The Synthesis of Aromatic Leukotriene Analogues; Regioselective Trapping of 2,4'-Dilithiophenylethyne

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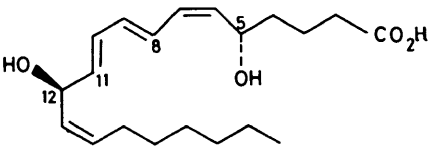
The 8,11-bridged aromatic leukotriene B_4 analogues (**3**), (**4**), and (**5**), in which conformational freedom is restricted, have been prepared by extremely short synthetic routes. Conditions are described which allow the regioselective electrophililic trapping of 2,4'-dilithiophenylethyne at the 4'-site. The application of this methodology to the preparation of LTB_4 analogues (**3**) and (**4**) is discussed.

There is a great deal of current interest in hydroxylated icosatetraenoic acids produced from arachidonic acid by lipoxygenase metabolic pathways.[1] Leukotriene B_4 (LTB_4) (**1**), produced by the 5-lipoxygenase pathway, has attracted particular attention due to its potent chemotactic properties and potential role in inflammation and allergy.[2] As part of a programme to prepare synthetic LTB_4 analogues for structure-activity studies,[3] we became interested in bridged leukotrienes[4] in which conformational freedom is restricted. Prime targets, in view of their accessibility, were 8,11-bridged LTB_4 analogues (**2**) in which the 8*E*,10*E*-diene unit is constrained by incorporation into an aromatic ring. In this paper we describe an extremely short synthetic route to the 8,11-etheno bridged compound (**2a**) exemplified by the synthesis of aromatic LTB_4 analogues (**3**) and (**4**). The preparation of the simple pyridine-based LTB_4 analogue (**5**) is also discussed.†

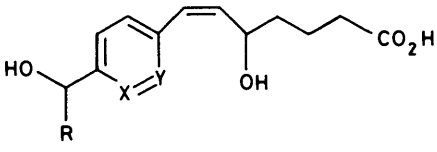
The strategy adopted for the synthesis of compound (**2a**) is shown in Scheme 1. Regioselective electrophilic trapping of 2,4'-dilithiophenylethyne (**7**), first by RCHO at the 4'-position, and then by methyl 5-oxopentanoate (**8**) at the 2-position should produce the acetylenic diol (**6**) in a single reaction. Acetylene (**6**) is readily convertible into target compound (**2a**) by Lindlar reduction and saponification. Although there is no control over the stereochemistry at C-5 and C-12 (leukotriene numbering), this procedure is extremely short and convergent and, by variation of the two aldehydes, applicable to the synthesis of a wide range of LTB_4 analogues.

A literature search revealed that 2,4'-dilithiophenylethyne (**7**) had been prepared by the treatment of 4-bromophenylethyne (**9**) with butyl-lithium and employed for the synthesis of the 4'-carboxylic acid (**11**) as shown in Scheme 2.[5] Rather than utilise regioselective carboxylation, however, the dilithio reagent (**7**) was treated with an excess of CO_2 to give the dicarboxylic acid (**10**) which was then partially decarboxylated to produce the monoacid (**11**).[5] We therefore began our investigation by examining the regioselective 4'-trapping of the dilithio reagent (**7**).[6] The results of this study are summarised in Scheme 2.

We first repeated the literature procedure for the lithiation of 4-bromophenylethyne (**9**) in which ether–THF (*ca.* 1:1) was employed as solvent. This gave the dilithio reagent (**7**) as an insoluble, viscous gum and all attempts to carry out regioselective trapping reactions using this material were unsuccessful. We found that a homogeneous solution was obtained when hexamethylphosphoramide (HMPA) was added to a solution of reagent (**7**) in THF but subsequent addition of nonanal as trapping agent gave the 4-butylphenyl adduct (**12**) as the sole product in 80% yield. Under these conditions it would appear

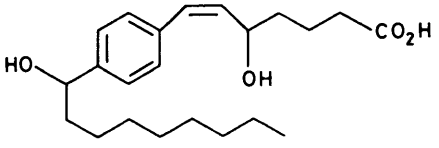


(**1**) LTB_4

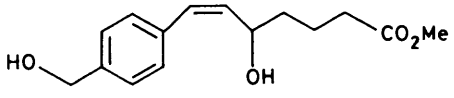


(**2**)

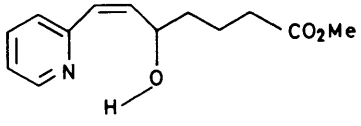
a X = Y = CH



(**3**)



(**4**)

