Synthesis of Analogues of Arachidonic Acid as Potential Inhibitors of Leukotriene Biosynthesis

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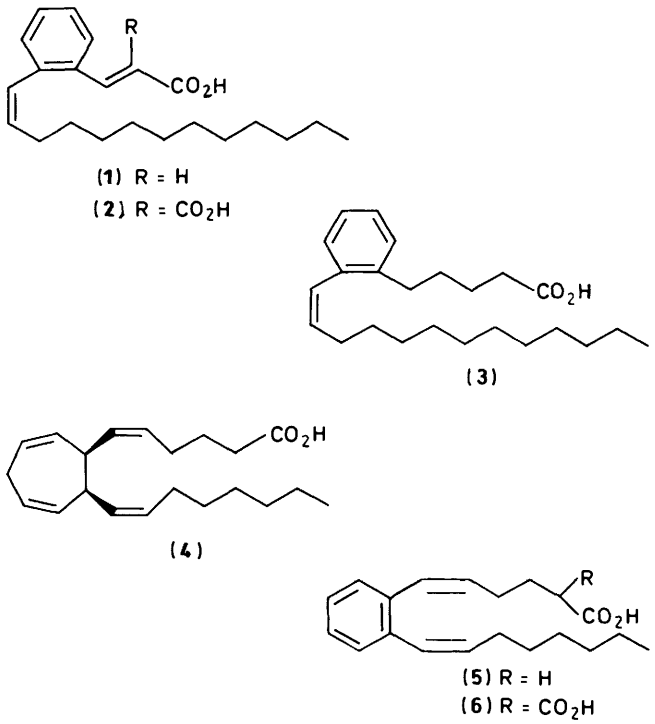
A versatile route to 1,2-disubstituted aromatic analogues of arachidonic acid of formulae (**5**) and (**6**) has been established involving the stepwise cross-coupling of alkynes to 1,2-dibromobenzene. Subsequent reduction allows good control over the degree of unsaturation and the stereochemistry of the resulting alkenes. Some of these compounds have been shown to inhibit the biosynthesis of leukotrienes *in vitro*.

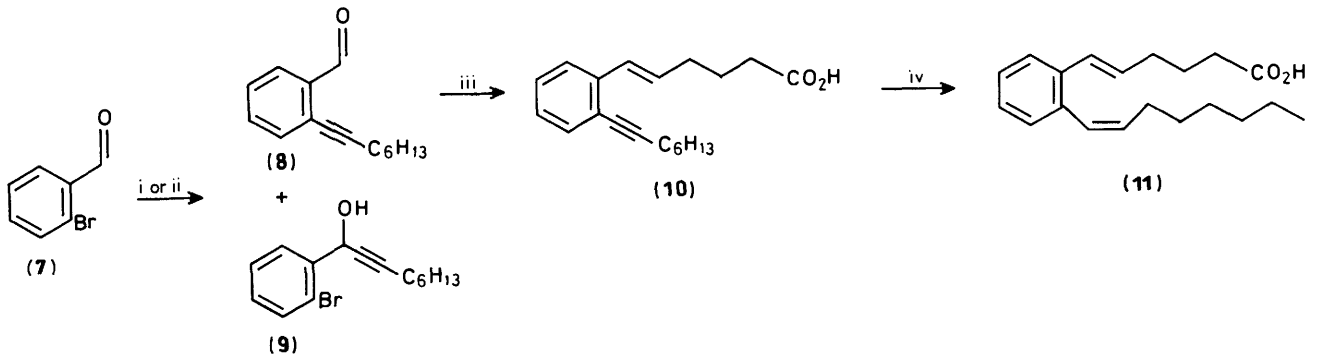
The realisation that the peptidoleukotrienes (LTC_4, LTD_4, and LTE_4) play an important role in allergic and inflammatory diseases[1] has stimulated considerable interest in the inhibition of their biosynthesis. Of the enzymes involved in their formation from arachidonic acid, the inhibition of 5-lipoxygenase has attracted most attention.[2]

As part of a programme designed to investigate metabolically stable analogues of arachidonic acid as inhibitors of 5-lipoxygenase, we have prepared a variety of aromatic alkanoic acids of the type (**1**)—(**3**).[3] The recent report by Nicolaou that 7,13-bridged arachidonic acid analogues, typified by compound (**4**), were potent inhibitors of 5-lipoxygenase,[4] prompted us to investigate compounds of this type in which the cycloheptadienyl moiety was replaced by an aromatic ring such as in compound (**5**). Such compounds avoid the need for stereochemical control at the junction of the ring system and alkyl chains, and have the potential for greater metabolic stability. Since our earlier work in this area[3c] had shown that the malonates (**2**) were biologically more potent than the corresponding alkenoates (**1**), we were particularly interested in the synthesis of compound (**6**).



