Synthesis of (2*E*,4*E*)-dienals by double formyl-olefination with an arsonium salt and its application in the syntheses of lipoxygenase metabolites of arachidonic acid

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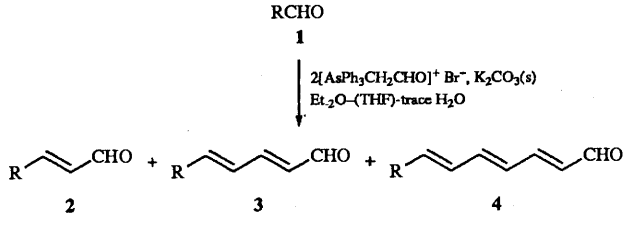
A new facile route to (2*E*,4*E*)-dienals by a double formyl-olefination with arsonium salts has been developed. By this method and with other arsonium reagents in the key step some lipoxygenase metabolites of arachidonic acid, lipoxin A_4 and B_4 and leukotriene B_4, have been synthesized.

Polyethylenic aldehyde has gained much attention in recent years because of its importance as useful intermediates in organic synthesis, especially in the syntheses of polyunsaturated natural products such as lipoxygenase metabolites of arachidonic acid, polyene antibiotics, pheromones and other bioactive compounds.

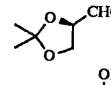
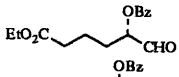
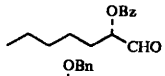
To date several reagents, such as 4-(triphenylphosphoranylidene)but-2-enal,[1] the arsonium salt of crotonaldehyde,[2] 1-lithio-4-ethoxybutadiene,[3] or 4-(diethylphosphono)crotonylcyclohexylimine,[4] 1-lithio-4-trimethylsiloxybutadiene[5] and, more recently, δ-alkoxy dienylzirconocene chloride[6] and γ-trimethylsily crotonaldimine,[7] have been introduced for the conversion of aldehydes into conjugated dienals. However, some of these reagents suffered from being difficult to prepare and/or lack stereoselectivity, whereas others demand rather drastic reaction conditions.

Huang *et al.* have developed a useful procedure[8] for the preparation of (α,β)-*E*-unsaturated aldehydes by the formyl-olefination of an aldehyde with the easily prepared arsonium salt of bromoacetaldehyde $[As(Ph_3)CH_2CHO]^+Br^-$. Occasionally, when an excess of the reagent was used, we also detected (2*E*,4*E*)-dienal in the crude product. Evidently, this compound was formed through one-pot double formyl-olefination of the aldehyde with the arsonium salt, a reaction similar to that with the corresponding formylmethylene(triphenyl)phosphorane, $Ph_3P{=}CHCHO$,[9] but under more drastic reaction conditions and in low yield. Since then we have been systematically exploring the possibility of performing double formyl-olefination in one pot. Herein we report some results of our study.



The results of our study are summarized in Table 1. Use of 2 equiv. of the arsonium salt and inorganic base, with aromatic aldehydes as the substrates, gave the double formyl-olefination product **3** together with, in some cases, the (2*E*,4*E*,6*E*)-trienal (entries a, b, c); the yield of the (2*E*,4*E*)-dienal was low. Although it is possible to ascribe these results to the low reactivity of the aromatic aldehyde, the results for aliphatic aldehyde were only a little better (entries e, d), with the selectivity still unsatisfactory. However, use of the more active α-alkoxy (acyloxy) aldehydes with portionwise addition of the arsonium salt as well as the base gave increased yields of the (2*E*,4*E*)-dienal (61–75%, entries f–i), with no (2*E*,4*E*,6*E*)-trienals detectable in the crude product. The products from entries f–i are very useful intermediates for the syntheses of natural products. It should be noted that only all-*E*-isomers could be detected (^1H NMR) in the products.

Table 1 Results of the one-pot double formyl-olefination of aldehyde

Entry	Substrate 1	Temp./°C	Time/h	Yield (%)[a] 2	3	4
a[b]	*p*-$NO_2C_6H_4CHO$	25	10	21	47	20
b[b,d]	PhCHO	40	30	34	35	24
c[b,d]	*p*-ClC_6H_4CHO	40	30	51	32	15
d[b]	n-$C_5H_{11}CHO$	40	17	48	46	
e[b]	n-$C_8H_{17}CHO$	25	40	39	49	
f[c]		10	12	21	75	
g[c]		0	10	24	72	
h[c]		10	12	35	61	
i[c]		20	12	23	66	

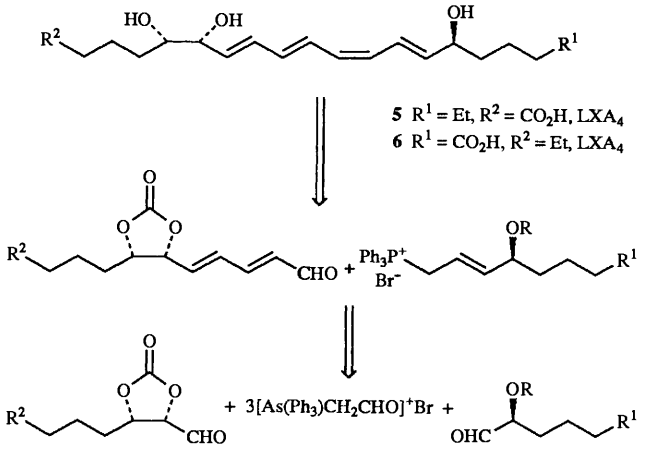
[a] Isolated yield. [b] The solvent used was Et_2O–THF (7:3). [c] The solvent was Et_2O alone. [d] KF-Al_2O_3 was used as the base instead of K_2CO_3.

In the present paper we have used our new facile route for construction of conjugated dienal of lipoxygenase metabolites of arachidonic acid. Thus, lipoxin A_4 **5** and B_4 **6** and leukotriene B_4 **34** have been synthesized.

Synthesis of lipoxin A_4 and B_4

Lipoxins, the lipoxygenase-derived eicosanoids discovered by Samuelsson,[10] contain an unusual conjugated tetraene system and three asymmetric carbons. LXA_4 **5** and LXB_4 **6** are the major lipoxins formed *in vivo*. Their all-*trans* isomers have also been detected, with the stereochemical structures determined by comparison of the biologically produced samples with synthetic ones.[11] These eicosanoids can be generated by oxidation of arachidonic acid by way of cell–cell interactions or by way of interactions between the 5- and 15-lipoxygenases or between the 5- and 12-lipoxygenases. This new group of compounds displays a profile of bioactions unique among eicosanoids,[12] and may play counter-regulatory roles. For example, they have been found to be involved in the stimulation of human neutrophils, inhibition of some 'pro-inflammatory' actions of the leukotrienes, and activation of isolated protein kinase.

Recent results even indicated that LX's formed *in vivo* may be associated with certain human diseases. Because the small quantities available from biological sources are incompatible with the great needs of further biological investigations, the chemical syntheses of these compounds have attracted much interest.[13] We intended to apply the formyl-olefination[8] and our double formyl-olefination of aldehydes using $[As(Ph_3)CH_2CHO]^+Br^-$ for construction of three *E*-double bonds in these molecules. Our retrosynthesis of these two molecules was based on the results of Depezay[13b] (see Scheme 1).



Scheme 1

We have developed a general strategy to prepare these compounds starting from a single chiral pool molecule, the readily available D-glyceraldehyde acetonide **1f**.[14] The syntheses of fully protected LXA_4 and LXB_4 as well as their all-*trans* isomers are depicted in Scheme 2. The reaction of D-glyceraldehyde acetonide **1f** with propynyl bromide and zinc in dimethylformamide (DMF)–ether gave the chiral homopropargylic alcohol **7** with an *erythro*/*threo* ratio of >10:1.[15] Treatment of the terminal alkyne **7** with 2 equiv. of BuLi and an excess of ethyl chloroformate afforded **8** and its *threo*-isomer (separable by flash column chromatography) in 80% total yield. Compound **8** was hydrogenated to give the acyclic carbonate **11**, which was then converted into the cyclic carbonate **18** by treatment with acid according to known procedures.[16] The key intermediate, the (2*E*,4*E*)-dienal **22**, was prepared from **18** by Swern oxidation followed by our double formyl-olefination in one pot, where triethylamine was used as the base instead of potassium carbonate; an overall product yield of 60–66% was obtained.

The phosphonium salt **25**, another segment of LXA_4, was also synthesized from the alkyne **7**. Alkylation of **7** followed by hydrogenation and chromatography gave the pure *erythro* compound **9**, silylation of which with $Ph_2BuSiCl$ followed by acetonide hydrolysis–glycol cleavage with periodic acid[17] afforded the desired aldehyde **19**. Formyl-olefination of **19** with arsonium salt and reduction, bromination and reaction with triphenylphosphine then gave the salt **25**.

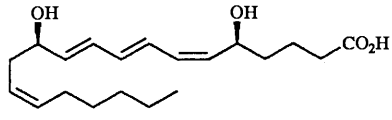
Alternatively, protection of compound **9** by ethyl chloroformate in pyridine afforded the acyclic carbonate **13** (97%); this, then, using the same reagents and conditions as described above for the transformation of **18** into **22**, gave, in similar overall yield, the (2*E*,4*E*)-dienal **26**, the key precursor of LXB_4.

The phosphonium salt **29**, another precursor of LXB_4, was prepared from the alkyne **7**. To obtain the pure *erythro*-isomer of **7**, we protected the alcohol with acetic anhydride to give the separable acetyl ester **10** and its *threo*-isomer. The alcohol protecting group of **10** was then changed into a silyl ether, after which an ester group was introduced into the terminal alkyne with BuLi and ethyl chloroformate; and the product hydrogenated to afford compound **17**. The phosphonium salt **29** was obtained from **17** using the same procedure described above for the transformation of **19** into **25**.

The ylide derived from **25** (BuLi, THF, −100 °C, 5 min) was treated with the dienal **22** and, after HMPA addition and increase of the temperature to −40 °C, the fully protected lipoxin A_4 **30** and its all-*trans* isomer **31** were obtained (61%); these could be easily isolated by flash column chromatography in a ratio of *ca.* 1.5:1. Similarly, the fully protected lipoxin B_4 **32** and its all-*trans* isomer **33** were obtained (76%, 1:1 ratio) by reaction of the ylide derived from **29** (LiHMDS, THF, −100 °C) with the dienal **26** following the same procedure. Since it has been reported[13b,18] that LXA_4 and LXB_4 can be obtained by removal of the protecting groups from compounds **32** and **33** so we have successfully completed the formal syntheses of LXA_4 and LXB_4. The reaction conditions of deprotection have, however, to be optimized.

