Titanium(II)-based *Z*-reduction of alkynes. Syntheses of deuterium labelled linolenic and oleic acids and (3*E*,8*Z*,11*Z*)-tetradeca-3,8,11-trienyl acetate, the sex pheromone of a tomato pest, *Scrobipalpuloides absoluta*

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An operationally simple Ti^{II}-mediated, stereo- and regio-specific reduction of isolated, conjugated and methylene 'skipped' polyynes to the corresponding *Z*-polyenes in a one-pot procedure is described and applied *inter alia* to the syntheses of deuterium labelled linolenic and oleic acids. Final quenching with D_2O (instead of H_2O) results in regio- and stereo-specific *Z*-dideuteration of the alkyne. The synthesis of (3*E*,8*Z*,11*Z*)-tetradeca-3,8,11-trienyl acetate, the major sex pheromone of *Scrobipalpuloides absoluta*, a destructive pest of tomatoes, and the (3*Z*,8*Z*,11*Z*)-isomer, utilises this methodology in key reduction steps, and under- or over-reduction are negligible.

A very large number of biologically important molecules incorporate carbon-carbon double bonds, in particular patterns and with defined (*Z* or *E*) configurations. An important illustrative series spans oleic, linoleic, linolenic and arachidonic acids, all with *Z*-configured double bonds, and excepting oleic acid, incorporate the methylene skipped polyene arrangement. There has been considerable interest in the acquisition of labelled polyunsaturated fatty acids for use in biosynthetic studies, particularly of insect pheromones, and in the synthesis of the pheromones themselves. The vast majority of *Lepidopteran* pheromones are straight chain, unsaturated esters, alcohols *etc.* with quite precise requirements regarding double-bond configuration for the maintenance of biological activity.[1] This general situation has stimulated much of the work directed towards the stereospecific creation of carbon-carbon double bonds.

Traditional methods for the formation of olefins include the Wittig reaction and the selective partial reduction of alkynes. However, these approaches are often unable to provide the geometric purity necessary for many studies, particularly physioactivity studies involving pheromones. Methods developed to provide increased stereocontrol have included the hydro- or carbo-metallation/hydrolysis of alkynes,[2] and the transition metal catalysed couplings of allylic substrates with vinylic organometallic reagents.[3] The use of cycloalkenes as starting materials, as a means of controlling the double bond geometry, has also found application.[4] Despite these developments, the reduction of polyynes to obtain the corresponding polyenes remains an attractive route, particularly for methylene skipped polyenes, as the required skipped polyynes are accessible by metal-mediated coupling of alk-1-ynes and prop-2-ynylic halides. In these reductions, the geometric purity of the resultant alkene is an abiding concern, as is the efficiency of the conversion that ideally should occur without under- or over-reduction of the triple bonds.

The partial reduction of alkynyl systems to give polyene systems was recently discussed by Meinwald and co-workers,[5] and a number of procedures for the reduction of the skipped triyne system to the corresponding skipped triene system were explored. Heterogeneous hydrogenation with Lindlar catalyst (Pd–$CaCO_3$, poisoned with quinoline), gave the product contaminated with other isomers, although after column chromatography on $AgNO_3$–SiO_2 the required compound was obtained in 40% yield.[5] Hydrogenation using a Cu–Zn couple also resulted in contamination with *trans*-isomers and products of under- and over-reduction.[6] Meinwald also observed that a modified P2-Nickel reduction of a substrate containing only a single triple bond, provided the desired compound (90%), mixed with starting material (5%) and the completely reduced material (5%).[5]

Trost and Braslau[7] obtained the *Z*-olefin from the corresponding alkyne by employing an homogenous Pd^0-catalysed reduction in the presence of acetic acid and a silicon hydride, and achieved the formation of a *Z*,*Z*-diene in about 93% geometric purity. A more selective transfer hydrogenation protocol was described by Tani *et al.*[8] and employed HCO_2H–NEt_3 as the hydrogen donor with a Pd^0-catalyst. A high *Z*:*E* ratio was achieved in the product and this method was promising for the synthesis of polyene systems.

Deuterium incorporation

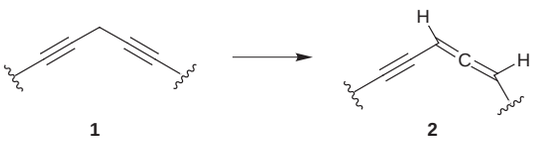
For some biosynthetic studies, the regioselective incorporation of deuterium is necessary. Deuteration *via* heterogeneous catalysis results in undesirable deuterium scrambling.[9] The homogeneous Wilkinson's catalyst, which reacts with alkynes in a sequence of two separate reductions (*i.e.* acetylene to olefin followed by olefin to saturated compound), overcomes this scrambling. Although the rate of alkene reduction is slowed, relative to the initial alkyne hydrogenation, by the addition of relatively acidic alcohols (2,2,2-trifluoroethanol or phenol),[10] further refinement of this method is required for it to become a synthetically useful preparation of alkenes. The methods described by Trost *et al.*[7] and Tani *et al.*,[8] while homogeneous and therefore amenable to regioselective deuterium incorporation, would require more expensive deuterium sources.

The methodology utilised by Meinwald and co-workers[5] to provide both stereoselective reduction and regioselective deuterium incorporation, involved the *Z*-reduction of the skipped triyne using bis(2-deuteriocyclohexyl)borane-D (formed *in situ* from $NaBD_4$, $BF_3{\cdot}Et_2O$ and cyclohexene) based on the procedure described by Brown and Zweifel,[11] and later modified by Brown and Molander.[12] The subsequent treatment with CH_3CO_2D cleaved the vinyl borane, and released the *Z*-dideuterio triene.

Skipped polyynes

In designing synthetic routes to these systems, consideration must be given to the reactivity of the skipped polyyne precursors which are reported, and have been observed in the current study, to be unstable and to decompose on standing.[13]

Necessarily, access to skipped polyenes *via* selective reduction of the corresponding polyynes requires efficient construction of the latter. Alka-1,4-diynes **1** are usually prepared *via* Cu^{I} catalysed cross-couplings between terminal acetylenes and prop-2-ynylic halides or toluene-*p*-sulfonates (tosylates). However, the basic conditions employed (*e.g.* Grignard reagents) often lead to isomeric products such as alka-1,2-dien-4-ynes **2**,[14] owing to the acidity of the doubly prop-2-ynylic methylene protons (see Scheme 1).



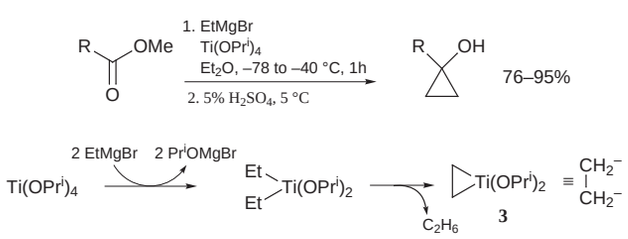
Scheme 1

This problem can be avoided by treatment of prop-2-ynylic halides or tosylates with alk-1-ynes in the presence of $Cu^{I}I$, $Bu^{n}_{4}NCl$ and Na_2CO_3 in DMF.[15] Similarly, alka-1,4-diynes were reported to be readily available *via* the mild $Cu^{I}I$ mediated coupling of alk-1-ynes and prop-2-ynylic chlorides or tosylates in the presence of NaI and K_2CO_3 in DMF at room temperature.[16] A similar procedure was used in the synthesis of (3*Z*,6*Z*,8*E*)-dodeca-3,6,8-trien-1-ol, a pheromone of *Reticulitermes* termites.[17] These methods therefore provide ready access to polyyne systems and consequently to the polyene system *via* appropriate reduction.

We now describe a method for the formation of *Z*-olefins, applicable to the formation of polyenes, including skipped systems (*i.e.* *Z*,*Z*-alka-1,4-dienes), in geometrically pure form. Deuterium can also be introduced regiospecifically *via* this reduction, which employs Ti^{II}-based chemistry and the formation of alkoxytitanium–acetylene complexes.

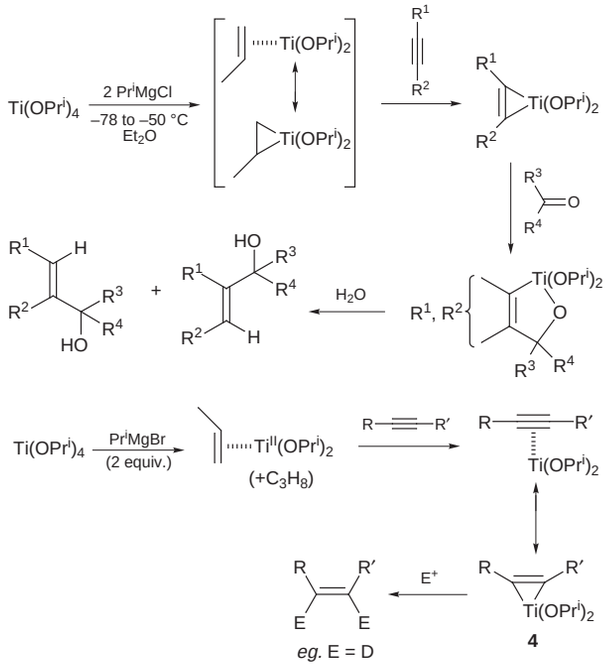
Results and discussion

Alkoxytitanium(II) mediated transformations are of increasing importance and much of the recent progress made can be traced to the remarkable observations of Kulinkovich and co-workers,[18] who described the formation of 1-substituted cyclopropanols from a $Ti(OPr^{i})_4$-catalysed reaction of esters with ethylmagnesium bromide. This system, which was postulated to involve a titanacyclopropane **3** functioning as a vicinal dicarbanion equivalent (Scheme 2), was then extensively developed by Corey *et al.*[19]



Scheme 2

A new general thrust in this area was provided by Sato and co-workers,[20] who described the formation of alkoxytitanium–alkyne complexes **4** by ligand exchange of the initially formed diisopropoxytitanocyclopropane complex with the appropriate alkyne. These derived complexes could be regarded as possessing titanacyclopropene characteristics, and hence viewed as a *cis-vicinal* alkene dianion synthon. This capability has been demonstrated in a variety of reactions, for example, to provide allylic alcohols (Scheme 3).[21] Although the isolation and characterisation of titanacyclopropene complexes have not been achieved, Sato[20] provided evidence for their intermediacy by cleavage with D_2O, which afforded the *Z*-configured [$^{2}H_2$]alkene



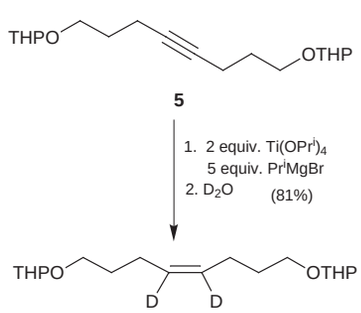
Scheme 3

as shown in Scheme 3. This is consistent with a titanacyclopropene **4** experiencing formal electrophilic substitution with retention of alkene configuration (Scheme 3).

In connection with our studies of the biosynthesis of fruit-fly pheromones, we required various ^{2}H-labelled methylene skipped trienes, and other *Z*-configured systems, and were considering procedures that were versatile enough to afford stereo- and regio-specific reduction of isolated, conjugated and methylene-skipped alkyne systems to the corresponding *Z*-dideuterio alkenes. This report describes these procedures and various applications.

Isolated systems

Initially the procedure was tested on the triple bond of the bis-THP ether of oct-4-yne-1,8-diol **5**. In the presence of an excess of $Ti(OPr^{i})_4$ (2 equiv.) and $Pr^{i}MgBr$ (5 equiv.) (with respect to the alkyne **5**), the reaction provided, upon D_2O quenching, a single product **6** (by GC analysis) in 81% yield (Scheme 4). No



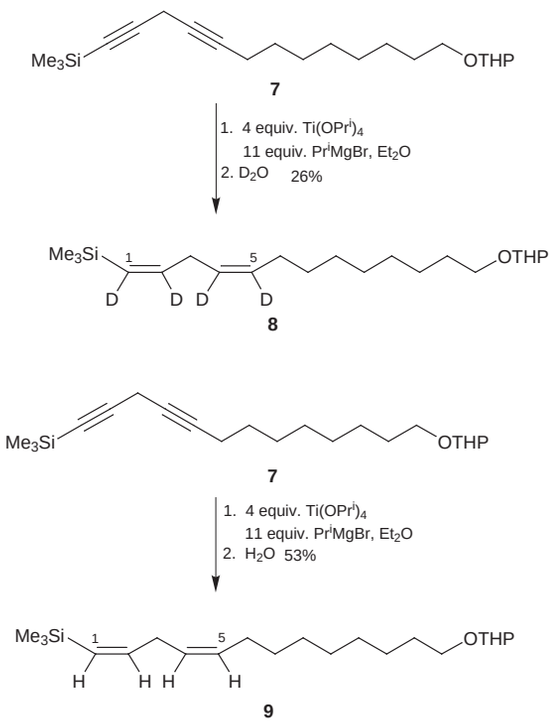
Scheme 4

vinylic hydrogens were present (^{1}H NMR spectral analysis), but in the ^{13}C NMR spectrum, a triplet was observed at δ 129.13 due to =CD, which exhibited a ^{13}C–^{2}H coupling constant of 22.9 Hz. Additionally, in the ^{2}H NMR spectrum, a single peak was observed at δ 5.41. Thus the spectra obtained were consistent with the formation of alkene **6**. The configuration of the double bond was not confirmed in this case, and because of the symmetrical nature of the product, incorporation of protium instead of deuterium would not provide further information.

A further application of this methodology to isolated alkenes, is discussed later when the synthesis of deuterated oleic acid (pure *Z* isomer) is described.

Skipped systems

Initial investigations involving the formation of skipped polyene systems from the corresponding polyynes were conducted with Me_3Si-protected skipped diyne **7** (refer to Scheme 5). In the



Scheme 5

presence of an excess of $Ti(OPr^i)_4$ (4 equiv.) and Pr^iMgBr (11 equiv.), the diyene **7** (1 equiv.), was transformed to a single tetradeuterio-product (by GC analysis) upon D_2O quenching. Following flash chromatography, the diene **8** was recovered in 26% yield. NMR spectral analysis showed only a small amount of residual protium on C5. No signals were observed for residual protium on C1, C2 or C4. In the ^1H NMR spectrum, residual H5 integrated for 0.2 protons, while in the ^{13}C NMR spectrum a C5 signal was observed at δ 130.59 due to residual =CH. (Signals due to =CD were not observed for C5.) The ^2H NMR spectrum exhibited only the expected four signals at δ 6.25, 5.53, 5.43 and 5.35 ppm (relative to $CDCl_3$ at δ 7.24). The reaction, when repeated with H_2O quenching, provided the corresponding protium containing product **9**, in 53% yield after flash chromatography. GC–MS Analysis indicated that a single isomer was formed. In this case, the ^1H NMR spectrum confirmed the *Z*,*Z*-configuration of the skipped diene. The coupling constant (^3J) between H4 and H5 was 10.7 Hz with that between H1 and H2 being 14.0 Hz. Although a coupling of 14 Hz might be considered high for a *Z*-double bond, typical ^1H–^1H coupling constants for vinylsilanes are 18–19 Hz for *E*- and 14 Hz for *Z*-configured systems.[22]

The reduction of **skipped enynes** was also examined, as shown in Scheme 6. Enynes **10** and **11** were synthesised *via* a coupling reaction between crotyl bromide and the THP ether of but-3-ynol in a modification of the procedure of Lapitskaya *et al.* (alkyne, bromide, Cu^II, K_2CO_3 and NaI in DMF).[16] This reaction provided a 3 : 1 mixture of **10** and the allylic rearrangement product **11** in 55% yield, following flash chromatography. Enyne **10** showed a coupling constant of 15.0 Hz for H6–H7 corresponding to the *E*-configured double bond.

Utilisation of this mixture in the Ti^{II}-reduction protocol, [$Ti(OPr^i)_4$ (5 equiv.) and Pr^iMgBr (13 equiv.)] and subsequent D_2O quenching, provided a mixture of dideuterio **12** and **13**, with no detectable signals assignable to vinylic protons attached to C3 and C4 (only the vinylic protons of C6 and C7 were observed in this region of the spectrum). In the ^{13}C NMR spectrum of octa-3,6-dienol derivative **12**, triplets were observed corresponding to deuterated C3 and C4 at δ 129.20 and 125.63 with a ^{13}C–^2H coupling of 23.5 Hz. The corresponding carbon signals of the hepta-3,6-dienol derivative **13** were not detected. Application of this methodology to the synthesis of deuterated linolenic acid (which contains the methylene-skipped *Z*,*Z*,*Z*-triene system) and to the syntheses of a *Z*,*Z*-8,11-diene and a *Z*,*Z*,*Z*-3,8,11-triene are described later.

Conjugated systems

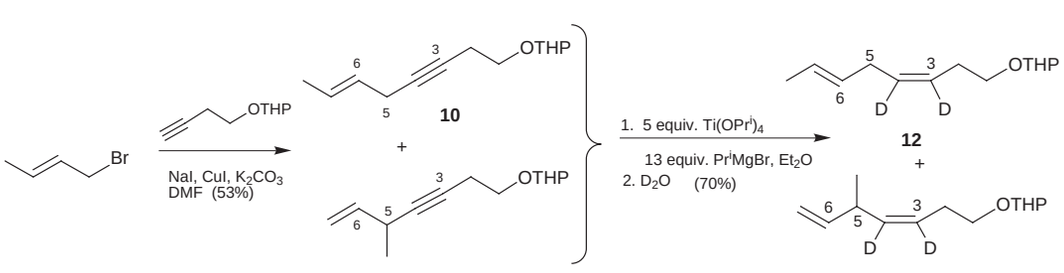
The Ti^{II} reduction procedure was also applied to a conjugated diyne system, as shown in Scheme 7. Treatment of conjugated diyne **14** with $Ti(OPr^i)_4$ (4 equiv.) and Pr^iMgBr (11 equiv.) resulted in the formation of conjugated tetradeuterio-**15** which was isolated in 46% yield. A single *Z*,*Z*-diene system was observed. In this case, small isotopically shifted signals were observed in the high field region due to two and possibly three bonded isotope effects of adjacent =CH or =CD units.

The reaction was repeated, this time using $Ti(OPr^i)_4$ (5 equiv.) and Pr^iMgBr (13 equiv.), with respect to the diyne **14**, to ensure completeness of the reaction. Addition of H_2O as the electrophile provided conjugated *Z*,*Z*-diene **16** in 41% yield after flash chromatography. Homodecoupling experiments enabled the identification of the overlapping signals for 9-H and 12-H, and also the H10 and H11 signals (also overlapping). Although the 10-H/11-H multiplets were not fully analysed, the largest coupling constants were *ca.* 9 Hz.

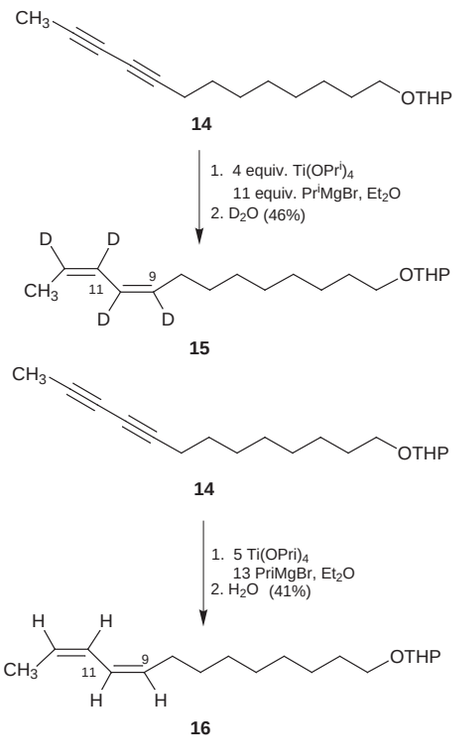
This is consistent with the formation of a *Z*,*Z*-configured system. The yield of this compound was increased to 55–60% (after chromatography) by quenching with H_2O–NH_4Cl or 10% aqueous HCl. A summary of the results with a variety of yne systems is presented in Table 1.

Synthesis of deuterated C_{18} fatty acids

The synthesis of isotopically labelled fatty acids has been reviewed.[23] In our work, we required both linolenic and oleic acids in geometrically pure form, and regiospecifically ^2H-labelled, for administration to certain insect species, and Ti^{II}-mediated reactions were employed.