Discussion

Our initial approach to these compounds was to introduce the hydrocarbon chain *via* coupling of an appropriate acetylene to 2-bromobenzaldehyde (**7**), and the acidic chain *via* a Wittig reaction (Scheme 1). However, cross-coupling of oct-1-ynyl zincate with compound (**7**) gave the expected aldehyde (**8**) in only 37% yield, together with an approximately equal amount of the alcohol (**9**). This result was surprising in the light of our previous experience with similar reactions on heteroaromatic aldehydes.[5] It also differs from the suggestion by Quintard and others[6] that the formyl group is compatible with the conditions of cross-coupling. Quintard, however, used alkylstannanes rather than alkyl zincates which may have resulted in a species of lower nucleophilicity. Nevertheless, products derived from attack at the formyl group were readily avoided using Heck

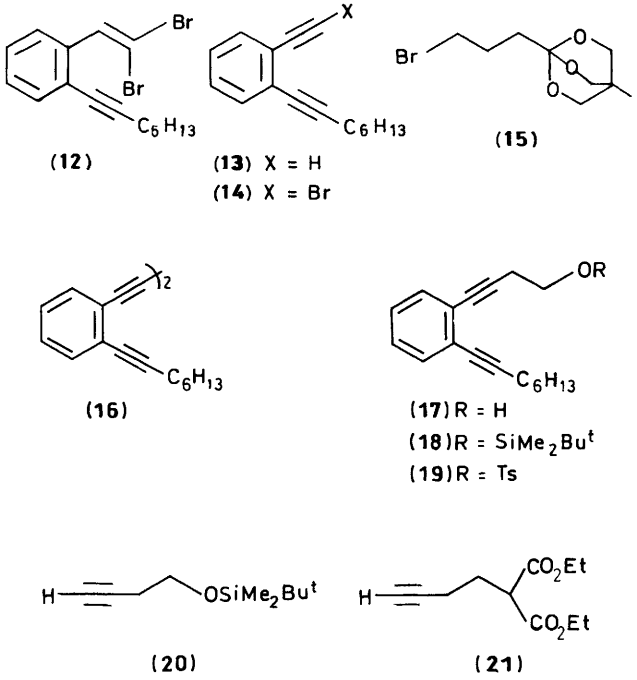


Scheme 1. *Reagents and conditions:* i, oct-1-yne, $Pd(OAc)_2$, Ph_3P, Et_3N, heat; ii, $ClZnC{\equiv}CC_6H_{13}$, $Pd(PPh_3)_4$; iii, $Ph_3P{=}CH[CH_2]_3CO_2Na$; iv, H_2/Pd, $BaSO_4$, Py

conditions.[7] Thus, the reaction of compound (**7**) with oct-1-yne afforded 62% of the coupled product (**8**) with no detectable alcohol (**9**) formed.

The reaction of aldehyde (**8**) with (4-carboxybutyl)triphenylphosphorane (generated in benzene using sodium t-pentoxide) gave almost exclusively the *E*-isomer (**10**) in 64% yield. This result was unexpected since similar systems have been shown to favour the formation of *Z*-isomers.[8] Indeed, Maryanoff[8b] reported that it was necessary to use lithium hexamethyldisilazide in tetrahydrofuran (THF) in order to achieve good selectivity for the *E*-isomer. Although not the preferred isomer, compound (**10**) could be partially hydrogenated with palladium on barium sulphate to furnish the diene (**11**) in high yield.

The formation of the undesired stereoisomer, and a need to establish a route which would also yield bisacetylenes, led us to consider an alternative approach based on the alkyne (**13**). Thus, using the procedure of Corey,[9] the aldehyde (**8**) was converted with tetrabromomethane and triphenylphosphine into the dibromide (**12**) in 77% yield. Treatment of compound (**12**) with 2 equiv. of alkyl-lithium gave only a poor yield of the terminal alkyne (**13**), although a more efficient two-step procedure, involving conversion into the bromo alkyne (**14**)