Synthesis of LTB_4

Leukotriene B_4 (LTB_4; **34**), also a biologically important arachidonic acid metabolite, has been implicated as a mediator in inflammation and allergic reactions.[19] Because of its biological importance and low natural abundance, LTB_4 has been an attractive synthetic target in recent years.[20] We have already reported a formal convergent synthesis of this compound.[21] In order to make LTB_4 more easily accessible for biological studies, we adopted a two-directional synthesis of the C-11–C-20 fragment described by Depezay[22] to facilitate large-scale synthesis. Since the isotopically labelled natural **34** had

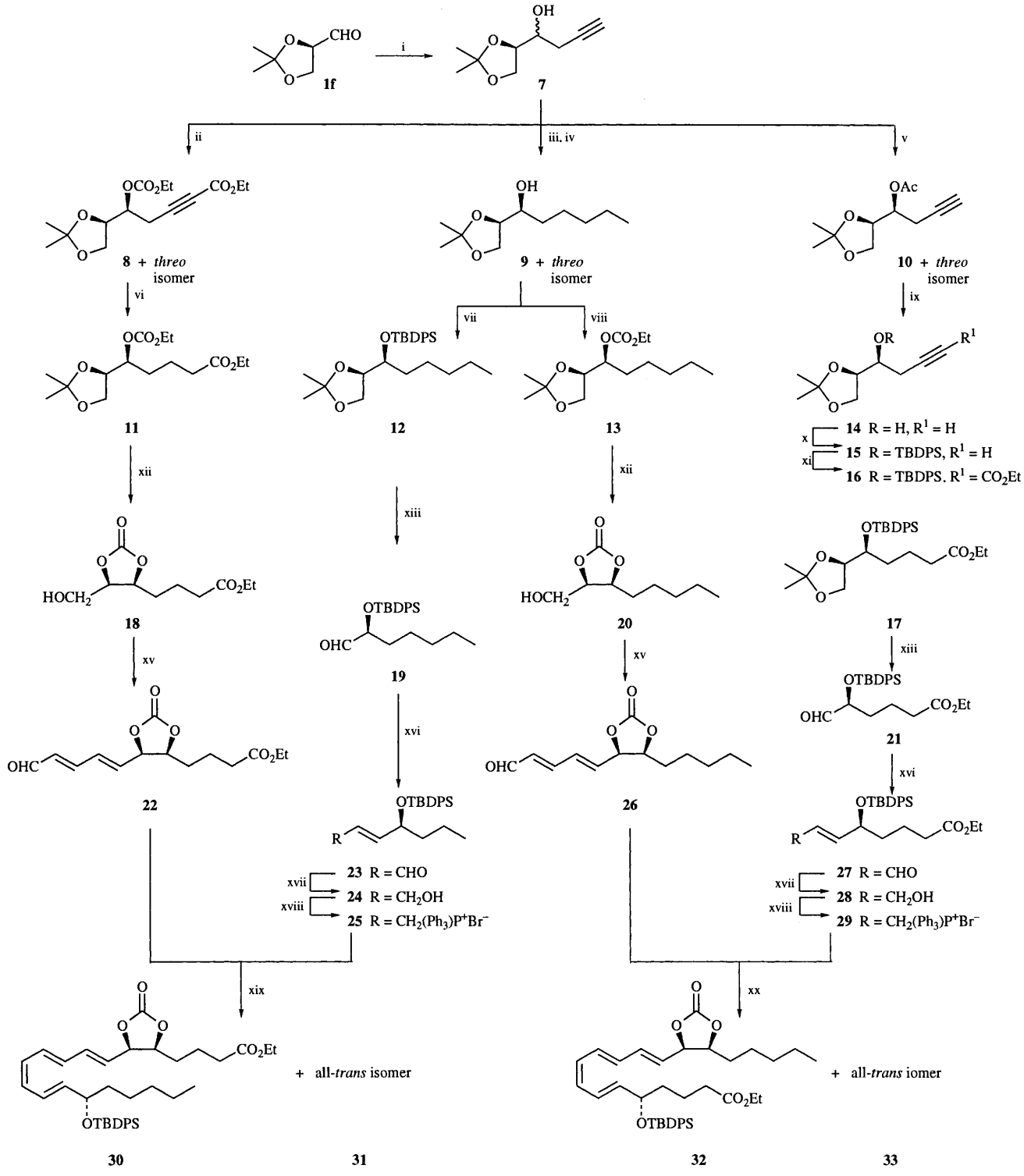


34 LTB_4

proven exceptionally useful in defining the physiological role of many biological mediators,[23] we designed a modified route to LTB_4, in which the 14,15-triple bond could be partially hydrogenated with hydrogen or tritium in later stages of the synthesis, to provide LTB_4 or [14,15-$^3H_2$]-LTB_4, respectively.

Compound **35**, prepared from D-mannitol, was converted into compound **36** according to known procedures[22] with some improvements. In the presence of the bulky *tert*-butyldiphenylsilyl (TBDPS) protecting group, hydrolysis of the acetonide in **36** has proved troublesome[22] under a wide variety of conditions. Either the procedures had no effect at all [*e.g.* conc. hydrochloric acid, THF, RT, 6 h;[24a] aq. $HClO_4$ (4 equiv.), THF, RT, 15 h;[24a] $NaIO_4$–AcOH, RT, 6 h;[24b] $NaBH_4$–AcOH; DDQ–water saturated EtOAc, RT, 7 h;[24c] H_5IO_6, Et_2O;[17] $HS(CH_2)_3SH$, $CoCl_2$;[24d] $HS(CH_2)_3SH$, PPTS, MeCN, 80 °C] or resulted in a complex mixture of products [*e.g.* Br_2, Et_2O;[24a] CF_3CO_2H, H_2O;[24a] PPTS, Bu^{t}OH, 80 °C, 1 h;[24e] $HO(CH_2)_2OH$, conc. hydrochloric acid, THF;[24f] $HS(CH_2)_3SH$, BF_3·OEt_2, MeCN, RT, 2 h;[24d] $HS(CH_2)_3SH$, Me_3SiCl, RT, 4 h;[24d] $HS(CH_2)_3SH$, CF_3CO_2H, 80 °C, 1 h; $HS(CH_2)_3SH$, *p*-TsOH]. Noticing the mediative effect of $AsPh_3$ on the reactivity of the strong Lewis acid $TiCl_4$,[25] we finally tried catalytic trans-thioketalization in the presence of the $TiCl_4$·$AsPh_3$ complex. The result was satisfactory, with glycol deprotection being achieved in 86% yield. The resulting diol was then cleaved by $Pb(OAc)_4$ to yield the aldehyde **38** (Scheme 3). The catalytic trans-thioketalization of **36** with $TiCl_4$ resulted in a complex mixture, from which **37** was isolated in only 34% yield. There was no reaction when the transthioketalization was performed with $Ti(OPr^i)_4$ or $Ti(OPr^i)_2Cl_2$ as Lewis acid catalysts.

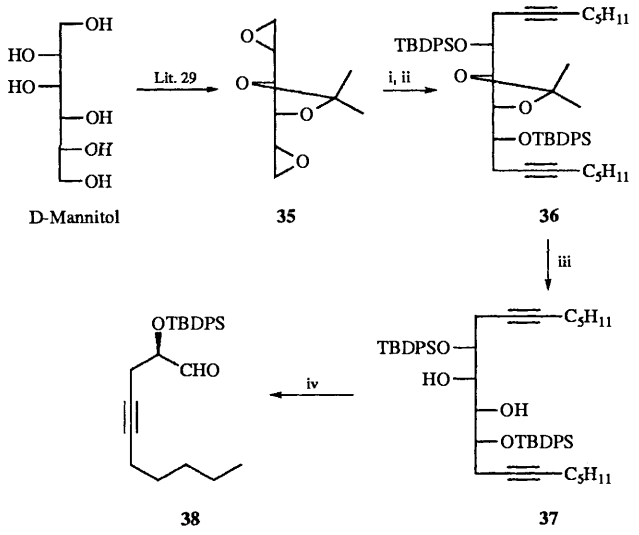
The key intermediate (2*E*,4*E*)-dienal **39** was obtained using our double formyl-olefination in 51% yield as a single isomer by reaction of the aldehyde **38** with 2.5 equiv. of the arsenic ylide



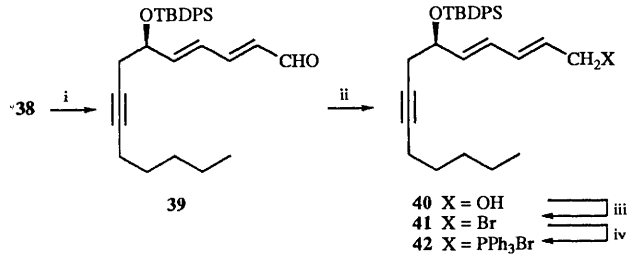
Scheme 2 *Reagents and conditions:* i, $BrCH_2C{\equiv}CH$, Zn, DMF–Et_2O (80%); ii, BuLi, $ClCO_2Et$ (80%); iii, BuLi, EtBr (87.5%); iv, H_2, 10% Pd–C, EtOH (98%); v, Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2 (97%); vi, H_2, 10% Pd–C, EtOH (95%); vii, Ph_2Bu^tSiCl, imidazole, DMF (86%); viii, $ClCO_2Et$, py, CH_2Cl_2 (97%); ix, K_2CO_3, MeOH (100%); x, Ph_2Bu^tSiCl, imidazole, DMF (84%); xi, BuLi, $ClCO_2Et$ (88%); xii, CF_3CO_2H–H_2O (1 : 1), then *p*-TsOH, PhMe (58–64%); xiii, H_5IO_6, Et_2O (95–99%); xiv, H_2, 5% Pd–C, EtOH (88%); xv, $(COCl)_2$, Me_2SO, THF, Et_3N −70 °C to −35 °C, then $[As(Ph_3)CH_2CHO]^+ Br^-$ (2 equiv.), Et_3N, −20 °C to 0 °C (60–66%); xvi, $[As(Ph_3)CH_2CHO]^+ Br^-$, K_2CO_3, Et_2O–trace water, −10 °C (75–79%); xvii, $NaBH_4$, $CeCl_3$, Pr^iOH, 0 °C (83–98%); xviii, CBr_4, Ph_3P, then Ph_3P, MeCN (61–64%); xix, LiHMDS, THF, −100 °C, HMPA (61%); xx, BuLi, THF, HMPA, −100 °C (76%)

($Ph_3As{=}CHCHO$) in a one-pot manner, together with the formyl-olefination product (15%) and the triple addition product (22%). Alternatively, compound **39** could also be obtained as a mixture of (2*E*,4*E*)- and (2*E*,4*Z*)- isomers in a ratio of 9:1 in 85% yield based on the consumed starting material by the method of formyl-enyl olefination.[2] From the mixture pure (2*E*,4*E*)-**39** could be isolated by isomerization followed by chromatography. The dienal **39** was then used in a series of known reactions, including $NaBH_4$ reduction in the presence of $CeCl_3$, bromination of the hydroxy group as well as a salt-forming reaction with PPh_3, to give the phosphonium salt **42**. Alternatively, the triple bond in compound **40** could be partially hydrogenated with 5% Pd–$CaCO_3$ in a toluene solution in 88% yield, and then transformed into corresponding phosphonium salt in the usual way (Scheme 4).