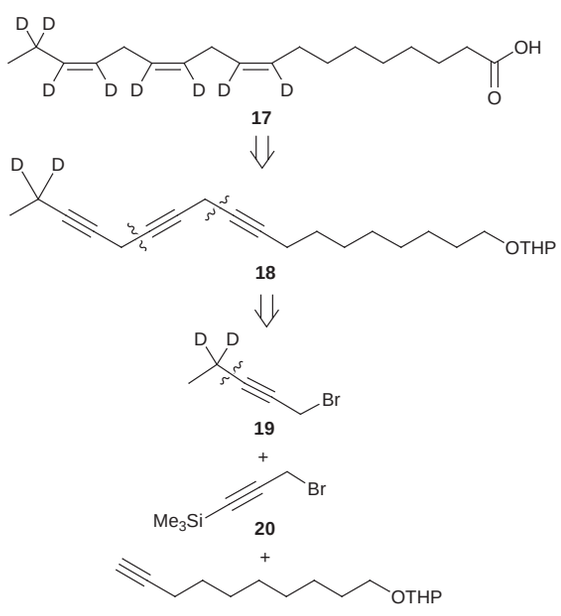
Scheme 6



Scheme 7

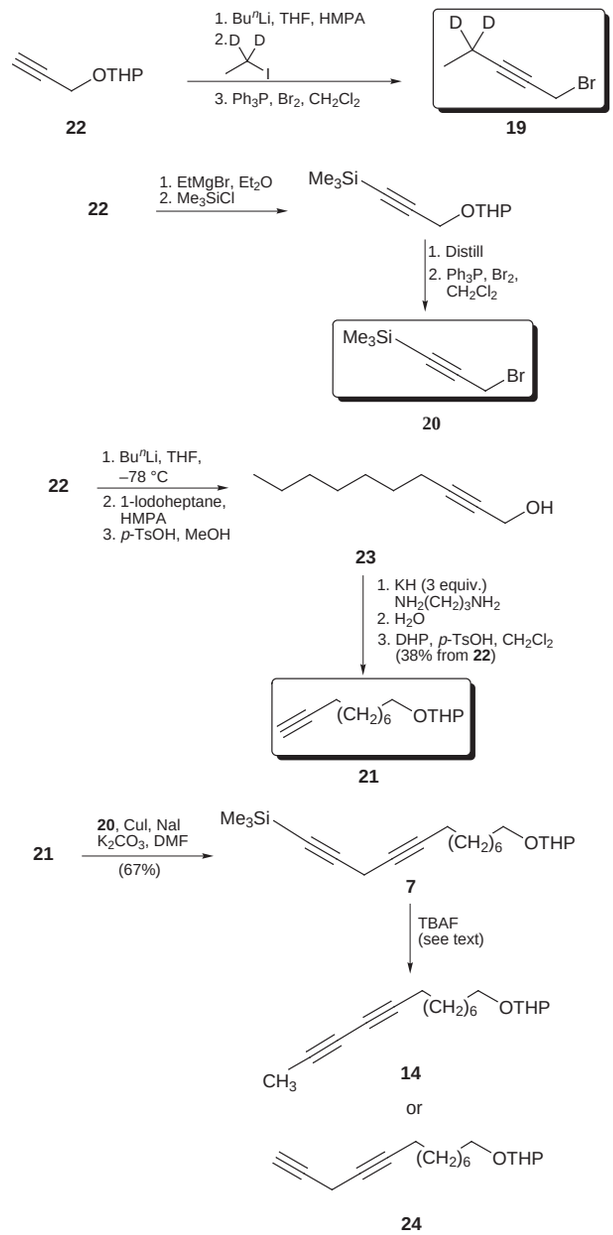
^{2}H-Labelled linolenic acid

Linolenic acid, deuterated in the C9–C17 portion of the molecule was required, along with the 9*Z*,12*Z*,15*Z*-triene system in geometrically pure form and with regiospecific deuterium incorporation. This is shown in **17** below (Scheme 8). Interestingly, syntheses of various deuterated [$^2H_3$, $^2H_6$ and $^2H_8$]-linolenic acids were reported recently by Meinwald and co-workers[5] for use in biosynthetic studies of insect derived alkaloids, and Haffner *et al.*[24] reported the use of [9,10,12,13,15,16-$^2H_6$]linolenic acid for studies of the formation of δ-lactones in yeast.



Scheme 8

Our plan was that skipped *Z*,*Z*,*Z*-triene would be obtained from the corresponding skipped triyne **18** with concomitant regiospecific introduction of deuterium, *via* the Ti^{II}-mediated reduction, using D_2O. The three retrosynthetic fragments (Scheme 8), **19**, **20** and **21** were to be linked to provide the triyne, by successive Cu^I mediated couplings in the presence of NaI and K_2CO_3 in DMF, as described by Lapitskaya *et al.*[16] This procedure avoids isomerisation of alka-1,4-diynes as can occur under basic conditions.[14] The fragments **19**, **20** and **21** all trace to the THP ether of prop-2-ynyl alcohol as summarised in Scheme 9.

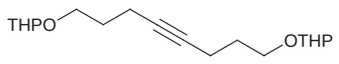
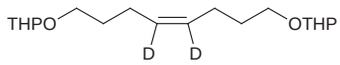
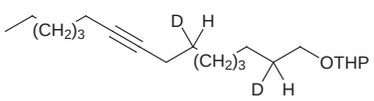
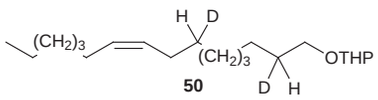
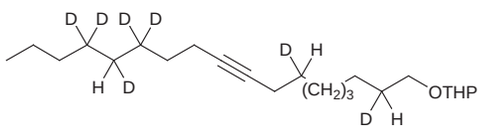
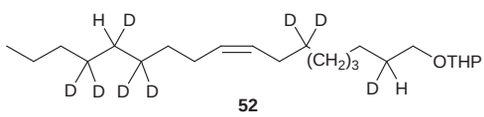
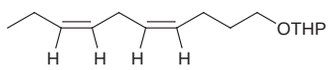
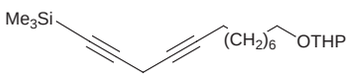
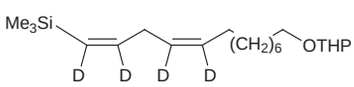
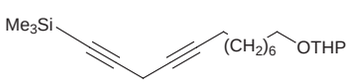
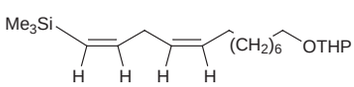
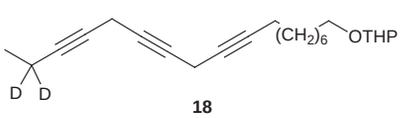
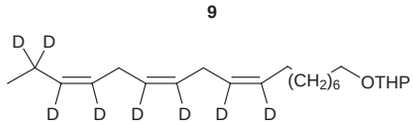
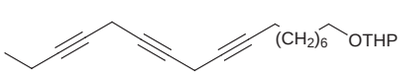
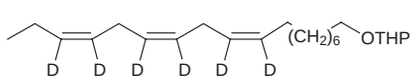
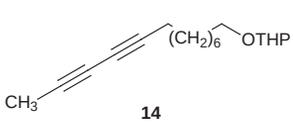
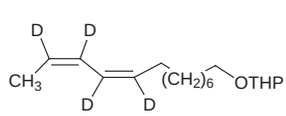
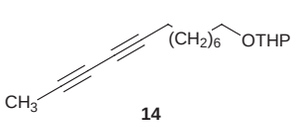
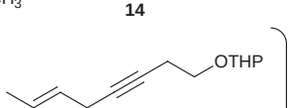
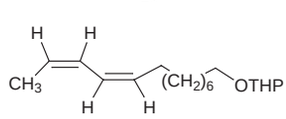
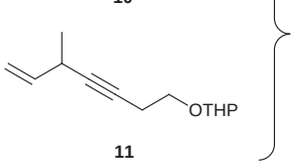
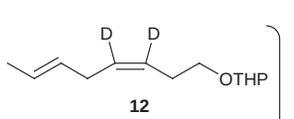
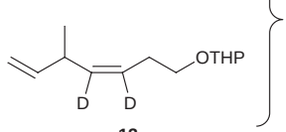


Scheme 9

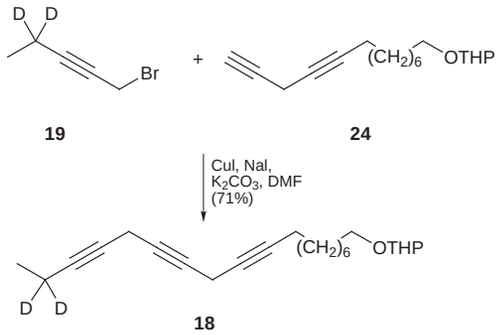
Clean removal of the Me_3Si group in **7** proved troublesome, and treatment with TBAF (2 equiv.) in THF (−5 °C for 1 h, then 25 °C for 2 h), resulted in the isomerised, conjugated diyne **14**, on the basis of mass spectra, and ^{1}H and ^{13}C NMR spectra. (The terminal CH_3 had δ_C 4.11 and δ_H 1.88). Repetition of the procedure with TBAF (1 equiv., 0 °C, 30 min), yielded the desired diyne **24** but in low yield (13%) after flash chromatography. However, this was sufficient to trial the next coupling reaction (Scheme 10) with the deuterated bromide **19**, using the CuI, K_2CO_3, NaI, DMF protocol.[16]

The desired triyne **18** was thus obtained in 71% yield, but on storage underwent decomposition. Further efforts were made to prepare diyne **24** in good yield, by varying the conditions for

Table 1 Ti^{II}-mediated reduction of alkynes to *Z*-alkenes

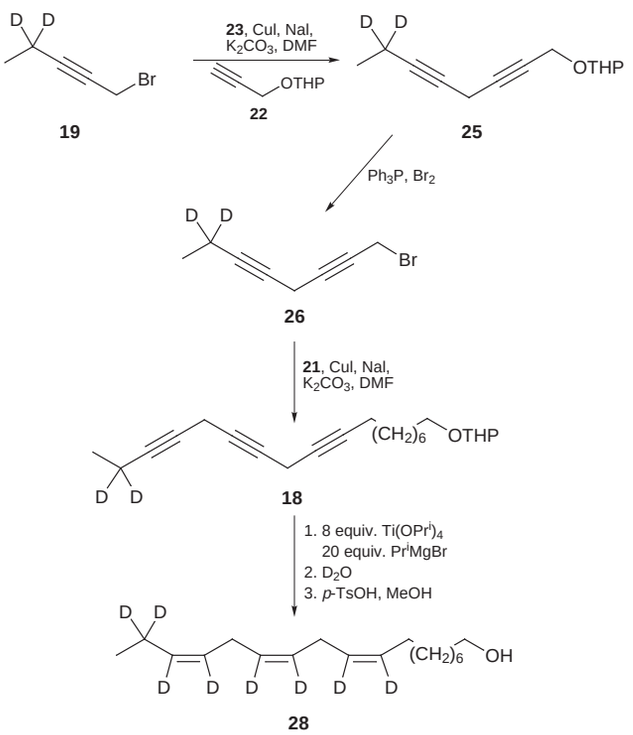
Entry	Starting alkyne	Reagents[a]	Product[b]	Isolated yield(%)[c]
1	 **5**	5:2	 **6**	81 (crude)
2	 **49**	5:2	 **50**	74[d,e]
3	 **51**	5:2	 **52**	53[d,e,f]
4	 **56**	13:5	 **57**	42
5	 **7**	11:4	 **8**	26
6	 **7**	11:4	 **9**	53
7	 **18**	20:8	 **27**	33
8		20:8	 **30**	25
9	 **14**	11:4	 **15**	46
10	 **14**  **10**	13:5	 **16**	55–60
11	 **11**	13:5	  **12** **13**	70 (crude)

[a] Ratio of $Pr^iMgBr:Ti(OPr^i)_4$. Per mole of starting alkynyl compound. Excess reagents were utilised to ensure complete reaction. These ratios were optimised in the indicated cases by titration of Grignard reagent. [b] Deuterium-containing *Z*-alkenes were obtained by quenching with *ca.* 99.5% D_2O; others from quenching with H_2O. [c] Refers to purified products after flash chromatography, except where indicated. [d] This yield was calculated (after chromatography) by quenching with 10% aqueous HCl. [e] The concentration of the Grignard reagent was determined by titration with menthol in the presence of 1,10-phenanthroline as indicator. Optimisation of the reagent ratio resulted. [f] This yield was lowered by the presence of an inert contaminant which was carried through from an earlier step.



Scheme 10

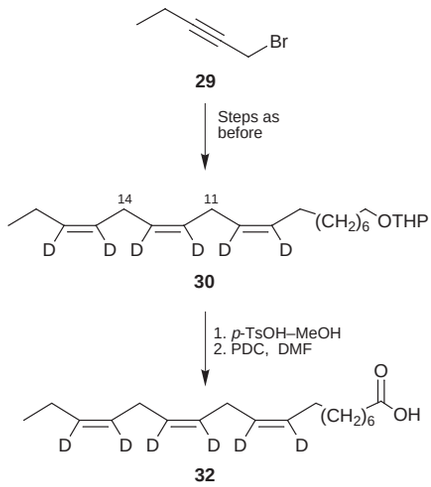
TBAF desilylation, but in addition to the desired skipped diyne **24**, conjugated diyne **14** and probably two allenes [on the basis of MS and IR (1941 cm^{-1}) data] were formed. With these impediments to obtention of the diyne **24**, a new approach to **18** was developed,, involving a change in the order of coupling, and avoidance of the trimethylsilyl (TMS)-protected alkyne **20**. The altered sequence is shown in Scheme 11.



Scheme 11

The above steps were conducted as expeditiously as possible to avoid polymerisation of diyne and triyne intermediates, which were stored if necessary, for short periods at low temperatures (−20 °C). The [$^2H_8$]alcohol **28** was characterised and used for biosynthetic studies.

Acquisition of labelled linolenic acid (Scheme 12) commenced with 1-bromopent-2-yne, **29**, rather than with [4,4-$^2H_2$]-1-bromopent-2-yne **19** utilised in the above sequence (Scheme 11). This led directly to the [$^2H_6$]-labelled tetrahydropyran-2′-yl ether **30**, after coupling and Ti^{II}-D_2O reduction of the skipped triyne. Normally under Jones' oxidation conditions, THP removal and oxidation to the carboxylic acid can be achieved in a 'one-pot' operation, but with THP ether **30**, this resulted in apparent rearrangement of the skipped trienyl system, as only a low intensity ^1H NMR signal for 11-H and 14-H was observed. Consequently, initial deprotection (*p*-TsOH–CH_3OH) was conducted, but again Jones' conditions largely removed the skipped trienyl system. The conversion to the carboxylic acid was best accomplished using PDC/DMF — conditions under



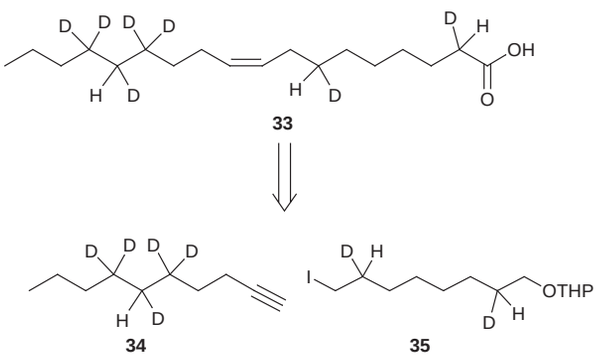
Scheme 12

which both acid- and base-sensitive functionality are stable.[25] The resulting [9,10,12,13,15,16-$^2H_6$]linolenic acid **32** was slightly contaminated with the aldehyde (an intermediate in the oxidation process).

Synthesis of ^2H-labelled oleic acid: (9*Z*)-[2,7,13,13,14,15,15-$^2H_7$]octadec-9-en-1-oic acid

Syntheses of deuterated oleic acid (*Z*-octadec-9-enoic acid) have been reported.[26] However, apart from the perdeuterated oleic acid produced by incubation of *S. obliquus* with D_2O[26] and syntheses that produce oleic acid deuterated at the double bond [26b–f] (C9 and C10), few reports have described the synthesis of oleic acid deuterated in both halves of the molecule.[26f,27,28] This is the focus of this report.

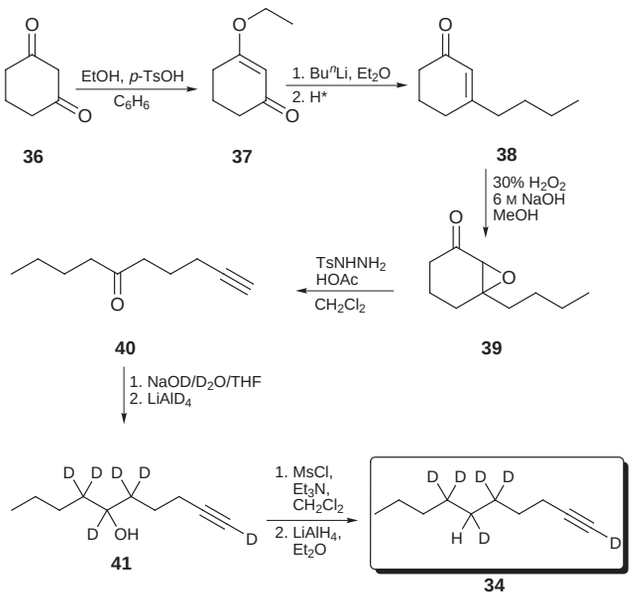
The present approach to geometrically pure, deuterium labelled oleic acid **33** was based on carbon-carbon coupling between the C_{10}-alkyne **34** and C_8-iodide **35** (shown in Scheme 13), and including deuterium content in both C9 portions of



Scheme 13

the molecule. The C_{10}–C_8 coupling then would provide the alkyne ready for Ti^{II} mediated *Z*-reduction, in contrast to Wittig linking of two C_9 fragments, for which *Z*-control of double bond configuration is more difficult.

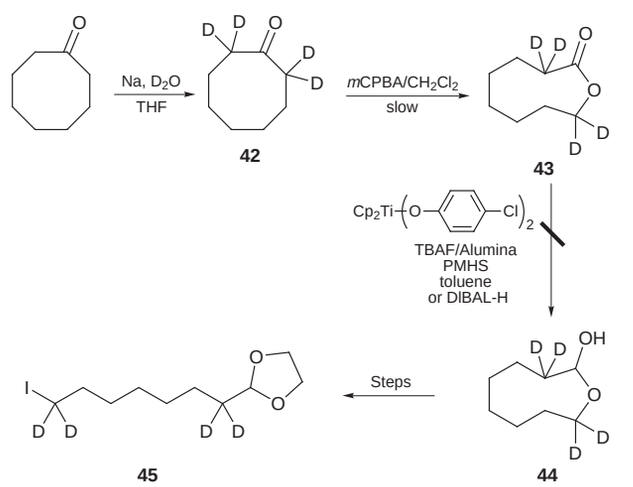
The synthesis of alkyne **34** (see Scheme 14) commenced with the inexpensive cyclohexane-1,3-dione **36** which was converted to the α,β-unsaturated ketone **38** in 90% yield from the enol ether **37**.[29] Epoxidation with alkaline H_2O_2 provided the epoxy ketone **39**[30] which was fragmented cleanly *via* the tosylhydrazone, according to the Eschenmoser procedure,[31] to give 6-oxodecyne **40**. The α-hydrogens (to the ketone function) were exchanged in the presence of a large excess of basic D_2O, and with the expected exchange of the terminal alkynyl hydrogen as well, the $^2H_5$-derivative ([$^2H_5$]-**40**) was obtained. Conversion to the required alkyne required reduction of the ketone without deuterium loss, and the most expedient route was $LiAlD_4$



Scheme 14

reduction followed by mesylation of the formed alcohol **41** and hydride displacement of the mesylate. (Deuteride displacement would permit further ^2H incorporation). In this way, alkyne **34** was obtained in 98% yield from deuterated 6-oxodecyne ([$^2H_5$]-**40**) and in 14% overall yield (8 steps) from cyclohexane-1,3-dione **36**.

A number of possibilities were available for the formation of deuterated iodide **35**. The use of cyclooctanone as the source of the C_8 system would enable the ready introduction of deuterium, again *via* exchange of the α-hydrogens in the presence of excess D_2O to provide **42** (see Scheme 15). Baeyer–Villiger



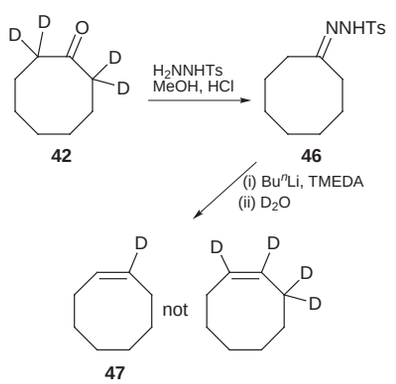
Scheme 15

oxidation would then provide the corresponding tetradeuteriolactone **43**, with chemo-differentiation of the ends of the C_8 chain. Reduction to the lactol **44** would enable the masked aldehydic function to be protected as the ethylene acetal, enabling the free alcohol to be converted to the iodide, **45**.

A report by Verdaguer *et al.*[32] described a method for the reduction of lactones to lactols which employed catalytic $Cp_2Ti(p\text{-}ClC_6H_4O)_2$ with polymethylhydrosiloxane (PMHS) in the presence of TBAF. A Ti^{III} hydride has been assumed to be the active catalyst for conversion of the lactone to the silyl lactol. This new procedure would avoid certain of the difficulties associated with use of DIBAL-H, the widely used reagent for this reduction.[33] Thus the route shown in Scheme 15 was performed (based on a successful trial reduction of δ-valerolactone to the corresponding lactol.)[32] [$^2H_4$]Cyclooctanone **42** underwent Baeyer–Villiger oxidation at a very slow rate to yield the lactone **43**, but the subsequent Ti-based reduction to the lactol was not successful. The deep-blue colour, which indicated the presence of the Ti^{III} species, disappeared rapidly upon addition of the lactone, which was then recovered unchanged. Despite thorough purification of the lactone **43**, including the recommended neutral alumina filtration,[32] premature quenching of the reductant still occurred. This method was not pursued, and although the method works well for five- and six-membered ring lactones, its application to other systems has not been developed.

Other methods for terminal differentiation of the deuterated C_8 system were considered, which might also circumvent the very slow Baeyer–Villiger oxidation of cyclooctanone. These included methods[34,35,36] which provide chemodifferentiated termini from symmetrical cyclic olefins.

Utilisation of the available [$^2H_4$]cyclooctanone **42** and application of one of Schreiber's chemodifferentiating ozonolysis procedures,[35] required Shapiro[37] conversion of the ketone **42** to cyclooctene, using TMEDA as the solvent[38] which enables high deuterium incorporation by exclusive reaction of the intermediate vinyllithium species with D_2O. In TMEDA, formation of the vinyllithium is fast compared to the rate of its protonation by solvent. [$^2H_4$]Cyclooctene should therefore be obtained. However, the procedure employed (see Scheme 16),

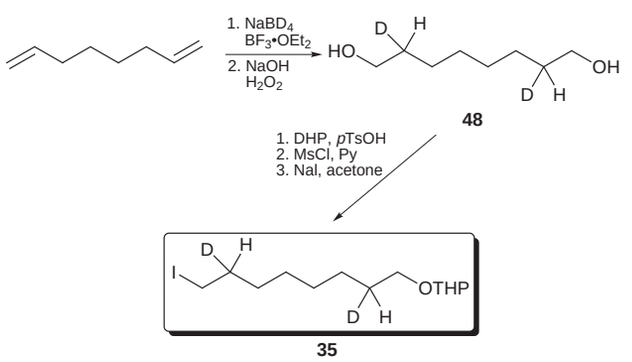


Scheme 16

resulted in [$^2H_1$]cyclooctene **47** and NMR spectral analysis of the intermediate tosylhydrazone **46** revealed deuterium loss during its formation. This problem could be overcome by using CH_3OD–DCl in the formation of the tosylhydrazone, but was not pursued.

