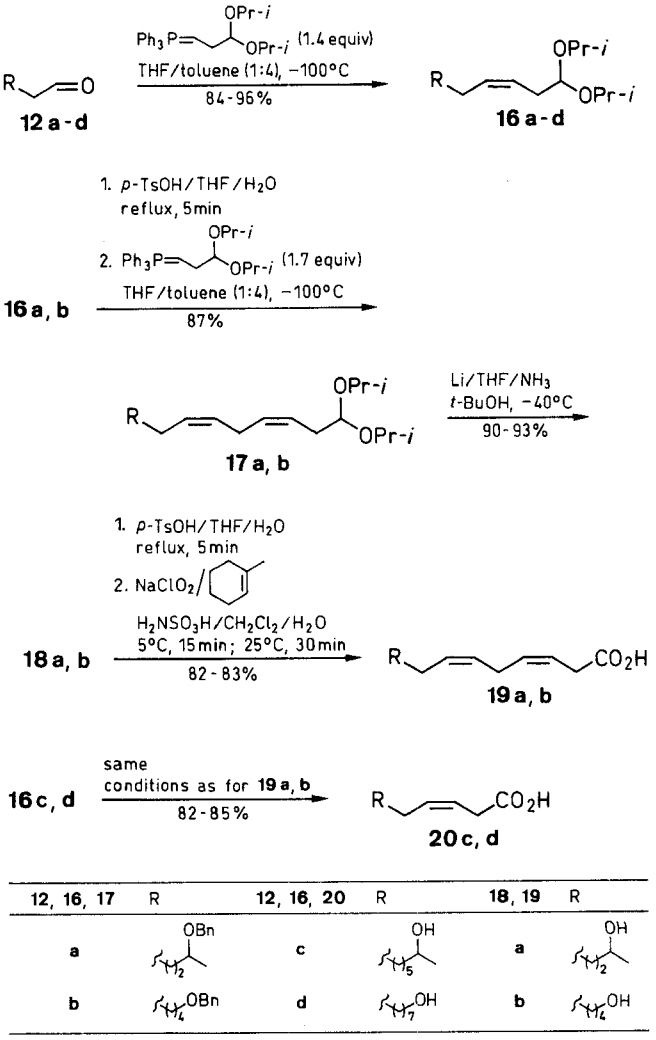
whereby the equivalent 1,4-diyne is formed and then reduced by catalytic hydrogenation to give the diene. However, this method has been supplanted recently by iterative methodology,[14] based on Wittig olefination with the ylid derived from **8**.[15] This represents a particularly attractive method for the synthesis of (*Z*,*Z*)-1,4-dienes and higher skipped polyenes; overall yields are high and the stereoselectivity of the alkene formations appears to be essentially complete. The method has already been applied to the preparation of some simple pheromones, and has given yields highly competitive with those of previous routes.[16]

We hypothesised that **1–4, 6** and **7** could be prepared by the use of this methodology, starting from the aldehydes **12a–d**. The synthesis of these aldehydes proved to be straightforward (Scheme 2). The aldehyde **12c** was obtained from cyclooctene[17,18] via ozonolysis to the aldehyde acetal **13**, followed by reaction with methylmagnesium bromide to give the hydroxy acetal **14**. Hydrolysis of the acetal functionality gave **12c** in near-quantitative yield. The aldehyde **12d** was obtained by ozonolysis of commercially available alkenol **15**. The aldehydes **12a** and **12b** were prepared from the hydroxy acetals **10a**[19] and **10b**,[20] by first benzylating the hydroxy groups to give **11a** and **11b** and then hydrolysing the acetal function. The hydroxy acetals **10a–b** were both prepared from **9**, itself easily obtained from acrolein on 250 g scale.[21] Metalation of **9** with magnesium in tetrahydrofuran (THF) in the presence of 5 mol% 1,2-dibromoethane at 5–15°C gave a Grignard reagent of sufficient stability for further use; reaction of this with excess propylene oxide at −20°C gave **10a** in 74% yield when catalysed with 10 mol% copper(I) cyanide.[22] Treatment of **9** with one equivalent of the chloromagnesium salt of 3-hydroxypropylmagnesium chloride, prepared as described by Normant,[23] in the presence of catalytic copper(I) iodide afforded **10b** in 78% yield. The stability of the Grignard derived from the *acyclic* β-bromoacetal **9** provides further evidence[24] of the usefulness of such reagents; the traditional reliance on β-bromodioxolanes[25] or dioxanes[26] seems to be unnecessary if the equivalent acyclic acetals are metalated under the correct conditions.[27]

Conversion of the aldehydes **12a–d** to the appropriate hydroxy acids was carried out as shown in Schemes 3 and 4. Reaction of **12a–b** with 1.4 equivalents of the ylid derived from **8** gave the acetals **16a–b**, both in excellent yields. Further homologation as described by Santelli,[14] gave the dienes **17a–b**. It was notable that attempts to carry out the diene-forming step without prior protection of the hydroxy group (using a 2.5 fold excess of ylid) resulted in extensive isomerisation of the skipped functionality, presumably due to the effect of the metal alkoxide (formed by deprotonation of the free hydroxy group by excess ylid). Removal of the protecting groups from **17a** and **17b** by lithium ammonia reduction gave the hydroxy acetals **18a–b**; hydrolysis of the acetal functionalities followed by oxidation of the aldehydes was employed to form the acids. Several methods of aldehyde oxidation were examined;[28] by far the best results were obtained using sodium chlorite (Lindgren oxidation).[29] This gave **19a–b** in 82–83% yields from **18a–b**, with no detectable isomerisation to the α,β-unsaturated acids taking place. The variant of the oxidation employed a two-phase water–dichloromethane[30] system, with 1-methylcyclohex-1-ene being employed as $HOCl/ClO_2$ scavenger[31–32] and sulfamic acid as catalyst.[33] The ease by which conversion of the acetal to the acid could be achieved makes **8** an attractive synthon for (*Z*)-β-alkenoic acids;[34] the ready availability of the phosphonium salt and the non-basic deprotection conditions probably make its use in this role preferable to the OBO-ester based technique developed by Corey[35] (and used recently by Keinan for the synthesis of **1**).[11]



12, 16, 17	R	12, 16, 20	R	18, 19	R
a	OBn	c	OH	a	OH
b	OBn	d	OH	b	OH

Scheme 3

The hydroxy aldehydes **12c–d** were converted to the hydroxy acids **20c–d** in similar fashion; olefination with 2.5 equivalents of the Santelli ylid gave hydroxy acetals **16c–d**, which were hydrolysed and then oxidised as above to give the acids. The fourteen carbon acids **22** and **23** were obtained from **16a** and **12c**, respectively, by use of the ylid **24**. Hydrolysis of **16a** followed by olefination in 4:1 THF/hexamethylphosphoric triamide (HMPA) at −100°C gave benzyloxy acid **21** in yields varying from 50–75%, with an average of 58–62%. Debenzylation as for **17a–b** gave hydroxy acid **22** in excellent yield. Treatment of **12c** with a threefold excess of ylid **24** under

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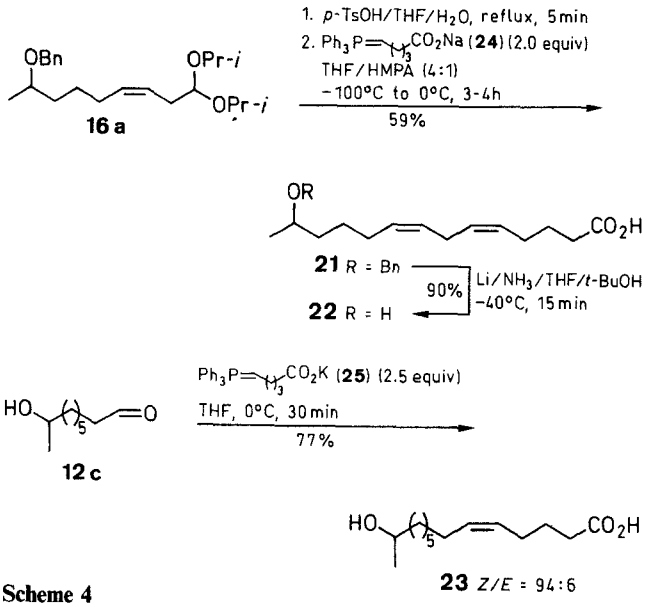
the conditions employed for the olefination of **16b** gave only moderate yields of the acid **23** (30–50%); use of the potassium salt **25** of the ylid[36] in THF at 0°C gave a much better yield (77%) but with significant (5–7%) contamination of the product with the *E*-isomer.



Scheme 4

Our first attempts to lactonise the hydroxy acids **20c–d, 19a–b, 22** and **23** utilised the Yonemitsu modification[37,38] of the Yamaguchi protocol,[39] which has been shown to be more effective than older methods[40–42] of acyl-activated cyclisation for a number of macrolide systems.[43–45] Indeed, a recent comparative study[46] of the lactonisation of Phoracantholide I cited the method as superior to all other methods with the exception of the Gerlach modification of the Corey procedure.[47] Owing to its reliance on the presence of silver(I) salts this last proved to be unsuitable for use with these sensitive dienes; attempts to cyclise **19b** by this method gave only traces of conjugated products. Use of the Yonemitsu method with **22** gave a yield of **4** of 74%, a clear improvement on the 47% reported by Oehlschlager.[4,48] However, unfortunately, the yields for **2** and **3** (10% and 18%, respectively) were little changed from previously reported values, and clearly unacceptable. On the other hand, a shift to the hydroxy activation method devised by Mitsunobu[49] (and modified recently by Steglich)[50] gave a dramatic improvement, with an essentially invariant yield of 70–72% being achieved for the four secondary lactones **1, 2, 4** and **7**. The unbranched lactones **3** and **6** gave yields of 66 and 81% respectively. The value of the change in methodology is reinforced by the fact that the lactonisation of **20** could be carried out on a 2.5 g scale using under a litre of solvent, making the method more practical than previous approaches in addition to being more efficient. Use of (*R*)- and (*S*)-propylene oxide allowed the enantiomers of **2** and **4** to be synthesised, underlining the value of using the epoxide as the starting point for the syntheses of these compounds.[51]

In summary, syntheses of greatly improved efficiency and practicality have been devised for the six targets – the overall yields are given in Table 1. The *Z*/*E* ratios for all the alkenes, other than that formed in the synthesis of **7**, were ≥ 99:1, the essentially complete *Z* selectivity reported by Santelli could be reproduced if comparable ylid concentrations were used, but traces (< 1%) of *E*-isomer were observed under the more concentrated conditions used here.