Wittig reaction of the C-1–C-6 segment[26,27] with the ylide



Scheme 3 *Reagents and conditions:* i, Hept-1-yne, BuLi, THF–HMPA; ii, Bu^tPh_2SiCl, imidazole, DMF (80% in 2 steps); iii, $HS(CH_2)_3SH$, $TiCl_4$·$AsPh_3$, CH_2Cl_2, −78 °C to RT (86%); iv, $Pb(OAc)_4$, PhH, RT, (74%)



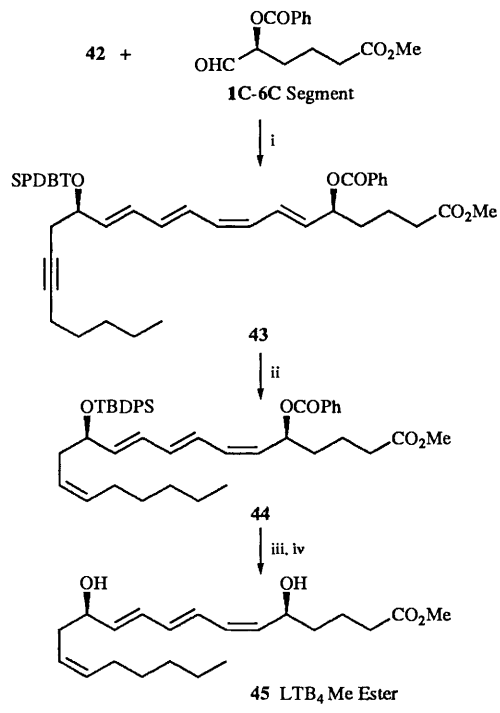
Scheme 4 *Reagents and conditions:* i, $[As(Ph_3)CH_2CHO]^+Br^-$, K_2CO_3, THF–Et_2O, H_2O (51%); or $[As(Ph_3)CH_2CH{=}CH_2CHO]^+Br^-$, K_2CO_3, THF–Et_2O, H_2O (85%), E/Z = 9:1; ii, $NaBH_4$, $CeCl_3/7H_2O$, Pr^iOH (89%); iii, CBr_4, PPh_3, CH_2Cl_2; iv, PPh_3, MeCN (70% in 2 steps)

from the salt **42** in the presence of HMPA afforded **43** (84%) as a 4.2:1 *Z*/*E* mixture at the newly formed double bond, which could be separated by careful column chromatography on silica gel (pre-treated with 5% Et_3N in light petroleum) with ethyl acetate–light petroleum (1:80) as eluent. The *cis* product is a direct precursor for both the natural and the isotopically labelled LTB_4. Thus, partial hydrogenation of (*Z*)-**43** with Pd–$CaCO_3$–Pb in a solution of ethyl acetate containing 1% quinoline gave **44** (78%), which was finally subjected to deprotection with K_2CO_3 in methanol to afford methyl ester of LTB_4 **45** (Scheme 5). The spectroscopic and physical data of our **45** were in good agreement with reported values.[28] The current preparative sequence is adaptable to a larger scale, and also allows access to the isotopically labelled compound analogous to the biologically important molecule.

In summary, the preparative method described here is facile, versatile, easy to perform and provides high stereoselectivity. In demonstration of this, the formal syntheses of the lipoxins A_4 and B_4 have been achieved utilizing the one-pot, double formyl-olefination of an aldehyde with the arsonium salt $[As(Ph_3)CH_2CHO]^+Br^-$ as the key step and D-glyceraldehyde acetonide as the same chiral pool. An improved synthesis of leukotriene B_4 was also achieved using $AsPh_3$-mediated $TiCl_4$-catalysed trans-thioketalization and a new double Wittig reaction employing the arsenic ylide ($Ph_3As{=}CHCHO$) as the key step for insertion of two *trans* C=C double bonds.

Experimental

Optical rotations, recorded in units of 10^{-1} deg cm^{-2} g^{-1}, were measured on a Perkin-Elmer 241 MC Autopol polarimeter.



Scheme 5 *Reagents and conditions:* i, BuLi, THF–HMPA, −80 °C (84%); ii, Pd–$CaCO_3$–Pb, 1% quinoline in EtOAc (78%); iii, Bu_4NF, THF; iv, K_2CO_3, MeOH (69% in 2 steps)

IR spectra were obtained on a Shimadzu IR-440 spectrophotometer. ^1H NMR spectra were taken on a Bruker AMX-300 or AMX-600 spectrometer and *J* values are given in Hz. Mass spectra were obtained on an HP 5989A spectrometer. High-performance liquid chromatography was carried out on an LKB 2000 liquid chromatograph. Microanalysis was carried out at the Microanalysis Laboratory of this Institute. Flash chromatography was performed on silica gel H (400 mesh).

Typical procedure for the double formyl-olefination of an aldehyde with $[As(Ph_3)CH_2CHO]^+Br^-$ and selected data for some (2*E*,4*E*)-dienal products

To a stirred solution of D-glyceraldehyde acetonide **1f** (130 mg, 1 mmol) in Et_2O (5 cm^3) and a trace of water (0.05 cm^3) was added $[As(Ph_3)CH_2CHO]^+Br^-$ (858 mg, 2 mmol) and K_2CO_3 (276 mg, 2 mmol) in portions. The reaction mixture was stirred at 10 °C under nitrogen for 12 h after which it was passed through a short pad of silica gel to remove most of the triphenylarsine oxide and the inorganic salt. The silica gel was eluted with ether, and the eluate was concentrated under reduced pressure. Flash chromatography of the residue afforded (4*S*,2*E*)-4,5-*O*-isopropylidene-4,5-dihydroxypent-2-enal **2f** (32 mg, 21% yield based on aldehyde) and (6*S*,2*E*,4*E*)-6,7-dihydroxy-6,7-*O*-isopropylidene-hepta-2,4-dienal **3f** (136 mg, 75%); **2** $[\alpha]_D$ +28.8 (*c* 0.5, $CHCl_3$) (Found: M, 182.0900. $C_{10}H_{14}O_3$ requires *M*, 182.0943); ν_{max}(neat)/cm^{-1} 1670, 1640, 1000 and 980; δ_H(300 MHz, C_6D_6) 1.40 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 3.37 (1 H, dd, $J_{6,7}$ 7.6, $J_{7,7}$ 7.9, 7-H), 3.79 (1 H, dd, $J_{6,7}$ 6.5, $J_{7,7'}$ 8.2, 7′-H), 4.24 (1 H, qd, $J_{4,6}$ 0.8, $J_{7,6} = J_{7',6} = J_{5,6}$ 6.5, 6-H), 5.64 (1 H, dd, $J_{6,5}$ 6.5, $J_{4,5}$ 15.2, 5-H), 5.95 (1 H, dd, $J_{1,2}$ 7.7, $J_{3,2}$ 15.4, 2-H), 6.03 (1 H, dd, $J_{3,4}$ 10.7, $J_{5,4}$ 15.2, 4-H), 6.39 (1 H, dd, $J_{4,3}$ 10.8, $J_{2,3}$ 15.4, 3-H) and 9.41 (1 H, d, $J_{2,1}$ 7.7, 1-H); *m*/*z* 182 (M^+, 1%), 167 (87), 152 (30), 125 (40), 95 (52), 81 (55), 72 (51) and 43 (100).

Ethyl (5*S*,6*E*,7*E*)-5-benzoyloxy-8-formylocta-6,7-dienoate 3g. This compound had $[\alpha]_D$ +88.9 (*c* 1.10, $CHCl_3$) [Found: *m*/*z* 208.1075. $C_{12}H_{16}O_3$ (M^+ − PhCOO − H) requires 208.1099]; ν_{max}(neat)/cm^{-1} 1720, 1680, 1640, 1600, 1450, 1260, 1100, 980 and 700; δ_H(300 MHz, C_6D_6) 0.95 (3 H, t, CH_3), 1.50–1.67 (4 H,

m, 3,4-H), 2.08 (2 H, m, 2-H), 3.95 (2 H, q, J 7.2, OCH_2), 5.49 (1 H, m, 5-H), 5.62 (1 H, dd, $J_{5,6}$ 6.1, $J_{7,6}$ 15.3, 6-H), 5.75 (1 H, dd, $J_{10,9}$ 7.7, $J_{8,9}$ 15.2, 9-H), 6.09 (1 H, dd, $J_{8,7}$ 10.9, $J_{6,7}$ 15.1, 7-H), 6.31 (1 H, dd, $J_{7,8}$ 10.8, $J_{9,8}$ 15.3, 8-H), 7.10 (3 H, m, ArH), 8.20 (2 H, m, ArH) and 9.35 (1 H, d, $J_{9,10}$ 7.7, 10-H); m/z 208 (5%), 179 (3), 143 (3), 105 (100) and 77 (19).

(6*S*,2*E*,4*E*)-6-benzoyloxyundeca-2,4-dienal 3h. This compound had $[\alpha]_D$ +115.4 (c 0.8, $CHCl_3$) (Found: C, 75.2; H, 7.7. $C_{18}H_{22}O_3$ requires C, 75.48; H, 7.75%); ν_{max}(neat)/cm^{-1} 1720, 1680, 1640, 1260, 1000, 980 and 700; δ_H(300 MHz, C_6D_6) 0.92 (3 H, t, J 6.9, CH_3), 1.20–1.48 (6 H, m, 8,9,10-H), 1.50–1.71 (2 H, m, 7-H), 5.65 (1 H, q, $J_{7,6} = J_{5,6}$ 6.2, 6-H), 5.78 (1 H, dd, $J_{6,5}$ 6.3, $J_{4,5}$ 15, 5-H), 5.88 (1 H, dd, $J_{1,2}$ 7.7, $J_{3,2}$ 15.3, 2-H), 6.19 (1 H, dd, $J_{3,4}$ 10.9, $J_{5,4}$ 14.9, 4-H), 6.41 (1 H, dd, $J_{4,3}$ 10.9, $J_{2,3}$ 15.2, 3-H), 7.18 (3 H, m, ArH), 8.26 (2 H, m, ArH) and 9.41 (1 H, d, J 7.7, 1-H); m/z 287 (M^+ + 1, 0.4%), 181 (0.7), 165 (1), 105 (100) and 77 (18).

(6*S*,2*E*,4*E*)-6-Benzyloxyhepta-2,4-dienal 3i. This compound had $[\alpha]_D$ −51.4 (c 1.05, $CHCl_3$) (Found: C, 77.4; H, 7.4. $C_{14}H_{16}O_2$ requires C, 77.74; H, 7.46%); ν_{max}(neat)/cm^{-1} 1680, 1640, 1100 and 980; δ_H(300 MHz, C_6D_6) 1.10 (3 H, d, $J_{6,7}$ 6.45, 7-H), 3.68 (1 H, m, 6-H), 4.20 (1 H, d, $J_{b,a}$ 12.08, OCH_2), 4.35 (1 H, d, $J_{a,b}$ 12.16, OCH_2), 5.64 (1 H, dd, $J_{6,5}$ 6.83, $J_{4,5}$ 15.43, 5-H), 5.88–5.96 (2 H, m, 2,4-H), 6.39 (1 H, dd, $J_{4,3}$ 10.81, $J_{2,3}$ 15.35, 3-H), 7.10–7.30 (5 H, m, ArH), 9.49 (1 H, d, $J_{2,1}$ 7.88, 1-H); m/z 174 (0.7%), 125 (2), 109 (3), 91 (100) and 77 (6).