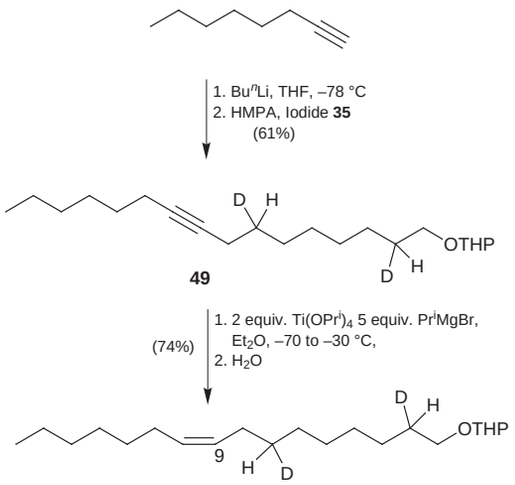
A more expedient route was then adopted which involved deuterioboration–oxidation[39] of octa-1,7-diene to form **48**. Monoprotection followed by flash chromatographic separation gave the mono-tetrahdropyran-2′-yl ether in 43% yield. The available hydroxy group was then mesylated and converted to the iodide **35** (Scheme 17).

The conditions for the alkyne–alkyl iodide coupling reaction were trialled using oct-1-yne and labelled iodide **35**, and use of



Scheme 17

salt-free Bu″ Li in hexane, a substantial proportion of HMPA (overall 60% of solvent) and a reaction temperature of −30 °C, led to the desired coupling. Alkyne **49** was obtained in satisfactory yield (61%) after flash chromatography, and was then reduced to *Z*-alkene **50**, using the $Ti(OPr^i)_4$–Pr^iMgBR–H_2O quench protocol, in good yield (74%) (see Scheme 18).



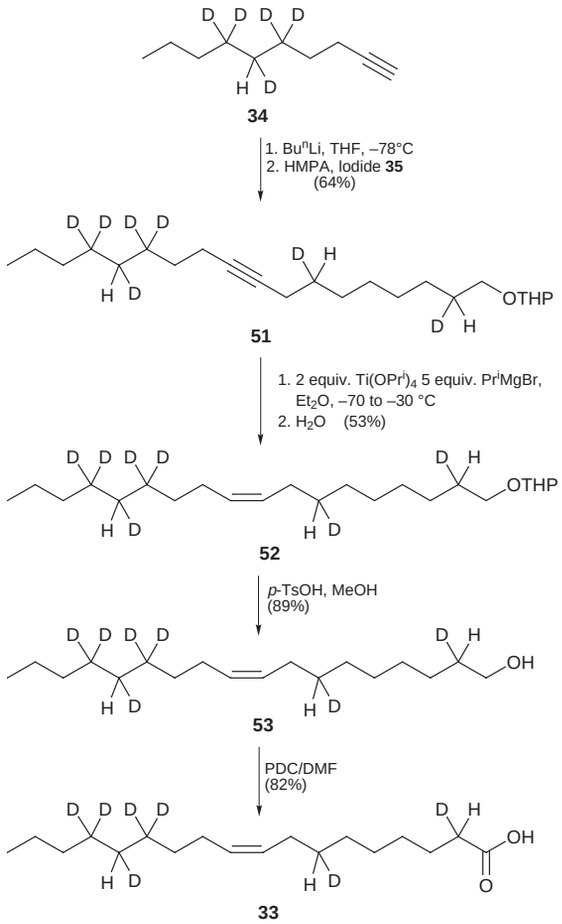
Scheme 18

Application of the above procedure to deuterated alkyne **34** and iodide **35**, provided the desired octadec-9-ynyl system **51** in satisfactory yield (Scheme 19). Reduction to the *Z*-alkene then afforded the deuterated *Z*-octadec-9-enyl compound **52** in 53% yield, after its separation by $AgNO_3$-impregnated silica gel chromatography from a minor contaminate, the THP ether of [2,7-$^2H_2$]dodecanol, apparently formed from reaction of Bu″Li with iodide **35**. Deprotection provided octadecenol **53** which was oxidised with PDC in DMF quite cleanly (82%) to the deuterated oleic acid **33** (Scheme 19). The ^1H and ^{13}C NMR spectra of **33** were consistent with the reported spectra[40] for oleic acid after allowances for the effects of the seven deuterium atoms. The signals for C9 and C10 were appropriate for *Z*-oleic acid with no signals to indicate the presence of the *E*-isomer. The resonances for allylic carbons in monoenoic acids in which the double bond is remote from CO_2H groups are particularly diagnostic,[41] with those in a *Z*-configured system found in the range of δ 27.2–27.4, and those for the *E*-isomer generally between δ 32.6–32.7. For the presently acquired oleic acid **33** these shifts for C8 and C11 were δ 27.05 and 27.16, confirming the *Z*-nature of the system and the specificity of the reduction. The overall yield of **33** was 3.5% for the twelve steps from cyclohexane-1,3-dione **36** or 4.7% from octa-1,7-diene (eight steps), with regiospecific deuterium incorporation in both 'halves' of the molecule. No scrambling of deuterium was detected by NMR or GC–MS analysis. Additionally, labelling at C9, C10 could have been effected merely by quenching with D_2O in the Ti-mediated reduction step.

Deuterated oleic acid acquired in this way has potential application in a number of biosynthetic studies and several of these are being pursued.

Synthesis of (3*E*,8*Z*,11*Z*)-tetradeca-3,8,11-trienyl acetate — the sex pheromone of *Scrobilpalpuloides absoluta*

The finding that skipped diynes are readily reduced to skipped *Z*,*Z*-dienes with no detectable isomerisation can now be applied to the synthesis of a natural system incorporating such a substructure. The moth species *Scrobipalpuloides absoluta* Meyrick (Lepidoptera : Gelechiidae : Gelechiinae) is a destructive pest of tomatoes in Brazil and a number of other South American countries and females of this species release a sex pheromone to attract conspecific males. The methylene skipped *Z*,*Z*-diene, (3*E*,8*Z*,11*Z*-tetradeca-3,8,11-trienyl acetate, was identified by



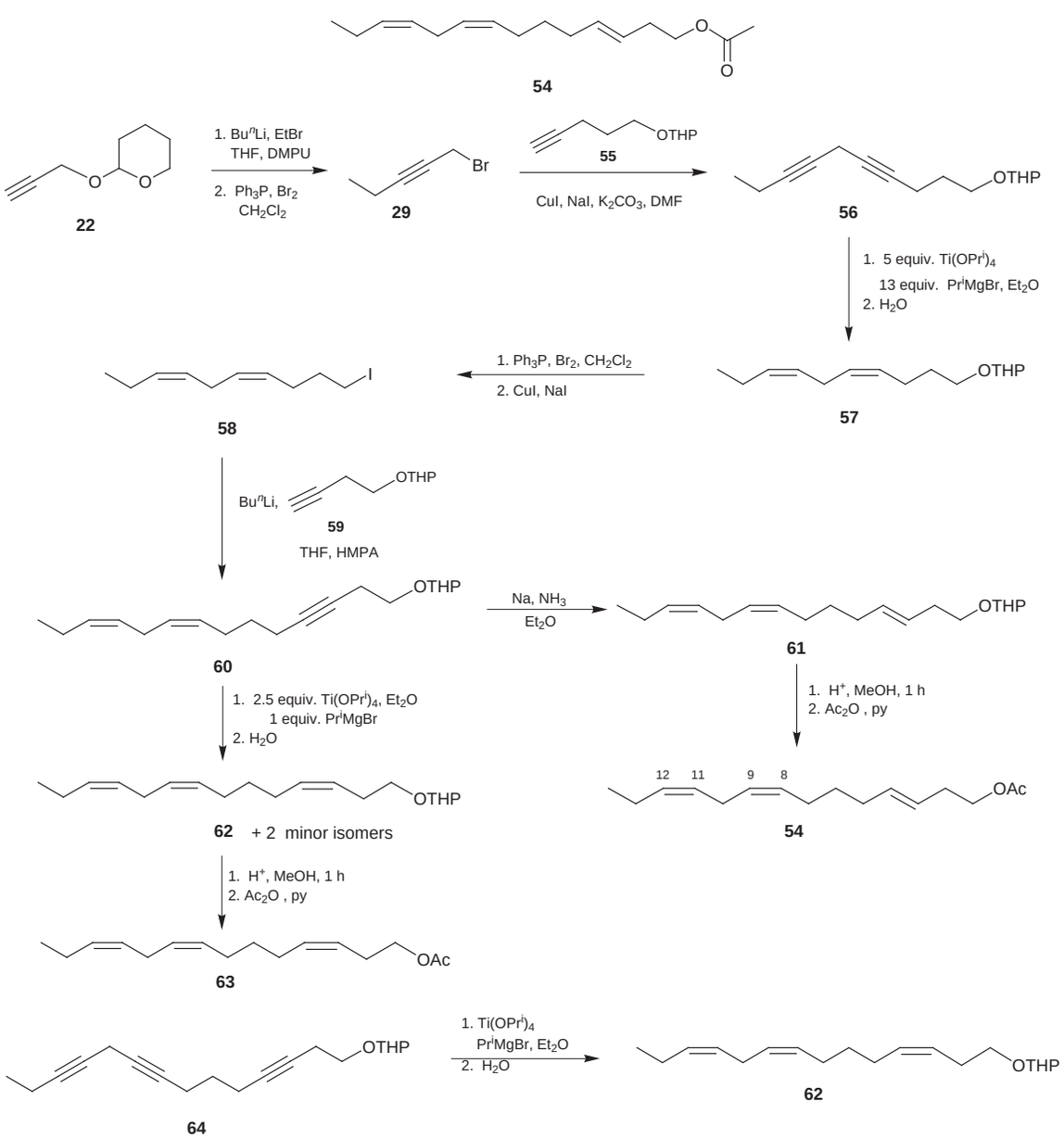
Scheme 19

Attygalle *et al.*,[13,42] who also synthesised the triene **54** (7% overall yield and 97% isomeric purity) to confirm its identity and to provide material for biological testing.

The important steps in the preparation of **54** relate to the specificity for *Z*-reduction of the methylene skipped diyne and isolated yne functions. Attygalle *et al.*[13,42] utilised hydroboration–acetic acid cleavage and $LiAlH_4$ reduction of a homoprop-2-ynylic alcohol to effect the specific *Z*- and *E*-reductions, respectively. Hydride reduction ($LiAlH_4$, diglyme, 120–140 °C, 2–5 h) was adopted because attempted Na–$NH_{3(l)}$ reduction to install the 3*E* double bond led to a hydrocarbon mixture associated with OTHP elimination.[13] A similar construction of the C_{14} chain was executed in the current work, but with different reduction methods. The synthesis of **54** is shown in Scheme 20.

Diyne **56** was obtained in 54% yield (after flash chromatography) *via* the coupling reaction between prop-2-ynylic bromide **29** and protected pentynol **55** [Cu^II/K_2CO_3/NaI/DMF protocol).[16] This unstable diyne was then reduced to the *Z*,*Z*-diene **57** using the Ti^{II}-methodology, in 42% yield following chromatography. Direct conversion to the bromide was achieved using triphenylphosphine dibromide in CH_2Cl_2. However, iodide exchange [Cu^II/K_2CO_3/NaI/DMF)[16] with this bromide provided iodide **58** which was employed in the Bu″Li-mediated coupling with THP-protected butynol **59** to yield dienyne **60** in 43% yield following flash chromatography (Scheme 20).

No elimination problems were encountered when Na in liquid NH_3 was employed to reduce the triple bond of dienyne **60** to the 3*E*-double bond and the triene **61** was obtained in quantitative yield. After deprotection, the trienol was then converted to the corresponding acetate **54** using acetic anhydride–pyridine. The overall yield from skipped diyne **56** was 8.4% over six steps, with purifications after each step. The ^1H and ^{13}C



Scheme 20

NMR and EI mass spectra for this compound were identical with those reported.[13]

The *Z*-configured isomer **63** was synthesised for comparative purposes. As also shown in Scheme 20, dienyne **60** was treated with Ti(OPr^i)$_4$ and Pr^{i}MgBr and then quenched with H_2O in the normal way to provide *Z*,*Z*,*Z*-triene **62**. Two other isomers of **62** were also formed as significant components. All three isomers were converted to the corresponding acetates as before, and the required **63** was purified by chromatography (on SiO_2–$AgNO_3$). The minor components were isomers of **63** but did not contain the methylene skipped diene system on the basis of ^{1}H NMR spectra. Some isomerisation of the *Z*,*Z*-methylene skipped diene system had therefore occurred. However, synthesis of the corresponding triene **64** would enable the direct formation of the *Z*,*Z*,*Z*-triene system **62** using the Ti^{II}-based chemistry, and should provide **63** as a single isomer, based on our results with conjugated systems. The ^{1}H NMR signal for 4-H (δ 5.49) in **63** was identified and exhibited ^3J couplings of 10.8 Hz with 3-H (*Z*-configured double bond), 7.3 Hz with H5 and 1.5 Hz with 2-H. Similarly the signal at δ 5.28 due to 9-H or 11-H showed a coupling of 10.6 Hz typical of the *Z*-configured double bond. The allylic resonances of the 3*E*- and 3*Z*-isomers in the ^{13}C NMR spectrum were diagnostic.[41] In the 3*E*-isomer **54**, C2 and C5 resonated at δ 31.95 and 32.13, respectively, while in the 3*Z*-isomer **63**, C2 and C5 resonances were observed between δ 26.79 and 26.91.

Summary

A Ti^{II}-based method for the *Z*-reduction of alkynes has been applied to a variety of alkyne systems, and this general approach is attractive as it employs cheap commercially available materials [Ti(OPr^i)$_4$ and Pr^{i}MgBr] and an inexpensive source of deuterium (D_2O), should labelling be required. The conversion appears to be regio- and stereo-specific, affording pure *Z*-configured alkenes, and no scrambling when ^{2}H-labelling is conducted. The method is also operationally simple and occurs with negligible under- or over-reduction.

Experimental

General experimental and instrumentation

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX500, Bruker AMX500, JEOL JMN-GX400, Bruker AMX400 or Bruker AC200F NMR spectrometer, with the individual frequencies indicated in the text. Chemical shifts, unless otherwise stated, are relative to residual $CHCl_3$ (δ 7.24) in deuterochloroform for ^{1}H NMR, and are relative to the central component of the $CDCl_3$ triplet at δ 77.00 for ^{13}C NMR spectroscopy; *J* values

are given in Hz. ^{2}H NMR were recorded on either a JEOL JMN-GX400 or a Bruker AMX400 in $CHCl_3$ with a small amount of $CDCl_3$ for reference at δ 7.24. All 2D NMR experiments were performed on a Bruker AMX500 or DRX500 spectrometer. GC–MS spectra were recorded using a 30 m × 0.25 mm BP5 column fitted in a Hewlett Packard HP5890 combined with a Hewlett Packard HP5970 mass selective detector. High resolution mass spectra were obtained on a Kratos MS25RFA instrument. IR spectra were recorded on a Perkin-Elmer Model 397 FTIR spectrometer using liquid films between 5 mm sodium chloride disks. Light petroleum refers to the fraction of bp 40–60 °C.

General procedure for Ti^{II}-based reductions[20]

Mg turnings (0.729 g, 0.03 mol) were dry-stirred for 30 min under an N_2 atmosphere and then Et_2O (5 ml) was added. 2-Bromopropane (3.075 g, 0.025 mol) in anhydrous Et_2O (10 ml) was added dropwise until the reaction commenced. Additional Et_2O (5 ml), was then added to the Mg turnings, while the 2-bromopropane addition was continued at such a rate as to maintain gentle refluxing. Occasional cooling in an ice-bath was required. After the addition was completed, the mixture was stirred for 30 min and then transferred to a graduated flask fitted with a rubber septum. Additional Et_2O was added to give 20 ml of a ~1..25 M Pr^iMgBr solution.

To the alkyne dissolved in Et_2O, was added $Ti(OPr^i)_4$ in Et_2O in one portion. The solution was cooled to −78 °C and Pr^iMgBr (~1.25 M solution in dry Et_2O) was added dropwise, *via* cannula, to give a bright yellow solution. The reaction mixture was then warmed to −30 °C for 2 h, during which time the reaction mixture turned dark brown. Upon re-cooling to −78 °C, D_2O (or H_2O) was added, and the mixture allowed to warm to room temperature overnight.

Work-up procedure A. After filtration through Celite and washing with Et_2O, the filtrate was dried ($MgSO_4$) and concentrated to yield an oil, which was purified by flash chromatography.

Work-up procedure B. H_2O–NH_4Cl or 10% aqueous HCl was added to quench the reaction. The organic layer was separated and the aqueous layer extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated to yield an oil, which was purified by flash chromatography.

1,8-Bis(tetrahydropyran-2′-yloxy)oct-4-yne 5

Prepared according to the known procedure.[43] Crude alkyne **5** was purified by flash chromatography (Et_2O–hexane, 1:5) (Found: M^+, 310.2132. $C_{18}H_{30}O_4$ requires M^+, 310.2144); δ_H(400 MHz, $CDCl_3$) 1.45–1.60 (8H, m), 1.62–1.85 (8H, m), 2.22 (4H, t, *J* 7.0, 3-H and 6-H), 3.43 (2H, dt, *J* 9.7, 6.2, 1-H and 8-H), 3.46 (2H, m, 2 × 6′-Ha), 3.77 (2H, dt, *J* 9.7, 6.5, 1-H and 8-H), 3.83 (2H, m, 2 × 6′b-H), 4.56 (2H, dd, *J* 4.0, 2.7, 2 × 2′-H); δ_C(100 MHz, $CDCl_3$) 98.72, 79.73, 66.05, 62.08, 30.67, 29.28, 25.48, 19.48, 15.62.

(4*Z*)-[4,5-$^2H_2$]-1,8-Bis(tetrahydropyran-2′-yloxy)oct-4-ene 6

From alkyne **5** (0.150 g, 0.484 mmol) in Et_2O (5 ml), $Ti(OPr^i)_4$ (0.275 g, 0.968 mmol) in Et_2O (5 ml), Pr^iMgBr (1.94 ml, 2.42 mmol, ~1.25 M solution in dry Et_2O) and D_2O (1.0 ml) according to the general procedure. Work-up procedure A provided **6** (0.123 g, 81%); δ_H(400 MHz, $CDCl_3$) 1.42–1.88 (16H, m), 2.09 (4H, m, H3, H6), 3.35 (2H, dt, *J* 9.7, 6.7, 1-Ha, 8-Ha), 3.45 (2H, m, 6′-Ha), 3.71 (2H, dt, *J* 9.7, 6.7, 1b-H, 8b-H), 3.84 (2H, m, 6′b-H), 4.54 (1H, dd, *J* 4.3, 2.7, 2′-H); δ_C(100 MHz, $CDCl_3$) 129.13 (t, $J_{^{13}C-^2H}$ 22.9), 98.83, 66.98, 62.25, 30.75, 29.72, 25.50, 23.71, 19.63; $\delta_{^2H}$(61.3 MHz, $CDCl_3$) 5.41; *m/z* 314 (M^+, 0.1%), 229 (1), 85 (100), 69 (6), 68 (5), 67 (12), 57 (13), 56 (8), 55 (9), 43 (14), 41 (19).

(1*Z*,4*Z*)-[1,2,4,5-$^2H_4$]-1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)trideca-1,4-diene 8

From alkyne **7** (0.100 g, 0.289 mmol) in Et_2O (5 ml), $Ti(OPr^i)_4$ (0.328 g, 1.16 mmol) in Et_2O (5 ml), Pr^iMgBr (2.54 ml, 3.18 mmol, ~1.25 M solution in dry Et_2O) and D_2O (1.0 ml) according to the general procedure. Work-up procedure A and flash chromatography (Et_2O–hexane, 1:20) provided deuterated diene **8** (0.027 g, 26%) (Found: C, 72.2, H, 11.4. $C_{21}H_{36}O_2SiD_4$($C_{21}H_{40}O_2Si$) requires C, 71.5, H, 11.4%); δ_H(400 MHz, $CDCl_3$) 0.11 (9H, s, $SiMe_3$), 1.22–1.38 (10H, m), 1.43–1.60 (6H, m), 1.69 (1H, m), 1.81 (1H, m), 2.01 (2H, t, *J* 6.7, 6-H), 2.84 (2H, s, 3-H), 3.36 (1H, dt, *J* 9.7, 6.7, 13-Ha), 3.46 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 6.9, 13-Hb), 3.85 (1H, m, 6′-Hb), 4.55 (1H, dd, *J* 4.6, 2.4, 2′-H), 5.38 (0.2H, t, *J* 7.2, residual 5-H); δ_C(100 MHz, $CDCl_3$) 130.59 (C5, residual CH=), 98.83, 67.66, 62.30, 31.42 (br), 30.79, 29.74, 29.61 (C7, 3 bond isotope effect when C9 is CH=), 29.59 (C7, 3 bond isotope effect when C9 is CH=), 29.45, 29.43, 29.23, 27.30 (C6, adjacent to residual CH=), 27.19 (C6, adjacent to residual CD=), 26.22, 25.52, 19.68, 0.14. Signals due to C1, C2 and C4 (CD=) were not detected; $\delta_{^2H}$(61.3 MHz, $CDCl_3$) 5.35, 5.43, 5.53, 6.25; *m/z* 356 (M^+, 0.2%), 173 (1), 159 (3), 156 (3), 103 (7), 101 (7), 85 (100), 83 (10), 75 (15), 73 (51), 67 (13).