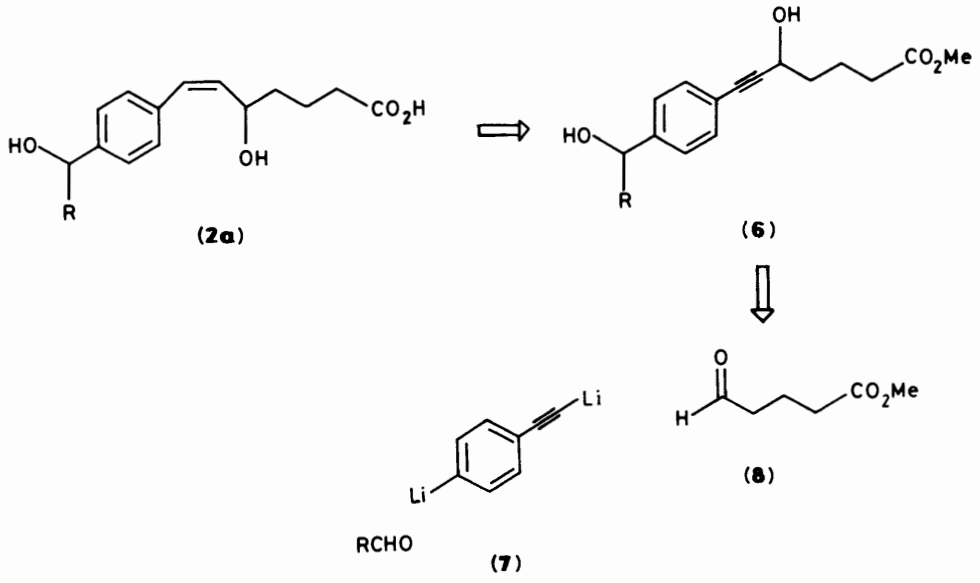


(**5**)

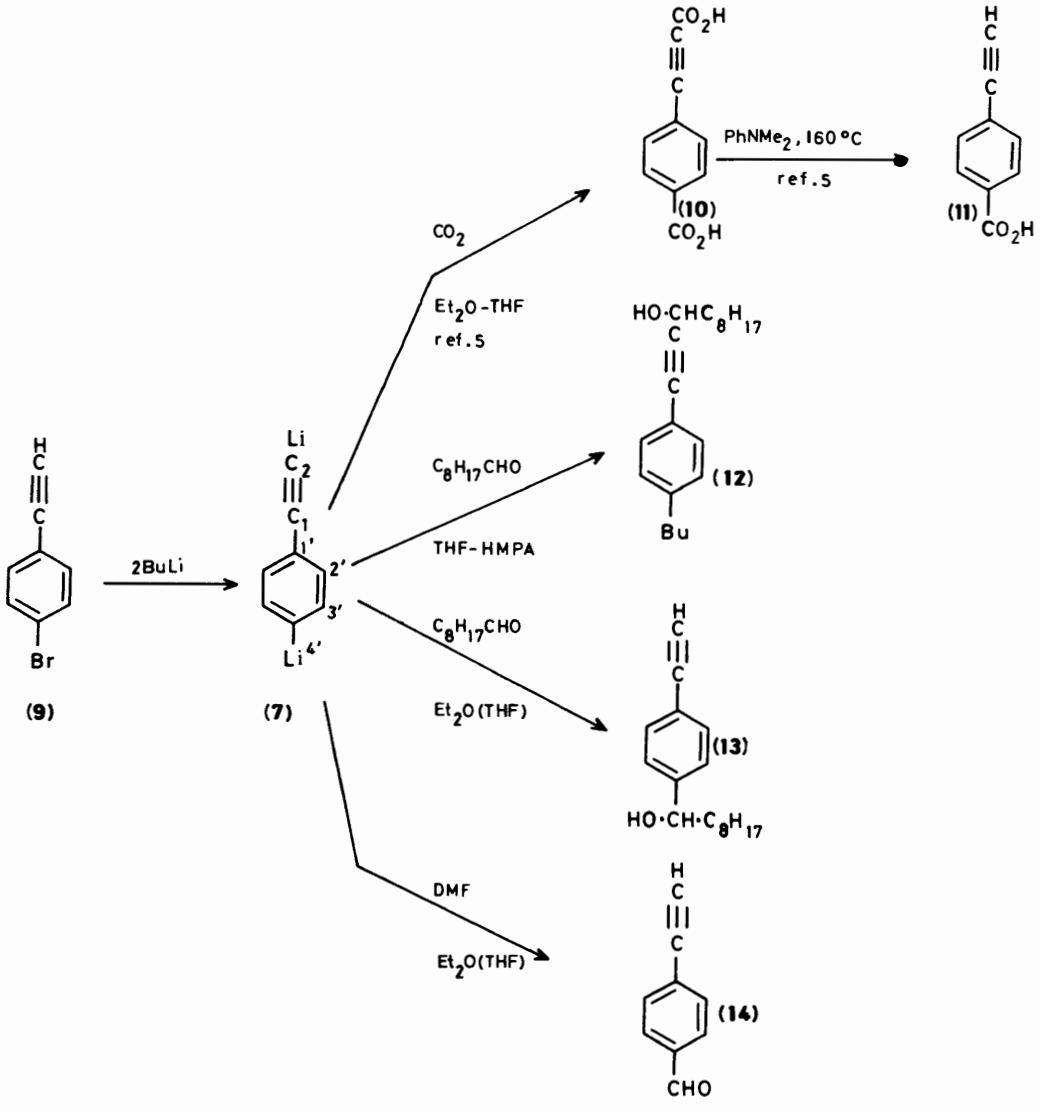
that the bromobutane generated during transmetallation acts as the initial trapping agent, nonanal then reacts at the acetylide site. Though unexpected, this result demonstrates that regioselective reaction at the 4'-position is possible.

Conditions which allow the controlled regioselective 4'-trapping of the dilithio reagent (**7**) were eventually devised. 4-Bromophenylethyne (**9**) in ether was treated with 2 molar equivalents of butyl-lithium in hexane at −70 °C. The reaction was then warmed to −40 °C and THF added dropwise until lithium/bromine exchange occurred. Under these

† All synthetic compounds are racemic.