Table 1. Macrolides **1–7** Prepared

New Syntheses				Best Previous Syntheses			
Lactone	Yield	Steps	From	Yield	Steps	From	Ref.
1	48	5	cyclooctene	18	6	oct-1-yne	5,7
2	32	7	acrolein	0.33	11	5-chloro-2-pentanone	4,5
3	35	7	acrolein	2.2	9	hept-1-yne	4,5
4	27	6	acrolein	13	9	5-chloro-2-pentanone	5,6
6	51	4	dec-9-en-1-ol	22	5	undec-10-en-1-ol	5,6
7	56	4	cyclooctene	15	9	hex-5-yn-1-ol	6

Behavioural testing of the synthetic materials with *O. surinamensis* is currently in progress and will be reported elsewhere; however, preliminary indications are that the compounds prepared by this route are at least as attractive as material synthesised via previously described routes, suggesting that the presence of trace amounts of *E*-alkenes is not a significant problem.

All reactions were monitored by TLC on Macherey-Nagel Düren ALUGRAM® SIL G/UV$_{254}$ plastic or aluminum backed silica gel plates with fluorescent stain for UV absorption indication. Visualisation was by molecular I_2 staining, followed by further development with either H_2SO_4/vanillin or phosphomolybdic acid. The flash silica used for column chromatography was May and Baker Sorbsil 60 (230–400 mesh), packed as a slurry and run under low pressure. All reactions were stirred magnetically using Teflon-coated bars. All solvents used in reactions were anhydrous unless otherwise stated; THF was distilled from Na wire under N_2 in the presence of benzophenone, toluene and benzene were dried with and stored over Na wire, CH_2Cl_2, DMF, HMPA, and hexane were all distilled from CaH_2 under N_2. Solvents used for aqueous work up and for chromatography were BDH reagent grade; light petroleum in all cases refers to the 40–60°C fraction. NMR spectra were recorded using a JEOL GX270 spectrometer at 20–25°C, running at 270 MHz for ^1H and 66.7 MHz for ^{13}C (using TMS as standard, coupling constants J are reported in Hz). IR spectra were acquired by means of a Perkin-Elmer 1600 series FT-IR; quoted values have an error of $\pm 4\ cm^{-1}$. Optical rotations were determined over a 10 cm path length using an Optical Activity AA-100 polarimeter, Fisons analytical grade $CHCl_3$ was used as the solvent in all cases. Melting points are uncorrected. All 1,4-diene, β,γ-unsaturated aldehyde, acid or ester containing compounds were stored frozen in anhydrous, deoxygenated benzene at −30°C under N_2 and in the dark. All phosphonium salts were stored under dry N_2 and dried three times in-flask by azeotropic distillation with anhydrous benzene, under reduced pressure, before being used in Wittig reactions.

(3,3-Diisopropoxypropyl)triphenylphosphonium Bromide (8):
The phosphonium salt **8** was prepared by the method of Santelli.[15] Data for **8** were as described therein, except for the ^{13}C NMR.
^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 134.6 (dd, J_{CCCP} = 3.0), 132.9

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(dd, J_{CCCP} = 9.8), 130.0 (dd, J_{CCP} = 12.7), 117.3 (d, J_{CP} = 86.1), 97.6 (dd, J_{CCCP} = 17.6), 69.0 (d), 28.3 (dt, J_{CCP} = 2.9), 22.6 (q), 22.1 (q), 17.2 (dt, J_{CP} = 54.8).

1-Bromo-3,3-dimethoxypropane (9):
The acetal **9** was prepared from acrolein (112.0 g, 2.00 mol) using the general procedure for β-bromo acetals described by Stowell.[21] Distillation of the crude acetal gave **9** as a colourless liquid with a distinctive odour (58–60 °C/14 Torr, 253.4 g, 1.385 mol, 69%). Spectroscopic data were as for the commercially available material.[52]

Synthesis of 2:
6,6-Dimethoxyhexan-2-ol (10a):
Mg turnings (7.30 g, 0.300 mol) were suspended in THF (350 mL) under N_2 and 1,2-dibromoethane (2 mL) added; after 5 min the suspension was cooled to 0 °C and the freshly distilled bromide **9** (45.88 g, 0.250 mol) added at such a rate as to maintain the temperature within the range 5–15 °C. After a further 30 min at 10 °C the solution was added to a cooled (−30 °C) suspension of CuCN (2.24 g, 25.0 mmol,10 mol%) in THF (100 mL) and propylene oxide (17.40 g, 0.300 mol, 20% excess)[51] at such a rate as to maintain the temperature in the range −25 to −15 °C. The resulting solution was allowed to warm to 25 °C and then quenched by the addition of half-sat. aq NH_4Cl (150 mL) and 33% aq NH_4OH (15 mL); after stirring for 15 min the layers were separated and the aqueous extracted with Et_2O (2 × 150 mL); the combined organics were washed with H_2O (50 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (Et_2O/light petroleum 1:1) gave **10a** (29.95 g, 184.6 mmol, 74%) as a colourless oil. Attempted distillation gave elimination of MeOH; accordingly the material was used directly.

IR (neat): ν = 3430, 2950, 2830, 1460, 1375, 1190, 1130, 1070, 1055, 985, 950, 920, 850 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.22 (1 H, t, J = 5.5), 3.61 (1 H, m), 3.16 (6 H, s), 2.93 (1 H, br s), 1.46 (2 H, m), 1.29 (4 H, m), 1.02 (3 H, d, J = 6).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 104.3 (d), 67.2 (d), 52.4 (q), 52.3 (q), 38.75 (t), 32.2 (t), 23.2 (q), 20.7 (t).

$[\alpha]_D^{25}$ for (*R*)-**10a** −4.0° (c = 2.09, $CHCl_3$); $[\alpha]_D^{25}$ for (*S*)-**10a** +4.2° (c = 2.18, $CHCl_3$).

5-Benzyloxy-1,1-dimethoxyhexane (11a):
NaH (7.20 g of 50% dispersion in mineral oil, 150.0 mmol, 1.2 equiv.) was washed with hexane (3 × 50 mL) and suspended in DMF (250 mL). After cooling to 5 °C the hydroxy acetal **10a** (20.28 g, 125.0 mmol) in DMF (20 mL) was added and the suspension allowed to warm to 20 °C over 1 h. After 30 min BnBr (25.60 g, 150.0 mmol) was added at 5–10 °C over 15 min and the resulting thick slurry quenched after 30 min by the careful addition of H_2O (200 mL). Pentane (250 mL) was added and the layers separated; the aqueous phase was extracted with pentane (3 × 100 mL) and the combined pentane layers washed with H_2O (2 × 100 mL) and brine (150 mL), dried ($MgSO_4$) and concentrated. Distillation gave pure **11a** (101–102 °C/0.05 Torr, 30.90 g, 122.4 mmol, 98%).

IR (neat): ν = 3030, 2945, 2830, 1495, 1455, 1375, 1340, 1190, 1130, 1070, 1030, 950, 735, 700 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.32 (4 H, m), 7.26 (1 H, m), 4.49 (2 H, AB q, J = 12.0, δ_A = 4.55, δ_B = 4.43), 4.34 (1 H, t, J = 5.5), 3.50 (1 H, m), 3.29 (6 H, s), 1.59 (3 H, m), 1.44 (3 H, m), 1.18 (3 H, d, J = 6).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 139.0 (s), 128.3 (d), 127.6 (d), 127.3 (d), 104.4 (d), 74.7 (d), 70.3 (t), 52.6 (q), 36.4 (t), 32.5 (t), 20.6 (t), 19.55 (q).

MS (NH_3 – CI mode) m/z (%) = 270 ($M^+ + NH_4$, 14), 238 (32), 221 (54), 206 (40), 115 (15), 99 (100), 91 (16), 75 (22).

$[\alpha]_D^{25}$ for (*R*)-**11a** −8.9° (c = 2.20, $CHCl_3$). $[\alpha]_D^{25}$ for (*S*)-**11a** +8.7° (c = 2.28, $CHCl_3$).

5-Benzyloxyhexanal (12a):
The acetal **11a** (25.2 g, 100.0 mmol) was dissolved in THF (200 mL), *i*-PrOH (20 mL) and H_2O (100 mL) and *p*-TsOH (500 mg) added; the resulting solution was refluxed for 1 h and then diluted with pentane (150 mL). The layers were separated and the aqueous phase was extracted with pentane (2 × 100 mL); the combined organics were washed with H_2O (50 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated to give **12a** (20.40 g, 99.0 mmol, 99% crude) in >95% purity.

IR (neat): ν = 3030, 2970, 2930, 2870, 2720, 1725, 1495, 1455, 1375, 1342 m, 1310, 1205, 1140, 1090, 1070, 1030, 915, 865, 810, 740, 700 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.73 (1 H, s), 7.35 (4 H, m), 7.30 (1 H, m), 4.52 (2 H, AB q, J = 11.6, δ_A = 4.59, δ_B = 4.43), 3.53 (1 H, m), 2.41 (2 H, m), 1.65 (4 H, m), 1.22 (3 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 202.6 (d), 138.85 (s), 128.3 (d), 127.7 (d), 127.5 (d), 74.3 (d), 70.3 (t), 43.8 (t), 36.0 (t), 19.5 (q), 18.1 (t).