Ethyl (5*S*,6*R*)-5-ethoxycarbonyloxy-6,7-*O*-isopropylidene-6,7-dihydroxyhept-2-ynoate 8

A solution of BuLi in hexane (40 mmol) was added dropwise to a solution of compound **7** (3.4 g, 20 mmol) in dry THF (100 cm^3) at −78 °C. After 1 h, ethyl chloroformate (9.5 cm^3, 100 mmol) was added to the mixture and stirring was continued at −60 °C for 1 h; the bath was then allowed to warm to room temperature over 2 h. The reaction was quenched by the addition of saturated aq. NH_4Cl to the mixture after which the phases were separated and the aqueous layer was extracted with ether. The organic layer and extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the *erythro*-isomer **8** (4.6 g, 73%); $[\alpha]_D$ +37.4 (c 1.45, CH_2Cl_2), {lit,[16] $[\alpha]_D$ +33 (c 1.39, CH_2Cl_2)} (Found: C, 57.0; H, 7.3. $C_{15}H_{22}O$ requires C, 57.32; H, 7.05); ν_{max}(neat)/cm^{-1} 2200, 1750, 1705 and 1250; δ_H(300 MHz, $CDCl_3$) 1.31 (6 H, m, 2 × CH_3), 1.37 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.80 (1 H, dd, $J_{5,4}$ 5.5, $J_{4',4}$ 18.0, 4-H), 2.88 (1 H, dd, $J_{5,4'}$ 4.6, $J_{4,4'}$ 18.4, 4′-H), 3.91 (1 H, dd, $J_{6,7}$ 5.9, $J_{7',7}$ 8.8, 7-H), 4.11 (1 H, dd, $J_{6,7'}$ 6.2, $J_{7,7'}$ 8.8, 7′-H), 4.23 (5 H, m, 6-H + 2 × OCH_2) and 4.77 (1 H, m, 5-H); m/z 299 (M^+ − CH_3, 82%), 271 (41), 229 (47), 165 (54), 121 (68), 101 (100) and 43 (89); and its *threo*-isomer (0.45 g, 7.1%); $[\alpha]_D$ +6.2 (c 1.48, CH_2Cl_2); ν_{max}(neat)/cm 2200, 1745, 1705 and 1250; δ_H(300 MHz, $CDCl_3$) 1.30 (6 H, m, 2 × CH_3), 1.36 (3 H, s, CH_3), 1.44 (3 H, s, CH_3), 2.70 (1 H, dd, $J_{5,4}$ 6.5, $J_{4',4}$ 17.4, 4-H), 2.79 (1 H, dd, $J_{5,4'}$ 6.5, $J_{4,4'}$ 17.4, 4′-H), 3.86 (1 H, dd, $J_{6,7}$ 5.6, $J_{7',7}$ 8.7, 7-H), 4.08 (1 H, dd, $J_{6,7'}$ 6.6, $J_{7,7'}$ 8.7, 7′-H), 4.23 (4 H, m, 2 × OCH_2), 4.35 (1 H, m, 6-H) and 4.90 (1 H, m, 5-H); m/z 299 (M^+ − CH_3, 34%), 271 (22), 229 (21), 183 (29), 165 (54), 121 (58), 101 (96) and 43 (100).

(2*R*,3*S*)-1,2-*O*-Isopropyldieneoctane-1,2,3-triol 9

BuLi in hexane (60 mmol) was added to a solution of **7** (5.1 g, 30 mmol) in dry THF (150 cm^3) at −60 °C under N_2 followed, after 0.5 h, by a solution of ethyl bromide (2.61 cm^3, 35 mmol) in HMPA (15 cm^3). Stirring was continued for 0.5 h at the same temperature and then at room temperature overnight. The reaction was quenched by the addition of saturated aq. NH_4Cl to the mixture which was then extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated and the residue chromatographed to give pure (2*R*)-1,2-isopropylideneoct-5-yne-1,2,3-triol (5.2 g, 88%); ν_{max}(neat)/cm^{-1} 3400 and 1060; δ_H(300 MHz, $CDCl_3$) 1.15 (3 H, t, J 7, 8-H), 1.36 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.18 (2 H, m, 7-H), 2.50 (2 H, m, 4-H), 3.70–3.80 (2 H, m, 3-H + 1-H) and 3.93–4.10 (2 H, m, 2-H + 1′-H); m/z 199 (M^+ + 1, 10%), 183 (32), 123 (68), 101 (100), 95 (46) and 43 (78). This compound (5.5 g, 27.8 mmol) was hydrogenated in ethanol (40 cm^3) under atmospheric pressure using 10% Pd–C (200 mg) as catalyst. After uptake of the theoretical amount of hydrogen, the mixture was filtered and the filtrate was evaporated under reduced pressure. Chromatography of the residue afforded the title compound **9** (4.67 g, 85%); $[\alpha]_D$ +13.1 (c 1.7, $CHCl_3$) [Found: m/z 187.1329. $C_{10}H_{19}O_3$ (M^+ − CH_3) requires 187.1334]; ν_{max}(neat)/cm^{-1} 3350 and 1050; δ_H(300 MHz, $CDCl_3$) 0.90 (3 H, t, CH_3), 1.38 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.27–1.57 (8 H, m, 4,5,6,7-H), 2.15 (1 H, br s, OH), 3.58 (1 H, m, 3-H), 3.74 (1 H, m, 1-H) and 3.90–4.05 (2 H, m, 1′-H + 2-H); m/z 203 (M^+, 2%), 187 (39), 127 (15), 101 (100) and 43 (58); and its *threo*-isomer (0.7 g, 13%); $[\alpha]_D$ +18.4 (c 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 and 1050; δ_H(300 MHz, $CDCl_3$) 0.90 (3 H, t, CH_3), 1.38 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.27–1.57 (8 H, m, 4,5,6,7-H), 2.20 (1 H, br s, OH), 3.48 (1 H, m, 3-H), 3.72 (1 H, m, 3-H) and 3.98 (2 H, m, 1′-H + 2-H); m/z 203 (M^+, 9%), 187 (25), 145 (2), 127 (29), 101 (100) and 43 (35).

(2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxy-1,2-*O*-isopropylideneoctane-1,2,3-triol 12

tert-Butylchlorodiphenylsilane (3.94 cm^3, 15 mmol) and imidazole (2.19 g, 32 mmol) were added successively to a solution of compound **9** (1.62 g, 8 mmol) in anhydrous DMF (50 cm^3) under N_2. The mixture was stirred at room temperature for 50 h, and then partitioned between Et_2O (200 cm^3) and water (20 cm^3). The organic layer was separated and washed with saturated aq. NH_4Cl and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue afforded the pure compound **12** (3.01 g, 85.5%); $[\alpha]_D$ +21.6 (c 0.65, $CHCl_3$) {lit,[16] $[\alpha]_D$ +12 (c 1.14, CH_2Cl_2)}; ν_{max}(neat)/cm^{-1} 1450, 1420, 1100, 1060, 810, 730 and 690; δ_H(300 MHz, $CDCl_3$) 0.78 (3 H, t, J 7.0, 8-H), 1.0–1.50 (23 H, m, 4-7-H + Bu^t + 2 × CH_3), 3.74–3.82 (2 H, m, 1-H + 3-H), 3.95 (1 H, dd, $J_{2,1'}$ 6.3, $J_{1,1'}$ 7.8, 1′-H), 4.06 (1 H, q, $J_{1,2} = J_{1',2} = J_{3,2}$ 6.3, 2-H), 7.35–7.47 (6 H, m, ArH) and 7.67–7.72 (4 H, m, ArH).

(2*R*,3*S*)-3-Acetoxy-1,2-*O*-isopropylidenehex-5-yne-1,2,3-triol 10

Et_3N (20.9 cm^3, 0.15 mol) was added to a solution of the alkyne **7** (17 g, 0.1 mol) in CH_2Cl_2 (300 cm^3). After being stirred at 0 °C for 10 min, the mixture was treated with DMAP (0.1 g) and acetyl anhydride (14.1 cm^3, 0.15 mol) and stirring continued at room temperature for 1.5 h. The mixture was then washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue afforded the acetyl ester **10** (19 g, 89.6%); $[\alpha]_D$ +35.1 (c 1.05, $CHCl_3$) [Found: m/z 197.0803. $C_{10}H_{13}O_4$ (M^+ − CH_3) requires 197.0814]; ν_{max}(neat)/cm^{-1} 3290, 1740, 1220 and 840; δ_H(300 MHz, $CDCl_3$) 1.36 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.01 (1 H, t, $J_{4,6}$ 3, 6-H), 2.58 (1 H, ddd, $J_{6,4}$ 2.7, $J_{3,4}$ 5.8, $J_{4',4}$ 17.4, 4-H), 2.66 (1 H, ddd, $J_{6,4'}$ 2.6, $J_{3,4'}$ 4.8, $J_{4,4'}$ 17.3, 4′-H), 3.86 (1 H, dd, $J_{2,1}$ 5.5, $J_{1',1}$ 8.6, 1-H), 4.08 (1 H, dd, $J_{2,1'}$ 6.4, $J_{1,1'}$ 8.6, 1′-H), 4.30 (1 H, q, $J_{1,2} = J_{1',2} = J_{3,2}$ 6.4, 2-H) and 4.95 (1 H, q, $J_{4,3} = J_{4',3} = J_{2,3}$ 5.1, 3-H); m/z 197 (M^+ − CH_3, 13%), 115 (5), 101 (18), 95 (10) and 43 (100); and its *threo* isomer (1.47 g, 7%); $[\alpha]_D$ +0.48 (c 1.15, $CHCl_3$) [Found: m/z 197.0809, $C_{10}H_{13}O_4$ (M^+ − CH_3) requires 197.0814]; ν_{max}(neat)/cm^{-1} 3290, 1740, 1220 and 840; δ_H(300 MHz, $CDCl_3$) 1.36 (3 H, s, CH_3), 1.44 (3 H, s, CH_3), 2.01 (1 H, t, $J_{4,6}$ 3, 6-H), 2.50 (1 H, ddd, $J_{6,4}$ 2.7, $J_{3,4}$ 6.5, $J_{4',4}$ 16.9, 4-H), 2.61 (1 H, ddd, $J_{6,4'}$ 2.7, $J_{3,4'}$ 6.4, $J_{4,4'}$ 16.9, 4′-H), 3.79 (1 H, dd, $J_{2,1}$ 5.9, $J_{1',1}$ 8.6, 1-H), 4.06 (1 H, dd, $J_{2,1'}$ 6.8, $J_{1,1'}$ 8.7, 1′-H), 4.37 (1 H, q, $J_{1,2}$ =

$J_{1'.2} = J_{3.2}$ 6.1, 2-H) and 5.03 (1 H, q, $J_{4.3} = J_{4'.3} = J_{2.3}$ 6.4, 3-H); *m/z* 197 ($M^+ - CH_3$, 30%), 169 (2), 115 (8), 101 (31), 95 (20) and 43 (100).