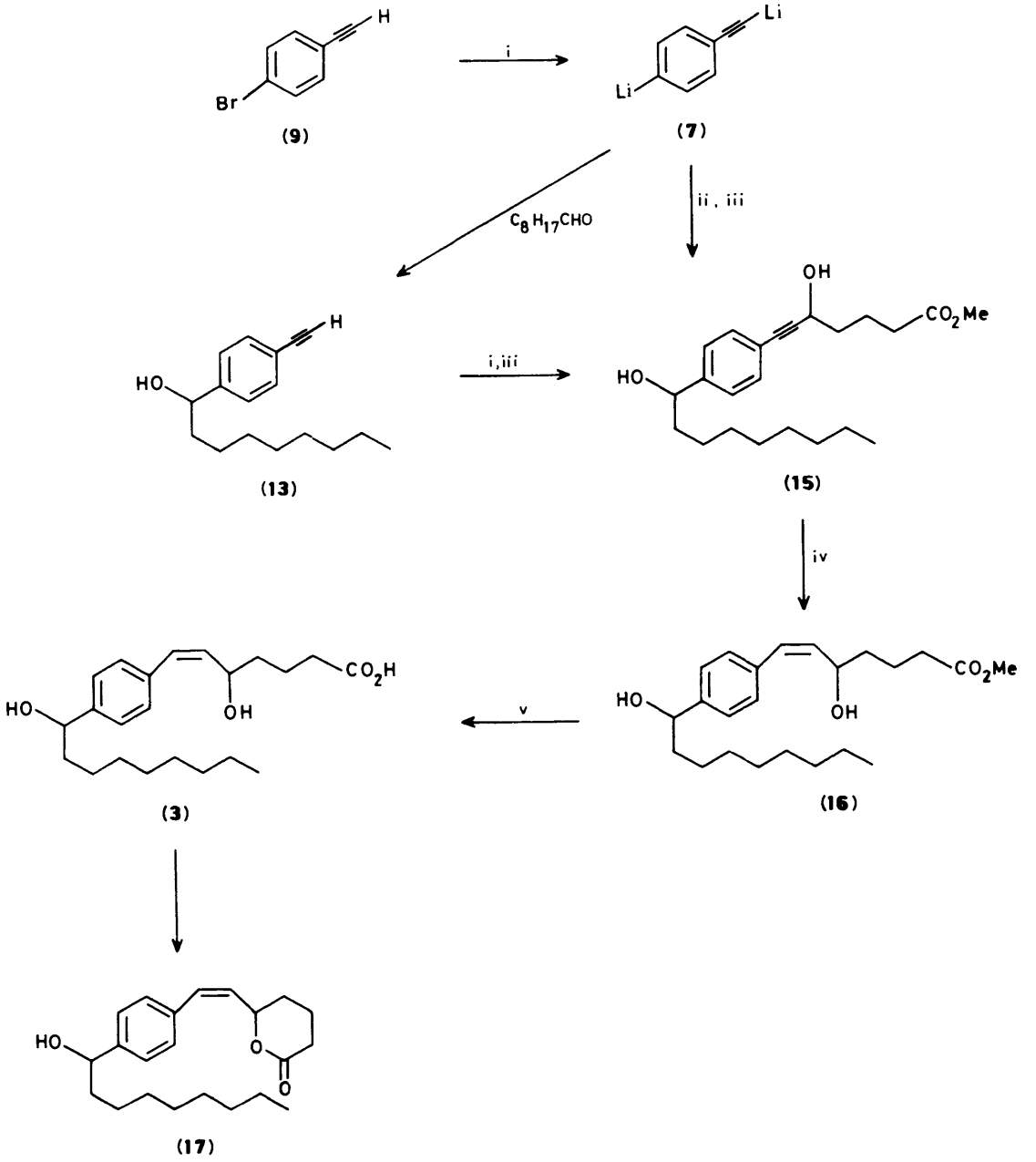
Scheme 1.