(1*Z*,4*Z*)-1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)trideca-1,4-diene 9

From alkyne **7** (0.050 g, 0.289 mmol) in Et_2O (3 ml), $Ti(OPr^i)_4$ (0.163 g, 0.575 mmol) in Et_2O (2 ml), Pr^iMgBr (1.26 ml, 1.58 mmol, ~1.25 M solution in dry Et_2O) and H_2O (1.0 ml) according to the general procedure. Work-up procedure A and flash chromatography (Et_2O–hexane, 1:20) provided diene **9** (0.027 g, 53%) (Found: C, 72.5, H, 11.5. $C_{21}H_{40}O_2Si$ requires C, 71.5, H, 11.4%); δ_H(500 MHz, $CDCl_3$) 0.11 (9H, s, $SiMe_3$), 1.24–1.36 [10H, m, 2 × (11-H, 10-H, 9-H, 8-H, 7-H)], 1.43–1.60 (6H, m, 2 × 12-H, 3′-Ha, 4′-Ha, 2 × 5′-H), 1.69 (1H, m, 3-Hb), 1.81 (1H, m, 4′-Hb), 2.02 (2H, q, *J* 7.0, 6-H), 2.85 (2H, br t, *J* 7.3, 3-H), 3.36 (1H, dt, *J* 9.6, 6.7, 13-Ha), 3.48 (1H, m, 6′-Ha), 3.71 (1H, dt, *J* 9.6, 6.9, 13b-H), 3.85 (1H, ddd, *J* 11.2, 7.7, 3.5, 6′-Hb), 4.55 (1H, dd, *J* 4.4, 2.9, 2′-H), 5.30 (1H, dtt, *J* 10.7, 7.1, 1.5, 4-H), 5.39 (1H, dtt, *J* 10.7, 7.2, 1.5, 5-H), 5.48 (1H, dt, *J* 13.9, 1.4, 1-H), 6.20 (1H, dt, *J* 14.0, 7.3, 2-H); δ_C(125 MHz, $CDCl_3$) 146.91 (C2), 130.74 (C5), 129.17 (C1), 127.24 (C4), 98.83 (C2′), 67.66 (C13), 62.31 (C6′), 31.69 (C3), 30.79 (C3′), 29.74, 29.60, 29.45, 29.43, 29.23, 26.22 (C12, C11, C10, C9, C8, C7), 27.33 (C6), 25.51 (C5′), 19.69 (C4′), 0.11 [$Si(CH_3)_3$]; *m/z* 352 (M^+, 0.1%), 279 (0.1), 103 (7), 101 (6), 95 (8), 85 (100), 73 (61), 59 (22), 43 (20), 41 (32).

(6*E*)-1-(Tetrahydropyran-2′-yloxy)oct-6-en-3-yne 10 and 5-methyl-1-(tetrahydropyran-2′-yloxy)hept-6-en-3-yne 11[16]

Illustrative alkyne-allylic/prop-2-ynylic halide, Cu^I mediated coupling procedure. Anhydrous sodium iodide (2.220 g, 14.81 mmol), copper(I) iodide (1.411 g, 7.41 mmol) and potassium carbonate (2.047 g, 14.81 mmol) were stirred in dry DMF (5 ml). 1-(Tetrahydropyran-2′-yloxy)but-3-yne (1.141 g, 7.41 mmol) in DMF (5 ml) was added, followed by (2*E*)-1-bromobut-2-ene (1.00 g, 7.41 mmol) in DMF (5 ml). The resultant heterogeneous yellow–green suspension was stirred under a N_2 atmosphere. Additional bromide (0.5 g) and copper(I) iodide (0.7 g) were added, and stirring was continued until the reaction was complete (GC analysis, 93% product, 48 h). Saturated aqueous NH_4Cl (100 ml) was added, followed by Et_2O (80 ml) and the layers were separated and the aqueous layer was further extracted with Et_2O (5 × 50 ml). The ethereal layers were combined and washed with 10% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl. The solution was dried over $MgSO_4$ and concentrated to give the crude products, as a 3:1 mixture. Purification by flash chromatography (Et_2O–hexane, 1:20) gave a 3:1 mixture of (6*E*)-1-(tetrahydropyran-2′-yloxy)oct-6-en-3-yne **10** and 5-methyl-1-(tetrahydropyran-2′-yloxy)hept-6-en-3-yne **11** (0.851 g, 55%).

(6*E*)-1-(Tetrahydropyran-2′-yloxy)oct-6-en-3-yne 10. δ_H(400 MHz, $CDCl_3$) 1.43–1.60 (4H, m), 1.64 (3H, ddt, *J* 6.5, 1.6, 1.6,

8-H), 1.69 (1H, m), 1.80 (1H, m), 2.46 (2H, m, 2-H), 2.82 (2H, m, 5-H), 3.43–3.54 (2H, m, 1-Ha, 6′-Ha), 3.77 (1H, dt, *J* 9.7, 7.3, 1-Hb), 3.85 (1H, m, 6′-Hb), 4.61 (1H, dd, *J* 3.5, 3.5, 2′-H), 5.37 (1H, dtq, *J* 15.0, 5.6, 1.6), 5.64 (1H, dqt, *J* 14.8, 6.5, 1.6, 7-H); δ_C(100 MHz, $CDCl_3$) 126.35, 125.65 (C6, C7), 98.67 (C2′), 78.71, 78.54 (C3, C4) 66.09 (C6′), 62.11 (C1), 30.55 (C3′), 25.42 (C5′), 21.92 (C5), 20.24 (C4′), 19.37 (C2), 17.53 (C8); *m*/*z* 207 (M^+-1, 0.1%), 193 (0.4), 91 (29), 85 (100), 57 (17), 55 (14), 43 (20), 41 (38), 39 (23).

5-Methyl-1-(tetrahydropyran-2′-yloxy)hept-6-en-3-yne 11. δ_H(400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 7.0, 5-Me), 1.43–1.60 (4H, m), 1.69 (1H, m), 1.80 (1H, m), 2.46 (2H, m, 2-H), 3.08 (1H, m, 5-H), 3.43–3.54 (2H, m, 1-Ha, 6′-Ha), 3.77 (1H, dt, *J* 9.7, 7.3, 1-Hb), 3.85 (1H, m, 6′-Hb), 4.61 (1H, dd, *J* 3.5, 3.5, 2′-H), 4.98 (1H, ddd, *J* 9.9, 1.6, ~1, 7-Ha), 5.22 (1H, ddd, *J* 16.9, 1.6, ~1, 7−Hb), 5.76 (1H, ddd, *J* 16.9, 10.2, 5.6, 6-H); δ_C(100 MHz, $CDCl_3$) 139.82 (C6), 113.56 (C7), 98.63 (C2′), 82.82, 79.09 (C3, C4), 66.09 (C6′), 62.04 (C1), 30.55 (C3′), 29.59 (C5), 25.42 (C5′), 21.41 (CH_3), 20.24 (C4′), 19.32 (C2); *m*/*z* 208 (M^+, 0%), 193 (0.2), 91 (31), 85 (100), 79 (19), 77 (13), 67 (17), 65 (9), 57 (15), 55 (12), 43 (19), 41 (33), 39 (18).

(3*Z*,6*E*)-[3,4-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)octa-3,6-diene 12 and (3*Z*)-[3,4-$^2H_2$]-5-methyl-1-(tetrahydropyran-2′-yloxy)hepta-3,6-diene 13

From alkyne mixture **10**–**11** (0.200 g, 0.962 mmol) in Et_2O (10 ml), $Ti(OPr^i)_4$ (1.367 g, 4.81 mmol) in Et_2O (10 ml), Pr^iMgBr (10.0 ml, 12.5 mmol, ~1.25 M solution in dry Et_2O) and D_2O (1.0 ml) according to the general procedure. Work-up procedure A provided the mixture of products **12**–**13** (0.146 g, 70%).

(3*Z*,6*E*)-[3,4-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)octa-3,6-diene 12. δ_H(400 MHz, $CDCl_3$) 1.43–1.60 (4H, m), 1.61 (3H, br d, *J* 5.4, 8-H), 1.67 (1H, m), 1.80 (1H, m), 2.32 (2H, br t, *J* 7.0, 2-H), 2.70 (2H, br d, *J* 4.8, 5-H), 3.37 (1H, dt, *J* 9.7, 7.0, 1-Ha), 3.46 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 7.3, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.56 (1H, dd, *J* 4.0, 3.0, 2′-H), 5.39 (2H, m, 6-H, 7-H); δ_C(100 MHz, $CDCl_3$) 129.30 (C6 or C7), 129.20 (C3 or C4, t, $J_{^{13}C-^2H}$ 23.5), 125.63 (C3 or C4, t, $J_{^{13}C-^2H}$ 23.5), 125.17 (C6 or C7), 98.65 (C2′), 66.92 (C6′), 62.16 (C1), 30.67, 30.32, 27.70, 25.46, 19.51, 17.78 (C8); *m*/*z* 212 (M^+, 0.1%), 128 (1), 111 (2), 110 (3), 101 (8), 95 (6), 85 (100).

(3*Z*)-[3,4-$^2H_2$]-5-Methyl-1-(tetrahydropyran-2′-yloxy)hepta-3,6-diene 13. δ_H(400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 7.0, 5-Me), 1.43–1.60 (4H, m), 1.67 (1H, m), 1.80 (1H, m), 2.32 (2H, br t, *J* 7.0, 2-H), 3.15 (1H, m, 5-H), 3.37 (1H, dt, *J* 9.7, 7.0, 1-Ha), 3.46 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 7.3, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.56 (1H, dd, *J* 4.0, 3.0, 2′-H), 4.88 (1H, ddd, *J* 10.5, 1.6, ~1, 7-Ha), 4.95 (1H, ddd, *J* 17.1, 1.6, ~1, 7-Hb), 5.74 (1H, ddd, *J* 16.9, 10.7, 6.2, 6-H); δ_C(100 MHz, $CDCl_3$) 142.76 (C6), 112.28 (C7). Other signals were not detected.

(9*Z*,11*Z*)-[9,10,11,12-$^2H_4$]-1-(Tetrahydropyran-2′-yloxy)-trideca-9,11-diene 15

From alkyne **14** (0.100 g, 0.362 mmol) in Et_2O (5 ml), $Ti(OPr^i)_4$ (0.412 g, 1.45 mmol) in Et_2O (5 ml), Pr^iMgBr (3.19 ml, 3.99 mmol, ~1.25 M solution in dry Et_2O) and D_2O (1.0 ml) according to the general procedure. Work-up procedure A and flash chromatography (Et_2O–hexane, 1:20) gave deuterated diene **15** (0.047 g, 46%) (Found: C, 78.4, H, 11.7. $C_{18}H_{28}O_2D_4$ ($C_{18}H_{32}O_2$) requires C, 77.1, H, 11.5%); δ_H(400 MHz, $CDCl_3$) 1.20–1.40 (10H, m), 1.43–1.63 (6H, m), 1.68 (1H, m), 1.71 (3H, s, 13-H), 1.80 (1H, m), 2.13 (2H, t, *J* 7.0, 8-H), 3.36 (1H, dt, *J* 9.4, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.4, 7.0, 1-Hb), 3.85 (1H, m, 6′-Hb), 4.55 (1H, dd, *J* 4.3, 2.7, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.83, 67.65, 62.30, 30.81, 29.76, 29.61, 29.43, 29.42, 29.22, 27.36, (26.23, 26.22− signals due to residual protium), 26.20, 25.53, 19.68, 12.98 (C13). No signals were detected for C9, C10, C11 or C12 (CD=); *m*/*z* 284 (M^+, 0.2%), 266 (1), 207 (1), 167 (1), 137 (1), 110 (3), 109 (3), 101 (9), 85 (100).

(9*Z*,11*Z*)-(Tetrahydropyran-2′-yloxy)trideca-9,11-diene 16

From alkyne **14** (0.100 g, 0.362 mmol) in Et_2O (5 ml), $Ti(OPr^i)_4$ (0.515 g, 1.81 mmol) in Et_2O (5 ml), Pr^iMgBr (3.8 ml, 4.71 mmol, ~1.25 M solution in dry Et_2O) and H_2O (1.0 ml) according to the general procedure. Work-up procedure A and flash chromatography (Et_2O–hexane, 1:100) gave diene **16** (0.041 g, 41%) (Found: M^+, 280.2400. $C_{18}H_{32}O_2$ requires *M*, 280.2402); δ_H(400 MHz, $CDCl_3$) 1.20–1.40 (10H, m), 1.43–1.61 (6H, m), 1.67 (1H, m), 1.72 (3H, br d, *J* 6.5, 13-H), 1.80 (1H, m), 2.12 (2 H, m, 8-H), 3.35 (1H, dt, *J* 9.7, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 7.0, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.54 (1H, dd, *J* 4.3, 2.7, 2′-H), 5.42 (1H, m, 9-H), 5.48 (1H, m, 12-H), 6.24 (1H, br d, *J* 9, 10-H), 6.24 (1H, br d, *J* 9, 11-H); 9-H/12-H *versus* 10-H/11-H were identified by homodecoupling experiments; δ_C(100 MHz, $CDCl_3$) 131.94, 125.83, 124.59, 123.29, 98.83, 67.65, 62.30, 30.79, 29.74, 29.60, 29.42, 29.40, 29.20, 27.48, 26.21, 25.52, 19.68, 13.07; *m*/*z* 280 (M^+, 0.4%), 262 (2), 196 (0.4), 135 (2), 121 (2), 85 (100), 41 (33).

Deuterated linolenic acid

1-(Tetrahydropyran-2′-yloxy)prop-2-yne 22

Prop-2-ynol (30.0 g, 0.535 mol) and toluene-*p*-sulfonic acid (10.179 g, 0.054 mol) were dissolved in dry CH_2Cl_2 (400 ml) and cooled to 0 °C. 3,4-Dihydro-2*H*-pyran (67.55 g, 0.803 mol) in CH_2Cl_2 (100 ml) was added dropwise. Stirring was continued at room temperature overnight. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was then extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated. Flash chromatography (Et_2O–hexane, 1:20) gave 1-(tetrahydropyran-2′-yloxy)prop-2-yne **22** (8.048 g, 11%); *m*/*z* 140 (M^+, 1%), 139 (8), 111 (1), 101 (4), 85 (88), 83 (11), 82 (13), 57 (32), 56 (53), 55 (43), 41 (74), 39 (100).

[4,4-$^2H_2$]-1-Bromopent-2-yne 19

[4,4-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)pent-2-yne.[44]. Alkyne **22** (4.03 g, 28.77 mmol) was dissolved in THF (80 ml) in a three-neck flask and cooled to −78 °C. Bu″Li (2.5 M, 13.8 ml, 34.52 mmol) was added dropwise *via* syringe. The reaction mixture was stirred at −60 to −50 °C for 1 h. Upon recooling to −78 °C, [1,1-$^2H_2$]iodoethane (5.0 g, 31.65 mmol), dissolved in a mixture of THF (2 ml) and HMPA (12 ml), was added dropwise from a dropping funnel. The resulting mixture was allowed to warm to RT overnight. Hexane (250 ml) and water (300 ml) were added, and the layers separated. The aqueous layer was extracted with hexane (3 × 100 ml). After washing with saturated aqueous NaCl, the combined organic layers were dried ($MgSO_4$) and concentrated (reduced pressure). Purification using flash chromatography (Et_2O–hexane, 1:20) yielded pure [4,4-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)pent-2-yne (2.759 g, 56%) (Found: $M^+ - 1$, 169.1214. $C_{10}H_{13}O_2{}^2H_2$ requires $M^+ - 1$, 169.1198); δ_H(400 MHz, $CDCl_3$) 1.10 (3H, s, 5-H), 1.55 (4H, m, 3′-H, 4′-H or 5′-H), 1.71 (1H, m, 3′-H, 4′-H or 5′-H), 1.81 (1H, m, 3′-H, 4′H or 5′-H), 3.50 (1H, m, 6′-Ha), 3.82 (1H, ddd, *J* 11.6, 9.1, 3.2, 6′-Hb), 4.16 (1H, d, *J* 15.3, 1-Ha), 4.27 (1H, d, *J* 15.3, 1-Hb), 4.78 (1H, t, *J* 3.5, 2′-H); δ_C(100 MHz, $CDCl_3$) 96.69, 87.95, 75.11, 61.95, 54.65, 30.29, 25.38, 19.10, 13.54, 11.95 (quintet, *J* 19.8); *m*/*z* 170 (M^+, 0.1%), 101 (37), 85 (100), 69 (86), 67 (56), 55 (61), 43 (87), 42 (68), 41 (88), 40 (46), 39 (43).

[4,4-$^2H_2$]-1-Bromopent-2-yne 19[45] (illustrative procedure for conversion of THP ether to the corresponding bromide). Triphenylphosphine (4.24 g, 16.2 mmol) was dissolved in dry CH_2Cl_2 (60 ml) and the solution was cooled to 0 °C. Bromine (0.83 ml, 2.59 g, 16.2 mmol) dissolved in CH_2Cl_2 (25 ml) was added dropwise from a dropping funnel and a white precipitate was formed. Towards the end of the addition, the yellow colour of bromine in solution persisted. The solution was stirred for 30 min, after which time the yellow colour remained. Sufficient triphenylphosphine was added to discharge the coloration.

[4,4-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)pent-2-yne (2.50 g, 14.7 mmol) in CH_2Cl_2 was added in one portion and stirring was continued overnight. Et_2O (10 ml) was added, followed by saturated aqueous $NaHCO_3$ (200 ml). This aqueous layer was extracted with CH_2Cl_2 (5 × 80 ml). The combined organic layers were then washed with saturated aqueous $Na_2S_2O_3$ and aqueous NaCl, dried ($MgSO_4$) and evaporated. Flash chromatography (100% light petroleum) gave [4,4-$^2H_2$]-1-bromopent-2-yne **19** (1.856 g, 85%); δ_H(500 MHz, $CDCl_3$) 1.10 (3H, s, 5-H), 3.90 (2H, s, 1-H); δ_C(125 MHz, $CDCl_3$) 89.38, 74.65, 15.66, 13.24, 12.01 (quintet, *J* 20.0); *m*/*z* 150, 148 (M^+, 10, 8%), 135 (2), 133 (1), 81 (9), 79 (8), 69 (100), 43 (45), 42 (46), 41 (28), 40 (33).

3-Bromo-1-trimethylsilylpropyne 20

3-(Tetrahydropyran-2′-yloxy)-1-trimethylsilylpropyne. 1-Bromoethane (55.0 g, 0.5 mol) in anhydrous THF (150 ml) was added dropwise to a mixture of Mg turnings (12.2 g, 0.12 mol) and THF (50 ml), under a N_2 atmosphere. Heat was evolved as the Grignard reagent formed. Upon completion of the addition, the mixture was stirred and immersed in a hot water bath for 30 min. 1-(Tetrahydropyran-2′-yloxy)prop-2-yne **22** (70.0 g, 0.5 mol) was dissolved in THF (150 ml) and added to the 0 °C Grignard solution. The reaction mixture was then stirred at 0 °C for 10 min and then at RT for 30 min. Chlorotrimethylsilane (11.95 g, 0.11 mol) in THF (50 ml) was added dropwise over a period of an hour. The mixture was then warmed to 50 °C for 1 h. The reaction mixture was poured into saturated aqueous NH_4Cl (800 ml), Et_2O was added and the layers separated before the aqueous portion was further extracted with Et_2O (3 × 400 ml). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated *in vacuo*. Distillation (80 °C, 1.5 mm Hg) afforded pure 3-(tetrahydropyran-2′-yloxy)-1-trimethylsilylpropyne (29.6 g, 36%); δ_H(400 MHz, $CDCl_3$) 0.13 (9H, s, $SiMe_3$), 1.44–1.85 (6H, m, 3′-H, 4′-H, 5′-H), 3.45–3.51 (1H, m, 6′-Ha), 3.79 (1H, ddd, *J* 3.0, 9.3, 12.2, 6′-Hb), 4.17 (1H, d, *J* 15.9, 3-Ha), 4.24 (1H, d, *J* 15.9, 3-Hb), 4.77 (1H, t, *J* 3.4, 2′-H); δ_C(100 MHz, $CDCl_3$) 101.51, 96.70, 90.77, 61.83, 54.74, 30.18, 25.32, 18.93, −0.23; *m*/*z* 212 (M^+, 0.4%), 211 (1), 173 (13), 111 (40), 103 (37), 101 (49), 85 (100), 83 (78), 75 (44), 73 (60), 55 (53), 43 (47), 41 (42).

3-Bromo-1-trimethylsilylpropyne 20. This was prepared from 3-(tetrahydropyran-2′-yloxy)-1-trimethylsilylpropyne (25.0 g, 0.118 mol) in the manner described for obtaining bromide **19**. Distillation under reduced pressure (46 °C, 2 mm Hg) gave pure 3-bromo-1-trimethylsilylpropyne **20** (18.3 g, 81%); δ_H(400 MHz, $CDCl_3$) 3.88 (2H, s, 3-H), 0.15 (9H, s, $SiMe_3$); δ_C(100 MHz, $CDCl_3$) 99.98, 92.29, 14.61, −0.37; *m*/*z* 192, 190 (M^+, 1%), 177 (100), 175 (98), 149 (95), 147 (87), 139 (51), 137 (49), 111 (30), 96 (41), 53 (52), 43 (84).

Dec-2-yn-1-ol 23

1-(Tetrahydropyran-2′-yloxy)dec-2-yne. 1-(Tetrahydropyran-2′-yloxy)prop-2-yne **22** (10.00 g, 71.4 mmol) was dissolved in THF (200 ml) in a three-necked flask and cooled to −78 °C. Bu^{n}Li (2.5 M, 34.3 ml, 85.7 mmol) was added dropwise *via* syringe and the reaction mixture was stirred for 3 h between −78 and −50 °C. After re-cooling to −78 °C, 1-iodoheptane (17.765 g, 78.6 mmol), dissolved in a mixture of THF (100 ml) and HMPA (10 ml), was added dropwise. The resulting mixture was allowed to warm to RT overnight. Hexane (300 ml) and iced-water (600 ml) were added, and the layers were separated. The aqueous layer was extracted with hexane (3 × 150 ml). After washing with H_2O and saturated aqueous NaCl, the combined organic layers were dried ($MgSO_4$) and concentrated (reduced pressure) to give the crude product which was used directly in the next reaction; *m*/*z* 238 (M^+, 0.1%), 237 (0.1), 209 (0.2), 183 (1), 167 (2), 154 (1), 153 (2), 111 (13), 101 (29), 95 (46), 85 (100), 81 (50), 79 (25), 67 (48), 55 (48), 43 (41), 41 (64), 39 (22).

Dec-2-yn-l-ol 23. The crude THP ether was dissolved in Analar MeOH (500 ml). Toluene-*p*-sulfonic acid (1.357 g, 7.14 mmol) was added and the mixture was stirred overnight. Saturated aqueous $NaHCO_3$ (1000 ml) and Et_2O (300 ml) were added. After separation of the layers, the aqueous layer was further extracted with Et_2O (3 × 200 ml). The combined organic layers were washed with aqueous NaCl, dried and concentrated. Purification of the crude product by flash chromatography (Et_2O–hexane, 1:7) yielded dec-2-yn-l-ol **23** (6.967 g, 63% over two steps) (Found: $M^+ - 1$, 153.1282. $C_{10}H_{17}O$ requires $M^+ - 1$, 153.1279); δ_H(400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.0, 10-H), 1.21–1.39 (8H, m, 6-H to 9-H), 1.48 (2H, quintet, *J* 7.1, 5-H), 1.52 (1H, br s, OH), 2.18 (2H, tt, *J* 7.1, 2.2, 4-H), 4.22 (2H, br s, 1-H); δ_C(100 MHz, $CDCl_3$) 86.66, 78.28, 51.42, 31.71, 28.82, 28.78, 28.61, 22.60, 18.72, 14.03; *m*/*z* 111 ($M^+ - 43$, 10%), 107 (12), 81 (44), 79 (44), 70 (46), 69 (33), 67 (61), 55 (83), 43 (73), 41 (100), 39 (62).