$[\alpha]_D^{25}$ for (*R*)-**12a** −14.2° (c = 1.72, $CHCl_3$). $[\alpha]_D^{25}$ for (*S*)-**12a** +13.8° (c = 2.17, $CHCl_3$).

(3*Z*)-8-Benzyloxy-1,1-diisopropoxynon-3-ene (16a):
Phosphonium salt **8** (19.53 g, 37.7 mmol) was suspended in THF (50 mL) and toluene (200 mL) under N_2, and sodium hexamethyldisilazide (NaHMDS, 17.18 mL of 1.92 M solution in 1:4 THF–toluene, 33.0 mmol) added over 5 min at 0 °C. Stirring at 25 °C for 2 h was followed by cooling to −100 °C and addition of aldehyde **12a** (4.86 g, 23.56 mmol) in THF (20 mL) dropwise over 5 min. Stirring at −100 °C for 30 min and then warming to 25 °C over 3 h, followed by quenching with half-sat. aq NH_4Cl (40 mL), extraction with Et_2O (3 × 150 mL), washing of the combined organics with H_2O (2 × 50 mL) and brine (100 mL), drying ($MgSO_4$) and concentration gave a thick oil. This was dissolved in CH_2Cl_2 (25 mL) and the solution poured into pentane (150 mL); filtration to remove precipitated Ph_3PO and reconcentration gave the crude product; purification by flash chromatography on silica gel (Et_2O/light petroleum, 1:9 eluant) gave **16a** as a colourless oil (7.88 g, 22.62 mmol, 96%).

IR (neat): ν = 2970, 2930, 2865, 1495, 1455, 1380, 1330, 1280, 1175, 1130, 1100, 1030, 970, 930, 875, 810, 735, 695 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.31 (4 H, m), 7.26 (1 H, m), 5.43 (2 H, m), 4.53 (1 H, t, J = 5.7), 4.49 (2 H, AB q, J = 11.8, δ_A = 4.55, δ_B = 4.43), 3.85 (2 H, sept, J = 6.2), 3.49 (1 H, m), 2.34 (2 H, dd, J = 6.6, 5.7), 2.04 (2 H, m), 1.51 (4 H, m), 1.18 (6 H, d, J = 6.2), 1.15 (3 H, d), 1.13 (6 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 139.0 (s), 131.7 (d), 128.2 (d), 127.5 (d), 127.3 (d), 124.5 (d), 99.9 (d), 74.7 (d), 70.2 (t), 67.7 (d), 36.2 (t), 33.7 (t), 27.4 (t), 25.4 (t), 23.3 (q), 22.5 (q), 19.6 (q).

MS (NH_3 – CI mode): m/z (%) = 366 ($M^+ + NH_4$, 13), 306 (42), 289 (100), 264 (12), 246 (7), 183 (8), 131 (18), 108 (6), 35 (35).

HRMS: m/z for $C_{22}H_{40}NO_3$ ($M^+ + NH_4$), calc.: 366.3008; found: 366.3002.

$[\alpha]_D^{25}$ for (*R*)-**16a** −5.35° (c = 2.36, $CHCl_3$). $[\alpha]_D^{25}$ for (*S*)-**16a** +5.4° (c = 2.03, $CHCl_3$).

(3*Z*,6*Z*)-11-Benzyloxy-1,1-diisopropoxydodeca-3,6-diene (17a):
The acetal **16a** (4.182 g, 12.00 mmol) was dissolved in THF (120 mL) and warmed to reflux; *p*-TsOH (6.0 mL of 0.1 M aqueous solution) was added and the resulting solution refluxed for 5 min, then cooled to 0 °C. Light petroleum (40 mL) was added, followed by washing with H_2O (2 × 20 mL) and brine (25 mL). The aq layers were re-extracted with light petroleum (30 mL) and the combined organics dried ($MgSO_4$) and concentrated. The resulting crude aldehyde was dissolved in THF (15 mL) and the solution added dropwise at −100 °C to a stirred solution of the ylide obtained by stirring the phosphonium salt **8** (10.02 g, 20.0 mmol, 1.66 equiv) in THF (40 mL) and toluene (140 mL) with NaHMDS (1.92 M in THF/toluene, 1:3, 9.25 mL, 17.8 mmol) at 20 °C for 1 h. Warming to 0 °C over 4 h was followed by quenching with half-sat. aq NH_4Cl (25 mL); the layers were separated and the aqueous layer extracted with Et_2O (2 × 30 mL); the combined organics were washed with

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H_2O (10 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated giving an oil which was then poured into pentane (100 mL). The precipitated Ph_3PO was removed by filtration and the filtrate concentrated, giving the crude product. Purification by flash chromatography on silica gel (Et_2O/light petroleum 1:7) gave acetal **17a** (4.04 g, 10.44 mmol, 87%) as a colourless oil.

(Z)-8-Benzyloxynon-3-enal:

IR (neat): ν = 3025, 2970, 2930, 2860, 2725, 1725, 1495, 1455, 1375, 1340, 1260, 1205, 1135, 1095, 1065, 1030, 915, 735, 695 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.64 (1 H, t, J = 1.9), 7.35 (4 H, m), 7.29 (1 H, m), 5.69 (1 H, m), 5.55 (1 H, m), 4.51 (2 H, AB q, J = 11.8, δ_A = 4.58, δ_B = 4.46), 3.52 (1 H, m), 3.15 (2 H, d, J = 7.1), 2.04 (2 H, dd, J = 6.8, 6.8), 1.52 (4 H, m), 1.21 (3 H, d, J = 6.0).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 199.65 (d), 139.0 (s), 135.1 (d), 128.35 (d), 127.7 (d), 127.5 (d), 118.3 (d), 74.6 (d), 70.3 (t), 42.6 (t), 36.2 (t), 27.6 (t), 25.2 (t), 19.6 (q).

(3Z,6Z)-11-Benzoyloxy-1,1-diisopropoxydodeca-3,6-diene **(17a)**:

IR (neat): ν = 3010, 2970, 2930, 2865, 1495, 1455, 1380, 1330, 1175, 1130, 1030, 975, 910, 875, 810, 735, 696 m, 670 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.28 (4 H, m), 7.23 (1 H, m), 5.38 (2 H, m), 5.32 (2 H, m), 4.50 (1 H, t, J = 6.5), 4.45 (2 H, AB q, J = 11.7, δ_A = 4.58, δ_B = 4.47), 3.81 (2 H, sept, J = 6.2), 3.45 (1 H, m), 2.74 (2 H, m), 2.32 (2 H, m), 2.00 (2 H, m), 1.42 (4 H, m), 1.12 (6 H, d, J = 6.2), 1.10 (3 H, d), 1.07 (6 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 139.1 (s), 130.2 (d), 130.1 (d), 128.35 (d), 127.95 (d), 127.65 (d), 127.4 (d), 124.7 (d), 99.9 (d), 74.5 (d), 70.3 (t), 67.9 (d), 36.3 (t), 33.8 (t), 27.3 (t), 26.0 (t), 25.6 (t), 23.4 (q), 22.6 (q), 19.7 (q).

MS (NH^3 – CI mode): m/z (%) = 406 ($M^+ + NH_4$, 9), 346 ($M^+ + NH_4 - i$PrOH, 33), 329 (100), 286 (27), 269 (40), 253 (17), 237 (8), 196 (7), 179 (32), 162 (14), 161 (15), 131 (54), 108 (12), 104 (10), 99 (16), 91 (14), 35 (44).

HRMS: m/z, for $C_{25}H_{44}NO_3$ ($M^+ + NH_4$) calc.: 406.3321; found: 406.3317.

$[\alpha]_D^{25}$ for (*R*)-**17a** – 4.5° (c = 2.04, $CHCl_3$), $[\alpha]_D^{25}$for (*S*)-**17a** + 4.4° (c = 2.14, $CHCl_3$).

(6Z,9Z)-12,12-Diisopropoxydodeca-6,9-dien-2-ol (18a):

The benzyl ether **17a** (2.66 g, 6.84 mmol) was dissolved in THF (35 mL) and NH_3 (30 mL) at – 40 °C, and *t*-BuOH (5 mL) added; to the resulting colourless solution was added Li metal (~ 300 mg, excess) until a persistent blue colour was obtained. Half-sat. aq NH_4Cl (20 mL) was slowly added, followed by warming to 20 °C over 2 h. Extraction with Et_2O (3 × 40 mL) followed by washing of the extracts with H_2O (2 × 5 mL) and brine (20 mL), drying ($MgSO_4$) and concentration gave the crude alcohol. Purification by chromatography on silica gel (Et_2O/light petroleum 1:1) gave **18a** (1.91 g, 6.31 mmol, 93%).

IR (neat): ν = 3420, 3010, 2970, 2930, 1465, 1380, 1330, 1225, 1175, 1125, 1030, 810, 665 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$: δ = 5.35 (2 H, m), 5.29 (2 H, m), 4.48 (1 H, t, J = 5.5), 3.80 (2 H, sept, J = 6.2), 3.70 (1 H, m), 2.72 (2 H, dd, J = 5.5, 5.5), 2.30 (2 H, dd, J = 5.5, 5.5), 2.16 (1 H, br s), 2.00 (2 H, m), 1.37 (4 H, m), 1.12 (6 H, d, J = 6.2), 1.10 (3 H, d), 1.07 (6 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 130.0 (d), 129.85 (d), 127.9 (d), 124.55 (d), 99.8 (d), 67.7 (d), 67.6 (d), 38.75 (t), 33.7 (t), 27.1 (t), 25.8 (t), 25.7 (t), 23.4 (q), 23.3 (q), 22.5 (q).