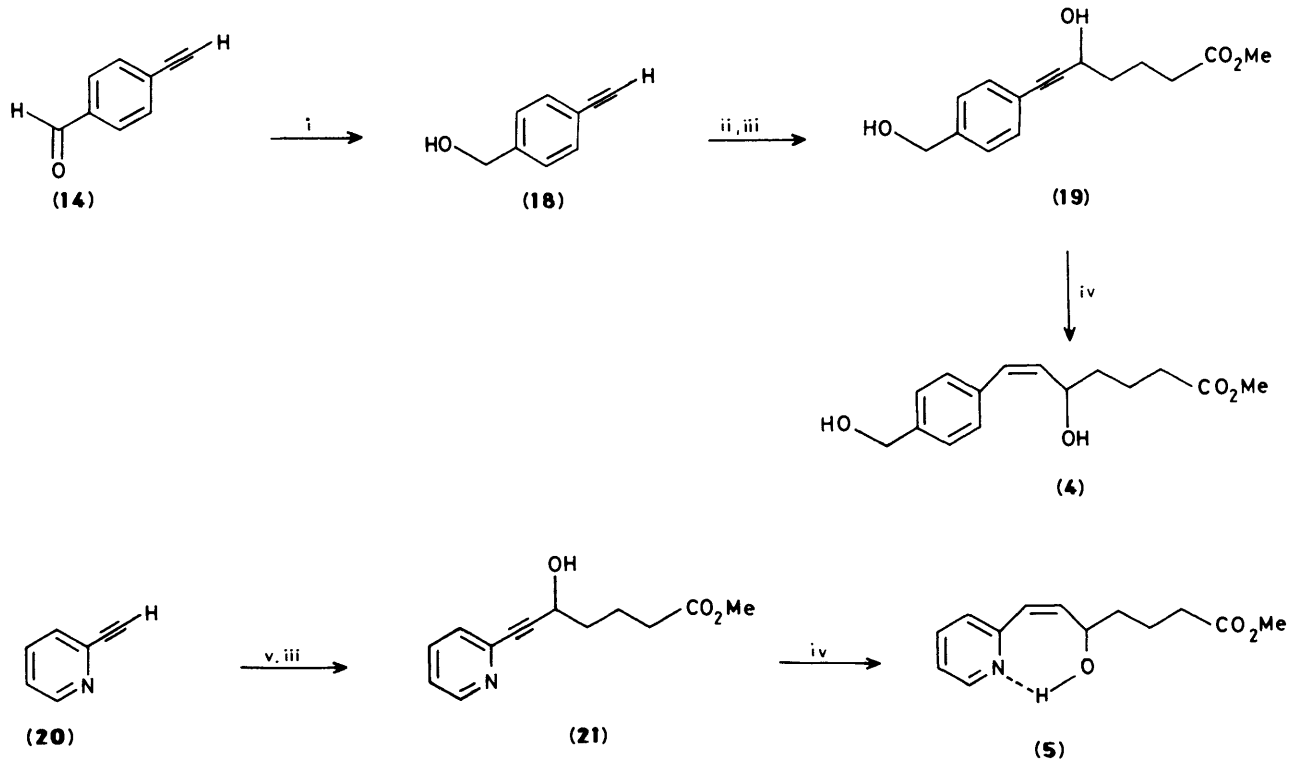
Scheme 2.

conditions the dilithio reagent (**7**) is formed as a bright-pink suspension. The addition of nonanal to this reagent gave regioselective 4′-trapping, the alcohol (**13**) being obtained in 82% yield after protonation. A small amount (<4%) of the regioisomeric product resulting from acetylide addition to nonanal was also observed. Dimethylformamide (DMF) was also used to trap the dilithio reagent (**7**), the 4′-aldehyde (**14**) being obtained in 93% yield after hydrolysis.

Having established conditions for the regioselective trapping of 2,4′-dilithiophenylethyne (**7**) our attention then turned to the synthesis of LTB_4 analogue (**3**) using this methodology (Scheme 3). The dilithio reagent (**7**) could be converted directly into the diol (**15**) by sequential trapping with nonanal followed by methyl 5-oxopentanoate (**8**). Using this 'one-pot' procedure the diol (**15**) was obtained in 41% overall yield from 4-bromophenylethyne (**9**). An improved yield was obtained when the transformation was carried out in two separate stages (Scheme 3). The alcohol (**13**) was therefore converted into the corresponding dianion which was treated with methyl 5-oxopentanoate (**8**). This procedure gave the diol (**15**) in 68% overall yield from the bromoalkyne (**9**). Lindlar reduction of the acetylene (**15**) proceeded smoothly to give the ester (**16**), hydrolysis then leading to the target aromatic LTB_4 analogue (**3**) in 85% overall yield. The 8,11-etheno bridged LTB_4 analogue (**3**) is therefore available in 3 or 4 steps from the readily available[7] 4-bromophenylethyne in up to 58% overall yield using this dianion-based route. The diastereoisomers of LTB_4 analogues (**15**), (**16**), and (**3**) were not distinguishable by ^1H n.m.r. (360 MHz) or ^{13}C n.m.r. (90.56 MHz) spectroscopy or by chromatography (t.l.c. and normal or reversed phase h.p.l.c.) in a range of solvents. However, when the hydroxy acid (**3**) was converted into lactone (**17**), h.p.l.c. revealed the presence of 2 diastereoisomers in approximately equal amounts.



Scheme 3. *Reagents:* i, 2BuLi; ii, $C_8H_{17}CHO$; iii, $MeO_2C(CH_2)_3CHO$ (**8**); iv, H_2, Lindlar; v, K_2CO_3, aq. MeOH; vi, Heat



Scheme 4. *Reagents:* i, $NaBH_4$; ii, 2BuLi; iii, $MeO_2C(CH_2)_3CHO$ (**8**); iv, H_2, Lindlar; v, BuLi

A range of aromatic LTB_4 analogues are available using the synthetic route shown in Scheme 3 by variation of the aldehydes used to trap the dilithio reagent (**7**). Alternatively, LTB_4 analogues can be prepared from 4-ethynylbenzaldehyde (**14**) by aldehyde addition followed by acetylide alkylation and Lindlar reduction. This approach is illustrated in Scheme 4. Aldehyde (**14**) was reduced to alcohol (**18**), dianion formation followed by treatment with methyl 5-oxopentanoate (**8**) then gave the diol (**19**). Lindlar reduction produced the aromatic LTB_4 analogue (**4**), lacking the hydrophobic C-13 to C-20 fragment, in 50% overall yield. Problems were encountered with the Lindlar reduction, over-reduced and isomeric contaminants being observed. These by-products were minimised (< 10%) by using hexane containing the minimum amount of THF needed to solubilise the alkyne (**19**) as solvent, employing a 20% excess of catalyst poison, carrying out the hydrogenation at 0 °C and stopping the reaction before all of the starting material had been consumed.