1-(Tetrahydropyran-2′-yloxy)dec-9-yne 21

Dec-9-yn-l-ol.[46] Potassium hydride (mineral oil dispersion, 2.4 ml, 35 wt%) was transferred to a three-necked flask (flame-dried under N_2). Dry Et_2O (20 ml) was added, with stirring, to wash the KH, which was then allowed to settle, before the Et_2O was drawn off with a syringe. This procedure was repeated twice. Residual Et_2O was removed *in vacuo*. The system was then flushed with N_2 again. 1,3-Diaminopropane (30 ml) was transferred to the flask and stirred for 1.5 h. A yellow–green solution resulted. Dec-2-yn-l-ol **23** (1.042 g, 6.77 mmol) in 1,3-diaminopropane (5 ml) was added dropwise, *via* syringe, to the reaction mixture, at 0 °C. A precipitate was observed to form and the reaction mixture was left to stir at RT overnight. A green–brown cloudy mixture resulted. The mixture was poured into iced-water and the aqueous layer was then extracted with Et_2O. The combined ethereal layers were washed with aqueous HCl (3 M) and then with H_2O until the washes were of neutral pH. After washing with saturated aqueous NaCl, the organic layers were dried ($MgSO_4$) and concentrated to yield crude dec-9-yn-1-ol which was used in the next step without further purification; δ_H(400 MHz, $CDCl_3$) 1.21–1.41 (8H, m), 1.45–1.58 (4H, m), 1.59 (1H, br s, OH), 1.90 (1H, t, *J* 2.7, 10-H), 2.15 (2H, dt, *J* 7.1, 2.7, 8-H), 3.60 (2H, t, *J* 6.6, 1-H); δ_C(100 MHz, $CDCl_3$) 84.69, 68.05, 62.97, 32.71, 29.22, 29.00, 28.62, 28.42, 25.64, 18.34; *m*/*z* 121 (4%), 95 (25), 94 (9), 93 (34), 91 (9), 81 (46), 80 (21), 79 (67), 67 (64), 55 (81), 41 (100), 39 (57).

1-(Tetrahydropyran-2′-yloxy)dec-9-yne 21. Crude dec-9-yn-l-ol (1.042 g, 6.77 mmol) was dissolved in dry CH_2Cl_2 (100 ml). Toluene-*p*-sulfonic acid (0.129 g, 0.67 mmol) was then added and dihydropyran (0.854 g, 10.15 mmol) in CH_2Cl_2 (20 ml) was added dropwise. The reaction mixture was left stirring overnight and then poured into saturated aqueous $NaHCO_3$, which was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic fractions were washed with saturated aqueous NaCl, dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash chromatography (Et_2O–hexane, 1:20) gave 1-(tetrahydropyran-2′-yloxy)dec-9-yne **21** (0.929 g, 58%) (Found: M^+, 238.1929; C, 77.4, H, 11.3%; $C_{15}H_{26}O_2$ requires M^+, 238.1933; C, 75.6, H, 11.0%); δ_H(400 MHz, $CDCl_3$) 1.22–1.41 (8H, m), 1.42–1.61 (8H, m), 1.62–1.85 (2H, m), 1.91 (1H, t, *J* 2.6, 10-H), 2.15 (2H, dt, *J* 7.0, 2.6, 8-H), 3.36 (1H, dt, *J* 9.7, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 6.9, 1-Hb), 3.85 (1H, ddd, *J* 11.3, 7.5, 3.7, 6′-Hb), 4.55 (1H, dd, *J* 4.6, 2.4, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.86, 84.74, 68.03, 67.64, 62.33, 30.81, 29.74, 29.31, 29.02, 28.68, 28.47, 26.19, 25.53, 19.70, 18.38; *m*/*z* 238 (M^+, 0.2%), 237 (1), 101 (29), 85 (100), 81 (18), 67 (22), 57 (11), 56 (20), 55 (27), 41 (40).

1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)trideca-1,4-diyne 7

This was formed from 1-(tetrahydropyran-2′-yloxy)dec-9-yne **21** (4.00 g, 16.8 mmol) and 3-bromo-1-trimethylsilylpropyne **20** (3.86 g, 20.0 mmol) according to the procedure described for

the preparation of **10** and **11**. The title compound **7** (3.63 g, 62%) was purified by flash chromatography (Et_2O–hexane, 1:19); δ_H(400 MHz, $CDCl_3$) 0.13 (9H, s, Me_3Si), 1.20–1.40 (8H, m), 1.41–1.61 (8H, m), 1.62–1.85 (2H, m), 2.12 (2H, tt, *J* 7.0, 2.4, 6-H), 3.15 (2H, t, *J* 2.3, 3-H), 3.35 (1H, dt, *J* 9.4, 6.7, 13-Ha), 3.45 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 7.0, 13-Hb), 3.84 (1H, ddd, *J* 11.0, 7.8, 3.8, 6′-Hb), 4.54 (1H, dd, *J* 4.3, 2.4, 2′-H); δ_C(100 MHz, $CDCl_3$) 100.84, 98.83, 84.59, 81.03, 73.34, 67.63, 62.30, 30.79, 29.73, 29.34, 29.06, 28.78, 28.65, 26.19, 25.53, 19.69, 18.71, 10.86, −0.09; *m*/*z* 275 (M^+ − 73, 1%), 173 (3), 159 (3), 145 (3), 135 (4), 133 (4), 131 (5), 103 (9), 101 (12), 85 (100), 75 (14), 73 (48).

Attempted formation of 1-(tetrahydropyran-2′-yloxy)trideca-9,12-diyne 24

Rearrangement of 7 to 1-(tetrahydropyran-2′yloxy)trideca-9,11-dinye 14. 1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)-trideca-1,4-diyne **7** (3.40 g, 9.83 mmol) was dissolved in THF (200 ml) and cooled to −5 °C. TBAF (19.7 ml, 1.0 M in THF) was added dropwise *via* syringe. The reaction mixture immediately went black, but was left to stir for 1 h at −5 °C and then at 25 °C for 2 h. It was then diluted with Et_2O (500 ml) and washed with saturated aqueous NaCl (2 × 100 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (Et_2O–hexane, 1:19) gave 1-(tetrahydropyran-2′-yloxy)trideca-9,11-diyne **14** (2.28 g, 94%) (Found: M^+, 276.2087. $C_{18}H_{28}O_2$ requires M^+, 276.2089); δ_H(400 MHz, $CDCl_3$) 1.20–1.86 (18H, m, 9 × CH_2), 1.88 (3H, s, 13-H), 2.20 (2H, t, *J* 7.0, 8-H), 3.35 (1H, dt, *J* 9.7, 6.7, 1-Ha), 3.46 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 7.0, 1-Hb), 3.85 (1H, ddd, *J* 11.0, 7.8, 3.8, 6′-Hb), 4.55 (1H, dd, *J* 4.3, 2.7, 2′-H); δ_C(100 MHz, $CDCl_3$), 98.85, 76.91, 72.91, 67.63, 65.30, 64.58, 62.32, 30.79, 29.72, 29.28, 29.00, 28.74, 28.31, 26.17, 25.52, 19.69, 19.12, 4.11; *m*/*z* 276 (M^+, 0.4%), 261 (9), 119 (12), 117 (11), 105 (20), 101 (11), 91 (32), 85 (100), 79 (18), 77 (21), 67 (23), 41 (46).

Rearrangement of 7 to 1-(tetrahydropyran-2′-yloxy)trideca-9,12-diyne 24. 1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)-trideca-1,4-diyne **7** (0.277 g, 0.801 mmol) was dissolved in THF (16 ml) and cooled to −10 °C. TBAF (0.801 ml, 1.0 M in THF) was added dropwise *via* syringe. The reaction mixture immediately went black, but was left to stir for 30 min between −10 and 0 °C. It was then diluted with Et_2O (50 ml) and washed with saturated aqueous NaCl (2 × 10 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (Et_2O–hexane, 1:19) gave 1-(tetrahydropyran-2′-yloxy)trideca-9,12-diyne **24** (0.030 g, 13%); δ_H(500 MHz, $CDCl_3$) 1.25–1.60 (18H, m), 1.65–1.72 (1H, m), 1.76–1.83 (1H, m), 2.03 (1H, t, *J* 2.5, 13-H), 2.13 (2H, tt, *J* 7.0, 2.4, 8-H), 3.13 (2H, q, *J* 2.5, 11-H), 3.36 (1H, dt, *J* 9.6, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.71 (1H, dt, *J* 9.6, 6.9, 1-Hb), 3.85 (1H, m, 6′-Hb), 4.54 (1H, dd, *J* 2.8, 4.5, 2′-H); *m*/*z* 275 (M^+ − 1, 0.4%), 237 (1), 119 (4), 117 (5), 105 (9), 101 (25), 91 (23), 85 (100), 55 (22), 41 (34).

Rearrangement of 7 to allenes and conjugated isomers. 1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)trideca-1,4-diyne **7** (0.504 g, 1.45 mmol) was dissolved in THF (30 ml) and cooled to −10 °C. TBAF (1.45 ml, 1.0 M in THF) was added dropwise *via* syringe. The reaction mixture immediately went black, but was left to stir for 30 min between −10 and 0 °C. The reaction was then diluted with Et_2O (50 ml) and washed with saturated aqueous NaCl (2 × 10 ml), dried ($MgSO_4$) and concentrated to give (0.41 g) of an oil which by GC–MS analysis was a mixture of four components, corresponding to 1-(tetrahydropyran-2′-yloxy)trideca-9,12-diyne **24** (12% by GC), and rearrangement products 1-(tetrahydropyran-2′-yloxy)trideca-9,11-diyne **14** (25%), 1-(tetrahydropyran-2′-yloxy)trideca-9,10-dien-12-yne (19%), and 1-(tetrahydropyran-2′-yloxy)trideca-11,12-dien-9-yne (43%). ν_{max}(thin film)/cm^{-1} 1941 (br, allene); 1-(*tetrahydropyran*-2′-*yloxy*)*trideca*-9,10-*dien*-12-*yne*; *m*/*z* 275 (M^+ − 1, 0.2%), 163 (1), 133 (2), 131 (2), 117 (5), 85 (100), 41 (39). 1-(*Tetrahydropyran*-2′-*yloxy*)*trideca*-11,12-*dien*-9-*yne*; *m*/*z* 276 (M^+ − 1, 0.1%), 163 (1), 135 (3), 133 (2), 131 (4), 117 (11), 115 (3), 105 (9), 91 (24), 85 (100), 41 (37).

Attempted rearrangement of 7 with HF. 1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)trideca-1,4-diyne **7** (0.015 g, 0.043 mmol) was dissolved in acetonitrile (1 ml) and aqueous HF (170 μl, 50%) was added dropwise *via* syringe at 0 °C. Stirring was continued for 30 min when solid $NaHCO_3$ was added, and the reaction mixture was then washed through a short plug of $MgSO_4$ with Et_2O, and concentrated *in vacuo*. GC–MS analysis indicated the presence of a new product which was not identified, but still exhibited *m*/*z* 85 (THP) and 73 ($SiMe_3$); *m*/*z* 173 (6%), 131 (9), 119 (8), 103 (13), 101 (13), 85 (100), 73 (53), 55 (23), 44 (62), 43 (24), 41 (22).

Attempted rearrangement of 7 with K_2CO_3. 1-Trimethylsilyl-13-(tetrahydropyran-2′-yloxy)trideca-1,4-diyne **7** (0.010 g, 0.029 mmol) was dissolved in MeOH (1 ml) and K_2CO_3 (10 mg) was added. Upon stirring overnight, GC–MS examination of the crude product showed that no reaction had occurred, with only starting material being observed.

[17,17-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)octadeca-9,12,15-triyne 18

Prepared according to the procedure described for the preparation of **10** and **11**, from 1-(tetrahydropyran-2′-yloxy)trideca-9,12-diyne **24** (30 mg, 0.109 mmol) and [4,4-$^2H_2$]-1-bromopent-2-yne **19** (19 mg, 0.130 mmol). The crude product was purified by flash chromatography (Et_2O–hexane, 1:20) to yield [17,17-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)octadeca-9,12,15-triyne **18** (0.029 g, 71%); δ_H(400 MHz, $CDCl_3$), 1.07 (3H, s, 18-H), 1.15–1.38 (8H, m), 1.42–1.60 (8H, m), 1.68 (1H, m), 1.80 (1H, m), 2.12 (2H, br t, *J* 6.7, 8-H), 3.11 (4H, m), 3.36 (1H, dt, *J* 9.7, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.7, 7.0, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.55 (1H, m, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.85, 82.03, 80.84, 74.89, 74.80, 73.76, 73.19, 67.66, 62.33, 30.79, 29.73, 29.33, 29.06, 28.81, 28.70, 26.19, 25.52, 19.69, 18.70, 13.62, 9.78, 9.74 [C17 (CD_2) not observed]; *m*/*z* 329 (M^+ − 15, 0.4%), 159 (5), 157 (5), 155 (4), 145 (7), 143 (10), 131 (13), 130 (16), 129 (15), 101 (15), 85 (100), 55 (25), 43 (20), 41 (36).

[7,7-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)octa-2,5-diyne 25

Formed according to the procedure described for the preparation of **10** and **11**, from 1-(tetrahydropyran-2′-yloxy)prop-2-yne **22** (0.473 g, 3.38 mmol) and [4,4-$^2H_2$]-1-bromopent-2-yne **19** (0.500 g, 3.38 mmol). Purification by flash chromatography (Et_2O–hexane, 1:20) yielded [7,7-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)octa-2,5-diyne **25** (0.292 g, 42%); δ_H(500 MHz, $CDCl_3$), 1.06 (3H, t, *J* 1.0, 8-H), 1.45–1.84 (6H, m), 3.14 (2H, t, *J* 2.1, 4-H), 3.49 (1H, m, 6′-Ha), 3.79 (1H, ddd, *J* 12.0, 9.2, 3.0, 6′-Hb), 4.17 (1H, dt, *J* 15.3, 2.1, 1-Ha), 4.26 (1H, dt, *J* 15.3, 2.2, 1-Hb), 4.76 (1H, t, *J* 3.5, 2′-H); δ_C(125 MHz, $CDCl_3$) 96.79, 82.20, 80.83, 75.98, 72.77, 61.89, 54.47, 30.20, 25.32, 19.01, 13.56, 9.83 [C7 (CD_2) not observed]; *m*/*z* 207 (M^+ − 1, 1%), 108 (23), 107 (30), 105 (31), 93 (42), 85 (100), 81 (50), 80 (49), 79 (51), 78 (55), 55 (48), 43 (45), 41 (70).

[7,7-$^2H_2$]-1-Bromoocta-2,5-diyne 26

Prepared from [7,7-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)octa-2,5-diyne **25** (0.250 g, 1.20 mmol) in the manner described for obtaining bromide **19**. Flash column chromatography (100% light petroleum) gave [7,7-$^2H_2$]-1-bromoocta-2,5-diyne **26** (0.107 g, 48%); δ_H(400 MHz, $CDCl_3$) 1.08 (3H, s, 8-H), 3.18 (2H, t, *J* 2.4, 4-H), 3.89 (2H, t, *J* 2.4, 1-H); δ_C(100 MHz, $CDCl_3$) 82.63, 82.10, 75.25, 72.19, 14.79, 13.56, 11.78 (C7, quintet, *J* 20.2), 10.05; *m*/*z* 188, 186 (M^+, 22, 21%), 173 (6), 171 (6), 107 (100), 105 (54), 81 (72), 80 (70), 79 (76), 78 (85), 77 (35), 52 (40), 51 (50).

[17,17-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)octadeca-9,12,15-triyne 18

Formed according to the procedure described for the preparation of **10** and **11**, from 1-(tetrahydropyran-2′-yloxy)dec-9-yne **21** (0.141 g, 0.591 mmol) and [7,7-$^2H_2$]-1-bromoocta-2,5-diyne

26 (0.092 g, 0.492 mmol). Purification by flash chromatography (Et_2O–hexane, 1:20) yielded [17,17-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)octadeca-9,12,15-triyne **18** (0.094 g, 56%). NMR and GC–MS spectra were identical to those reported earlier.

(9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16,17,17-$^2H_8$]-1-(Tetrahydropyran-2′-yloxy)octadeca-9,12,15-triene 27

From triyne **18** (0.085 g, 0.247 mmol) in Et_2O (5 ml), $Ti(OPr^i)_4$ (0.562 g, 1.98 mmol) in Et_2O (5 ml), Pr^iMgBr (3.95 ml, 0.94 mmol, ~1.25 M solution in dry Et_2O) and D_2O (1.0 ml) according to the general procedure. Work-up procedure A and flash chromatography (Et_2O–hexane, 1:20) provided pure triene **27** (33 mg, 38%) (Found: M^+, 356.3533. $C_{23}H_{32}O_2{}^2H_8$ requires M^+, 356.3530); δ_H(500 MHz, $CDCl_3$) 0.93 (3H, br s, 18-H), 1.22–1.48 (12H, m), 1.46–1.61 (6H, m), 1.66–1.72 (1H, m), 1.77–1.85 (1H, m), 2.02 (2H, br t, *J* 7.0, 8-H), 2.77 (4 H, m, 11-H, 14-H), 3.36 (1H, dt, *J* 9.6, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.6, 6.9, 1-Ha), 3.85 (1H, m, 6′-Hb), 4.55 (1H, dd, *J* 4.4, 2.8, 2′-H); δ_C(125 MHz, $CDCl_3$) 98.83 (C2′), 67.67, 62.31, 30.79 (C3′), 29.75, 29.62, 29.48, 29.45, 27.87, 27.09, 26.23, 25.51 (C5′), 25.26, 22.14, 19.69 (C4′), 14.03 (C18); *m*/*z* 356 (M^+, 0.2%), 101 (11), 85 (100), 83 (19), 82 (14), 55 (13), 43 (16), 41 (22).

(9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16,17,17-$^2H_8$]Octadeca-9,12,15-trienol 28

Deuterated triene **27** (0.033 g, 0.093 mmol) and toluene-*p*-sulfonic acid (1.8 mg, 0.009 mmol) were dissolved in MeOH (1 ml), and stirred for 90 min at RT when TLC analysis indicated the absence of starting material. Solid $NaHCO_3$ was then added and left to stir for 1 h. Solid $MgSO_4$ was then added and the solution was filtered. The MeOH was removed on the rotary evaporator. Flash chromatography (Et_2O–hexane, 1:5) provided pure **28** (0.008 g, 32%); δ_H(400 MHz, $CDCl_3$) 0.94 (3H, br s, 18-H),1.22–1.38 (10 H, m), 1.53 (1H, s, OH), 1.55 (2H, m, 2-H), 2.03 (2H, br t, *J* 7.1, 8-H), 2.78 (4H, m, 14-H), 3.62 (2H, br t, *J* 6.5, 1-H).

1-Bromopent-2-yne 29

1-(Tetrahydropyran-2′-yloxy)pent-2-yne. 1-(Tetrahydropyran-2′-yloxy)prop-2-yne **22** (4.08 g, 29.14 mmol) was dissolved in THF (80 ml) in a three-necked flask and cooled to −78 °C. Bu″Li (2.5 M, 14.0 ml, 35.0 mmol) was added dropwise *via* syringe and the reaction mixture was stirred at −60 °C to −50 °C for 2 h. Upon recooling to −78 °C, iodoethane (5.0 g, 32.1 mmol), dissolved in a mixture of THF (5 ml) and DMPU (5 ml), was added dropwise from a dropping funnel. The resulting mixture was allowed to warm to RT overnight. Hexane (250 ml) and water (300 ml) were added, and the layers were separated. The aqueous layer was extracted with hexane (3 × 100 ml). After washing with saturated aqueous NaCl, the combined organic layers were dried ($MgSO_4$) and concentrated (reduced pressure). Purification using flash chromatography (Et_2O–hexane, 1:20) yielded pure fractions of 1-(tetrahydropyran-2′-yloxy)pent-2-yne (2.287 g, 47%); δ_H(500 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.7, 5-H), 1.51 (2H, m), 1.58 (2H, m), 1.71 (1H, m), 1.81 (1H, m), 2.21 (2H, qt, *J* 7.6, 2.1, 4-H), 3.50 (1H, m, 6′-Ha), 3.82 (1H, ddd, *J* 11.6, 9.2, 3.0, 6′-Hb), 4.16 (1H, dt, *J* 15.0, 2.1, 1-Ha), 4.26 (1H, dt, *J* 15.0, 2.1, 1-Hb), 4.78 (1H, t, *J* 3.5, 2′-H); δ_C(125 MHz, $CDCl_3$) 96.67, 87.96, 75.09, 61.93, 54.64, 30.28, 25.37, 19.09, 13.74, 12.49; *m*/*z* 167 ($M^+ - 1$, 0.3%), 111 (12), 101 (30), 85 (63), 83 (13), 79 (10), 67 (74), 66 (22), 65 (30), 55 (40), 41 (100), 39 (52).

1-Bromopent-2-yne 29. Prepared from 1-(tetrahydropyran-2′-yloxy)pent-2-yne (4.80 g, 28.6 mmol) utilising the general procedure described for bromide **19**. Flash chromatography (100% light petroleum) gave purified 1-bromopent-2-yne **29** (3.66 g, 87%); δ_H(500 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.5, 5-H), 2.24 (2H, qt, *J* 7.5, 2.4, 4-H), 3.90 (2H, t, *J* 2.4, 1-H); δ_C(125 MHz, $CDCl_3$) 89.43, 74.63, 15.66, 13.45, 12.64; *m*/*z* 148, 146 (M^+, 8, 8%), 133 (1), 131 (1), 81 (12), 79 (11), 67 (100), 41 (94), 39 (67).