(5*S*,6*R*)-5-Ethoxycarbonyloxy-6,7-*O*-isopropylidene-5,6,7-trihydroxyheptanoate 11

Compound **8** (942 mg, 3 mmol) was hydrogenated under atmospheric pressure using 10% Pd–C (80 mg) as catalyst and anhydrous ethanol (20 cm^3) as solvent. After the theoretical amount of hydrogen had been taken up, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give the product **11** (910 mg, 95%), which was used in the next step without further purification; $[\alpha]_D$ −5.8 (*c* 0.64, CH_2Cl_2) {lit,[16] $[\alpha]_D$ −4 (*c* 1.1, CH_2Cl_2)}; ν_{max}(neat)/cm^{-1} 1715 and 1250; δ_H(300 MHz, $CDCl_3$) 1.27–1.37 (6 H, m, 2 × CH_3), 1.34 (3 H, s, CH_3), 1.39 (3 H, s, CH_3), 1.62–1.85 (4 H, m, 3,4-H), 2.35 (2 H, m, 2-H), 3.85 (1 H, m, 7-H), 4.05 (1 H, m, 7′-H), 4.10–4.25 (5 H, 6-H + 2 × OCH_2) and 4.85 (1 H, m, 5-H).

(2*R*,3*S*)-1,2-*O*-Isopropylidenehex-5-yne-1,2,3-triol 14

Potassium carbonate (300 mg) was added to a solution of the acetyl ester **10** (9.4 g, 43.5 mmol) in anhydrous methanol (60 cm^3) and the mixture was stirred at room temperature for 1 h. After the methanol had been evaporated, the residue was diluted with Et_2O (200 cm^3), washed with saturated aqueous NH_4Cl and brine, dried (Na_2SO_4) and concentrated. Compound **14** (pure *erythro* isomer of **7**), was obtained in quantitative yield (7.39 g); $[\alpha]_D$ +6.4 (*c* 1.4, $CHCl_3$) [Found: *m/z* 155.0736. $C_8H_{11}O_3$ requires (M − CH_3), 157.0708]; ν_{max}(neat)/cm^{-1} 3350, 3200, 1050 and 840; δ_H(300 MHz, $CDCl_3$) 1.36 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 2.08 (1 H, t, $J_{4.6}$ 2.6, 6-H), 2.29 (1 H, br s, OH), 2.46 (1 H, ddd, $J_{6.4}$ 2.5, $J_{3.4}$ 5.6, $J_{4'.4}$ 17.2, 4-H), 2.54 (1 H, ddd, $J_{6.4'}$ 2.5, $J_{3.4'}$ 5.6, $J_{4.4'}$ 17.2, 4′-H), 3.78 (1 H, m, 1-H), 4.01 (1 H, m, 1′-H) and 4.05–4.15 (2 H, m, 2,3-H); *m/z* 155 ($M^+ - CH_3$, 38%), 101 (77), 95 (44), 81 (18), 73 (23), 59 (35) and 43 (100).

(2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxy-1,2-*O*-isopropylidenehex-5-yne-1,2,3-triol 15

tert-Butylchlorodiphenylsilane (2.41 cm^3, 9.18 mmol) and imidazole (1.93 g, 28.2 mmol) were added successively to a solution of compound **14** (1.2 g, 7.06 mmol) in anhydrous DMF (5 cm^3). The mixture was stirred at room temperature for 30 h, and then partitioned between Et_2O (50 cm^3) and water (10 cm^3). The organic layer was separated and washed with saturated aq. NH_4Cl and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue afforded the pure title compound (2.37 g, 83.6%); $[\alpha]_D$ +37.6 (*c* 1.2, $CHCl_3$) [Found: *m/z* 393.1871. $C_{24}H_{29}O_3Si$ requires ($M^+ - CH_3$), 393.1885]; ν_{max}(neat)/cm^{-1} 3200, 1420, 1100, 730 and 690; δ_H(300 MHz, $CDCl_3$) 1.08 (9 H, s, Bu^t), 1.29 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 1.98 (1 H, t, $J_{4.6}$ 2.6, 6-H), 2.23 (1 H, ddd, $J_{6.4}$ 2.8, $J_{3.4}$ 5.4, $J_{4'.4}$ 17.4, 4-H), 2.36 (1 H, ddd, $J_{6.4'}$ 2.8, $J_{3.4'}$ 3.7, $J_{4.4'}$ 16.9, 4′-H), 3.78–3.85 (2 H, m, 1,3-H), 4.02 (1 H, dd, $J_{2.1'}$ 6.5, $J_{1.1'}$ 8.2, 1′-H), 4.29 (1 H, q, $J_{1.2} = J_{1'.2} = J_{3.2}$ 6.5, 2-H), 7.38–7.44 (6 H, m, ArH) and 7.69–7.75 (4 H, m, ArH); *m/z* 393 ($M^+ - CH_3$, 5%), 351 (M^+ − Bu^t, 3), 293 (47), 249 (70), 215 (100), 199 (58), 183 (54), 105 (32) and 43 (21).

Ethyl (5*S*,6*R*)-5-*tert*-Butyldiphenylsilyloxy-6,7-*O*-isopropylidenehept-2-ynoate 16

BuLi in hexane (6 mmol) was added to a stirred solution of compound **15** (2.2 g, 5 mmol) in THF (40 cm^3) at −70 °C. After being stirred for 2 h at the same temperature, the mixture was treated with ethyl chloroformate (0.78 cm^3, 8 mmol) at −70 °C. After an additional 3 h at −70 °C, the mixture was allowed to warm to room temperature when it was treated with saturated brine to quench the reaction. The phases were separated and the aqueous phase was back-extracted with ether. The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue afforded **16** (2.1 g, 88.2%); $[\alpha]_D$ +73.3 (*c* 1.2, $CHCl_3$) (Found: C, 71.30; H, 7.89. $C_{28}H_{36}O_5Si$ requires C, 69.97; H, 7.58); ν_{max}(neat)/cm^{-1} 2170, 1700, 1580, 1420, 1240, 730 and 690; δ_H(300 MHz, $CDCl_3$) 1.08 (9 H, s, Bu^t), 1.27–1.33 (9 H, m, 3 × CH_3), 2.39 (1 H, dd, $J_{3.4}$ 4.2, $J_{4'.4}$ 17.5, 4-H), 2.52 (1 H, dd, $J_{3.4'}$ 4.2, $J_{4.4'}$ 17.5, 4′-H), 3.75–3.82 (2 H, m, 5,7-H), 4.01 (1 H, dd, $J_{6.7'}$ 6.6, $J_{7.7'}$ 8.3, 7′-H), 4.17–4.25 (3 H, m, 6-H + OEt), 7.36–7.50 (6 H, m, ArH) and 7.69–7.74 (4 H, m, ArH); *m/z* 465 ($M^+ - CH_3$, 4%), 423 (M^+ − Bu^t, 2), 365 (30), 319 (350), 291 (47), 199 (100), 183 (65), 135 (55) and 43 (18).

Ethyl (5*S*,6*R*)-5-*tert*-Butyldiphenylsilyloxy-6,7-*O*-isopropylideneheptanoate 17

Ethyl (5*S*,6*R*)-5-*tert*-Butyldiphenylsilyloxy-6,7-*O*-isopropylidenehept-2-ynoate (1.9 g, 4 mmol) was hydrogenated under atmospheric pressure using 5% Pd–C (200 mg) as catalyst and anhydrous ethanol (20 cm^3) as solvent. After the theoretical amount of hydrogen had been taken up, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Chromatography of the residue afforded **17** (1.7 g, 88.5%); $[\alpha]_D$ +19.6 (*c* 0.75, $CHCl_3$) (Found: *m/z* 469.2412, $C_{27}H_{37}O_5Si$ requires ($M^+ - CH_3$) 469.2410); ν_{max}(neat)/cm^{-1} 1720, 1420, 1100, 720 and 690; δ_H(300 MHz, $CDCl_3$) 1.05 (9 H, s, Bu^t), 1.22 (3 H, t, *J* 7.1, OEt), 1.29 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.39–1.70 (4 H, m, 3,4-H), 2.00–2.07 (2 H, m, 2-H), 3.69 (1 H, t, $J_{6.7} = J_{7'.7}$ 7.2, 7-H), 3.76 (1 H, m, 5-H), 3.94 (1 H, t, $J_{6.7'} = J_{7.7'}$ 7.5, 7′-H), 4.08 (3 H, m, 6-H + OEt), 7.36–7.43 (6 H, m, ArH) and 7.6–7.70 (4 H, m, ArH); *m/z* 469 ($M^+ - CH_3$, 2%), 369 (42), 323 (30), 281 (32), 263 (33), 199 (100), 183 (57) and 135 (59).

(6*R*,7*S*,2*E*,4*E*)-6,7-dihydroxy-6,7-*O*-oxomethylenedodeca-2,4-dienal 22

To a solution of oxalyl chloride (0.228 cm^3, 2.6 mmol) in THF (10 cm^3) was slowly added, over 2 min, DMSO (0.370 cm^3, 5.2 mmol) in THF (4 cm^3) at −70 °C. After being stirred at −35 °C for 1 h, the mixture was re-cooled to −70 °C before the alcohol carbonate **18** (376 mg, 2 mmol) in THF (4 cm^3) was added over 2 min. After 1 h at −35 °C, the mixture was treated with Et_3N (1.4 cm^3, 10 mmol) at −70 °C and its temperature slowly raised to −10 °C over 1 h. The arsonium salt (1.72 g, 4 mmol) and Et_3N (0.560 cm^3, 4 mmol) were then added at 0 °C in portions to the mixture after which it was stirred at 0 °C for 8 h. The mixture was then diluted with ether, filtered through silica gel to remove triphenylarsine oxide and triethylammonium halides and concentrated under reduced pressure. Flash chromatography of the residue afforded the dienal **22** (310 mg, 65%); $[\alpha]_D$ +7.3 (*c* 0.4, CH_2Cl_2), {lit,[16] $[\alpha]_D$ +12 (*c* 1.4, CH_2Cl_2)}; ν_{max}(neat)/cm^{-1} 1790, 1710, 1680, 1640, 1160 and 980; δ_H(300 MHz, $CDCl_3$) 1.01 (3 H, t, CH_3), 1.30–1.60 (4 H, m, 3,4-H), 2.01 (2 H, m, 2-H), 3.83 (1 H, m, 5-H), 3.98 (2 H, q, *J* 7.1, OCH_2), 4.20 (1 H, t, $J_{5.6} = J_{7.6}$ 7.4, 6-H), 5.28 (1 H, dd, $J_{11.10}$ 7.2, $J_{9.10}$ 15.3, 10-H), 5.82–5.91 (2 H, m, 7,8-H), 6.27 (1 H, dd, $J_{8.9}$ 10.8, $J_{10.9}$ 15.5, 9-H) and 9.36 (1 H, d, $J_{10.11}$ 7.6, 11-H); *m/z* 283 ($M^+ - 1$), 193 (14%), 149 (45), 99 (91), 81 (100) and 55 (94).

The dienal **26** was obtained in a similar way (60%); $[\alpha]_D$ +7.7 (*c* 0.8, CH_2Cl_2), {lit,[16] $[\alpha]_D$ +10 (*c* 1.92, CH_2Cl_2)}; ν_{max}(neat)/cm^{-1} 1790, 1680, 1640 and 980; δ_H(300 MHz, C_6D_6) 0.88 (3 H, t, *J* 7, 12-H), 1.0–1.5 (8 H, m, 8, 9, 10, 11-H), 3.95 (1 H, m, 7-H), 4.34 (1 H, t, $J_{5.6} = J_{7.6}$ 7.5, 6-H), 5.36 (1 H, dd, $J_{1.2}$ 7.2, $J_{3.2}$ 15.2, 2-H), 5.85–5.98 (2 H, m, 4,5-H), 6.32 (1 H, dd, $J_{4.3}$ 10.8, $J_{2.3}$ 15.3, 3-H) and 9.38 (1 H, d, $J_{2.1}$ 7.6, 1-H); *m/z* 239 ($M^+ - 1$, 23%), 213 (4), 195 (7), 81 (75) and 66 (100).