Finally, the pyridine LTB_4 analogue (**5**) lacking the whole C-12 to C-20 chain, was prepared from 2-ethynylpyridine (**20**) as shown in Scheme 4. Treatment of acetylene (**20**) with butyl-lithium, to generate the corresponding acetylide, followed by addition to methyl 5-oxopentanoate (**8**) gave the hydroxyalkyne (**21**) in 9% yield. The alkyne (**21**) rapidly polymerises when set aside and this presumably accounts for the low yield obtained for its preparation. Lindlar reduction of alkyne (**21**) occurred in high yield (86%) and, in contrast to the reduction of the analogous phenyl compound (**19**), no over-reduced or isomerised products were detectable by g.c.m.s. I.r. dilution studies and ^1H n.m.r. spectroscopy (hydroxy proton at δ 7.32) indicate that intramolecular hydrogen bonding occurs in the alcohol (**5**). LTB_4 analogues (**3**), (**5**), (**15**), (**16**), and (**17**) have been subjected to preliminary screening and all show some biological activity, particularly as inhibitors of 5-lipoxygenase enzymes. Other synthetic applications of the dilithio reagent (**7**) are currently under investigation.

Experimental

All organometallic and low temperature reactions were conducted in flame-dried glassware under an atmosphere of dry, oxygen-free nitrogen. Butyl-lithium was purchased from Aldrich as a solution in hexane and was standardized at regular intervals and transferred using gas-tight syringes. Light petroleum is the fraction with b.p. 40—60 °C, and ether refers to diethyl ether. Ether and THF were distilled from sodium benzophenone ketyl, hexane and triethylamine from lithium aluminium hydride and HMPA from calcium hydride. 4-Bromophenylethyne (**9**),[7] 2-ethynylpyridine (**20**),[8] Lindlar catalyst,[9] and methyl 5-oxopentanoate (**8**)[10] were prepared according to literature procedures. A standard work-up consisted of the addition of saturated aqueous ammonium chloride and extraction of the aqueous layer with the specified solvent. The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed on a rotary evaporator under reduced pressure.

Chromatography refers to column chromatography using silica gel 60 (Merck 7734). ^1H N.m.r. spectra were recorded on a Bruker WP 80 or Bruker AM 360 spectrometer and ^{13}C spectra on a Bruker AM 360 spectrometer. All n.m.r. spectra were recorded using $CDCl_3$ as solvent. I.r. spectra were obtained on a Perkin-Elmer 297 spectrophotometer, u.v. spectra on a Pye-Unicam SP800A spectrophotometer, and mass spectra on Kratos MS25 (low resolution) and Kratos MS30 or VG ZAB-IF (high resolution) instruments.

1-(4-*Butylphenyl*)*undec*-1-*yn*-3-*ol* (**12**).—To a stirred solution of 4-bromophenylethyne (**9**)[7] (0.553 g, 3.06 mmol) in THF (30 ml) at −40 °C, was added butyl-lithium (1.65 M; 3.8 ml, 6.3 mmol). A thick viscous precipitate of the dianion (**7**) developed, preventing stirring. HMPA (2 ml) was added and the dianion slowly dissolved to give a deep purple solution. After cooling the solution to −70 °C, nonanal (0.53 ml, 3.09 mmol) was added dropwise. The mixture was stirred for 30 min and then

subjected to a standard ether work-up. Chromatography on silica (CH_2Cl_2–light petroleum, 10:1) gave the *title alcohol* (**12**) as an oil (0.735 g) (80%); $\nu_{max.}$(film) 3 350 and 2 225 cm^{-1}; δ 7.26 (4 H, m) 4.63 (1 H, m), 2.63 (2 H, t, *J* 7 Hz), 2.10—1.00 (19 H, m), and 0.90 (6 H, m). [Found: *m/z* (Me_3Si–derivative) 372.2827 (M^+). $C_{24}H_{40}OSi$; requires M^+, 372.2848].

1-(4-*Ethynylphenyl*)*nonan*-1-*ol* (**13**).—To a stirred solution of 4-bromophenylethyne (**9**)[7] (4.00 g, 22.1 mmol) in ether (50 ml) at −70 °C, was added butyl-lithium (1.6 M; 27.6 ml, 44.2 mmol). The solution was stirred at −70 °C to −40 °C for 10 min after which THF (7 ml) was added dropwise to give a bright-pink suspension of the dianion (**7**). After being stirred for 20 min at −40 °C, the mixture was cooled to −70 °C and a solution of nonanal (3.8 ml, 22.1 mmol) in ether (20 ml) was added dropwise. The mixture was stirred for 30 min at −70 °C after which the temperature was allowed to rise to 0 °C when it was subjected to a standard ether work-up. Chromatography on silica (CH_2Cl_2–light petroleum, 4:1) gave the *title alcohol* (**13**) as an oil (4.43 g, 82%); $\nu_{max.}$(film) 3 350, 3 300, and 2 110 cm^{-1}; δ 7.45 (4 H, m), 4.73 (1 H, t, *J* 6.5 Hz), 3.10 (1 H, s), 2.00 (1 H, br s, exchangeable), 1.75 (2 H, m), 1.30 (12 H, m), and 0.90 (3 H, t, *J* 6 Hz) [Found: *m/z* (Me_3Si–derivative) 316.1983 (M^+). $C_{20}H_{32}OSi$ requires M^+, 316.2222].