(9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16-$^2H_6$]-1-(Tetrahydropyran-2′-yloxy)octadeca-9,12,15-triene 30

1-(Tetrahydropyran-2′-yloxy)octa-2,5-diyne. Prepared according to the procedure described for the preparation of **10** and **11**, from 1-(tetrahydropyran-2′-yloxy)prop-2-yne **22** (1.417 g, 10.12 mmol) and 1-bromopent-2-yne **29** (1.488 g, 10.12 mmol). Purification of the crude product by flash chromatography (Et_2O–hexane, 1:2) yielded 1-(tetrahydropyran-2′-yloxy)octa-2,5-diyne (0.696 g, 33%); *m*/*z* 205 ($M^+ - 1$, 1%), 121 (5), 119 (5), 117 (5), 111 (8), 105 (30), 103 (37), 91 (65), 85 (88), 79 (75), 78 (39), 77 (100), 41 (83), 39 (61).

1-Bromoocta-2,5-diyne. Prepared from 1-(tetrahydropyran-2′-yloxy)octa-2,5-diyne (0.696 g, 3.38 mmol) according to the general procedure described for bromide **19**. Purification by flash chromatography (100% light petroleum) gave 1-bromooca-2,5-diyne (0.416 g, 67%); δ_H(200 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.5, 8-H), 2.15 (2H, qt, *J* 7.5, 2.4, 7-H), 3.19 (2H, tt, *J* 2.4, 2.3, 4-H), 3.89 (2H, t, *J* 2.3, 1-H); δ_C(50 MHz, $CDCl_3$) 82.68, 82.06, 75.24, 72.15, 14.86, 13.77, 12.33, 10.06.

1-(Tetrahydropyran-2′-yloxy)octadeca-9,12,15-triyne. Formed according to the procedure described for the preparation of **10** and **11**, from 1-(tetrahydropyran-2′-yloxy)dec-9-yne **21** (0.545 g, 2.29 mmol) and 1-bromoocta-2,5-diyne (0.400 g, 2.17 mmol). The product was purified by flash chromatography (Et_2O–hexane, 1:20) to yield 1-(tetrahydropyran-2′-yloxy)octadeca-9,12,15-triyne (0.407 g, 55%); δ_H(500 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.5, 18-H), 1.23–1.36 (8H, m), 1.42–1.59 (8H, m), 1.68 (1H, m), 1.81 (1H, m), 2.13 (4H, m, 8-H, 17-H), 3.11 (4H, m, 11-H and 14-H), 3.35 (1H, dt, *J* 9.6, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.6, 6.9, 1-Hb), 3.84 (1H, ddd, *J* 11.2, 7.7, 3.6, 6′-Hb), 4.55 (1H, dd, *J* 4.3, 2.8, 2′-H); δ_C(125 MHz, $CDCl_3$) 98.83, 82.09, 80.82, 74.86, 74.77, 73.73, 73.14, 67.64, 62.32, 30.78, 29.72, 29.33, 29.06, 28.81, 28.68, 26.19, 25.50, 19.69, 18.68, 13.83, 12.35, 9.77, 9.74.

(9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16-$^2H_6$]-1-(Tetrahydropyran-2′-yloxy)octadeca-9,12,15-triene 30. From the triyne prepared above (0.202 g, 0.591 mmol) in Et_2O (5 ml), $Ti(OPr^i)_4$, (1.343 g, 4.73 mmol) in Et_2O (10 ml), Pr^iMgBr (9.45 ml, 11.81 mmol, ~1.25 M solution in Et_2O) and D_2O (1.0 ml) according to the general procedure. Work-up procedure A and flash chromatography (Et_2O–hexane, 1:20) provided pure **30** (52 mg, 25%) (Found: M^+, 354.3401. $C_{23}H_{34}O_2{}^2H_6$ requires M^+, 354.3405). δ_H(500 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.6, 18-H), 1.22–1.40 (12H, m), 1.45–1.60 (6H, m), 1.65–1.72 (1H, m), 1.76–1.85 (1H, m), 2.02 (4H, m, 8-H, 17-H), 2.77 (4H, m, 11-H, 14-H), 3.36 (1H, dt, *J* 9.6, 6.7, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dt, *J* 9.6, 6.9, 1-Hb), 3.85 (1H, m, 5′-Hb), 4.55 (1H, dd, *J* 4.4, 2.9, 2′-H); δ_C(125 MHz, $CDCl_3$) 98.81, 67.65, 62.29, 30.77 (C3′), 29.74, 29.61, 29.46, 29.44, 29.24, 27.87, 27.08, 26.22, 25.50 (C5′), 25.25, 21.11, 20.39, 19.67 (C4′), 14.22 (C18); δ_{2_H} (61 MHz, $CHCl_3$) 5.40, 5.37, 5.32; *m*/*z* 354 (M^+, 0.1%), 112 (6), 111 (4), 101 (7), 97 (7), 96 (7), 85 (100), 83 (18), 82 (16), 43 (19), 41 (29).

(9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16-$^2H_6$]Octadeca-9,12,15-trienoic acid 32

Attempted oxidation of 30. [9,10,12,13,15,16-$^2H_6$]-1-(Tetrahydropyran-2′-yloxy)octadeca-9,12,15-triene **30** (0.005 g, 0.014 mmol) was dissolved in dry acetone (1 ml) and excess Jones' reagent was added dropwise to the stirred solution until the orange colour persisted for a period of 20 min. Concentration of the solution *in vacuo* gave a residue, to which water (5 ml) and Et_2O (5 ml) were added. Further extracts (Et_2O, 2 × 3 ml) were combined with the initial extract, dried over $MgSO_4$ and concentrated, but **32** was not present in the product mixture on the basis of ^1H NMR analysis.

(9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16-$^2H_6$]Octadeca-9,12,15-trienol 31. THP ether **30** (0.043 g, 0.12 mmol) and toluene-*p*-sulfonic acid (2.3 mg, 0.012 mmol) were stirred in MeOH (2 ml) for 1 h at RT. Solid $NaHCO_3$ was added and left to stir for 1 h. Solid $MgSO_4$ was then added to dry the solution which was

then filtered. MeOH was removed on the rotary evaporator and the oil obtained was subjected to flash chromatography (Et_2O–hexane, 1 : 5) to provide pure product trienol **31** (0.030 g, 91%) (Found: M^+, 270.2830. $C_{18}H_{26}O^2H_6$ requires M^+, 270.2830); δ_H(400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, 18-H), 1.2–1.4 (10H, m, 3-H to 7-H), 1.54 (2H, m, 2-H), 2.04 (4H, m, 8-H, 17-H), 2.77 (4H, m, 11-H, 14-H), 3.61 (2H, t, *J* 6.6, 1-H); δ_C(100 MHz, $CDCl_3$) 63.05 (C1), 32.78, 29.60, 29.47, 29.38, 29.22, 27.08, 25.72, 25.35, 25.26, 20.39, 14.21 (C18); δ_{2_H}(61 MHz, $CHCl_3$) 5.40, 5.37, 5.33; *m*/*z* 270 (M^+, 2%), 212 (3), 154 (3), 140 (5), 112 (34), 98 (36), 97 (42), 83 (100), 82 (92), 81 (60), 43 (60), 41 (73).

Attempted oxidation of trienol 31. To a stirred solution of [9,10,12,13,15,16-$^2H_6$]octadeca-9,12,15-trienol **31** (0.005 g, 0.019 mmol) in dry acetone (1 ml) was added Jones' reagent (dropwise). Addition of excess Jones' reagent was indicated by the persistence of the orange colour of Cr^{VI}. Concentration *in vacuo* gave a residue, to which water (5 ml) and Et_2O (5 ml) were added. Further extracts (Et_2O, 2 × 3 ml) were combined with the initial extract, dried over $MgSO_4$ and concentrated. This product was extracted from Et_2O into an alkaline solution, which was then reacidified and extracted with Et_2O. This Et_2O solution was dried over $MgSO_4$ and concentrated to give a mixture of unidentified rearrangement products, on the basis of ^{1}H NMR analysis.

(9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16-$^2H_6$]Octadeca-9,12,15-trienoic acid 32.[25] [9,10,12,13,15,16-$^2H_6$]Octadeca-9,12,15-trienol **31** (0.026 g, 0.0963 mmol) was dissolved in DMF (2 ml) and PDC (0.163 g, 0.43 mmol) was added in one portion. The reaction mixture was left stirring for 24 h. GC–MS Analysis showed the absence of starting alcohol, but indicated the presence of some aldehyde *en route* to acid **32**. A small amount of additional PDC was added and stirring was continued for another 2 h before Et_2O (10 ml) and H_2O (20 ml) were added. Upon separation of the layers, the aqueous layer was further extracted with Et_2O. The combined ether extracts were washed with saturated aqueous NaCl and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave acid **32** and a trace amount of the corresponding aldehyde (0.015 g, 56%). *Acid* **32**; δ_H(400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.6, 18-H), 1.20–1.40 (8H, m), 1.54–1.67 (2H, m, 3-H), 1.95–2.08 (4H, m, 8-H, 17-H), 2.33 (2H, t, *J* 7.4, 2-H), 2.78 (4H, br s, 11-H, 14-H). (9*Z*,12*Z*,15*Z*)-[9,10,12,13,15,16-$^2H_6$]*Octadeca*-9,12,15-*trienal*; *m*/*z* 268 (4), 210 (5), 155 (3), 154 (3), 153 (3), 112 (34), 99 (45), 98 (44), 97 (44), 84 (55), 83 (100), 82 (92), 70 (53), 69 (53), 43 (57), 41 (62).

Synthesis of deuterated oleic acid

3-Ethoxycyclohex-2-enone 37

In a flask fitted with a Dean-Stark trap, was placed cyclohexane-1,3-dione **36** (20.0 g, 0.178 mmol), toluene-*p*-sulfonic acid (0.406 g, 0.0021 mol), ethanol (95 ml) and benzene (340 ml). The mixture was refluxed for 6 h, and the benzene–ethanol–water azeotrope was collected. Upon cooling, the residual solution was washed with 10% aqueous NaOH which had been saturated with NaCl (4 × 80 ml). It was then washed with H_2O until the washes were of neutral pH. Concentration under reduced pressure gave 24.56 g of crude product which was distilled (88–90 °C, 1.6 mbar) to yield (12.67 g, 51%) pure **37**; δ_H(400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.0, 2′-H), 1.91 (2H, m, 5-H), 2.27 (2H, dd, *J* 7.3, 6.0, 3-H or 5-H), 2.34 (2H, br t, *J* 6.3, 3-H or 5-H), 3.84 (2H, q, *J* 7.0, 1′-H), 5.28 (1H, br s, 2-H); δ_C(100 MHz, $CDCl_3$) 199.62, 177.75, 102.61, 64.04, 36.67, 29.00, 21.16, 14.01; *m*/*z* 140 (M^+, 45%), 112 (45), 84 (100), 69 (81), 68 (64), 43 (49), 39 (53).

3-Butylcyclohex-2-enone 38

3-Ethoxycyclohex-2-enone **37** (5.0 g, 35.7 mmol) was dissolved in Et_2O (250 ml) in a three-necked flask under a dry N_2 atmosphere, and cooled to 0 °C. Bu^{n}Li (21.1 ml, 38.0 mmol) was added dropwise *via* cannula to the reaction flask. The resulting mixture was stirred at 0 °C for 30 min and at room temperature for 2 h. It was then poured into iced ~1 M HCl (~300 ml). The Et_2O layer was separated and washed with saturated aqueous $NaHCO_3$ (2 × 100 ml) and saturated aqueous NaCl (1 × 100 ml). The Et_2O solution was then dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (Et_2O–light petroleum, 1 : 6) gave 3-butylcyclohex-2-enone **38** (4.866 g, 90%); δ_H(400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3, 4′-H), 1.46 (2H, m), 1.31 (2H, ~sextet, *J* ~7.3), 1.95 (2H, ~quintet, *J* 6.2), 2.18 (2H, br t, *J* 7.6), 2.25 (2H, ~br t, *J* ~6.2), 2.32 (2H, dd, *J* 7.1, 6.3), 5.84 (1H, ~quintet, *J* 1.3, 2-H); δ_C(100 MHz, $CDCl_3$) 199.91, 166.66, 125.65, 37.74, 37.34, 29.66, 29.05, 22.73, 22.32, 13.79; *m*/*z* 152 (M^+, 10%), 123 (10), 110 (9), 82 (100), 67 (12), 53 (10), 41 (19), 39 (22).

3-Butyl-2,3-epoxycyclohexanone 39

Enone **38** (3.00 g, 19.7 mmol) was dissolved in MeOH (160 ml) and to the solution was added H_2O_2 (13.42 ml, 118.4 mmol) and 6 M NaOH (1.55 ml, 9.28 mmol). The reaction mixture was left to stir overnight and then water (350 ml) was added and the mixture was extracted with Et_2O (3 × 150 ml). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to yield crude product. Purification *via* flash chromatography (Et_2O–light petroleum, 1 : 9) provided 3-butyl-2,3-epoxycyclohexanone **39** (2.663 g, 80%); δ_H(400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.2, 4′-H), 1.25–1.41 (4H, m), 1.54–1.71 (2H, m), 1.79–2.11 (4H, m), 2.45 (1H, t, *J* 4.5, 6-Ha), 2.49 (1H, t, *J* 4.7, 6-Hb), 3.04 (1H, s, 2-H); δ_C(100 MHz, $CDCl_3$) 206.95, 65.43, 61.17, 35.91, 35.69, 26.74, 26.39, 22.56, 17.38, 13.85; *m*/*z* 168 (M^+, 17%), 139 (12), 126 (14), 112 (20), 111 (18), 97 (76), 71 (83), 55 (95), 53 (17), 43 (40), 41 (100), 39 (52).

6-Oxodec-1-yne 40

Epoxy ketone **39** (1.2 g, 7.14 mmol) was dissolved in a mixture of CH_2Cl_2 (16 ml) and acetic acid (8 ml) and cooled to 0 °C. Toluene-*p*-sulfonylhydrazide (1.330 g, 7.14 mmol) was added in one portion and the reaction mixture left to stir for 3 h at 0 °C. After continued stirring for 3 h at room temperature, the mixture was poured into water (100 ml), light petroleum was added and the layers separated. Further extraction of the aqueous layer with light petroleum (2 × 50 ml) was performed and the combined organic extracts were washed with H_2O (20 ml), $NaHCO_3$ (20 ml) and NaCl (20 ml) and then dried over $MgSO_4$. Concentration and flash chromatography (Et_2O–light petroleum, 1 : 9) gave 6-oxodec-1-yne **40** (1.061 g, 98%). δ_H(400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3, 10-H), 1.28 (2H, sextet, *J* 7.3, 9-H), 1.53 (2H, quintet, *J* 7.5, 4-H or 8-H), 1.76 (2H, quintet, *J* 7.0, 4-H or 8-H), 1.92 (1H, t, *J* 2.6, 1-H), 2.20 (2H, dt, *J* 6.9, 2.6, 3-H), 2.38 (2H, t, *J* 7.5, 5-H or 7-H), 2.52 (2H, t, *J* 7.2, 5-H or 7-H); δ_C(100 MHz, $CDCl_3$) 210.56, 83.62, 68.93, 42.68, 40.99, 25.96, 22.33, 22.25, 17.76, 13.80; *m*/*z* 152 (M^+, 6%), 123 (7), 110 (12), 109 (10), 95 (62), 85 (65), 67 (59), 58 (57), 57 (98), 55 (54), 41 (100), 39 (61).

[1,5,5,6,7,7-$^2H_6$]Dec-1-yn-6-ol 41

[1,5,5,7,7-$^2H_5$]-6-Oxodec-1-yne. Alkynyl ketone **40** (0.512 g, 3.37 mmol) was stirred vigorously overnight in a THF (10 ml) and D_2O (25 ml) mixture to which Na metal (50 mg) had been added. DCl (38%) in D_2O was added to achieve pH 1–2. Extraction with Et_2O (3 × 100 ml) gave the combined ethereal extracts which were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated under reduced pressure to give a product (0.496 g, 94%) which exhibited only one GC peak and was used in the subsequent step without further purification; *m*/*z* 157 (M^+, 10%), 128 (6), 115 (13), 114 (12), 98 (68), 87 (81), 70 (49), 68 (34), 67 (14), 62 (74), 59 (100).

[1,5,5,6,7,7-$^2H_6$]Dec-1-yn-6-ol 41. $LiAlD_4$ (200 mg, 4.8 mmol) was stirred in dry Et_2O (10 ml) and cooled to −20 °C. In a separate flask, [1,5,5,7,7-$^2H_5$]-6-oxodec-1-yne (0.755 g, 4.81 mmol) was dissolved in Et_2O (5 ml) and transferred *via* cannula

to the $LiAlD_4$ suspension. The reaction was stirred at room temperature for 5 h. GC–MS analysis suggested the reaction was complete and $Na_2SO_4 \cdot 10\ H_2O$ was added portionwise to quench the reaction, with stirring continued until a free-moving white solid resulted. The mixture was filtered through a sinter and washed through with Et_2O. Concentration *in vacuo* gave crude material which was purified by flash chromatography (Et_2O–hexane, 1:4) to give decynol as a mixture of **41** and [5,5,6,7,7-$^2H_5$]-**41** (0.211 g, 56%); δ_H(400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, 10-H), 1.25–1.36 (4H, m, 8-H, 9-H), 1.54 (1H, dt, *J* 13.8, 6.9, 4-Ha), 1.65 (1H, dt, *J* 13.7, 7.1, 4-Hb), 1.92 (0.1H, t, *J* 2.6, 1-H), 2.18 (2H, t, *J* 7.1, 3-H), 4-Ha and 4-Hb were identified by irradiation of 3-H in a homodecoupling experiment; δ_C(100 MHz, $CDCl_3$) 84.40 (C1, residual ≡CH), 83.92 (C1, t, $J_{^{13}C-^2H}$ 7.5, ≡CD), 70.77 (C6, t, $J_{^{13}C-^2H}$ 21.4), 68.42 (C2), 36.26 (C5 or C7, quintet, $J_{^{13}C-^2H}$ 19.0), 35.38 (C5 or C7, quintet, $J_{^{13}C-^2H}$ 19.1), 27.53, 24.35, 22.65, 18.32, 14.02 (C10).

[1,5,5,6,7,7-$^2H_6$]Dec-1-yne 34

[1,5,5,6,7,7-$^2H_6$]-6-(Methanesulfonyloxy)-dec-1-yne. To a 0 °C solution of alcohol **41** (0.334 g, 2.1 mmol) in CH_2Cl_2 (5 ml), was added Et_3N (0.35 ml, 0.255 g, 2.52 mmol), followed by methanesulfonyl chloride (0.179 ml, 0.265 g, 2.3 mmol) *via* syringe. The reaction mixture was stirred for 2 h at room temperature, when TLC indicated complete conversion. Concentration *via* rotary evaporation gave an oily white solid. Flash chromatography (Et_2O–hexane, 1:5) gave the [1,5,5,6,7,7-$^2H_6$]mesylate, together with the [5,5,6,7,7-$^2H_5$]mesylate (0.409 g, 82%). [1,5,5,6,7,7-$^2H_6$]Mesylate; δ_H(400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, 10-H), 1.32 (4H, m, 8-H, 9-H), 1.59 (2H, m, 4-H), 1.94 (0.1H, t, *J* 2.7, residual 1-H), 2.21 (2H, t, *J* 6.9, 3-H), 2.98 (3H, s, $MeSO_3$); δ_C(100 MHz, $CDCl_3$) 83.56 (C1, residual ≡*CH*), 83.09 (C1, t, $J_{^{13}C-^2H}$ 7.6, ≡CD), 68.94 (C2), 38.70 (CH_3SO_3), 33.63 (C5 or C7, quintet, $J_{^{13}C-^2H}$ 18.5), 32.39 (C5 or C7, quintet, $J_{^{13}C-^2H}$ 18.6), 26.78, 23.48, 22.35, 18.02, 13.84 (C10) [no signal for C6 (CDOMs) was observed]; *m*/*z* 238 (M^+, 0%), 194 (2), 179 (6), 168 (12), 112 (12), 111 (8), 101 (100), 100 (47), 83 (50), 82 (49), 79 (73), 72 (65), 71 (53), 43 (66), 42 (61), 41 (60).

[1,5,5,6,7,7-$^2H_6$]Dec-1-yne 34. $LiAlH_4$ (0.062 g, 1.65 mmol) was stirred in Et_2O and cooled to 0 °C. In a separate flask, the mesylate (0.390 g, 1.65 mmol) was dissolved in Et_2O and transferred *via* cannula to the $LiAlH_4$ suspension. The reaction was stirred at room temperature for 90 min. GC–MS analysis revealed that starting material remained. Additional $LiAlH_4$ was added to the reaction mixture at 0 °C. Upon stirring for an additional 5 min, GC–MS analysis showed that the reaction was still not complete. The reaction was then left to stir overnight, after which time the conversion was complete. $Na_2SO_4 \cdot 10\ H_2O$ was added portionwise to quench the reaction, with stirring continued until the white solid moved freely. The mixture was washed through a sinter with Et_2O and concentration of this solution gave crude material which was purified *via* flash chromatography to give decyne **34** and [5,5,6,7,7-$^2H_5$]-**34** (0.211 g, 90%); δ_H(400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.1, 10-H), 1.19–1.31 (5H, m, 6-H, 8-H, 9-H), 1.49 (2H, m, 4-H), 1.91 (0.5H, t, *J* 2.6, 1-H), 2.16 (1H, dt, *J* 7.2, 2.5, 3-H adjacent to ≡CH), 2.16 (1H, t, *J* 7.2, 3-H adjacent to ≡CD); δ_C(100 MHz, $CDCl_3$) 84.84 (C1, residual ≡*CH*), 84.36 (C1, t, $J_{^{13}C-^2H}$ 7.6, ≡*CD*), 67.98 (C2), 31.60, 28.30, 28.24 (C6, t, $J_{^{13}C-^2H}$ 19.1), 28.16 (C5 and C7, quintet, $J_{^{13}C-^2H}$ 19.1), 22.59, 18.32, 14.08 (C10); *m*/*z* 143 (M^+, 0%), 114 (8), 101 (8), 100 (29), 85 (74), 84 (100), 70 (84), 69 (78), 58 (54), 57 (60), 56 (59), 44 (62), 43 (89), 42 (83), 41 (75), 39 (57).