(2*S*)-*tert*-Butyldiphenylsilyloxyheptaldehyde 19

The acetol **12** (2.9 g, 6.6 mmol) was added to a well-stirred suspension of periodic acid (3.0 g, 13.2 mmol) in dry ether (50

cm^3) under a nitrogen atmosphere, at room temperature. After being stirred for 10 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Flash chromatography of the residue gave the aldehyde **19** (2.4 g, 98.8%); $[\alpha]_D$ +2.7 (*c* 1.05, $CHCl_3$) {lit.,[16] $[\alpha]_D$ −1 (*c* 1.25, CH_2Cl_2)}; ν_{max}(neat)/cm^{-1} 1720, 1450, 1420, 1100, 810, 730 and 690; δ_H(300 MHz, $CDCl_3$) 0.84 (3 H, t, *J* 6.8, 7-H), 1.00–1.40 (15 H, m, 4–7-H + Bu^t), 1.52–1.70 (2 H, m, 3-H), 4.03 (1 H, td, $J_{3.2}$ 5.9, $J_{1.2}$ 1.5, 2-H), 7.34–7.46 (6 H, m, ArH), 7.62–7.69 (4 H, m, ArH) and 9.59 (1 H, d, $J_{2.1}$ 1.5, 1-H).

The aldehyde **21** was prepared in a similar way (95%); $[\alpha]_D$ −3.5 (*c* 1.4, $CHCl_3$) {lit.,[16] $[\alpha]_D$ +0.6 (*c* 1.16, CH_2Cl_2)};† ν_{max}(neat)/cm^{-1} 1720, 1450, 1100, 730 and 690; δ_H(300 MHz, $CDCl_3$) 1.12 (9 H, t, Bu^t), 1.23 (3 H, t, *J* 7, OEt), 1.58–1.78 (4 H, m, 3,4-H), 2.16–2.24 (2 H, m, 2-H), 4.01–4.19 (3 H, m, 5-H + OEt), 7.32–7.49 (6 H, m, ArH), 7.60–7.73 (4 H, m, ArH) and 9.58 (1 H, s, 6-H).

(4*S*,2*E*)-4-*tert*-Butyldiphenylsiloxynon-2-enal 23

To a stirred solution of the aldehyde **19** (1.84 g, 5 mmol) in Et_2O (30 cm^3) and a trace of water (0.300 cm^3) at −10 °C were added, in turn, portions of the arsonium salt (2.15 g, 5 mmol) and potassium carbonate (0.67 g, 5 mmol). After being stirred for 7 h under nitrogen, the mixture was passed through a short pad of silica gel and concentrated. Flash chromatography of the residue gave compound **23** (1.55 g, 79%); $[\alpha]_D$ −18.5 (*c* 1.4, $CHCl_3$) {lit.,[13b] $[\alpha]_D$ −18 (*c* 0.5, $CHCl_3$)}, ν_{max}(neat)/cm^{-1} 1680, 1450, 1420, 1100, 960, 810, 730 and 690; δ_H(300 MHz, $CDCl_3$) 0.75 (3 H, t, *J* 7.1, 9-H), 1.0–1.25 (15 H, m, 6–8-H + Bu^t), 1.40–1.50 (2 H, m, 5-H), 4.38 (1 H, q, $J_{5.4} = J_{3.4}$ 5.3, 4-H), 6.06 (1 H, ddd, $J_{4.2}$ 0.9, $J_{1.2}$ 7.9, $J_{3.2}$ 15.5, 2-H), 6.61 (1 H, dd, $J_{4.3}$ 5.3, $J_{2.3}$ 15.7, 3-H), 7.24–7.39 (6 H, m, ArH), 7.51–7.60 (4 H, m, ArH) and 9.38 (1 H, d, $J_{2.1}$ 8.0, 1-H).

Ethyl (5*S*,6*E*)-5-tert-Butyldiphenylsilyloxy-8-formyloct-6-enoate 27

This compound was prepared in a similar way (75.3%); $[\alpha]_D$ −13.2 (*c* 0.5, $CHCl_3$) [Found: *m*/*z* 381.1485, $C_{22}H_{25}O_4Si$ requires (M^+ − Bu^t), 381.1522]; ν_{max}(neat)/cm^{-1} 1720, 1680, 1420, 1100, 730 and 690; δ_H(300 MHz, $CDCl_3$) 1.11 (9 H, t, Bu^t), 1.25 (3 H, t, *J* 7, OEt), 1.50–1.75 (4 H, m, 3,4-H), 2.19 (2 H, t, $J_{3.2}$ 6.9, 2-H), 4.11 (2 H, q, *J* 7.2, OEt), 4.50 (1 H, m, 5-H), 6.17 (1 H, ddd, $J_{5.7}$ 1.5, $J_{8.7}$ 7.9, $J_{6.7}$ 15.7, 7-H), 6.69 (1 H, dd, $J_{5.6}$ 5.0, $J_{7.6}$ 15.5, 6-H) and 9.47 (1 H, d, $J_{7.8}$ 7.8, 8-H); *m*/*z* 393 (7%), 381 (100), 335 (12), 227 (24), 199 (93), 183 (39), 139 (44), 77 (18) and 55 (20).

Protected LXA_4 30 and its (8*E*)-isomer 31

To a solution of the phosphonium salt **25** (133 mg, 0.185 mmol) in dry THF (4 cm^3) at −100 °C was added an LHMDS solution in THF (0.5 mol dm^{-3}; 0.336 cm^3, 0.168 mmol). After 5 min, the aldehyde **19** (40 mg, 168 mmol) in THF (1.5 cm^3) and HMPA (0.270 cm^3) were added. The mixture was stirred for 5 min and then warmed to −50 °C and stirred for 1 h. Aqueous NH_4OAc (25% w/v; 5 cm^3) was added to the mixture at −50 °C to quench the reaction after which it was extracted with ether (20 cm^3 × 4). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue afforded the protected LXA_4 **30** (33 mg) and its (8*E*)-isomer **31** (49 mg, 76% total yield) Physical data for protected LXA_4 **30**: $[\alpha]_D$[2] −7.8 (*c* 0.7, CH_2Cl_2) {lit:[13b] $[\alpha]_D$ −9.8 (*c* 0.38, CH_2Cl_2)}; ν_{max}(neat)/cm^{-1} 1805, 1733, 1428, 1175, 1111, 998, 822, 772, 741 and 703; δ_H($CDCl_3$, 600 MHz) 0.89 (3 H, t, *J* 6.5, 20-H), 1.08 (9 H, t, Bu^t), 1.23–1.60 (15 H, m, 3,4,16–19-H + OEt), 2.19 (2 H, t, *J* 6.8, 2-H), 4.09 (3 H, q, *J* 7.1, OEt), 4.28 (1 H, q, $J_{4.5} = J_{6.5}$ 6.1, 5-H), 4.69 (1 H, td, $J_{14.15}$ 3.2, $J_{16.15}$ 8.6, 15-H), 5.15 (1 H, t, $J_{13.14} = J_{15.14}$ 7.8, 14-H), 5.64 (1 H, dd, $J_{14.13}$ 8.1, $J_{12.13}$ 16.7, 13-H), 5.67 (1 H, dd, $J_{5.6}$ 6.7, $J_{7.6}$ 15.4, 6-H), 5.90–5.97 (2 H, ABMN, $J_{A.B}$ 10.9, 8,9-H), 6.20 (1 H, dd, $J_{12.11}$ 10.8, $J_{10.11}$ 14.7, 11-H), 6.32 (1 H, dd, $J_{8.7}$ 10.2, $J_{6.7}$ 15, 7-H), 6.38 (1 H, dd, $J_{11.12}$ 10.7, $J_{13.12}$ 15.1, 12-H), 6.50 (1 H, dd, $J_{9.10}$ 10.5, $J_{11.10}$ 14.7, 10-H), 7.33–7.42 (6 H, m, ArH) and 7.63–7.67 (4 H, m, ArH); *m*/*z* (CI, CH_4) 645 (M + 1, 17%), 601 (M − C_3H_7, 15), 583 (51), 383 (100), 327 (98), 305 (27), 281 (28), 199 (23), 179 (10), 99 (9) and 79 (9); λ_{max}(EtOH)/nm 294, 306 and 320. Physical data for (8*E*)-isomer **31**; $[\alpha]_D$ −88.4 (*c* 0.39, CH_2Cl_2), {lit.,[13b] $[\alpha]_D$ −81 (*c* 0.43, CH_2Cl_2)}; δ_H($CDCl_3$, 600 MHz) 0.89 (3 H, t, *J* 6, 20-H), 1.07 (9 H, t, Bu^t), 1.21–1.68 (15 H, m, 3,4,16–19-H + OEt), 2.16 (2 H, t, *J* 7.2, 2-H), 4.08 (2 H, q, *J* 7.1, OEt), 4.21 (1 H, q, $J_{4.5} = J_{6.5}$ 5.3, 5-H), 4.67 (1 H, td, $J_{14.15}$ 3.2, $J_{16.15}$ 8.6, 15-H), 5.12 (1 H, t, $J_{13.14} = J_{15.14}$ 7.8, 14-H), 5.62 (1 H, dd, $J_{14.13}$ 8.2, $J_{12.13}$ 15.1, 13-H), 5.67 (1 H, dd, $J_{5.6}$ 6.6, $J_{7.6}$ 15.1, 6-H), 5.92 (1 H, dd, $J_{8.7}$ 10.7, $J_{6.7}$ 15.2, 7-H), 6.07 (1 H, dd, $J_{10.9}$ 10.8, $J_{8.9}$ 14.9, 9-H), 6.18 (1 H, dd, $J_{7.8}$ 10.6, $J_{9.8}$ 15.4, 8-H), 6.21 (1 H, dd, $J_{12.11}$ 10.6, $J_{10.11}$ 15.4, 11-H), 6.31 (1 H, dd, $J_{9.10}$ 10.8, $J_{11.10}$ 14.9, 10-H), 6.40 (1 H, dd, $J_{11.12}$ 10.7, $J_{13.12}$ 15.1, 12-H), 7.26–7.42 (6 H, m, ArH) and 7.61–7.66 (4 H, m, ArH); λ_{max}(EtOH) 294, 306 and 320 nm.