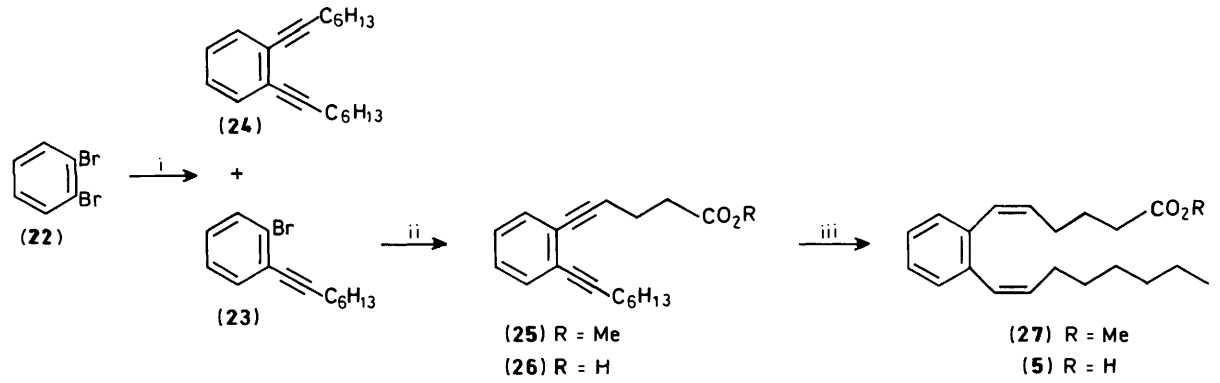
with potassium t-pentoxide and subsequent metal–halogen exchange, gave reasonable yields. Unfortunately, attempts to alkylate alkyne (**13**) with 4-bromobutyric acid, 1-(3-bromopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**15**),[10] or tris-(4-methoxycarbonylbutyl)borane were unsuccessful due to the unreactive nature of the acetylenic anion. Similarly, attempts to cross-couple the zincate of alkyne (**13**) with ethyl 4-bromobutyrate or the bromide (**15**) also failed. In both of these cases the only isolable product was the dimeric alkyne (**16**). Alkylation of alkyne (**13**) with ethylene oxide, however, gave 66% of the alcohol (**17**), although this compound could be prepared more conveniently in better overall yield by cross-coupling of the zincate of the silyl alkyne (**20**) with 2-(oct-1-ynyl)bromobenzene (**23**) followed by desilylation. Whilst it has not been possible to elaborate the alcohol (**17**) to compounds of type (**5**), it does serve as a useful intermediate in the synthesis of the malonates (**6**) (see below).

Since 2-bromobenzaldehyde (**7**) failed to provide a useful precursor to 1,2-diynes such as (**25**), we considered the stepwise displacement of halogen from 1,2-dibromobenzene (**22**) under Heck or cross-coupling conditions (Scheme 2). It was reasoned that under Heck conditions the displacement of one halogen atom should render the second less labile, since it is well documented that this reaction is favoured by electron-withdrawing substituents.[7] As expected therefore, the reaction of oct-1-yne with dibromide (**22**) selectively afforded the mono-addition product (**23**), although in only 40% yield. More vigorous conditions increased the yield to 60% but also resulted in the formation of 12% of the di-addition product (**24**).* The cross-coupling of oct-1-ynyl zincate with dibromide (**22**) was surprisingly selective and gave 80% of mono-addition product (**23**) together with 10% of the diyne (**24**). Further elaboration of compound (**23**) with the zincate of methyl hex-5-ynoate[11] resulted in a modest yield (33%) of the required product (**25**) with 23% of unchanged (**23**) being reclaimed. Although no other product was isolated, it seems likely that the low yield in this instance is due to competing reactions of the zincate with the ester function in the product (**25**) and in itself. Both diyne (**25**) and its partial reduction product (**27**) gave the corresponding acids (**26**) and (**5**) in excellent yield on treatment with lithium hydroxide in aqueous THF.