[2,7-$^2H_2$]Octane-1,8-diol 48

Octa-1,7-diene (5.00 g, 45.4 mmol) was dissolved in dry THF (100 ml), and $NaBD_4$ (1.90 g, 45.4 mmol) was added in one portion. The reaction was cooled to 0 °C and $BF_3 \cdot OEt_2$ (7.44 ml, 8.59 g, 60.4 mmol) was added dropwise *via* syringe. Stirring was continued at 0 °C for 15 min and then at room temperature for 2 h. GC analysis then showed the absence of diene. Water (20 ml) was added dropwise, followed by, in one portion, NaOH solution (3 M, 20 ml) and aqueous H_2O_2 (30% w/v, 21 ml). The resultant mixture was refluxed at 80 °C for 30 min. Upon cooling, additional H_2O (300 ml) was added to the mixture, which was then extracted with Et_2O (3 × 100 ml). The combined Et_2O extracts were washed with unsaturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (ethyl acetate) gave pure [2,7-$^2H_2$]octane-1,8-diol **48** (5.042 g, 75%); δ_H(400 MHz, $CDCl_3$) 1.29–1.33 (8H, m), 1.46 (2H, br s, OH), 1.52 (2H, m, 2-H), 3.61 (4H, d, *J* 6.6, 1-H); δ_C(100 MHz, $CDCl_3$) 62.94 (C1), 32.32 (C2, t, $J_{^{13}C-^2H}$ 19.2), 29.30, 25.53 (C3, C4).

[2,7-$^2H_2$]-1,8-Bis(trimethylsilyloxy)octane

A small amount of [2,7-$^2H_2$]octane-1,8-diol **48** was treated with TMSI reagent (*N*-trimethylsilylimidazole) in CH_2Cl_2 for 30 min under reflux. GC–MS analysis revealed the presence of a peak due to [2,7-$^2H_2$]-1,8-bis(trimethylsilyloxy)octane; *m*/*z* 292 (M^+, 0%), 202 (2), 187 (5), 177 (5), 150 (6), 149 (22), 147 (69), 103 (21), 75 (74), 73 (78), 71 (47), 70 (100), 56 (43).

[2,7-$^2H_2$]-1-Iodo-8-(tetrahydropyran-2′-yloxy)octane 35

[2,7-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)octan-8-ol. Diol **48** (5.042 g, 34.1 mmol) was dissolved in dry CH_2Cl_2 (100 ml) and toluene-*p*-sulfonic acid (0.324 g, 1.7 mmol) was added in one portion. 3,4-Dihydro-2*H*-pyran (2.866 g, 34.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise to the solution at 0 °C. The reaction mixture was left stirring overnight, and then poured into saturated aqueous $NaHCO_3$. Upon separation of the layers, the aqueous fraction was further extracted with CH_2Cl_2 (3 × 60 ml). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated. Flash chromatography yielded pure mono-THP-protected diol (3.414 g, 43%); δ_H(400 MHz, $CDCl_3$) 1.26–1.34 (8H, m), 1.45–1.58 (6H, m), 1.62–1.72 (1H, m), 1.75–1.84 (1H, m), 3.34 (1H, dd, *J* 9.4, 7.0, 1-Ha), 3.46 (1H, m, 6′-Ha), 3.59 (2H, d, *J* 6.6, 8-H), 3.68 (1H, dd, *J* 9.4, 7.0, 1-Hb), 3.83 (1H, m, 6′-Hb), 4.53 (1H, dd, *J* 4.4, 2.6, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.82 (C2′), 67.55, 62.86, 62.29 (C6′, C1, C8), 32.32 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.2), 30.74, 29.35, 29.29 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.2), 29.28, 26.02, 25.55, 25.46, 19.64; *m*/*z* 232 (M^+, 0.1%), 231 (1), 159 (1), 147 (1), 131 (1), 113 (4), 101 (20), 85 (100), 70 (31), 56 (41), 41 (39).

[2,7-$^2H_2$]-1-(Methanesulfonyloxy)-8-(tetrahydropyran-2′-yloxy)octane. The mono-THP-protected diol (2.00 g, 8.62 mmol) was dissolved in CH_2Cl_2 (20 ml), and the solution was cooled to 0 °C. Et_3N (1.44 ml, 1.047 g, 10.34 mmol), followed by mesyl chloride (0.734 ml, 1.086 g, 9.48 mmol) were added *via* syringe and the reaction mixture was stirred for 2 h at RT, when TLC indicated complete conversion. Concentration *via* rotary evaporation gave an oily white solid. Flash chromatography (Et_2O–hexane, 1:1) gave the desired mesylate (2.317 g, 87%); δ_H(400 MHz, $CDCl_3$) 1.28–1.41 (8H, m), 1.45–1.58 (5H, m), 1.64–1.72 (2H, m), 1.75–1.81 (1H, m), 2.97 (3H, s, CH_3), 3.35 (1H, dd, *J* 9.5, 6.7, 8-Ha), 3.46 (1H, m, 6′-Ha), 3.69 (1H, dd, *J* 9.5, 6.9, 8-Hb), 3.84 (1H, m, 6′-Hb), 4.18 (2H, d, *J* 6.5, 1-H), 4.54 (1H, dd, *J* 4.5, 2.7, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.88 (C2′), 70.04, 67.50, 62.36 (C6′, C1, C8), 37.34 (Me), 30.76, 29.27 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.4), 29.18, 28.90, 28.71 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.4), 25.98, 25.47, 25.23, 19.69; *m*/*z* 310 (M^+, 0.4%), 309 (2), 227 (2), 113 (14), 97 (14), 86 (9), 85 (100), 84 (48), 70 (53), 58 (100), 56 (71), 55 (60).

[2,7-$^2H_2$]-1-Iodo-8-(tetrahydropyran-2′-yloxy)octane 35. NaI (2.90 g, 19.35 mmol) was added to the mesylate (1.507 g, 4.84 mmol) dissolved in dry acetone and the mixture was refluxed overnight. Upon cooling, the acetone was removed on the rotary evaporator. H_2O (50 ml) and Et_2O (30 ml) were added and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was further

extracted with Et_2O (3 × 30 ml). The Et_2O extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$ and concentrated to give a dark brown oil. Flash chromatography (Et_2O–hexane, 1:11) gave pure **35** (1.118 g, 67%); δ_H(400 MHz, $CDCl_3$) 1.28–1.40 (8H, m), 1.47–1.59 (5H, m), 1.66–1.72 (1H, m), 1.73–1.85 (2H, m), 3.15 (2H, d, *J* 7.0, 1-H), 3.36 (1H, dd, *J* 9.6, 6.7, 8-Ha), 3.48 (1H, m, 6′-Ha), 3.70 (1H, dd, *J* 9.6, 6.9, 8-Hb), 3.85 (1H, m, 6′-Hb), 4.55 (1H, dd, *J* 4.4, 2.7, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.88 (C2′), 67.55, 62.37 (C6′, C8), 33.16 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.6), 30.79, 30.34, 29.31 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.2), 29.21, 28.45, 26.04, 25.51, 19.71, 7.06 (C1); *m*/*z* 342 (M^+, 4%), 341 (23), 101 (14), 85 (100), 71 (11), 70 (24), 56 (36), 41 (32).

Attempted formation of [2,7-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)-hexadec-9-yne 49

Formation of [2,7-$^2H_2$]-1-bromo-8-(tetrahydropyran-2′-yloxy)-octane. Octyne (0.012 g, 0.11 mmol) was dissolved in THF (5 ml) and cooled to −78 °C. Bu^{n}Li (1.6 M in Et_2O, 0.068 ml, 0.11 mmol) was added dropwise *via* syringe to the reaction mixture which was stirred for 90 min at −50 °C. A small amount of the reaction mixture was quenched with D_2O, with GC–MS analysis indicating complete deprotonation. The reaction mixture was re-cooled to −78 °C. In a separate flask, iodide **35** (0.037 g, 0.11 mmol) was dissolved in HMPA (0.5 ml, freshly distilled from CaH_2) and THF (5 ml) and then transferred *via* cannula to the flask containing the deprotonated alkyne. The reaction was left stirring at room temperature overnight, and then quenched by pouring into H_2O (20 ml), which was extracted with hexane (3 × 30 ml). The combined hexane extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$ and concentrated. Flash chromatography (Et_2O–hexane, 1:10) gave [2,7-$^2H_2$]-1-bromo-8-(tetrahydropyran-2′-yloxy)octane (0.022 g, 63%) and none of the desired product **49**; δ_H(500 MHz, $CDCl_3$) 1.27–1.38 (8H, m), 1.47–1.59 (5H, m), 1.65–1.72 (1H, m), 1.77–1.85 (2H, m), 3.35 (1H, dd, *J* 9.6, 6.6, 8-Ha), 3.37 (2H, d, *J* 6.8, 1-H), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dd, *J* 9.6, 6.9, 8-Hb), 3.84 (1H, m, 6′-Hb), 4.55 (1H, dd, *J* 4.3, 2.7, 2′-H); δ_C(125 MHz, $CDCl_3$) 98.86 (C2′), 67.53, 62.35 (C6′, C8), 33.85 (C1), 32.41 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.6), 30.78, 29.29 (C2 or C7, t, $J_{^{13}C-^2H}$ 19.2), 29.21, 28.66, 28.00, 26.02, 25.49, 19.70; *m*/*z* 296, 294 (M^+, 0.4, 1%), 295 (3), 293 (2), 223 (1), 221 (1), 195 (1), 151 (1), 149 (1), 115 (1), 113 (3), 101 (6), 86 (6), 85 (100).

[2,7-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)hexadec-9-yne 49

Octyne (0.040 g, 0.363 mmol) was dissolved in THF (0.5 ml) and cooled to −30 °C. Bu^{n}Li (1.11 M, 0.359 ml, 0.399 mmol) was added dropwise *via* syringe to the reaction mixture which was stirred between −30 and −10 °C for 1 h. A small amount of the reaction mixture was quenched with D_2O, with GC–MS analysis indicating complete deprotonation. The reaction mixture was re-cooled to −30 °C. In a separate flask, iodide **35** (0.136 g, 0.399 mmol) was dissolved in HMPA (1 ml, freshly distilled from CaH_2) and THF (0.5 ml) and then transferred *via* cannula to the flask containing the deprotonated alkyne. The reaction was left stirring at room temperature overnight, and then quenched by pouring into H_2O (20 ml), which was extracted with hexane (3 × 30 ml). The combined hexane extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$ and concentrated. Flash chromatography (Et_2O–hexane, 1:20) gave pure **49** (0.079 g, 61%); δ_H(400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.0, 16-H), 1.20–1.58 (22H, m), 1.64–1.72 (1H, m), 1.75–1.82 (1H, m), 2.08–2.12 (4H, m, 8-H, 11-H), 3.34 (1H, dd, *J* 9.5, 6.7, 1-Ha), 3.69 (1H, dd, *J* 9.5, 6.9, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.54 (1H, dd, *J* 4.3, 2.6, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.83 (C2′), 80.22, 80.16 (C9, C10), 67.59, 62.30 (C1, C6′), 31.36, 30.78, 29.34, 29.12, 29.07, 28.68, 28.51, 26.09, 25.50, 22.55, 19.68, 18.74, 18.63, 14.01 (C16) [C2 and C7 (CDH) were not detected]; *m*/*z* 324 (M^+, 0.3%), 253 (1), 239 (1), 124 (3), 110 (4), 109 (3), 101 (17), 97 (5), 96 (10), 95 (7), 94 (4), 86 (6), 85 (100).

[2,7-$^2H_2$]-1-(Tetrahydropyran-2′-yloxy)hexadec-9-ene 50

Pr^{i}MgBr was titrated at 0.97 M by its reaction with menthol in the presence of 1,10-phenanthroline indicator. From alkyne **49** (0.070 g, 0.216 mmol) in Et_2O (5 ml), Ti(O^{i}Pr)$_4$ (0.123 g, 0.423 mmol) in Et_2O (15 ml), Pr^{i}MgBr (0.97 M, 1.11 ml, 1.08 mmol) and H_2O (1 ml) according to the general procedure. Work-up procedure B and flash chromatography (Et_2O–light petroleum, 1:25) gave **50** (0.052 g, 74%). δ_H(400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.1, 16-H), 1.20–1.32 (17H, m), 1.45–1.59 (5H, m), 1.63–1.72 (1H, m), 1.77–1.85 (1H, m), 1.98 (4H, m, 8-H, 11-H), 3.35 (1H, dd, *J* 9.5, 6.9, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.70 (1H, dd, *J* 9.5, 6.9, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.54 (1H, dd, *J* 4.3, 2.6, 2′-H), 5.32 (2H, m, 9-H, 10-H); δ_C(100 MHz, $CDCl_3$) 129.89, 129.82 (C9, C10), 98.82 (C2′), 67.60, 62.28 (C1, C6′), 31.76, 30.78 (C3′), 29.72, 29.44, 29.42, 29.13, 28.96, 27.20, 27.08, 26.12, 25.51 (C5′), 22.63, 19.67 (C4′), 14.06 (C16) [C2 and C7 (CDH) were not detected]; *m*/*z* 326 (M^+, 0.2%), 253 (1), 240 (1), 101 (8), 98 (5), 97 (7), 96 (6), 86 (7), 85 (100), 83 (12), 69 (13), 67 (11), 57 (12), 56 (21), 55 (24), 41 (26).

[2,7,13,13,14,15,15-$^2H_7$]-1-(Tetrahydropyran-2′-yloxy)octadec-9-yne 51

Deuterated decyne **34** (0.147 g, 1.03 mmol) was dissolved in THF (1.8 ml) and cooled to −30 °C. Bu^{n}Li (1.11 M, 1.018 ml, 1.13 mmol) was added dropwise *via* syringe to the reaction mixture which was stirred between −30 and −10 °C for 1 h. A small amount of the reaction mixture was quenched with D_2O, with GC–MS analysis indicating complete deprotonation. The reaction mixture was re-cooled to −30 °C. In a separate flask, iodide **35** (0.387 g, 1.13 mmol) was dissolved in HMPA (3.6 ml, freshly distilled from CaH_2) and THF (1.8 ml) and then transferred *via* cannula to the flask containing the deprotonated alkyne. The reaction was left stirring at room temperature overnight, and then quenched by pouring into H_2O (40 ml), which was extracted with hexane (3 × 30 ml). The combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$ and concentrated. Flash chromatography (Et_2O–hexane, 1:30) gave **51** (0.233 g, 64%) and minor amounts of [2,7-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)dodecane; δ_H(400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.0, 18-H), 1.18–1.37 (14H, m), 1.42 (2H, t, *J* 6.8), 1.45–1.59 (5H, m), 1.67 (1H, m), 1.80 (1H, m), 2.10 (4H, m, 8-H, 11-H), 3.34 (1H, dd, *J* 7.0, 9.4, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.69 (1H, dd, *J* 7.0, 9.5, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.55 (1H, m, *J* 4.4, 2.6, 2′-H); δ_C(100 MHz, $CDCl_3$) 98.81 (C2′), 80.23, 80.12 (C9, C10), 67.58, 62.28, 31.60, 30.77 (C3′), 29.34, 29.06, 28.94, 28.68, 26.09, 25.50 (C5′), 22.58, 19.67 (C4′), 18.69, 18.63 (C8, C11), 14.06 (C18); *m*/*z* 357 (M^+, 0.4%), 239 (2), 137 (2), 125 (2), 112 (3), 111 (4), 110 (3), 101 (18), 85 (100), 83 (14), 82 (13), 70 (10), 69 (12), 68 (13), 67 (13), 57 (17), 56 (22), 41 (25).

(9*Z*)-[2,7,13,13,14,15,15-$^2H_7$]-1-(Tetrahydropyran-2′-yloxy)-octadec-9-ene 52

Pr^{i}MgBr was titrated at 0.99 M by its reaction with menthol in the presence of 1,10-phenanthroline indicator. From alkyne **51** {mixed with unreactive [2,7-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)-dodecane} (0.150 g, 0.42 mmol) in Et_2O (5 ml), Ti(OPr^i)$_4$ (0.239 g, 0.84 mmol) in Et_2O (25 ml), Pr^{i}MgBr (0.99 M, 2.12 ml, 2.10 mmol) and H_2O (2 ml) according to the general procedure. Work-up procedure B and flash chromatography (Et_2O–light petroleum, 1:50) gave a mixture of **52** and [2,7-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)dodecane (0.121 g, 80%). Separation of **52** from [2,7-$^2H_2$]-1-(tetrahydropyran-2′-yloxy)dodecane using SiO_2–$AgNO_3$ based flash chromatography (Et_2O–light petroleum, 1:50) gave **52** (0.052 g, 53%) (Found: M^+, 359.3786. $C_{23}H_{37}D_7O_2$ requires M^+, 359.3781); δ_H(400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.0, 18-H), 1.17–1.32 (16H, m), 1.45–1.59 (5H, m), 1.64–1.72 (1H, m), 1.76–1.84 (1H, m), 1.97 (4H, m, 8-H, 11-H), 3.34 (1H, dd, *J* 9.5, 6.9, 1-Ha), 3.47 (1H, m, 6′-Ha), 3.69 (1H, dd, *J* 9.5, 7.0, 1-Hb), 3.84 (1H, m, 6′-Hb), 4.54 (1H, dd, *J* 4.3, 2.6, 2′-H), 5.31 (2H, m, 9-H, 10-H); δ_C(100 MHz, $CDCl_3$)

129.90, 129.79 (C9, C10), 98.80 (C2′), 67.59, 62.28 (C1, C6′), 31.66, 30.75 (C3′), 29.52, 29.44, 29.41, 29.12, 27.13 (C8 or C11), 27.07 (C8 or C11), 26.11, 25.48 (C5′), 22.61, 19.66 (C4′), 14.09 (C18) [C2, C7, C13, C14, and C15 (CD_2 or CDH) were not detected]; *m/z* 359 (M^+, 0.2%), 286 (1), 127 (1), 126 (1), 125 (1), 112 (3), 111 (2), 101 (9), 98 (5), 97 (5), 86 (10), 85 (100), 83 (10), 57 (14), 56 (19), 55 (14), 43 (13), 42 (11), 41 (20).

(9*Z*)-[2,7,13,13,14,15,15-$^2H_7$]Octadec-9-en-1-ol 53

THP-Protected alkene **52** (0.078 g, 0.217 mmol) was dissolved in MeOH (2 ml), and toluene-*p*-sulfonic acid (215 μl, 0.11 M in MeOH, 4.13 mg, 0.022 mmol) was added. The reaction was monitored by TLC and stirred for 2 h. Solid $NaHCO_3$ was then added and stirring was continued for an additional hour. The solvent was then removed *in vacuo* before Et_2O (5 ml) and H_2O (5 ml) were added. The Et_2O and aqueous layers were separated and the latter was further extracted with Et_2O (3 × 5 ml). The combined extracts were washed (saturated aqueous NaCl), dried ($MgSO_4$) and concentrated to give an oil which was purified by flash chromatography (Et_2O–hexane, 1:5), giving octadecenol **53** (0.053 g, 89%); δ_H(400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.0, 18-H), 1.18–1.32 (16H, m), 1.47–1.55 (1H, m, 2-H), 1.59 (1H, br s, OH), 1.95–2.01 (4H, m, 8-H, 11-H), 3.60 (2H, d, *J* 6.6, 1-H), 5.32 (2H, m, 9-H, 10-H); δ_C(100 MHz, $CDCl_3$) 129.94, 129.76 (C9, C10), 62.94 (C1), 32.34 (C2, C7 or C14, t, $J_{^{13}C-^2H}$ 19.1), 31.65, 29.52, 29.46, 29.36, 29.11, 27.13 (C8 or C11), 27.06 (C8 or C11), 25.61, 22.61, 14.09 (C18) (the other deuterated carbon signals were not detected); *m/z* 257 ($M^+ - 1$, 4%), 256 (3), 255 (2), 228 (1), 227 (1), 200 (1), 199 (1), 198 (1), 185 (1), 171 (1), 170 (1), 157 (2), 156 (2), 155 (2), 140 (6), 139 (5), 128 (6), 127 (7), 126 (11), 125 (11), 112 (17), 111 (18), 110 (12), 98 (45), 97 (52), 96 (37), 86 (26), 85 (32), 83 (87), 82 (65), 81 (26), 70 (52), 69 (68), 68 (78), 59 (27), 58 (46), 57 (62), 56 (100), 55 (71), 54 (45), 45 (37), 44 (57), 43 (65), 42 (90), 41 (81).

(9*Z*)-[2,7,13,13,14,15,15-$^2H_7$]Octadec-9-enoic acid 33

Octadecenol **53** (0.050 g, 0.182 mmol) was dissolved in dry DMF (3 ml). Freshly prepared PDC (0.308 g, 0.818 mmol) was added in one portion and the reaction was stirred for 16 h at room temperature. GC analysis showed the reaction had reached completion. H_2O (20 ml) was added and the mixture extracted with Et_2O (3 × 10 ml). The Et_2O extracts were washed with saturated aqueous $CuSO_4$, H_2O and saturated aqueous NaCl and then dried ($MgSO_4$) and concentrated. Purification involved the use of alkaline extraction. The resulting oil was dissolved in Et_2O (10 ml) and extracted with 0.1 M NaOH solution (3 × 10 ml). This basic solution was acidified to pH 1–2 with aqueous HCl and extracted again with Et_2O (3 × 10 ml). The combined Et_2O extracts were dried over $MgSO_4$ and concentrated to give deuterated oleic acid **33** (0.043 g, 82%) (Found: M^+, 289.2997; C, 74.8; H, 11.9%. $C_{18}H_{27}O_2D_7$ ($C_{18}H_{34}O_2$) requires M^+, 289.2998; C, 76.5; H, 12.1%); δ_H(400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.0, 18-H), 1.18–1.32 (14H, m), 1.61 (2H, m, 3-H), 1.98 (4H, m, 8-H, 11-H), 2.31 (1H, m, 2-H), 5.32 (2H, m, 9-H, 10-H); δ_C(100 MHz, $CDCl_3$) 180.08 (C1), 130.03, 129.69 (C9, C10), 33.74 (C2, t, $J_{^{13}C-^2H}$ 19.5), 31.67 (C16), 29.54, 29.26 (C7, t, $J_{^{13}C-^2H}$ 19.2), 29.10, 29.00, 28.95 (C4, C5, C6, C12), 28.68 (C14, t, $J_{^{13}C-^2H}$ 19.0), 27.16, 27.05 (C8, C11), 24.59 (C3), 22.61 (C17), 14.08 (C18) [C13 and C15 (CD_2) were not detected]; *m/z* 289 (M^+, 2%), 288 (2), 271 (11), 270 (9), 269 (4), 227 (5), 226 (5), 212 (2), 185 (3), 184 (3), 171 (3), 169 (3), 168 (3), 167 (3), 126 (12), 125 (12), 115 (19), 114 (19), 113 (18), 112 (18), 99 (45), 86 (42), 85 (57), 84 (45), 72 (47), 71 (52), 70 (65), 69 (52), 58 (58), 57 (72), 56 (100), 55 (78), 54 (42), 45 (59), 44 (72), 43 (81), 42 (96), 41 (88).