MS (NH_3 – CI mode): m/z (%) = 239 ($M^+ + H - i$PrOH, 100), 196 (88), 179 (46), 163 (25), 131 (45), 35 (34).

$[\alpha]_D^{25}$ for (*R*)-**18a** – 2.1° (c = 1.046, $CHCl_3$); $[\alpha]_D^{25}$ for (*S*)-**18a** + 2.2° (c = 1.024, $CHCl_3$).

(3Z,6Z)-11-Hydroxydodeca-3,6-dienoic Acid (19a):

The hydroxy acetal **18a** (1.490 g, 5.00 mmol) was dissolved in THF (70 mL) and the solution warmed to reflux. *p*-TsOH (1.75 mL of 0.1 M aqueous solution) was added; after 10 min the solution was cooled to 0 °C and Et_2O (50 mL) and H_2O (20 mL) added. The layers were separated and the aqueous extracted with Et_2O (3 × 40 mL), the combined ethereal layers were washed with H_2O (15 mL) and brine (30 mL) and concentrated. The crude hydroxy aldehyde was dissolved in CH_2Cl_2 (40 mL); 1-methylcyclohex-1-ene (2.50 g, 25.0 mmol) was added followed by the water washing from the hydrolysis. The two-phase mixture was cooled to 0 °C and H_2NSO_3H (5.0 mL of 1.0 M aq solution) added, followed by $NaClO_2$ (15.30 mL of 1.0 M aq solution) with rapid stirring. After 15 min the temperature was allowed to rise to 25 °C over 30 min; the layers were separated and the aqueous extracted with more CH_2Cl_2 (2 × 30 mL). The combined organic layers were concentrated and the residue redissolved in Et_2O (30 mL); the solution was extracted with 0.5 M aq Na_2CO_3 (3 × 25 mL) and the combined extracts washed with Et_2O (20 mL), acidified to pH1 with 2 M HCl and then extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were washed with 2 M HCl (10 mL), H_2O (5 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated to give the hydroxy acid **19a** (880 mg, 4.15 mmol, 83%).

(3Z,6Z)-11-Hydroxydodeca-3,6-dienal:

IR (neat): ν = 3390, 3010, 2970, 2930, 2860, 2730, 1725, 1455, 1375, 1335, 1175, 1110, 1035, 915, 830, 735 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.65 (1 H, t, J = 2.95), 5.61 (2 H, m), 5.35 (2 H, m), 3.77 (1 H, m), 3.21 (2 H, dm, J = 6.0), 2.76 (2 H, dd, J = 6.4, 6.8), 2.38 (1 H, s), 2.06 (2 H, m), 1.43 (4 H, m), 1.16 (3 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 199.7 (d), 133.5 (d), 130.7 (d), 127.0 (d), 118.4 (d), 70.0 (d), 42.55 (t), 38.55 (t), 27.2 (t), 26.0 (t), 25.7 (t), 23.6 (q).

(3Z,6Z)-11-Hydroxydodeca-3,6-dienoic Acid **(19a)**:

IR (neat): ν = 3395, 3010, 2965, 2935, 1715, 1560, 1400, 1375, 1295, 1210, 1130, 1075, 1015, 940, 825, 665 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 6.60 (2 H, br s), 5.57 (2 H, m), 5.37 (2 H, m), 3.82 (1 H, m), 3.14 (2 H, d, J = 5.2), 2.78 (2 H, dd, J = 5.2, 5.2), 2.05 (2 H, m), 1.43 (4 H, m), 1.18 (3 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 176.7 (s), 131.9 (d), 130.5 (d), 128.4 (d), 120.7 (d), 68.2 (d), 38.6 (t), 32.8 (t), 27.2 (t), 25.85 (t), 25.65 (t), 23.2 (q).

MS (NH_3 – CI mode, for methyl ester): m/z = 244 ($M^+ + NH_4$, 100), 227 ($M^+ + H$, 37), 209 (22), 194 (3), 177 (5), 135 (8), 35 (15).

HRMS: m/z, for $C_{13}H_{23}O_3$ ($M^+ + H$) calc.: 227.1647; found: 227.1634.

$[\alpha]_D^{25}$ for (*R*)-**19a** – 2.9° (c = 2.428, $CHCl_3$). $[\alpha]_D^{25}$ for (*s*)-**19a** + 2.85° (c = 2.350, $CHCl_3$).

(3Z,6Z)-Dodeca-3,6-dien-11-olide (2):

Ph_3P (656 mg, 2.50 mmol) was dissolved in anhydr. deoxygenated toluene (200 mL) under N_2 and diethyl azodicarboxylate (DEAD) (445 mg, 2.55 mmol) added; after stirring for 5 min the hydroxy acid **19a** (106 mg, 500 μmol) in toluene (30 mL) was added dropwise via syringe drive over 9 h, with the addition of further Ph_3P (328 mg, 1.25 mmol) and DEAD (222 mg, 1.275 mmol) after 4 h. On completion of addition the resulting mixture was stirred for a further h and then concentrated; purification by flash chromatography on silica gel (Et_2O/light petroleum 1:39) gave **2** as a colourless oil (73 mg, 371 μmol, 74%).

IR (neat): ν = 3005, 2975, 2930, 2860, 1730, 1445, 1380, 1250, 1210, 1185, 1155, 1140, 1095, 1065, 1035, 970, 950, 910, 850, 810, 745, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.56 (1 H, dddt, J = 10.5, 9.2, 6.25, 1.15), 5.41 (2 H, 23 line m), 5.20 (1 H, dddt, J = 10.9, 9.15, 6.1, 1.4), 4.89 (1 H, dqd, J = 7.6, 6.45, 2.75), 3.13 (1 H, ddt, J = 13.9, 9.0, 0.8), 3.08 (1 H, dtt, J = 13.9, 9.15, 1.2), 2.87 (1 H, ddd, J = 13.9, 7.5, 1.2), 2.53 (1 H, dtq, J = 14.0, 6.4, 1.7), 2.37 (1 H, 20 line sym m), 1.97 (1.97 (1 H, dqt, J = 13.0, 6.8, 0.8), 1.67 (1 H, m) 1.58 (1 H, m), 1.41 (1 H, m), 1.26 (1 H, m), 1.22 (3 H, d, J = 6.45).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 171.3 (s), 132.9 (d), 130.3 (d), 126.6 (d), 119.6 (d), 72.4 (d), 34.0 (t), 31.6 (t), 26.75 (t), 26.3 (t), 25.0 (t), 19.7 (q).

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MS (EI, 70 eV): m/z (%) = 194 (M^+, 3), 176 (4), 91 (44), 79 (100), 77 (36), 67 (40).

HRMS: m/z, for ($C_{12}H_{18}O_2$, M^+), calc.: 194.1307; found: 194.1302.

$[\alpha]_D^{25}$ for (*R*)-**2** − 58.4° (c = 1.052, $CHCl_3$). $[\alpha]_D^{25}$ for (*S*)-**2** + 62.5° (c = 0.930, $CHCl_3$).

Synthesis of 3:

6,6-Dimethoxyhexan-1-ol (10b):

Acetal **9** (18.31 g, 100.0 mmol) was dissolved in THF (100 mL) and CuI (9.52 mg, 5.0 mmol, 5 mol%) added; the suspension was cooled to − 15 °C and a warm (40 °C) 0.60 M THF solution of 3-hydroxypropylmagnesium chloride chloromagnesium salt (166 mL, 100.0 mmol, freshly prepared as described by Normant)[23] added over 15 min. After 30 min at − 15 °C the suspension was warmed to 0 °C over 2 h and sat. aq NH_4Cl (50 mL) and 33% aq NH_4OH (10 mL) added. After stirring for 15 min the layers were separated and the aqueous extracted with Et_2O (2 × 100 mL); the combined organics were washed with H_2O (30 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated to give an oil. Purification by flash chromatography on silica gel (Et_2O/light petroleum 1 : 1) gave **10b** as a colourless oil which eliminated MeOH on attempted distillation (12.65 g, 78.0 mmol, 78%).

IR (neat): ν = 3415, 2940, 2860, 1460, 1385, 1370, 1190, 1130, 1055, 915 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.28 (1 H, t, J = 5.7), 3.51 (2 H, t, J = 6.5), 3.23 (6 H, s), 2.72 (1 H, s), 1.49 (4 H, m), 1.28 (4 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 104.4 (d), 62.4 (t), 52.5 (q), 32.5 (t), 32.3 (t), 25.6 (t), 24.3 (t).

6-Benzyloxy-1,1-dimethoxyhexane (11b):

Hydroxy acetal **10b** (12.165 g, 75.0 mmol) was benzylated using the same procedure as for **10a**, giving **11b** as a colourless oil (102–104 °C/0.05 Torr, 18.47 g, 73.2 mmol, 98%).

IR (neat): ν = 3065, 3030, 2940, 2860, 1495, 1455, 1385, 1365, 1305, 1190, 1120, 1075, 1055, 1030, 915, 825, 735, 700 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.33 (4 H, m), 7.28 (1 H, m), 4.49 (2 H, s), 4.35 (1 H, t, J = 5.5), 3.47 (2 H, t, J = 6.5), 3.30 (6 H, s), 1.61 (4 H, m), 1.40 (4 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 138.6 (s), 128.2 (d), 127.5 (d), 127.35 (d), 104.3 (d), 72.7 (t), 70.2 (t), 52.4 (q), 32.3 (t), 29.6 (t), 26.0 (t), 24.4 (t).

6-Benzyloxyhexanal (12b):

Acetal **11b** (14.01 g, 55.5 mmol) was hydrolysed by the same procedure as for **11a**, giving crude **12b** as a colourless oil (10.98 g, 53.2 mmol, 96%).