4-*Ethynylbenzaldehyde* (**14**).—To a stirred solution of 4-bromophenylethyne (**9**)[7] (0.99 g, 5.46 mmol) in ether (35 ml) at 70 °C, was added butyl-lithium (1.6 M; 6.8 ml, 10.9 mmol). The temperature of the mixture was then allowed to warm to −40 °C when THF (2 ml) was added dropwise to give a bright-pink suspension of the dianion (**7**). The mixture was stirred at this temperature for 5 min and then re-cooled to −70 °C and treated with dimethylformamide (0.42 ml, 5.46 mmol) by dropwise addition. After being stirred at −70 °C—−30 °C for 30 min, the reaction mixture was subjected to a standard ether work-up. Filtration through a plug of silica (CH_2Cl_2–light petroleum, 2:1) gave the *aldehyde* (**14**) (0.66 g, 93%) as a colourless solid, m.p. 78 °C; $\nu_{max.}$(KBr) 3 220, 2 100, 1 685, and 1 605 cm^{-1}; δ 10.15 (1 H, s), 7.90 (4 H, m), and 3.40 (1 H, s); *m/z* 130 (M^+) (Found: C, 82.9; H, 4.6. C_9H_6O requires C, 83.06; H, 4.65%). The yield quoted in this reaction is the highest obtained from several experiments. In other runs yields as low as 60% were recorded.

Methyl 5-*Hydroxy*-7-[4-(1-*hydroxynonyl*)*phenylhept*-6-*ynoate* (**15**).—(*a*) *From* 4-*bromophenylethyne* (**9**).—To a stirred solution of 4-bromophenylethyne (**9**)[7] (0.4 g, 2.21 mmol) in ether (25 ml) at −70 °C, was added butyl-lithium (1.5 M; 3 ml, 4.5 mmol). The temperature was allowed to rise to −40 °C and THF (3 ml) added dropwise to give a bright-pink suspension of dianion (**7**). After being stirred at −40 °C for 5 min, the mixture was re-cooled to −70 °C and a solution of nonanal (0.36 ml, 2.1 mmol) in ether (2 ml) was added dropwise. The mixture was stirred at −70 °C—−50 °C for 30 min, re-cooled to −70 °C and then treated with methyl 5-oxopentanoate (**8**)[10] (0.29 g, 2.23 mmol). After being stirred at −70 °C to 0 °C for 30 min, the reaction mixture was subjected to a standard ether work-up. Chromatography (twice) on silica (CH_2Cl_2–EtOAc, 4:1) gave the *diol* (**15**) (0.339 g, 41%) as an oil, R_F 0.67 (CH_2Cl_2–EtOAc, 1:2); $\nu_{max.}$(film) 3 400 and 1 740 cm^{-1}; δ 7.38 (2 H, d, *J* 6 Hz), 7.27 (2 H, d, *J* 6 Hz), 4.66 (1 H, m), 4.61 (1 H, td, *J* 7 Hz, 5 Hz), 3.69 (3 H, s) 2.41 (2 H, t, *J* 7 Hz), 2.30 (1 H, d, *J* 6 Hz, exchangeable), 2.05 (1 H, d, *J* 5 Hz, exchangeable), 1.85 (4 H, m), 1.73 (2 H, m), 1.25 (12 H, m), and 0.87 (3 H, t, *J* 6 Hz) [Found: *m/z* (di-Me_3Si–derivative) 518.3232 (M^+). $C_{29}H_{50}O_4Si_2$ requires M^+, 518.3247].

(*b*) *From* 4-(1-*Hydroxynonyl*)*phenylethyne* (**13**). To a stirred solution of the acetylenic alcohol (**13**) (1.176 g, 4.82 mmol) in THF (30 ml) at −70 °C, was added butyl-lithium (1.6 M; 6 ml, 9.6 mmol). The solution was stirred at −70 °C—−50 °C for 20 min, cooled to −70 °C and then treated with methyl 5-oxopentanoate (**8**)[10] (0.75 g, 5.77 mmol). After 1 h at −70 °C the reaction mixture was subjected to a standard ether work-up. Chromatography on silica (CH_2Cl_2–ether, 7:1) gave the diol (**15**) (1.496 g, 83%) identical to the sample obtained in (*a*).