Synthesis of trienyl acetate pheromone

1-(Tetrahydropyran-2′-yloxy)deca-4,7-diyne 56

Formed according to the procedure described for the preparation of **10** and **11**, from 1-(tetrahydropyran-2′-yloxy)pent-4-yne **55** (2.08 g, 12.38 mmol) and 1-bromopent-2-yne **29** (1.92 g, 12.38 mmol). The crude product was purified by flash chromatography (Et_2O–hexane, 1:20) to yield 1-(tetrahydropyran-2′-yloxy)deca-4,7-diyne **56** (1.56 g, 54%); δ_H(500 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.5, 10-H), 1.75 (2H, quintet, *J* 6.5, 2-H), 1.44–1.85 (6H, m, 3′-H, 4′-H,5′-H), 2.15 (2H, qt, *J* 7.5, 2.4, 9-H), 2.24–2.30 (2H, m, 3-H), 3.08 (2H, quintet, *J* 2.4, 6-H), 3.40–3.51 (2H, m, 1-Ha and 6′-Ha), 3.78 (1H, dt, *J* 9.8, 6.4, 1-Hb), 3.84 (1H, ddd, *J* 11.4, 8.2, 3.1, 6′-Hb), 4.57 (1H, dd, *J* 3.0, 4.1, 2′-H); δ_C(125 MHz, $CDCl_3$) 98.74, 81.79, 79.74, 74.80, 73.76, 66.01, 62.13, 30.66, 28.88, 25.48, 19.48, 15.64, 13.87, 12.37, 9.68; *m/z* 233 ($M^+ - 1$, 0.2%), 219 (0.4), 205 (1), 177 (2), 175 (2), 167 (22), 150 (6), 149 (6), 117 (15), 115 (16), 91 (44), 85 (100), 79 (21), 77 (30), 67 (25), 57 (24), 55 (29), 43 (32), 41 (76), 39 (31).

(4*Z*,7*Z*)-1-(Tetrahydropyan-2′-yloxy)deca-4,7-diene 57

From alkyne **56** (1.559 g, 6.66 mmol) in Et_2O (40 ml), $Ti(OPr^i)_4$ (9.469 g, 33.3 mmol) in Et_2O (40 ml), Pr^iMgBr (69.3 ml, 86.6 mmol, ~1.25 M solution in dry Et_2O) and H_2O (2.5 ml) according to the general procedure. Work-up procedure A and flash column chromatography (Et_2O–hexane, 1:20) provided pure **57** (0.669 g, 42%) (Found: M^+, 238.1932; C, 77.3; H, 11.3%; $C_{15}H_{26}O_2$ requires M^+, 238.1933; C, 75.6; H, 11.0%); δ_H(500 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, 10-H), 1.46–1.60 (4H, m, 3′-Ha, 5′-Ha, 4′-Ha, 5′-Hb), 1.65 (2H, ~quintet, *J* 6.8, 2-H), 1.67–1.73 (1H, m, 3′-Hb), 1.76–1.86 (1H, m, 4′-Hb), 2.01–2.09 (2H, m, 9-H), 2.09–2.20 (2H, m, 3-H), 2.77 (2H, br t, *J* 6.5, 6-H), 3.38 (1H, dt, *J* 9.7, 6.6, 1-Ha), 3.48 (1H, m, 6′-Ha), 3.73 (1H, dt, *J* 9.7, 6.7, 1-Hb), 3.85 (1H, ddd, *J* 11.2, 7.8, 3.4, 6′-Hb), 4.56 (1H, dd, *J* 4.3, 2.9, 2′-H), 5.28 (1H, dtt, *J* 1.5, 7.2, 10.6, 5-H or 7-H), 5.32–5.41 [3H, m, 4-H, 8-H and (5-H or 7-H)]; δ_C(125 MHz, $CDCl_3$) 131.84, 129.32, 128.61, 127.29, 98.85, 66.95, 62.30, 30.77, 29.69, 25.51, 25.50, 23.89, 20.53, 19.65, 14.26; *m/z* 238 (M^+, 0%), 1.55 (1), 154 (1), 136 (2), 126 (1), 121 (2), 108 (3), 107 (5), 95 (8), 94 (4), 93 (6), 91 (4), 85 (100), 79 (19), 67 (31), 57 (15), 55 (18), 43 (18), 41 (41), 39 (12).

(4*Z*,7*Z*)-1-Iododeca-4,7-diene 58

(4*Z*,7*Z*)-1-Bromodeca-4,7-diene. Obtained according to the procedure described for bromide **19** from (4*Z*,7*Z*)-1-(tetrahydropyran-2′-yloxy)deca-4,7-diene **57** (0.660 g, 2.77 mmol). Flash chromatography (100% light petroleum) gave 1-bromodeca-4,7-diene (0.536 g, 89%) (Found: M^+, 216.0508. $C_{10}H_{17}{}^{79}Br$ requires M^+, 216.0514); δ_H(500 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.5, 10-H), 1.91 (2H, quintet, *J* 6.7, 2-H), 2.06 (2H, qdd, *J* 7.5, 7.1, 1.6, 9-H), 2.21 (2H, tdd, *J* 6.7, 7.3, 1.6, 3-H), 2.79 (2H, dddd, *J* 7.2, 7.5, 1.6, 1.6, 6-H), 3.39 (2H, t, *J* 6.7, 1-H), 5.28 (1H, dtt, *J* 10.7, 1.6, 7.2, 7-H), 5.31 (1H, dtt, *J* 10.6, 7.3, 1.6, 4-H), 5.38 (1H, dtt, *J* 10.6, 7.1, 1.6, 8-H), 5.41 (1H, dtt, *J* 10.7, 1.6, 7.5, 5-H); δ_C(125 MHz, $CDCl_3$) 132.04, 129.86, 127.66, 126.97, 33.26, 32.52, 25.62, 25.57, 20.55, 14.24; *m/z* 218, 216 (M^+, 5, 6%), 189 (3), 187 (3), 176 (4), 174 (3), 162 (2), 160 (2), 109 (11), 107 (12), 95 (58), 93 (12), 91 (13), 82 (13), 81 (53), 79 (40), 77 (20), 68 (31), 67 (100), 65 (14), 55 (31), 54 (15), 53 (23), 41 (71), 39 (50).

(4*Z*,7*Z*)-1-Iododeca-4,7-diene 58. Formed when 1-bromodeca-4,7-diene (0.530 g, 2.44 mmol) and 1-(tetrahydropyran-2′-yloxy)but-3-yne **59** (0.451 g, 2.93 mmol) were treated according to the procedure described for the preparation of **10** and **11**. Flash chromatography (Et_2O–hexane, 1:20) yielded a fraction containing the recovered halide, as 1-iododeca-4,7-diene **58** (0.502 g, 78%); δ_H(400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.5, 10-H), 1.87 (2H, quintet, *J* 6.9, 2-H), 2.06 (2H, br quintet, *J* 7.6, 9-H), 2.16 (2H, br q, *J* 7.3, 3-H), 2.80 (2H, m, 6-H), 3.18 (2H, t, *J* 6.9, 1-H), 5.25–5.45 (4H, m, 4-H, 5-H, 7-H and 8-H); δ_C(100 MHz, $CDCl_3$) 132.04, 129.87, 127.51, 127.00, 33.30, 27.93, 25.68, 20.57, 14.24, 6.39; *m/z* 264 (M^+, 5%), 222 (2), 155 (11), 127 (8), 109 (7), 95 (46), 81 (44), 79 (28), 77 (17), 67 (100), 55 (37), 53 (22), 41 (73), 39 (58).

Eluting with a more polar solvent system (Et_2O–hexane, 1 : 1) gave 1,8-*Bis*(*tetrahydropyran*-2′-*yloxy*)*octa*-3,5-*diyne* (0.078 g); δ_C(100 MHz, $CDCl_3$) 98.67, 74.37, 66.05, 65.15, 62.07, 30.42, 25.32, 20.65, 19.24.

(8*Z*,11*Z*)-1-(Tetrahydropyran-2′-yloxy)tetradeca-8,11-dien-3-yne 60

1-(Tetrahydropyran-2′-yloxy)but-3-yne **59** (0.060 g, 0.39 mmol) was dissolved in THF (5 ml) in a three-necked flask and cooled to −78 °C. Bu″Li (2.5 M, 1.56 μl, 0.39 mmol) was added dropwise *via* syringe and the reaction mixture was stirred at −60 to −50 °C for 2 h. Upon recooling to −78 °C, 1-iododeca-4,7-diene **58** (0.074 g, 0.28 mmol), dissolved in a mixture of THF (0.5 ml) and HMPA (0.5 ml), was added dropwise. The resulting mixture was allowed to warm to RT overnight. Hexane (20 ml) and water (20 ml) were added, and the layers were separated. The aqueous layer was extracted with hexane (3 × 10 ml). After washing with saturated aqueous NaCl, the combined organic layers were dried ($MgSO_4$) and concentrated (reduced pressure). Purification using flash chromatography (Et_2O–hexane, 1 : 20) yielded pure fractions of dienyne **60** (0.034 g, 43%); δ_H(400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, 14-H), 1.51 (2H, quintet, *J* 7.2, 6-H), 1.40–1.83 (6H, m, 3′-H, 4′-H, 5′-H), 2.05 (2H, m, 13-H), 2.10–2.16 (4H, m, 5-H and 7-H), 2.43 (2H, tt, *J* 7.3, 2.4, 2-H), 2.76 (2H, br t, *J* 6.4, 10-H), 3.50 (1H, dt, *J* 9.6, 7.3, 1-Ha), 3.45–3.55 (1H, m, 6′-Ha), 3.76 (1H, dt, *J* 9.6, 7.2, 1-Hb), 3.86 (1H, ddd, *J* 11.4, 8.2, 3.2, 6′-Hb), 4.61 (1H, dd, *J* 4.1, 3.0, 2′-H), 5.20–5.40 (4H, m, 8-H, 9-H, 1-H and 12-H); δ_C(100 MHz, $CDCl_3$) 131.83, 128.93, 128.93, 127.24, 98.70, 80.98, 76.98, 66.18, 62.16, 30.54, 28.82, 26.22, 25.50, 25.40, 20.50, 20.19, 19.40, 18.21, 14.27; *m*/*z* 290 (M^+, 0.1%), 261 (0.1), 217 (1), 205 (1), 175 (1), 159 (5), 117 (5), 91 (14), 85 (100), 79 (15), 67 (24), 57 (13), 55 (13), 43 (17), 41 (36).

(3*E*,8*Z*,11*Z*)-1-(Tetrahydropyran-2′-yloxy)tetradeca-3,8,11-triene 61

Sodium (0.016 g, 0.703 mmol) was added to liquid NH_3 (2 ml) in a three-necked flask fitted with a dry-ice condenser, and immersed in a bath at −78 °C. A deep blue solution resulted. (8*Z*,11*Z*)-1-(Tetrahydropyran-2′-yloxy)tetradeca-8,11-dien-3-yne **60** in Et_2O (0.2 ml) was added and after 1 h, additional NH_3. The mixture was then stirred at −30 °C for 3 h and NH_4Cl (0.4 g) was added to quench the reaction. Additional Et_2O was added and stirring continued overnight while the NH_3 evaporated. Water (20 ml) was added and the product extracted with Et_2O (3 × 10 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ and aqueous NaCl, then dried with $MgSO_4$ and concentrated to yield (3*E*,8*Z*,11*Z*)-1-(tetrahydropyran-2′-yloxy)tetradeca-3,8,11-triene **61** (0.034 g, 100%). Further purification was not necessary prior to subsequent reaction; δ_H(400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, 14-H), 1.40 (2H, quintet, *J* 7.3, 6-H), 1.45–1.85 (6H, m, 3′-H, 4′-H, 5′-H), 1.95–2.10 (6H, m, 5-H, 7-H and 13-H), 2.27 (2H, br q, *J* 7.1, 2-H), 2.75 (2H, br t, *J* 6.3, 10-H), 3.39 (1H, dt, *J* 9.6, 7.0, 1-Ha), 3.44–3.51 (1H, m, 6′-Ha), 3.71 (1H, dt, *J* 9.6, 7.1, 1-Hb), 3.85 (1H, ddd, *J* 11.2, 7.6, 3.6, 6′-Hb), 4.57 (1H, dd, *J* 4.2, 2.9, 2′-H), 5.24–5.52 (6H, m, 3-H, 4-H, 8-H, 9-H, 11-H and 12-H); δ_C(100 MHz, $CDCl_3$) 132.18, 131.78, 129.80, 128.26, 127.36, 126.64, 98.74, 67.37, 62.27, 33.07, 32.20, 30.72, 29.42, 26.65, 25.53, 25.51, 20.52, 19.60, 14.24; *m*/*z* 292 (M^+, 0.1%), 219 (0.1), 208 (0.1), 175 (0.1), 149 (1), 121 (2), 101 (7), 85 (100), 67 (24), 57 (9), 55 (12), 43 (10), 41 (27).

(3*E*,8*Z*,11*Z*)-Tetradeca-3,8,11-trien-1-yl acetate 54

(3*E*,8*Z*,11*Z*)-Tetradeca-3,8,11-trien-1-ol. (3*E*,8*Z*,11*Z*)-1-(Tetrahydropyran-2′-yloxy)tetradeca-3,8,11-triene **61** (0.034 g, 0.1 mmol) and toluene-*p*-sulfonic acid (2 mg, 0.011 mmol) were dissolved in MeOH (1 ml), and stirred for 1 h, at room temperature. Solid $NaHCO_3$ was added and the solvent was removed *in vacuo*. Et_2O (5 ml) and H_2O (5 ml) were then added. After separation of the two layers, the aqueous layer was further extracted with Et_2O (2 × 5 ml). The combined extracts were then washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to give crude (3*E*,8*Z*,11*Z*)-tetradeca-3,8,11-trien-1-ol (~0.025 g), which was used in the next step without further purification; *m*/*z* 179 (M^+ − 29, 1%), 165 (2), 163 (3), 161 (2), 140 (3), 126 (6), 121 (10), 108 (10), 107 (13), 95 (19), 93 (42), 81 (37), 79 (81), 67 (100), 55 (54), 41 (96).

(3*E*,8*Z*,11*Z*)-Tetradeca-3,8,11-trien-1-yl acetate 54. Crude (3*E*,8*Z*,11*Z*)-tetradeca-3,8,11-trien-1-ol (~0.025 g, 0.12 mmol) was dissolved in dry pyridine (0.2 ml, 1.92 mmol) and to this solution was added acetic anhydride (0.073 g, 0.72 mmol). Stirring was continued for 1 h, after which time GC–MS analysis indicated complete conversion to the acetate. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (20 ml), and extracted with Et_2O (3 × 20 ml). The combined ethereal extracts were washed with H_2O and saturated aqueous $CuSO_4$, dried ($MgSO_4$) and concentrated under reduced pressure to give, after flash chromatographic purification, pure **54** (0.020 g, 67%) (Found: M^+, 250.1928; C, 76.4, H, 10.5%; $C_{16}H_{26}O_2$ requires M^+, 250.1933; C, 76.8; H, 10.5%); δ_H(400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, 14-H), 1.40 (2H, tt, *J* 7.7, 7.3, 6-H), 2.01 (3H, s, COMe), 2.03 (6H, m, 5-H, 7-H and 13-H), 2.29 (2H, br qd, *J* 6.8, 1.2, 2-H), 2.75 (2H, br tt, *J* 7.1, 1.3, 10-H), 4.04 (2H, t, *J* 6.9, 1-H), 5.27 (1H, dtt, *J* 10.7, 7.1, 1.4, 9-H or 11-H), 5.34 [3H, m, 8-H, 12-H and (9-H or 11-H)], 5.36 (1H, dtt, *J* 15.3, 6.8, 1.3, 3-H), 5.50 (1H, dtt, *J* 15.3, 6.6, 1.2, 4-H); δ_C (100 MHz, $CDCl_3$) 171.06 (C=O), 133.17 (C4), 131.82 (CH=), 129.69 (CH=), 128.35 (CH=), 127.33 (CH=), 125.39 (CH=), 64.10 (C1), 32.13 (C5), 31.95 (C2), 29.31 (C6), 26.62 (C7), 25.53 (C10), 20.93 ($COCH_3$), 20.52 (C13), 14.24 (C14); *m*/*z* 190 (M^+ − 60, 2%), 161 (5), 147 (6), 133 (7), 119 (9), 108 (17), 93 (35), 80 (34), 79 (62), 67 (57), 43 (100), 41 (46).

(3*Z*,8*Z*,11*Z*)-1-(Tetrahydropyran-2′-yloxy)tetradeca-3,8,11-triene 62

From alkyne **60** (0.162 g, 0.56 mmol) in dry Et_2O (2 ml), $Ti(OPr^i)_4$ (0.401 g, 1.41 mmol) in Et_2O (3 ml), Pr^iMgBr (2.71 ml, 3.39 mmol, ~1.25 M solution in dry Et_2O), H_2O (1.0 ml) according to the general procedure. Work-up Procedure A and flash chromatography (Et_2O–hexane, 1 : 20) provided **62** (0.025 g, 42%) mixed with minor amounts of isomeric products, which lacked the 'methylene-skipped' diene system by ^1H NMR spectroscopy. Major component **62**, δ_H(400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, 14-H), 1.20–1.85 (8H, m, 6-H, 3′-H, 4′-H, 5′-H), 1.98–2.10 (6H, m, 5-H, 7-H, 13-H), 2.33 (2H, m, 2-H), 2.75 (2H, br t, *J* 6.4, 10-H), 3.39 (1H, dt, *J* 9.6, 7.1, 1-Ha), 3.44–3.51 (1H, m, 6′-Ha), 3.71 (1H, dt, *J* 9.5, 7.2, 1-Hb), 3.86 (1H, ddd, *J* 11.2, 7.9, 3.6, 6′-Hb), 4.58 (1H, dd, *J* 4.3, 2.7, 2′-H), 5.24–5.50 (6H, m, 3-H, 4-H, 8-H, 9-H, 11-H, 12-H); δ_C(100 MHz, $CDCl_3$) 131.81, 131.57, 129.75, 128.36, 127.36, 125.92, 98.77, 67.10, 62.29, 30.74, 29.63, 28.00, 26.98, 26.85, 25.55, 25.50, 20.54, 19.61, 14.26; *m*/*z* 292 (M^+, 0.1%), 149 (1), 121 (2), 115 (1), 101 (7), 93 (5), 85 (100), 67 (24), 41 (28).

(3*Z*,8*Z*,11*Z*)-Tetradeca-3,8,11-trien-1-yl acetate 63

(3*Z*,8*Z*,11*Z*)-Tetradeca-3,8,11-trien-1-ol. (3*Z*,8*Z*,11*Z*)-1-(Tetrahydropyran-2′-yloxy)tetradeca-3,8,11-triene **62** (and isomers) (0.025 g, 0.086 mmol) and toluene-*p*-sulfonic acid (1.6 mg, 0.009 mmol) were dissolved in MeOH (1 ml), and stirred for 1 h, at room temperature. Solid $NaHCO_3$ was added and the solvent removed *in vacuo*. Et_2O (5 ml) and H_2O (5 ml) were then added. After separation of the two layers, the aqueous layer was further extracted with Et_2O (2 × 5 ml). The combined extracts were then washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to give crude (3*Z*,8*Z*,11*Z*)-tetradeca-3,8,11-trien-1-ol (~0.018 g), which was used in the next step without further purification.

(3*Z*,8*Z*,11*Z*)-Tetradeca-3,8,11-trien-1-yl acetate 63. Crude (3*Z*,8*Z*,11*Z*)-tetradeca-3,8,11-trien-1-ol (and isomers) (~0.018

g, 0.086 mmol) was dissolved in dry pyridine (0.2 ml, 1.92 mmol) and to this solution was added acetic anhydride (0.073 g, 0.72 mmol). Stirring was continued for 1 h, after which time GC–MS analysis indicated complete conversion to the acetate. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ (20 ml), which was then extracted with Et_2O (3 × 20 ml). The combined ethereal extracts were washed with H_2O, saturated aqueous $CuSO_4$, then dried ($MgSO_4$) and concentrated under reduced pressure. Flash column purification on SiO_2–$AgNO_3$ yielded pure **63** (0.010 g, 46%) (Found: M^+, 250.1932. $C_{16}H_{26}O_2$ requires M^+, 250.1933); δ_H(500 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, 14-H), 1.41 (2H, tt, *J* 7.7, 7.3, 6-H), 2.02 (3H, s, COMe), 2.05 (6H, m, 5-H, 7-H and 13-H), 2.36 (2H, br qd, *J* 7.0, 1.0, 2-H), 2.76 (2H, br tt, *J* 7.2, 1.5, 10-H), 4.04 (2H, t, *J* 6.9, 1-H), 5.28 (1H, dtt, *J* 10.6, 7.2, 1.4, 9-H or 11-H), 5.35 [4H, m, 3-H, 8-H, 12-H and (9-H or 11-H)], 5.49 (1H, dtt, *J* 10.8, 7.3, 1.5, 4-H); δ_C(125 MHz, $CDCl_3$) 171.11 (C=O), 132.54 (C4), 131.84 (CH=), 129.60 (CH=), 128.46 (CH=), 127.29 (CH=), 124.67 (CH=), 63.95 (C1), 32.13 (C5), 29.54 (C6), 26.91, 26.84, 26.79 (C2, C5, C7), 25.54 (C10), 20.97 ($CO\mathit{C}H_3$), 20.54 (C13), 14.26 (C14); *m/z* 250 (M^+, 0.1%), 190 (1), 161 (4), 147 (5), 133 (6), 119 (8), 108 (13), 93 (30), 91 (16), 81 (21), 80 (28), 79 (54), 67 (51), 43 (100), 41 (42).

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