IR (neat): ν = 3065, 3030, 2935, 2860, 2720, 1725, 1495, 1480, 1455, 1410, 1390, 1365, 1310, 1250, 1205, 1175, 1100, 1030, 910, 820, 735, 700 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.73 (1 H, t, J = 2.1), 7.34 (4 H, m), 7.29 (1 H, m), 4.50 (2 H, s), 3.47 (2 H, t, J = 6.4), 2.42 (2 H, dt, J = 2.1, 7.5), 1.64 (4 H, m), 1.43 (4 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 202.5 (d), 138.5 (s), 128.3 (d), 127.5 (d), 127.4 (d), 72.8 (t), 69.9 (t), 43.7 (t), 29.4 (t), 25.7 (t), 21.8 (t).

(3*Z*)-9-Benzyloxy-1,1-diisopropoxynon-3-ene (16b):

Crude **12b** (3.773 g, 18.29 mmol) was olefinated by the procedure described for **12a**, giving **16b** as a colourless oil (6.12 g, 17.56 mmol, 96%).

IR (neat): ν = 2970, 2930, 2855, 1495, 1450, 1370, 1365, 1330, 1225, 1175, 1105, 1030, 970, 880, 810, 735, 695 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.35 (4 H, m), 7.29 (1 H, m), 5.44 (2 H, m), 4.54 (1 H, t, J = 5.6), 4.50 (2 H, s), 3.87 (2 H, sept, J = 6.2), 3.47 (2 H, t, J = 6.6), 2.35 (2 H, dd, J = 5.7, 5.6), 2.06 (2 H, m), 1.63 (2 H, m), 1.39 (4 H, m), 1.20 (6 H, d, J = 6.2), 1.15 (6 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 138.7 (s), 131.9 (d), 128.4 (d), 127.7 (d), 127.5 (d), 124.5 (d), 100.0 (d), 72.9 (t), 70.45 (t), 67.8 (d), 33.8 (t), 29.75 (t), 29.5 (t), 27.5 (t), 25.95 (t), 23.4 (q), 22.6 (q).

MS (NH_3 – CI mode): m/z (%) = 366 ($M^+ + NH_4$, 7), 306 (28), 289 (100), 246 (4), 131 (20), 100 (4), 91 (7), 35 (10).

HRMS: m/z for $C_{22}H_{36}O_3$ ($M^+ + NH_4$), calc.: 366.3008; found: 366.3000.

(3*Z*,6*Z*)-12-Benzyloxy-1,1-diisopropoxydodeca-3,6-diene (17b):

Benzyloxy acetal **16b** (5.14 g, 14.75 mmol) was homologated by the same method used for the conversion of **16a** to **17a**, giving **17b** as a colourless oil (4.97 g, 12.80 mmol, 87%).

(3Z)-9-Benzyloxynon-3-enal:

IR (neat): ν = 3065, 3025, 2935, 2855, 2720, 1725, 1495, 1455, 1390, 1360, 1305, 1255, 1205, 1100, 1030, 910, 735, 700 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.64 (1 H, t, J = 2.7), 7.35 (4 H, m), 7.30 (1 H, m), 5.69 (1 H, m), 5.55 (1 H, m), 4.51 (2 H, s), 3.47 (2 H, t, J = 6.6), 3.18 (2 H, d, J = 7.2), 2.05 (2 H, m), 1.63 (2 H, m), 1.40 (4 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 199.65 (d, 138.7 (s), 135.2 (d), 128.4 (d), 127.6 (d), 127.5 (d), 118.2 (d), 72.9 (t), 70.3 (t), 42.55 (t), 29.6 (t), 29.1 (t), 27.6 (t), 25.85 (d).

(3Z,6Z)-12-Benzyloxy-1,1-diisopropoxydodeca-3,6-diene **(17b)**:

IR (neat): ν = 3010, 2970, 2930, 2860, 1495, 1455, 1380, 1365, 1330, 1225, 1205, 1175, 1105, 1030, 970, 910, 875, 810, 735, 685, 670 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.34 (4 H, m), 7.29 (1 H, m), 5.45 (4 H, m), 4.56 (1 H, t, J = 5.6), 4.50 (2 H, s), 3.875 (2 H, sept, J = 6.2), 3.47 (2 H, t, J = 6.6), 2.81 (2 H, dd, J = 5.2, 5.0), 2.39 (2 H, dd, J = 5.6, 5.4), 2.07 (2 H, m), 1.64 (2 H, m), 1.39 (4 H, m), 1.21 (6 H, d, J = 6.2), 1.15 (6 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 138.7 (s), 130.1 (d), 130.1 (d), 128.3 (d), 127.8 (d), 127.6 (d), 127.5 (d), 124.6 (d), 99.9 (d), 72.8 (t), 70.4 (t), 67.8 (d), 33.8 (t), 29.7 (t), 29.6 (t), 29.5 (t), 27.2 (t), 25.9 (t), 25.4 (q), 22.6 (q).

MS (NH_3 – CI mode): m/z (%) = 406 ($M^+ + MH_4$, 5), 346 (23), 329 (100), 286 (22), 271 (25), 251 (11), 179 (9), 161 (9), 131 (68), 108 (11), 91 (23), 35 (16).

HRMS: m/z for $C_{25}H_{44}NO_3$ ($M^+ + NH_4$) calc.: 406.3321; found: 406.3314.

(6*Z*,9*Z*)-12,12-Diisopropoxydodeca-6,9-dien-1-ol (18b):

The benzyl ether **17b** (3.15 g, 8.10 mmol) was reductively cleaved by the same procedure used for **17a**, giving **18b** (2.17 g, 7.27 mmol, 90%) as a colourless oil.

IR (neat): ν = 3420, 3010, 2970, 2930, 2860, 1465, 1380, 1330, 1225, 1175, 1125, 1030, 970, 910, 875, 810, 725, 665 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 5.38 (2 H, m), 5.30 (2 H, m), 4.49 (1 H, t, J = 5.5), 3.81 (2 H, sept, J = 6.2), 3.54 (2 H, t, J = 6.5), 2.73 (2 H, dd, J = 5.5, 5.5), 2.42 (1 H, br s), 2.33 (2 H, dd, J = 5.5, 5.5), 2.005 (2 H, d, J = 6), 1.49 (2 H, m), 1.32 (4 H, m), 1.13 (6 H, d, J = 6), 1.08 (6 H, d, J = 6).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 130.1 (d), 130.0 (d), 127.7 (d), 124.5 (d), 99.85 (d), 67.8 (d), 62.5 (t), 33.7 (t), 32.6 (t), 29.4 (t), 27.1 (t), 25.8 (t), 25.4 (t), 23.3 (q), 22.5 (q).

MS (NH_3 – CI mode): m/z (%) = 239 (M^+ + H – *i*PrOH, 98), 196 (100), 179 (50), 163 (21), 161 (21), 131 (50), 35 (37).

(3*Z*,6*Z*)-12-Hydroxydodeca-3,6-dienoic Acid (19b):

The hydroxy acetal **18b** (2.417 g, 8.11 mmol) was hydrolysed and oxidised as described for the preparation of **19a**, giving the acid **19b** (1.412 g, 6.65 mmol, 82%) as a pale yellow oil.

(3Z,6Z)-12-Hydroxydodeca-3,6-dienal:

IR (neat): ν = 3390, 3010, 2970, 2930, 2860, 2730, 1725, 1455, 1375, 1335, 1175, 1110, 1035, 915, 830, 735 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.66 (1 H, t, J = 2.0), 5.62 (2 H, m), 5.37 (2 H, m), 3.63 (2 H, t, J = 6.6), 3.22 (2 H, dd, J = 7.0, 2.0), 2.78 (2 H, dd, J = 6.5, 6.0), 2.05 (2 H, m), 1.85 (1 H, br s), 1.57 (2 H, m), 1.37 (4 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 199.7 (d), 133.6 (d), 130.85 (d), 126.8 (d), 118.4 (d), 62.9 (t), 42.6 (t), 32.7 (t), 29.4 (t), 27.3 (t), 26.05 (t), 25.5 (t).

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(3Z,6Z)-12-Hydroxydodeca-3,6-dienoic Acid **(19b)**:

IR (neat): ν = 3410, 3010, 2930, 2860, 1710,1400, 1260, 1175, 1050, 730 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 7.44 (2 H, br s), 5.53 (2 H, m), 5.33 (2 H, m), 3.60 (2 H, t, J = 6.5), 3.11 (2 H, d, J = 4.8), 2.76 (2 H, dd, J = 5.2, 5.2), 2.02 (2 H, m), 1.53 (2 H, m), 1.33 (4 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 176.7 (s), 131.9 (d), 130.6 (d), 126.9 (d), 120.6 (d), 62.6 (t), 32.75 (t), 32.2 (t), 29.3 (t), 27.2 (t), 25.8 (t), 25.3 (t).

MS (NH_3 – CI mode, for methyl ester): m/z (%) = 244 ($M^+ + NH_4$, 100), 227 ($M^+ + H$, 37), 195 (5), 177 (4), 35 (15).

HRMS: m/z, for $C_{13}H_{26}NO_3$, ($M^+ + NH_4$), calc.: 244.1913; found: 244.1920.

(3Z,6Z)-Dodeca-3,6-dien-12-olide (3):

Hydroxy acid **19b** (601 mg, 2.830 mmol) was dissolved in THF (20 mL) and half of the resulting solution added dropwise over a period of 4 h to a stirred solution of DEAD (2.521 g, 14.30 mmol) and Ph_3P (3.71 g, 14.10 mmol) in toluene 400 mL). Once addition had been completed further DEAD (1.263 g, 7.16 mmol) and Ph_3P (1.651 g, 7.04 mmol) were added, followed by addition of the remaining **19b** solution over a further 4 h. Workup as for the lactonisation of **19a** gave crude lactone **3**; purification by flash chromatography on silica gel (Et_2O/light petroleum, 1 : 19) gave the pure lactone as a colourless oil (374 mg, 1.925 mmol, 68 %).