Protected LXB_4 32 and its (11*E*)-isomer 33

BuLi (2.5 mol dm^{-3} in hexane; 0.065 cm^3, 0.150 mmol) was added to a solution of the phosphonium salt **29** (107 mg, 0.150 mmol) in dry THF (10 cm^3) at −100 °C followed after 5 min, by a solution of the aldehyde **21** (40 mg, 0.140 mmol) in THF (2 cm^3) and HMPA (0.1 cm^3). After being stirred for 1 h at −40 °C, the reaction mixture was treated with aqueous NH_4OAc (25% w/v, 3 cm^3) to quench the reaction and then extracted with ether (20 cm^3 × 3). The combined extracts were washed with brine, dried and concentrated. Flash chromatography of the residue on silica gel afforded the protected LXB_4 **32** (35 mg) and its (11*E*)-isomer **33** (20 mg, 61% total yield); Physical data for protected LXB_4 **32**: $[\alpha]_D$ −3.5 (*c* 0.5, CH_2Cl_2) {lit,[13b] $[\alpha]_D$ −4.7 (*c* 0.55, CH_2Cl_2)}; ν_{max}(neat)/cm^{-1} 1807, 1732, 1471, 1428, 1390, 1180, 1111, 998, 822, 741 and 703; δ_H($CDCl_3$, 600 MHz) 0.83 (3 H, t, *J* 7.3, 20-H), 1.07 (9 H, t, Bu^t), 1.14–1.90 (15 H, m, 3, 4, 16–19-H, OEt), 2.34 (2 H, m, 2-H), 4.13 (2 H, q, *J* 6.6, OEt), 4.23 (1 H, m, 15-H), 4.70 (1 H, m, 5-H), 5.17 (1 H, m, 6-H), 5.63 (1 H, dd, $J_{6.7}$ 8.2, $J_{8.7}$ 15.3, 7-H), 5.69 (1 H, dd, $J_{15.14}$ 6.2, $J_{13.14}$ 14.8, 14-H), 5.94 (2 H, AB, $J_{A.B}$ 11, 11,12-H), 6.18 (1 H, dd, $J_{8.9}$ 11, $J_{10.9}$ 15, 9-H), 6.25–6.41 (2 H, m, 8,13-H), 6.51 (1 H, dd, $J_{11.10}$ 11, $J_{9.10}$ 15, 10-H), 7.34–7.40 (6 H, m, ArH) and 7.67–7.72 (4 H, m, ArH); *m*/*z* (CI, CH_4) 645 (M + 1, 14%), 583 (25), 567 (9), 523 (9), 389 (26), 339 (100), 327 (82), 299 (20), 281 (28), 239 (25) 199 (46), 179 (38) and 79 (22); λ_{max}(EtOH)/nm 294, 306 and 320 nm; Physical data for its (11*E*)-isomer **33**; $[\alpha]_D$ −91.8 (*c* 0.4, CH_2Cl_2) {lit.,[13b] $[\alpha]_D$ −114 (*c* 0.51, CH_2Cl_2)}; δ_H($CDCl_3$, 600 MHz) 0.76 (3 H, t, *J* 7.2, 20-H), 1.01 (9 H, t, Bu^t), 1.05–1.90 (15 H, m, 3, 4, 16–19-H, OEt), 2.37 (2 H, m, 2-H), 4.08 (2 H, q, *J* 7.1, OEt), 4.13 (1 H, q, $J_{14.15} = J_{16.15}$ 6, 15-H), 4.63 (1 H, m, 5-H), 5.10 (1 H, t, $J_{7.6} = J_{5.6}$ 7.9, 6-H), 5.55 (1 H, dd, $J_{6.7}$ 8.1, $J_{8.7}$ 15, 7-H), 5.65 (1 H, dd, $J_{15.14}$ 6.8, $J_{13.14}$ 15.2, 14-H), 5.88 (1 H, dd, $J_{10.11}$ 10.7, $J_{12.11}$ 15.1, 11-H), 6.15 (2 H, m, 9, 12-H), 6.27 (1 H, dd, $J_{11.10}$ 11, $J_{9.10}$ 14.8, 10-H), 6.35 (1 H, dd, $J_{9.8}$ 10.8, $J_{7.8}$ 15.1, 8-H), 7.29–7.32 (6 H, m, ArH) and 7.57–7.62 (4 H, m, ArH); λ_{max}(EtOH)/nm 294, 306 and 322.

(9*R*,10*S*,11*S*,12*R*)-Bis(*tert*-butyldiphenylsilyloxy)icosa-6,14-diyne-10,11-diol 37

$TiCl_4$ (0.58 cm^3, 5.27 mmol) was added to a stirred solution of Ph_3As (1.61 g, 5.27 mmol) in dry CH_2Cl_2 (30 cm^3) at −78 °C, to give a purple solution which was immediately added to a solution of the acetonide **36** (4.50 g, 5.27 mmol) and propane-1,3-dithiol (2.34 cm^3, 23.3 mmol) in CH_2Cl_2 (90 cm^3) also at

† The value of the optical rotation is small and somewhat different from the reported value probably owing to experimental error. The values recorded for the products in subsequent steps were, however, coincident with those in literature.

−78 °C. The mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature. Stirring was continued for 2 h after which the mixture was treated with saturated aqueous NH_4Cl. The organic phases were separated and the aqueous phase was back-extracted with CH_2Cl_2. The combined organic layer and extracts were washed successively with aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Chromatography of the residue gave the title compound **37** as a colourless oil (3.69 g, 86%); $[\alpha]_D$ −52.2 (*c* 0.9, $CHCl_3$) (Found: 76.2; H 8.7. $C_{52}H_{70}O_6Si_2$ requires C, 76.60; H, 8.65%); ν_{max}(film)/cm^{-1} 3450, 1410, 1100, 710 and 700; δ_H(300 MHz, $CDCl_3$) 0.87 (6 H, t, *J* 7.0), 1.10 (18 H, s, Bu^t), 1.24–1.44 (12 H, m), 2.04 (4 H, t, *J* 6.8), 2.27 (4 H, m), 3.95 (2 H, m), 4.20 (2 H, d, *J* 6.3) and 7.35–7.80 (20 H, m); *m/z* (FAB) 815 (M^+ + 1) and 559 (M^+ − $OSiPh_2Bu^t$).

(2*R*)-2-(*tert*-Butyldiphenylsilyloxy)dec-4-ynal 38

Lead tetraacetate (2.40 g, 5.38 mmol) was added to a solution of the diol **37** (3.50 g, 4.3 mmol) in dry benzene (30 cm^3) under nitrogen and the mixture stirred for 2 h at room temp. It was then filtered through a short column of silica gel and evaporated under reduced pressure to afford the crude aldehyde. Flash chromatography of this afforded the title compound **38** as a colourless oil (2.58 g, 74%); $[\alpha]_D$ −21.9 (*c* 3.5, $CHCl_3$), {lit.,[20] $[\alpha]_D$ −24.7 (*c* 0.03, $CHCl_3$)}; ν_{max}(film)/cm^{-1} 2100w, 1740 and 1105; δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.1), 1.08 (9 H, s, Bu^t), 1.22–1.46 (6 H, m), 2.10 (2 H, m), 2.48 (2 H, dd, *J* 2.0 and 5.8), 4.08 (1 H, dt, *J* 1.2 and 5.8), 7.34–7.44 (6 H, m), 7.65–7.71 (4 H, m) and 9.63 (1 H, d, *J* 1.2).

(6*R*,2*E*,4*E*)-(*tert*-Butyldiphenylsilyloxy)tetradeca-2,4-dien-8-ynal 39

Method A. To a solution of the aldehyde **38** (1.64 g, 4.04 mmol) in Et_2O (35 cm^3) and THF (15 cm^3) under nitrogen were added successively formylmethylene(triphenyl)arsonium bromide (4.50 g, 10.1 mmol), K_2CO_3 (1.40 g, 10.1 mmol) and water (0.15 cm^3). After being stirred at room temp. for 24 h, the reaction mixture was filtered through a short silica gel column. The filtrate was concentrated and chromatographed directly to yield the title compound **39** (0.94 g, 51%), the formyl-olefination product (0.26 g, 15%) and the triple addition product (0.43 g, 22%); physical and spectroscopic data of the title compound **39**: $[\alpha]_D$ +30.3 (*c* 1.1, $CHCl_3$) (Found: 76.2; H 8.7. $C_{52}H_{70}O_6Si_2$ requires C, 76.60; H, 8.65%); ν_{max}(film)/cm^{-1} 2700, 1690, 1585, 1100 and 970; δ_H(300 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 7.1), 1.09 (9 H, s, Bu^t), 1.27–1.44 (6 H, m, 11,12,13-H), 2.08 (2 H, m, 10-H), 2.38 (2 H, m, 7-H), 4.40 (1 H, m, 6-H), 6.04 (1 H, dd, *J* 7.9 and 15.3, 2-H), 6.30 (2 H, m, $J_{4,5}$ 15.3, 4,5-H), 7.02 (1 H, dd, *J* 10.1 and 15.3, 3-H), 7.38 (6 H, m, PhH), 7.66 (4 H, m, PhH) and 9.54 (1 H, d, *J* 7.9, 1-H); *m/z* 459 (M^+ + 1), 458 (M^+), 401 (M^+ − Bu^t), 349, 199 (100%) and 135. Physical and spectroscopic data of the formyl-olefination product (2*E*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)dodec-2-en-6-ynal: $[\alpha]_D$ −26.4 (*c* 3.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 2700, 1695, 1640, 1585 and 970; δ_H(300 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 7.1), 1.09 (9 H, s, Bu^t), 1.21–1.45 (6 H, m), 2.07 (2 H, m, 8-H), 2.37 (2 H, m, 5-H), 4.52 (1 H, m, 4-H), 6.31 (1 H, dd, *J* 7.8 and 15.5, 2-H), 6.85 (1 H, dd, *J* 4.7 and 15.5, 3-H), 7.34–7.47 (6 H, m, PhH), 7.60–7.70 (4 H, m, PhH) and 9.51 (1 H, d, *J* 7.8, 1-H); *m/z* 433 (M^+ + 1), 443 (M^+), 376 (M^+ − Bu^t + 1), 324, 199 and 135 (100%). Physical and spectroscopic data of the triple addition product (2*E*,4*E*,6*E*,8*R*)-8-(*tert*-butyldiphenylsilyloxy)hexadeca-2,4,6-trien-10-ynal: $[\alpha]_D$ −4.8 (*c* 3.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3050, 2700, 1700, 1640, 1590, 1100 and 990; δ_H(300 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 7.1), 1.06 (9 H, s, Bu^t), 1.26–1.44 (6 H, m, 13,14,15-H), 2.08 (2 H, m, 12-H), 2.35 (2 H, m, 9-H), 4.36 (1 H, m, 8-H), 6.09 (3 H, m, $J_{2,3}$ 15.2, $J_{6,7}$ 15.4, 2,6,7-H), 6.45 (1 H, dd, *J* 11.1 and 14.8, 4-H), 6.59 (1 H, dd, *J* 10.4 and 14.8, 5-H), 7.09 (1 H, dd, *J* 11.1 and 15.2, 3-H), 7.38 (6 H, m, PhH), 7.68 (4 H, m, PhH) and 9.56 (1 H, d, *J* 7.9, 1-H); *m/z* 484 (M^+), 427 (M^+ − Bu^t), 375, 199 (100%), 135.