(Z)-*Methyl* 5-*Hydroxy*-7-[4-(1-*hydroxynonyl*)*phenyl*]*hept*-6-*enoate* (**16**).—A solution of the acetylene diol (**15**) (1.26 g, 3.37 mmol) in hexane (7 ml) and THF (5 ml) was hydrogenated at atmospheric pressure over Lindlar catalyst (38 mg) poisoned with Et_3N (0.475 ml). Hydrogen uptake ceased at the theoretical amount (75 ml) after which the catalyst was filtered off (Whatman GFA) and the product concentrated under reduced pressure to yield the cis-*alkene* (**16**) (1.22 g 96%) as an oil, R_F 0.58 (CH_2Cl_2–EtOAc, 1:2); $\nu_{max.}$(film) 3 400, 3 015, 1 740, 1 640, and 860 cm^{-1}; $\lambda_{max.}$(EtOH) 246 nm (ε 14 970); δ_H 7.31 (2 H, d, *J* 8 Hz), 7.24 (2 H, d, *J* 8 Hz), 6.53 (1 H, d, *J* 11.5 Hz), 5.65 (1 H, dd, *J* 11.5 and 9 Hz), 4.65 (1 H, t, *J* 6.5 Hz), 4.55 (1 H, dt, *J* 9 and 6 Hz), 3.65 (3 H, s), 2.31 (2 H, t, *J* 7.5 Hz), 2.20 (1 H, br s, exchangeable), 2.05 (1 H, br s, exchangeable), 1.70 (6 H, m), 1.25 (12 H, m), and 0.87 (3 H, t, *J* 7 Hz); δ_c 174.26, 144.35, 135.90, 134.44, 131.12, 129.03, 126.15, 74.58, 67.63, 51.80, 39.34, 37.11, 34.03, 32.11, 29.81, 29.77, 29.52, 26.09, 22.91, 21.06, and 14.35 (Found: C, 73.4; H, 9.5. $C_{23}H_{36}O_4$ requires C, 73.36; H, 9.64%).

(Z)-5-*Hydroxy*-7-[4-(1-*hydroxynonyl*)*phenyl*]*hept*-6-*enoic Acid* (**3**).—A solution of the ester (**16**) (0.05 g, 1.38 mmol) was dissolved in a solution of K_2CO_3 in methanol–water (4:1) (1.5M; 20 ml) and stirred at room temperature for 4 h. The methanol was removed under reduced pressure, the product diluted with water (10 ml) and the aqueous solution washed with ether (2 × 10 ml). After acidification to pH 4 with dilute hydrochloric acid, the product was extracted with ether (4 × 25 ml) followed by ethyl acetate (2 × 30 ml). The combined extracts were washed with brine (30 ml) and dried ($MgSO_4$). Concentration under reduced pressure gave the *acid* (**3**) as a yellow syrup (0.43 g, 89%); $\nu_{max.}$($CHCl_3$) 3 400, 3 010, 1 700, 860, and 760 cm^{-1} [Found: *m/z* (tri-Me_3Si–derivative) 563.4340 (M^+ − Me). $C_{30}H_{55}O_4Si_3$ requires M^+ − Me, 563.3408]. Full characterisation was not possible as this product was prone to lactonisation.

(Z)-6-[4-(1-*Hydroxynonyl*)*styryl*]*tetrahydropyran*-2-*one* (**17**).—The hydroxy acid (**3**) (50 mg, 0.14 mmol) was heated for 6 h at 80 °C/0.5 mmHg, to give complete consumption of the starting material according to t.l.c. Chromatography on silica (CH_2Cl_2–ether, 5:1) gave the *lactone* (**17**) (40 mg, 85%) as an oil; $\nu_{max.}$(film) 3 450, 3 020, 1 740, 1 240, and 1 040 cm^{-1}; δ 7.33 (2 H, d, *J* 8 Hz), 7.25 (2 H, d, *J* 8 Hz), 6.70 (1 H, d, *J* 11.5 Hz) 5.71 (1 H, dd, *J* 11.5 and 10 Hz), 5.16 (1 H, ddd, *J* 10, 10 and 5 Hz), 4.67 (1 H, t, *J* 7 Hz), 2.55 (2 H, m), 2.10—1.60 (7 H, m), 1.25 (12 H, m), and 0.87 (3 H, t, *J* 7 Hz); *m/z* 344 (M^+). (Found: C, 76.5; H, 9.3, $C_{22}H_{32}O_3$ requires C, 76.70; H, 9.36%). H.p.l.c. on Partisil PXS 10 (CH_2Cl_2–EtOAc, 9:1; 3 ml min^{-1}) showed the presence of two diastereoisomers (*ca.* 1:1) with retention times of 7.19 min and 7.67 min.

p-*Ethynylbenzyl Alcohol* (**18**)[11].—To a stirred solution of the aldehyde (**14**) (2.0 g, 15.4 mmol) in ethanol (30 ml), was added sodium borohydride (2 g, 53 mmol). Reduction was almost instantaneous at room temperature. After a standard CH_2Cl_2 work-up, the product was concentrated under reduced pressures to yield alcohol (**18**)[11] (1.97 g, 97%) as an oil; $\nu_{max.}$(film) 3 400, 3 300, and 2 100 cm^{-1}; δ 7.40 (4 H, m), 4.70 (2 H, br s), 3.10 (1 H, s), and 2.10 (1 H, br s, exchangeable); *m/z* 132 (M^+). (Found: C, 81.4; H, 6.1; C_9H_8O requires C, 81.79; H, 6.10%).