IR (neat): ν = 3010, 2935, 2860, 1735, 1445, 1395, 1380, 1340, 1280, 1245, 1170, 1150, 1065, 1030, 985, 915, 840, 720, 690 cm^{-1}.

^1H NMR (360 MHz, $CDCl_3$): δ = 5.47 (4 H, 9 line sym m) 4.08 (2 H, t, J = 4.9), 3.07 (2 H, J = 7.5), 2.90 (2 H, td, J = 6.8, 1.0), 2.04 (2 H, dt, J = 7.5, 7.5), 1.70 (2 H, 11 line m), 1.44 (2 H, m), 1.35 (2 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 171.1 (s), 133.4 (d), 131.4 (d), 126.9 (d), 119.0 (d), 65.8 (t), 34.1 (t), 27.6 (t), 26.2 (t), 25.7 (t), 25.6 (t).

MS (EI, 70 eV): m/z (%) = 194 (M^+, 8), 167 (15), 149 (35), 107 (26), 94 (40), 79 (53).

HRMS: m/z for $C_{12}H_{18}O_2$ (M^+) calc.: 194.1307; found: 194.1310.

Synthesis of 4:

(5Z,8Z)-13-Benzyloxytetradeca-5,8-dienoic Acid (21):

The acetal **16a** (3.485 g, 10.00 mmol) was hydrolysed using the general procedure, and the crude aldehye dissolved in THF (10 mL) and added dropwise with *pre-cooling by contact with the flask walls* at – 100 °C to a solution of the ylid **24**, formed by stirring the phosphonium salt (8.86 g, 20.00 mmol) in THF (50 mL) and HMPA (8.5 mL) with a solution of NaHMDS in THF/toluene (1 : 3, 43.2 mL of 0.92 M solution) at 25 °C for 2 h. The resulting slurry was allowed to warm to 0 °C over 3–4 h, then quenched by the addition of sat. aq NH_4Cl (20 mL), acidified to pH1 with aq HCl and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with 2 M HCl (10 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated to give a thick oil. Purification by flash chromatography on silica gel (Et_2O/light petroleum ether/AcOH, 50 : 50 : 1, eluant) gave the acid **21** (1.94 g, 58.9 mmol, 59 %).

IR (neat): ν = 3400–2800, 3010, 2935, 2860, 1710, 1495, 1455, 1375, 1340, 1240, 1205, 1135, 1090, 1065, 1030, 915, 735, 695 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 10.48 (1 H, br s), 7.36 (4 H, m), 7.31 (4 H, m), 5.40 (4 H, m), 4.55 (2 H, AB q, J = 11.9, δ_A = 4.57, δ_B = 4.45), 3.55 (1 H, m), 2.79 (2 H, t, J = 5.8), 2.38 (2 H, t, J = 7.3), 2.11 (4 H, m), 1.73 (2 H, m), 1.62 (2 H, m), 1.50 (2 H, m), 1.22 (3 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 179.6 (s), 139.0 (s), 130.1 (d), 129.35 (d), 128.6 (d), 128.4 (d), 128.0 (d), 127.8 (d), 127.5 (d), 74.9 (d), 70.3 (t), 36.25 (t), 33.5 (t), 27.3 (t), 26.5 (t), 25.7 (t), 25.6 (t), 24.6 (t), 19.65 (q).

MS (NH_3 – CI mode): m/z (%) = 348 ($M^+ + NH_4$, 17), 331 ($M^+ + H$, 24), 264 (14), 212 (50), 195 (36), 168 (72), 150 (27), 132 (30), 124 (50), 116 (24), 108 (23), 106 (21), 99 (100), 94 (12), 91 (18), 78 (56), 61 (90), 44 (74).

HRMS: m/z for $C_{22}H_{31}O_3$ ($M^+ + H$) calc.: 331.2273; found: 331.2220.

$[\alpha]_D^{25}$ for (*R*)-**21** – 4.3° (c = 1.054, $CHCl_3$). $[\alpha]_D^{25}$ for (*S*)-**21** + 3.95° (c = 2.380, $CHCl_3$).

(5Z,8Z)-13-Hydroxytetradeca-5,8-dienoic Acid (22):

The benzyloxy acid **21** (4.808 g, 14.55 mmol) was dissolved in THF/NH_3 (1 : 1, (60 mL) at – 40 °C; *t*-BuOH (10 mL) was added followed by the addition of Li metal (~ 300 mg, excess) in small pieces until a consistent dark blue colour was obtained. After 15 min the reaction was quenched by the addition of NH_4Cl (1 g); the resulting suspension was allowed to warm to 0 °C (with concomitant evaporation of NH_3) over 1 h. H_2O (20 mL) was added, followed by Et_2O (30 mL); residual NH_4OH was neutralised by addition of 2 M HCl to pH1. The layers were separated and the aqueous extracted with Et_2O (2 × 20 mL); the combined ethereal layers were washed with 2 M HCl (10 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography on silica gel (Et_2O/light petroleum ether/AcOH, 50 : 50 : 1, eluant) gave the hydroxy acid **22** (3.158 g, 13.14 mmol, 90 %) as a colourless oil.

IR (neat): ν = 3360, 3010, 2935, 2860, 1710, 1455, 1410, 1375, 1240, 1155, 1130, 1085, 1045, 980, 925, 860, 830, 730, 695 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 8.01 (2 H, br s), 5.33 (4 H, m), 3.79 (1 H, m), 2.74 (2 H, dd, J = 5.5, 5.5), 2.31 (2 H, t, J = 7.5), 2.07 (4 H, m), 1.66 (2 H, quint, J = 7), 1.43 (4 H, m), 1.15 (3 H, d, J = 6).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 178.8 (s), 129.8 (d), 129.2 (d), 128.6 (d), 128.1 (d), 68.1 (d), 38.5 (t), 33.4 (t), 27.1 (t), 26.4 (t), 26.4 (t), 25.6 (t), 24.6 (t), 23.1 (q).

$[\alpha]_D^{25}$ for (*R*)-**22** – 3.1° (c = 1.012, $CHCl_3$). $[\alpha]_D^{25}$ for (*s*)-**22** + 3.2° (c = 2.214, $CHCl_3$).

(5Z,8Z)-Tetradeca-5,8-dien-13-olide (4):

Ph_3P (12.82 g, 48.9 mmol) was dissolved in toluene (950 mL) and DEAD (8.69 g, 49.9 mmol) added over 2 min. A solution of the hydroxy acid **22** (2.350 g, 9.778 mmol) in toluene (50 mL) was added dropwise over 7 h, with the addition of more Ph_3P (6.41 g, 24.4 mmol) and DEAD (4.35 g, 25.0 mmol) after 4 h. After stirring for a further 30 min the solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (30 mL); the resulting solution was poured into light petroleum (300 mL) resulting in precipitation of an amorphous solid. The supernatant was filtered through a short column of silica gel, the precipitate redissolved in CH_2Cl_2 and the cycle repeated until no further product could be detected in the supernatant. The combined filtrates were concentrated and the residue purified by flash chromatography on silica gel to give the lactone **4** (1.543 g, 6.940 mmol, 70 %).

IR (neat): ν = 3010, 2935, 2860, 1730, 1460, 1415, 1400, 1375, 1315, 1280, 1245, 1210, 1160, 1135, 1085, 1045, 1000, 975, 940, 920, 885, 815, 715 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.335 (3 H, 28 line multiplet) 5.18 (1 H, ddddd, J = 10.7, 10.6, 5.0, 2.1, 1.1), 4.94 (1 H, dqd, J = 10.1, 6.3, 3.2), 3.05 (1 H, dtd, J = 15.0, 9.7, 1.1), 2.32 (1 H, ddd, J = 14.6, 9.6, 3.1), 2.18 (1 H, ddd, J = 14.6, 10.6, 3.1), 2.30–2.12 (3 H, m), 1.90 (1 H, ddtd, J = 16.5, 9.6, 4.9, 2.1), 1.74 (1 H, dtdd, J = 13.9, 9.3, 4.7, 3.1), 1.61 (2 H, m), 1.50 (2 H, m), 1.30 (2 H, m), 1.09 (3 H, d, J = 6.3).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 173.4 (s), 129.0 (d), 128.8 (d), 128.1 (d), 127.8 (d), 69.2 (d), 35.15 (t), 33.8 (t), 26.2 (t), 26.1 (t), 25.8 (t), 25.6 (t), 24.9 (t), 20.7 (q).

MS (EI, 70 eV): m/z (%) = 222 (M^+, 31), 180 (32), 166 (15), 140 (28), 121 (24), 93 (66), 79 (100), 67 (75), 55 (38), 41 (67).

HRMS: m/z, for $C_{14}H_{22}O_2$ (M^+), calc.: 222.1620; found: 222.1623.

$[\alpha]_D^{25}$ for (*R*)-**4** – 30.4° (c = 1.240, $CHCl_3$). $[\alpha]_D^{25}$ for (*S*)-**4** + 31.0° (c = 1.410, $CHCl_3$).

Synthesis of 1:

(*R*/*S*)-9,9-Dimethoxynonan-2-ol (14):

MeMgBr (6.80 mL of 3.0 M solution in Et_2O, 20.40 mmol), was added to anhydrous THF (30 mL) under N_2. The solution was cooled to 0 °C and a solution of aldehyde **13** (1.920 g, 10.19 mmol) in

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THF (10 mL) added dropwise over 10 min. After a further 30 min at 0 °C half-sat. aq NH_4Cl (15 mL) was added slowly, followed by Et_2O (30 mL). The layers were separated and the aqueous extracted with Et_2O (3 × 30 mL); the combined ethereal layers were washed with H_2O (15 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude product. Purification by flash chromatography on silica gel (Et_2O/light petroleum 1:1) gave **14** as a colourless oil (1.821 g, 8.91 mmol, 89%).