Method B. To a solution of the aldehyde **38** (3.59 g, 8.83 mmol) in Et_2O (108 cm^3) and THF (12 cm^3) under nitrogen were added, successively, 3-formylallyl(triphenyl)arsonium bromide (5.99 g, 13.1 mmol), K_2CO_3 (1.81 g, 13.1 mmol) and water (0.185 cm^3). After being stirred at room temperature for 24 h, the reaction mixture was filtered through a short silica gel column and the filtrate was concentrated and chromatographed directly to afford the title compound **39** as a (2*E*,4*E*)- and (2*E*,4*Z*)-isomeric mixture (2.61 g, 64%; 85% based on recovered starting material) and recovered starting aldehyde **38** (0.87 g). The ratio between the (2*E*,4*E*)- and (2*E*,4*Z*)-isomer was determined as *ca.* 9:1. Isomerization of the mixture was induced with I_2 in CH_2Cl_2 and in the presence of sunlight, to give the pure (2*E*,4*E*)-product (2.52 g) after flash chromatography.

(2*E*,4*E*,6*R*)-(*tert*-Butyldiphenylsilyloxy)tetradeca-2,4-dien-8-yn-1-ol 40

Sodium borohydride (73 mg, 1.92 mmol) was added to a cold (0 °C) mixture of the aldehyde **39** (0.88 g, 1.92 mmol) and $CeCl_3 \cdot 7H_2O$ (0.71 g, 1.92 mmol) in Pr^{i}OH (10 cm^3) and the resulting reaction mixture was stirred at 0 °C for 6 h. It was then neutralized with 10% HOAc and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue gave the alcohol **40** as a colourless oil (0.787 g, 89%); $[\alpha]_D$ +22.1 (*c* 0.24, $CHCl_3$); ν_{max}(film)/cm^{-1} 3300, 1590, 1450, 1110 and 940; δ_H(300 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.8), 1.07 (9 H, s, Bu^t), 1.27–1.52 (6 H, m), 2.08 (2 H, m), 2.33 (2 H, m), 4.12 (2 H, d, *J* 5.9), 4.29 (1 H, m), 5.68–5.80 (2 H, m), 5.97–6.21 (2 H, 2dd, $J_{3,4}$ 10.4, $J_{2,3}$ and $J_{4,5}$ 15.0), 7.34–7.42 (6 H, m, PhH) and 7.63–7.71 (4 H, m, PhH); *m/z* 460 (M^+), 403 (M^+ − Bu^t), 349, 199 (100%), 197, 135 and 77.

(2*E*,4*E*,6*R*)-6-(*tert*-Butyldiphenylsilyloxy)-tetradeca-2,4-dien-8-ynyl(triphenyl)phosphonium bromide 42

The alcohol **40** (0.75 g, 1.63 mmol) was added to a solution of CBr_4 (1.47 g, 4.41 mmol) and Ph_3P (1.47 g, 5.59 mmol) in dry CH_2Cl_2 (5 cm^3) at 0 °C and the mixture was stirred for 5 min. It was then evaporated under reduced pressure at room temperature and the resulting solid residue was repeatedly washed with dry diethyl ether. The combined filtrates were evaporated to yield the labile bromide **41** (0.728 g) as an oil, which was used without further purification.

Triphenylphosphine (0.692 g, 2.66 mmol) was added to a solution of the crude bromide **41** in MeCN (12 cm^3) and the mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure. After addition of ether (3 × 10 cm^3) to the residue the mixture was centrifuged and the supernatant was discarded. The resulting phosphonium salt was washed twice with ether and dried *in vacuo* to afford the title salt **42** as a pale yellow syrup (0.90 g, 70%); δ_H(300 MHz, $CDCl_3$) 0.85 (3 H, t, *J* 7.1), 1.04 (9 H, s), 1.23–1.39 (6 H, m), 2.02 (2 H, m), 2.29 (2 H, m), 4.56 (1 H, m), 4.89 (2 H, m), 5.30 (1 H, m), 5.69–5.77 (2 H, m), 6.22 (1 H, m) and 7.25–7.87 (25 H, 3m, PhH).

(5*S*,12*R*,6*Z*,8*E*,10*E*)-Methyl 5-(benzoyloxy)-12-(*tert*-butyldiphenylsilyloxy)icosa-6,8,10-trien-14-ynoate 43

To a stirred solution of the phosphorane generated from the phosphonium salt **42** (0.90 g, 1.15 mmol) with BuLi (2.5 mol dm^{-3} in hexane; 0.46 cm^3, 1.15 mmol) in dry THF (10 cm^3) containing HMPA (1.5 cm^3) at −100 °C was added a solution of the C-1–C-6 segment[27] (457 mg, 1.73 mmol) in THF (5 cm^3). The resulting mixture was stirred at −100 °C for 1 h, allowed to warm to room temperature and then stirred for 0.5 h. After this the reaction mixture was poured into a mixture of 25% aqueous

ammonium acetate (150 cm^3), ether (150 cm^3) and triethylamine (9 cm^3). The aqueous phase was separated and extracted with ether, and the combined organic layer and extracts were then washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was chromatographed on a silica gel column (washed with 5% triethylamine in light petroleum) with ethyl acetate–light petroleum (1:80) as the eluent to give the desired title compound **43** (0.538 g, 68%) and the corresponding (6*E*)-isomer (0.128 g, 16%). For compound **43**: $[\alpha]_D$ +235.7 (*c* 0.03, Me_2CO); ν_{max}(film)/cm^{-1} 1740, 1720, 1430, 1270, 1110, 940 and 710; δ_H(300 MHz, C_6D_6) 0.86 (3 H, t, *J* 7.1), 1.10–1.40 (15 H, m), 1.58 (4 H, m), 2.06 (4 H, m), 2.50 (2 H, m), 3.31 (3 H, s), 4.45 (1 H, m), 5.34 (1 H, dd, *J* 9.8 and 10.2), 5.86 (1 H, dd, *J* 7.3 and 14.2), 5.97 (1 H, m), 6.01 (1 H, m), 6.06 (1 H, m), 6.10 (1 H, m), 6.69 (1 H, dd, *J* 12.3 and 12.7), 7.28, 7.80 (10 H, m, SiPh) and 7.05, 8.16 (5 H, 2m, COPh); *m/z* (FAB) 671 ($M^+ + 1$), 460, 135 (100), 104. For the (6*E*)-isomer: ν_{max}(film)/cm^{-1} 1740, 1720, 1430, 1270, 1110, 940 and 710; δ_H(300 MHz, C_6D_6) 0.86 (3 H, t, *J* 7.1), 1.10–1.40 (15 H, m), 1.59 (4 H, m), 2.07 (4 H, m), 2.48 (2 H, m), 3.33 (3 H, s), 4.48 (1 H, m), 5.52 (1 H, dd, *J* 7.1 and 14.1), 5.63 (1 H, m), 5.85 (1 H, dd, *J* 6.5 and 14.9), 5.97–6.00 (2 H, m), 6.14 (1 H, m), 6.29 (1 H, m), 7.22, 7.81 (10 H, m, SiPh) and 7.08, 8.18 (5 H, 2m, COPh); *m/z* (FAB) 691 ($M^+ + 1$), 460, 197, 134 and 105 (100%).

(5*S*,12*R*,6*Z*,8*E*,10*E*,14*Z*)-Methyl 5-benzoyloxy-12-(*tert*-butyldiphenylsilyloxy)icosa-6,8,10,14-tetraenoate 44

A suspension of compound **43** (40 mg, 0.058 mmol), Lindlar catalyst (Aldrich; 58 mg) and quinoline (0.1 cm^3) in ethyl acetate (10 cm^3) was magnetically stirred under a hydrogen atmosphere. The reaction was constantly monitored and after the starting material had been consumed (*ca.* 2 h) the suspension was filtered and then evaporated. The residue was flash chromatographed (the silica gel column was pre-treated as mentioned above) to provide the title compound **44** (31.4 mg, 78%); HPLC (using a silica gel column; mobile phase, ethyl acetate–light petroleum 1:25 with UV detection at 270 nm) of the sample showed it to be >95% purity, the retention time of compound **44** under these conditions was 14 min; ν_{max} (film)/cm^{-1} 1740, 1719, 1426, 1270, 1111, 997 and 709; δ_H(600 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 7.2), 1.07–1.29 (15 H, m), 1.74 (4 H, m), 1.84 (2 H, m), 2.16 (2 H, m), 2.37 (2 H, m), 3.65 (3 H, s), 4.21 (1 H, m), 5.27 (1 H, m), 5.37 (1 H, m), 5.42 (1 H, dd, *J* 9.8 and 10.2), 5.70 (1 H, dd, *J* 6.8 and 15.2), 5.91 (1 H, dd, *J* 10.2 and 11.6), 5.99 (1 H, dd, *J* 10.8 and 15.2), 6.15 (2 H, m), 6.49 (1 H, dd, *J* 11.6 and 14.4), 7.36–77.43 (9 H, m), 7.66 (2 H, m) and 8.05 (1 H, m).

(5*S*,12*R*,6*Z*,8*E*,10*E*,14*Z*)-Methyl 5,12-dihydroxyicosa-6,8,10,-14-tetraenoate (LTB_4 methyl ester) 45

Bu_4NF (1 mol dm^{-3} solution in THF; 0.127 cm^3, 0.127 mmol) was added to a magnetically stirred solution of compound **44** (18 mg, 0.026 mmol) in dry THF (3 cm^3) at 0 °C under nitrogen. The reaction mixture was stirred overnight at room temperature and then treated with brine (3 cm^3) to quench the reaction. The mixture was extracted with ether and the extract dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was dissolved in MeOH (4 cm^3) and treated with solid K_2CO_3 (47 mg, 0.33 mmol). After being stirred overnight at room temperature the reaction mixture was poured into a vigorously stirred mixture of ether (50 cm^3) and aqueous buffer (pH 6, 50 cm^3). The organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed to provide LTB_4 methyl ester (6.3 mg, 69%); $[\alpha]_D^{20}$ +4.9 (*c* 0.15, CCl_4) {lit.,[28] $[\alpha]_D^{20}$ +4.6 (*c* 0.39, CCl_4)}; ν_{max}(film)/cm^{-1} 3446, 1736, 1595, 1462, 1376, 1260, 1162 and 1070; δ_H($CDCl_3$, 600 MHz) 6.48 (1 H, dd, $J_{8,9}$ 14.5, $J_{8,7}$ 11.0, 8-H), 6.31 (1 H, dd, $J_{10,9}$ 10.9, $J_{10,11}$ 14.9, 10-H), 6.22 (1 H, dd, $J_{9,10}$ 10.9, $J_{9,8}$ 14.5, 9-H), 6.08 (1 H, t, $J_{7,8} = J_{7,6}$ 6.2, 7-H), 5.76 (1 H, ddd, $J_{11,12}$ 6.4, $J_{11,10}$ 14.9, 11-H), 5.56 (1 H, m, 15-H), 5.43 (1 H, dd, $J_{6,5}$ 9.7, $J_{6,7}$ 6.2, 6-H), 5.37 (1 H, m, 14-H), 4.59 (1 H, dt, $J_{5,6}$ 9.7, $J_{5,4}$ 6.6, 5-H), 4.12 (1 H, dt, $J_{12,13} = J_{12,11}$ 6.4, 12-H), 3.67 (3 H, s, OMe), 2.33 (4 H, m), 2.03 (2 H, m), 1.72–1.60 (5 H, m), 1.36–1.21 (7 H, m) and 0.88 (3 H, t, *J* 6.9).

Acknowledgements

We are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China and State Committee of Science and Technology of China for financial support.

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Paper 5/03780H
Received 12*th June* 1995
Accepted 6*th October* 1995