Methyl 5-Hydroxy-7-[4-(1-hydroxymethyl)phenyl]hept-6-ynoate (**19**).—To a stirred solution of the acetylenic alcohol (**18**) (0.60 g, 4.55 mmol) in THF (30 ml) at −70 °C, was added BuLi (1.55M; 5.9 ml, 9.1 mmol). A thick precipitate of the dianion developed which was solubilized by the addition of HMPA (2 ml). After being stirred for 20 min at −70 °C—−40 °C, the solution was re-cooled to −70 °C and treated with methyl 5-oxopentanoate (**8**)[10] (0.60 g, 4.62 mmol). The mixture was stirred at −70 °C for 30 min after which it was subjected to a standard ether work-up. Chromatography on silica (CH_2Cl_2–EtOAc, 1:2) gave the *diol* (**19**) (0.8455 g, 71%) as an oil, R_F 0.43 (CH_2Cl_2–EtOAc, 1:2); $\nu_{max.}$(film) 3 400, 2 230, and 1 730 cm^{-1}; δ 7.40 (4 H, m), 4.70 (2 H, br s), 3.70 (3 H, s), 2.40 (4 H, m), and 1.85 (4 H, m) [Found: *m/z* (di-Me_3Si–derivative) 406.2289 (M^+). $C_{21}H_{34}O_4Si_2$ requires M^+, 406.2000].

(Z)-*Methyl 5-Hydroxy-7-[4-(1-hydroxymethyl)phenyl]hept-6-enoate* (**4**).—A solution of the acetylenic diol (**19**) (0.50 g, 1.90 mmol) in THF (3 ml) and Et_3N (0.3 ml) was diluted with hexane until the diol began to separate; a few drops of THF were then added to achieve solubilization. The acetylene was reduced over Lindlar catalyst[9] (20.7 mg) at 0 °C, and the reaction stopped at *ca.* 80% completion (by t.l.c.) The catalyst was filtered (Whatman GFA) and the product chromatographed on silica (CH_2Cl_2–EtOAc, 1:1) to give *cis*-alkene (**4**) (0.369 g, 73%), as an oil, $\nu_{max.}$ 3 400, 3 020, 1 740, and 1 640 cm^{-1}; δ 7.33 (2 H, d, *J* 9 Hz), 7.26 (2 H, d, *J* 9 Hz), 6.55 (1 H, d, *J* 11 Hz), 5.65 (1 H, dd, *J* 11 and 10 Hz), 4.69 (2 H, br s), 4.55 (1 H, m), 3.66 (3 H, s), 2.32 (2 H, t, *J* 7.5 Hz), 2.13 (1 H, br s, exchangeable), 2.00 (1 H, br s, exchangeable), and 1.90—1.50 (4 H, m); *m/z* (di-Me_2SiBu^t–derivative) 435 ($M^+ - Bu^t$). The 360 MHz ^1H n.m.r. spectrum indicated the presence of over-reduced and isomerised contaminants (maximum 10%).

(Z)-*Methyl 5-Hydroxy-7-(2-pyridyl)hept-6-enoate* (**5**).—To a stirred solution of 2-ethynylpyridine[8] (**20**) (5 g, 48.54 mmol) in THF (200 ml) at −70 °C, was added butyl-lithium (1.55M; 31.3 ml, 48.5 mmol) in one portion. After 30 min at −70 °C, methyl 5-oxopentanoate (**8**)[10] (7.57 g, 58 mmol) was added. T.l.c. after 5 min showed a single product. After a further 15 min at −70 °C the reaction was quenched with water (100 ml). The mixture was extracted with ether (5 × 200 ml) and the extract dried (K_2CO_3) and concentration under reduced pressure to yield a dark brown oil (11.73 g). Chromatography of this on silica (CH_2Cl_2–EtOAc, 1:2) gave methyl 5-hydroxy-7-(2-pyridyl)hept-6-ynoate (**21**) (1.003 g, 9%) as a syrup, R_F 0.22 (CH_2Cl_2–EtOAc, 1:2); $\nu_{max.}$(film) 3 350, 2 250, and 1 740 cm^{-1}; *m/z* (Me_3Si–derivative) 305 (M^+). Since this product was very unstable it was reduced immediately.

A solution of the alkyne (**21**) (0.97 g, 4.16 mmol) in hexane (5 ml) and THF (5 ml) was reduced over Lindlar catalyst[9] (45 mg) poisoned with Et_3N (0.56 ml). Once the theoretical amount of hydrogen (93 ml) had been taken up, the reaction was stopped, the catalyst filtered off, and the product concentrated under reduced pressure. Chromatography on silica (CH_2Cl_2–EtOAc, 1:2) yielded cis-*alkene* (**5**) (0.84 g, 86%) as an oil, R_F 0.6 (CH_2Cl_2–EtOAc, 1:2); $\nu_{max.}$(film) 3 700—2 500 (no change on dilution), 3 020, 1 740, 1 640, and 1 600 cm^{-1}; $\lambda_{max.}$(EtOH) 238 nm (ε 12 180), 281 nm (ε 6 180); δ 8.57 (1 H, d, *J* 5 Hz), 7.715 (1 H, ddd, *J* 7.5, 7.5 and 2 Hz), 7.32 (1 H, s, exchangeable), 7.26 (1 H, d, *J* 7.5 Hz), 7.18 (1 H, ddd, *J* 7.5, 5 and 1 Hz), 6.49 (1 H, dd, *J* 12 and 1.75 Hz), 6.06 (1 H, dd, *J* 12 and 6 Hz), 4.48 (1 H, dt, *J* 6 and 6 Hz), 3.66 (3 H, s), 2.40 (2 H, t, *J* 7 Hz), and 1.80 (4 H, m); *m/z* (Me_3Si–derivative) 307 (M^+). (Found: C, 66.2; H, 7.35; N, 6.2. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.28; N, 5.95%).

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