IR (neat): ν = 3420, 2930, 2855, 1465, 1370, 1300, 1190, 1130, 1055, 945, 915, 850, 795, 725 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 4.32 (1 H, t, J = 5.7), 3.74 (1 H, m), 3.27 (6 H, s), 1.80 (1 H, br s), 1.55 (2 H, br m), 1.40–1.20 (10 H, br m), 1.14 (3 H, d, J = 6.0).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 104.55 (d), 68.05 (d), 52.6 (q), 39.3 (t), 32.5 29.6 (t), 29.5 (t), 25.7 (t), 24.6 (t), 23.5 (q).

(*R*/*S*)-8-Hydroxynonanal (12c):

Hydroxy acetal **14** (817 mg, 4.00 mmol) was dissolved in THF (15 mL), H_2O (40 mL) and *i*-PrOH (5 mL); the solution was warmed to reflux and *p*-TsOH (250 mg, 1.32 mmol) added. After 30 min the solution was cooled to 0 °C and NaOAc (0.5 g, excess) added followed by Et_2O (50 mL). The layers were separated and the aqueous extracted with Et_2O (3 × 30 mL), the combined ethereal layers were washed with sat. aq $NaHCO_3$ (15 mL), H_2O (10 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated to give the crude product. Distillation at reduced pressure gave **12c** as a colourless oil (100–120 °C/0.1 Torr, 612 mg, 3.867 mmol, 97%).

IR (neat): ν = 3395, 2930, 2865, 2720, 1720, 1460, 1410, 1375, 1340, 1105, 1065, 1030, 940, 845, 725 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.68 (1 H, s), 3.70 (1 H, m), 2.34 (3 H, br m), 1.56 (2 H, br m), 1.40–1.20 (8 H, br m), 1.10 (3 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 203.1 (d), 67.8 (d), 43.8 (t), 39.1 (t), 29.3 (t), 29.0 (t), 25.5 (t), 23.4 (q), 21.9 (t).

(9*Z*)-12,12-Diisopropoxydodec-9-en-2-ol (16c):

Hydroxy aldehyde **12c** (291 mg, 1.839 mmol) was reacted with the ylide formed from **8** (2.401 g, 4.80 mmol) and NaHMDS (4.87 mL of 0.92 M solution in THF/toluene, 1:4, 4.50 mmol) in THF (12 mL) and toluene (60 mL) using the procedure described for **16a**. Workup and purification by flash chromatography on silica gel gave **16c** as a colourless oil (471 mg, 1.567 mmol, 85%).

IR (neat): ν = 3420, 2970, 2930, 2855, 1465, 1380, 1330, 1225, 1175, 1130, 1030, 970, 880, 810, 725 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 5.38 (2 H, 9-line sym m), 4.50 (1 H, t, J = 5.6), 3.83 (2 H, sept, J = 6.2), 3.74 (1 H, m), 2.30 (2 H, dd, J = 5.7, 5.7), 1.99 (2 H, m), 1.81 (1 H, br s), 1.40–1.20 (10 H, br m), 1.15 (6 H, d, J = 6.0), 1.13 (3 H, d), 1.10 (6 H, d, J = 6.0).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 132.0 (d), 124.3 (d), 100.1 (d), 68.0 (d), 67.8 (d), 39.3 (t), 33.7 (t), 29.6 (t), 29.5 (t), 29.3 (t), 27.5 (t), 25.8 (t), 23.5 (q), 23.4 (q), 22.3 (q).

MS (NH_3 – CI mode): m/z (%) = 318 ($M^+ + NH_4$, 4), 241 (94), 198 (100), 181 (10), 153 (8), 131 (13), 35 (40).

(3*Z*)-11-Hydroxydodec-3-enoic Acid (20c):

Hydroxy acetal **16c** (361 mg, 1.201 mmol) was hydrolysed and then oxidised using the method described for **16a**, to give **20c** as a viscous oil (210 mg, 0.980 mmol, 82%).

(3Z)-11-Hydroxydodec-3-enal:

IR (neat): ν = 3385, 3020, 2930, 2855, 1725, 1465, 1375, 1335, 1265, 1105, 1035, 880, 800, 730 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.64 (1 H, s), 5.68 (1 H, 4 line m), 5.53 (1 H, 4 line m), 3.77 (1 H, m), 3.17 (2 H, d, J = 7.1), 2.01 (2 H, m), 1.80 (1 H, br s), 1.45–1.20 (10 H, br m), 1.16 (3 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 199.9 (d), 135.5 (d), 118.1 (d), 68.1 (d), 42.6 (t), 39.3 (t), 29.5 (t), 29.3 (t), 27.65 (t), 25.75 (t), 23.6 (q).

(3Z)-11-Hydroxydodec-3-enoic Acid **(20c)**:

IR (neat): ν = 3380–2600, 3025, 2930, 2855, 1715 br s, 1460, 1410, 1375, 1300, 1215, 1180, 1130, 1065, 935, 910, 840, 735 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 6.53 (2 H, br s), 5.55 (2 H, 8 line sym m), 3.79 (1 H, m), 3.10 (2 H, d, J = 5.8), 2.02 (2 H, m), 1.50–1.22 10 H, m), 1.17 (3 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 177.2 (s), 133.9 (d), 120.4 (d), 68.4 (d), 39.05 (t), 32.8 (t), 29.4 (t), 29.1 (t), 29.1 (t), 27.3 (t), 25.6 (t), 23.2 (q).

(3*Z*)-Dodec-3-en-11-olide (1):

The hydroxy acid **20c** (374 mg, 1.745 mmol) was dissolved in toluene (25 mL) and added dropwise to a solution of DEAD (1.631 g, 8.90 mmol) and Ph_3P (2.290 g, 8.725 mmol) in toluene (350 mL) over 6 h. Workup as for **2** gave the lactone **1** as a colourless mobile oil (243 mg, 1.238 mmol, 72%).

IR (neat): ν = 3020, 2935, 2855, 1730, 1145, 1400, 1375, 1355, 1300, 1250, 1215, 1185, 1150, 1140, 1095, 1060, 1035, 1010, 975, 950, 900, 855, 815, 790, 740, 725, 700 cm^{-1}.

^1H NMR was as reported by Oehlschlager.[6]

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 171.3 (s), 134.9 (d), 121.5 (d), 72.8 (d), 33.9 (t), 30.8 (t), 27.3 (t), 25.5 (t), 25.35 (t), 24.8 (t), 24.3 (t), 19.7 (q).

MS (EI, 70 eV): m/z (%) = 196 (M^+, 17), 136 (18), 110 (26), 109 (16), 96 (25), 95 (29), 82 (45), 81 (51), 69 (22), 68 (38), 67 (67), 55 (66), 54 (100), 41 (57), 39 (25), 29 (17).

HRMS: m/z, for $C_{12}H_{20}O_2$ (M^+) calc.: 196.1463; found: 196.1459.

Synthesis of 6:

9-Hydroxynonanal (12d):

Dec-9-en-1-ol (**15**; 540 mg, 3.445 mmol) was dissolved in CH_2Cl_2 (50 mL) and MeOH (15 mL) and Sudan III (2 mg) added; the solution was cooled to − 80 °C and O_3 bubbled through until the red colour of the dye discharged. The yellow solution was immediately purged of O_3 by passage of a stream of dry N_2 for 15 min; Ph_3P (906 mg, 3.45 mmol) was then added and the solution allowed to warm to 25 °C over 1 h. Concentration and purification by flash chromatography on silica gel (Et_2O/light petroleum 3:1) gave the product as a yellow solid; distillation (bulb-to-bulb, 100–120 °C bath/0.1 Torr) gave **12d** as a white, waxy solid (436 mg, 2.76 mmol, 80%).

IR (paraffin): ν = 3420, 1720, 1375, 1150, 1100, 1075, 1050, 1015, 960, 905, 850, 720 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 9.67 (1 H, s), 3.52 (2 H, t, J = 6.6), 2.68 (1 H, br s), 2.35 (2 H, dt, J = 2.6, 7.3), 1.50 (4 H, m), 1.24 (8 H, br s).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 203.2 (d), 62.6 (t), 43.8 (t), 32.6 (t), 29.2 (t), 29.1 (t), 29.0 (t), 25.6 (t), 21.9 (t).

(9*Z*)-12,12-Diisopropoxydodec-9-en-1-ol (16d):

Phosphonium salt **8** (1.601 g, 3.20 mmol) in THF (8 mL) and toluene (40 mL), was treated with NaHMDS (3.25 mL of 0.92 M solution in THF/toluene, 1:3) as previously described; the resulting ylide solution was cooled to − 100 °C. A solution of **12d** (194 mg, 1.226 mmol) in THF (5 mL), prepared by warming to ca. 40 °C, was added dropwise to the cooled ylid solution (*not* via the flask walls) over 5 min. Warming to 25 °C over 2 h was followed by quenching with sat. aq NH_4Cl chloride solution (10 mL) and addition of Et_2O (30 mL). The layers were separated and the aqueous extracted with Et_2O (2 × 30 mL), the combined ethereal layers were washed with H_2O (15 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated to give the crude product. Purification by flash chromatography on silica gel (Et_2O/light petroleum, 1:1) gave **16d** as a colourless oil (307 mg, 1.022 mmol, 84%).

IR (neat): ν = 3410, 2970, 2930, 2855, 1465, 1380, 1330, 1230, 1175, 1125, 1030, 875, 810, 725 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 5.42 (2 H, 9 line sym m), 4.53 (2 H, t, J = 5.7), 3.86 (2 H, sept, J = 6.2), 3.62 (2 H, t, J = 6.7), 2.33 (2 H, dd, J = 6.0, 6.0), 2.02 (2 H, m), 1.54 (2 H, m), 1.30 (10 H, br s), 1.19 (6 H, d, J = 6.2), 1.13 (6 H, d, J = 6.2).

^{13}C NMR (66.7 MHz, $CDCl_3$): δ = 132.2 (d), 124.4 (d), 100.1 (d), 67.9 (d), 63.1 (t), 33.8 (t), 32.9 (t), 29.6 (t), 29.6 (t), 29.5 (t), 29.3 (t), 27.6 (t), 25.8 (t), 23.5 (q), 22.35 (q).

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MS (NH_3 – CI mode): *m/z* (%) = 318 ($M^+ + NH_4$, 12), 241 (64), 198 (100), 131 (28).

(3*Z*)-12-Hydroxydodec-3-enoic Acid (20d):
The hydroxy acetal **16d** (306 mg, 1.018 mmol) was dissolved in THF (20 mL) and the solution warmed to reflux. *p*-TsOH (500 μL of 0.1 M aqueous solution) was added; after 10 min the solution was cooled to 0 °C and Et_2O (30 mL) and H_2O (10 mL) added. The layers were separated and the aqueous extracted with Et_2O (3 × 20 mL), the combined ethereal layers were washed with H_2O (10 mL) and brine (20 mL) and concentrated. The crude hydroxy aldehyde was dissolved in CH_2Cl_2(15 mL); 1-methylcyclohex-1-ene (250 mg, 2.50 mmol) was added followed by the H_2O washing from the hydrolysis. The two-phase mixture was cooled to 0 °C and H_2NSO_3H (1.0 mL of 1.0 M aqueous solution) added, followed by $NaClO_2$ (3.10 mL of 1.0 M aqueous solution) with rapid stirring. After 15 min the temperature was allowed to rise to 25 °C over 30 min; the layers were separated and the aqueous extracted with more CH_2Cl_2 (2 × 15 mL). The combined organic layers were concentrated and the residue redissolved in Et_2O (25 mL); the solution was extracted with 0.5 M Na_2CO_3 and the combined extracts washed with Et_2O (10 mL), acidified to pH1 with 2 M HCl and then extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were washed with 2 M HCl (10 mL), H_2O (5 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated to give **20d** in > 95% purity by NMR (183 mg, 854 μmol, 85%).

(3Z)-12-Hydroxydodec-3-enal:
IR (neat): *ν* = 3380, 2925, 2855, 1725, 1465, 1260, 1105, 1025, 875, 800 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): *δ* = 9.66 (1 H, t, *J* = 1.8), 5.69 (1 H, 4 line sym m), 5.54 (1 H, 4 line sym m), 3.63 (2 H, t, *J* = 6.7), 3.19 (2 H, d, *J* = 7.0), 2.00 (2 H, m), 1.66 (1 H, br s), 1.56 (2 H, br m), 1.30 (10 H, br m).

^{13}C NMR (66.7 MHz, $CDCl_3$): *δ* = 200.0 (d), 135.6 (d), 118.1 (d), 63.1 (t), 42.7 (t), 32.8 (t), 29.5 (t), 29.4 (t), 29.35 (t), 29.2 (t), 27.7 (t), 25.8 (t).

(3Z)-12-Hydroxydodec-3-enoic Acid **(20d)**:
IR (paraffin): *ν* = 3600–2600, 1705, 1385, 1310, 1260, 1215, 1060, 1025, 980, 910, 725, 705 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): *δ* = 7.46 (2 H, br s), 5.53 (2 H, 8 line sym m), 3.59 (2 H, t, *J* = 6.6), 3.07 (2 H, d, *J* = 5.6), 2.00 (2 H, m), 1.50 (2 H, m), 1.26 (10 H, br m).

^{13}C NMR (66.7 MHz, $CDCl_3$): *δ* = 177.0 (s), 133.7 (d), 120.4 (d), 62.65 (t), 32.7 (t), 32.3 (t), 29.35 (t), 29.3 (t), 29.2 (t), 29.05 (t), 27.3 (t), 25.6 (t).

(3*Z*)-Dodec-3-en-12-olide (6):
The hydroxy acid **20d** (164 mg, 765 μmol) was dissolved in toluene (25 mL) and added dropwise over 6 h to a stirred solution of Ph_3P (1.00 g, 3.825 mmol) and DEAD (680 mg, 3.90 mmol) in toluene (120 mL) under N_2. After stirring for a further 30 min the solution was concentrated and the crude product purified by flash chromatography on silica gel (Et_2O/light petroleum, 1:19) to give the lactone **6** as a colourless, mobile oil (22 mg, 620 μmol, 81%).

IR (neat): *ν* = 3020, 2930, 2855, 1735, 1460, 1400, 1380, 1345, 1295, 1250, 1180, 1145, 1110, 1025, 980, 795, 775 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): *δ* = 5.54 (2 H, m), 4.08 (2 H, t, *J* = 5.2), 3.04 (2 H, dd, *J* = 3.5, 3.5), 2.13 (2 H, ddt, *J* = 2.8, 6.7, 6.1), 1.65 (2 H, tt, *J* = 6.6, 5.2), 1.41 (2 H, m), 1.28 (6 H, m).

^{13}C NMR (66.7 MHz, $CDCl_3$): *δ* = 171.95 (s), 134.8 (d), 121.3 (d), 64.4 (t), 33.9 (t), 26.9 (t), 26.6 (t), 26.4 (t), 25.8 (t), 25.2 (t), 24.7 (t), 23.6 (t).

MS (EI, 70 eV): *m/z* (%) = 196 (M^+, 18), 178 (8), 136 (17), 126 (8), 121 (10), 112 (23), 95 (29), 81 (50), 67 (75), 54 (100), 41 (74).

HRMS: *m/z* for $C_{12}H_{20}O_2$ (M^+) calc.: 196.1463; found: 196.1467.

Synthesis of 7:
(5*Z*)-13-Hydroxytetradec-5-enoic Acid (23):
The hydroxy acetal **14** (282 mg, 1.380 mmol) was hydrolysed as previously described and the crude hydroxy aldehyde **12c** in THF (5 mL) added dropwise at 0 °C to a stirred suspension of the ylid **25**, forming by treating the (4-carboxybutyl)triphenylphosphonium bromide (2.62 g, 6.00 mmol) in THF (30 mL) with KOBu-*t* (15.0 mL of 0.78 M solution in THF, 11.70 mmol) at 25 °C for 30 min. After 30 min at 0 °C sat. aq NH_4Cl (10 mL) was added, followed by acidification to pH1 using 2 N aq HCl, the layers were separated and the aqueous extracted with Et_2O (3 × 30 mL), the combined ethereal layers were washed with H_2O (10 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated to give the crude product. Purification by flash chromatography on silica gel (Et_2O/light petroleum/AcOH, 50:50:1) gave the hydroxy acid **23** (258 mg, 1.064 mmol, 82%) (*Z*/*E* of 94:6, contaminated with ca. 5% (*Z*-dec-5-endioic acid).

IR (neat): *ν* = 3600–2400, 2930, 2855, 1710, 1495, 1455, 1410, 1375, 1240, 1130, 1045, 935, 800, 730, 695 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): *δ* = 7.44 (2 H, br s), 5.36 (2 H, 9 line sym m), 3.78 (1 H, m), 2.315 (2 H, t, *J* = 7.3), 2.05 (2 H, m), 1.97 (2 H, m), 1.66 (2 H, m), 1.45–1.20 (10 H, br m), 1.15 (3 H, d, *J* = 6.0).

^{13}C NMR (66.7 MHz, $CDCl_3$): *δ* = 178.9 (s), 131.2 (d), 128.4 (d), 68.3 (d), 39.1 (t), 33.55 (t), 29.5 (t), 29.4 (t), 29.2 (t), 27.2 (t), 26.45 (t), 25.6 (t), 24.7 (t), 23.2 (q).

(5*Z*)-Tetradec-5-en-13-olide (7):
The hydroxy acid **23** (206 mg, 850 μmol) was dissolved in toluene (25 mL) and the solution added dropwise over 5 h to a solution of DEAD (890 mg, 5.15 mmol) and Ph_3P (1.313 g, 5.00 mmol) in toluene (75 mL). Workup as before gave lactone **7** as a colourless mobile oil (138 mg, 615 μmol, 72%).

IR (neat): *ν* = 2930, 2860, 1730, 1460, 1415, 1375, 1345, 1325, 1295, 1245, 1205, 1185, 1170, 1155, 1130, 1110, 1085, 1040, 1015, 995, 970, 935, 915, 900, 875, 805, 770, 705, 665 cm^{-1}.

^1H NMR was as reported by Oehlschlager.[6]

^{13}C NMR (66.7 MHz, $CDCl_3$): *δ* = 173.5 (s), 131.0 (d), 128.95 (d), 69.4 (d), 34.7 (t), 33.9 (t), 27.0 (t), 26.7 (t), 26.3 (t), 25.3 (t), 25.0 (t), 25.0 (t), 23.3 (t), 20.8 (q).

MS (EI, 70 eV): *m/z* (%) = 224 (M^+, 47), 195 (9), 183 (9), 181 (10), 164 (15), 150 (11), 140 (17), 126 (56), 110 (37), 95 (47), 81 (100), 67 (93), 55 (68), 41 (89), 29 (26).

HRMS: *m/z* for $C_{14}H_{24}O_2$ (M^+) calc.: 224.1776; found: 224.1773.

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(52) Compound **9** (technical grade) may be purchased from Aldrich Chemical Co.

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