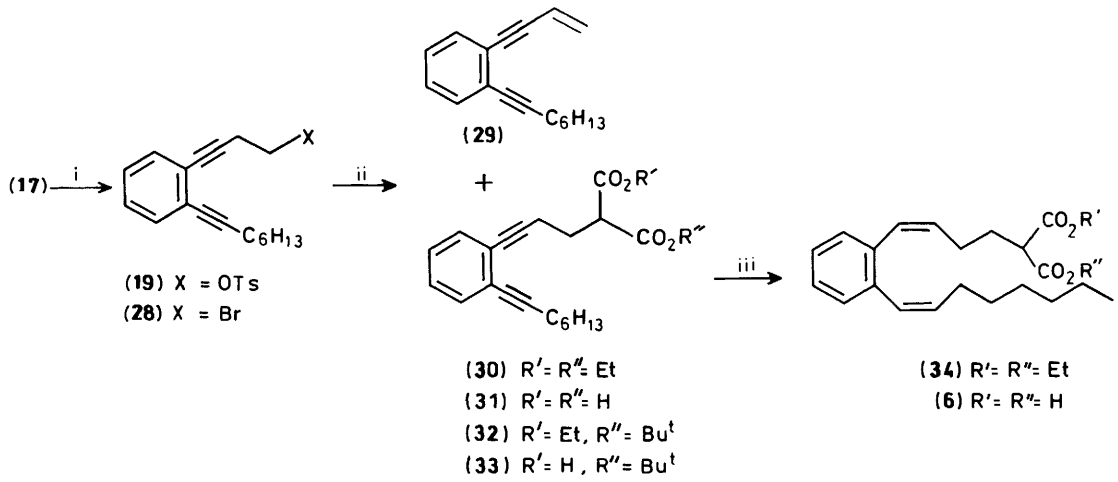
Attempts to apply a similar route to the malonates (**6**) were unsuccessful in that cross-coupling of the acetylenic malonate (**21**)[12] and the bromide (**23**) gave only a complex mixture. The previously prepared acetylenic alcohol (**17**), however, provided an alternative precursor for the introduction of the malonate group (Scheme 3). Reaction of the alcohol (**17**) with tosyl chloride in pyridine gave 53% of the tosylate derivative (**19**), which on treatment with diethyl sodiomalonate in THF gave the malonate (**30**) in 24% yield, together with 49% of the elimination product (**29**) and 20% unchanged sulphonate (**19**). A similar reaction using the lithiomalonate in 1,2-dimethoxyethane (DME) produced the same yield of the enyne (**29**) but a substantially lower yield of malonate (**30**). Higher yields of compound (**30**) (63%) were eventually obtained using the potassium salt of diethyl malonate in the presence of 18-crown-6. In this instance, only 28% of the elimination product (**29**) was formed and these results suggest that a delicate balance exists between substitution and elimination reactions in this system. Indeed, increasing the steric bulk of the malonate gave 51% of the enyne (**29**) and only 26% of the substitution product (**32**), even under optimal conditions. Surprisingly, the bromide (**28**), formed in 90% yield from the alcohol (**17**) on reaction with tetrabromomethane and triphenylphosphine, gave only the elimination product (**29**) on reaction with malonate anion. As with the monoesters, partial reduction of malonate (**30**) readily furnished the diene (**34**). Hydrolysis of diesters (**30**) and (**34**) gave the corresponding diacids (**31**) and (**6**), although the ethyl t-butyl diester (**32**) gave the monoester (**33**) under similar conditions.

The syntheses described here provide versatile routes to a variety of 1,2-disubstituted aromatic compounds. The possibility of coupling alkenyl or alkynyl zincates should allow the synthesis of mixed enyne systems with complete control over the level of unsaturation and the stereochemistry of both chains. The compounds described were tested in *in vitro* cell-free systems for their ability to inhibit the 5-lipoxygenase and phospholipase A_2 enzymes. Whilst most were disappointing as 5-lipoxygenase inhibitors, some proved to be potent inhibitors of phospholipase A_2.[13] Compound (**5**), in particular, inhibited this enzyme by ~70% at a concentration of 20μM.

* A similar report appeared during the preparation of this manuscript (G. Just and R. Singh, *Tetrahedron Lett.*, 1987, **28**, 5981).



Scheme 2. *Reagents and conditions:* i, $ClZnC{\equiv}CC_6H_{13}$, $Pd(PPh_3)_4$, THF; ii, $ClZnC{\equiv}C[CH_2]_3CO_2Me$, $Pd(PPh_3)_4$, THF; iii, H_2/Pd, $BaSO_4$, Py



Scheme 3. *Reagents and conditions:* i, TsCl, Py; ii, CBr_4, PPh_3, CH_2Cl_2; iii, $CH_2(CO_2R')(CO_2R'')$, KH, 18-Crown-6, THF; iv, H_2/Pd, $BaSO_4$, Py

Experimental

M.p.s were determined using a Büchi apparatus and are recorded uncorrected. I.r. spectra were measured as liquid films (for oils) or as dispersions in Nujol (for solids) using a Perkin-Elmer 197 spectrometer. N.m.r. spectra were obtained with a Perkin-Elmer EM390 (90 MHz) spectrometer or Jeol 270 GMX (270 MHz) spectrometer with solutions in deuteriochloroform containing Me_4Si as standard. Mass spectral data were obtained from a VG-Micromass 70-70F instrument using electron-impact ionisation technique. Yields for all products are for chromatographically homogeneous material.

Heck Reaction: General Procedure.—A mixture of the aryl halide (40 mmol), triphenylphosphine (2 mmol), palladium(II) acetate (0.7 mmol), and oct-1-yne (1.8 mol equiv.) in triethylamine (150 ml) was degassed then heated to 110 °C, under nitrogen, overnight. After cooling, the precipitate of triethylamine hydrobromide was removed by filtration and washed with ether. The filtrate was concentrated under reduced pressure and the residue chromatographed on silica (dichloromethane–hexane, 1:3) to give the coupled product.

Cross-coupling: General Procedure.—To the acetylene (10 mmol) at −78 °C was added butyl-lithium (1.05 mol equiv.). The mixture was warmed to 0 °C during 30 min and a solution of anhydrous zinc chloride (10 mmol) in THF (10 ml) was added. The mixture was stirred for 30 min during which time the temperature was increased to 25 °C. Solutions of the aryl bromide (10 mmol) in THF (5 ml) and tetrakis(triphenylphosphine)palladium(0) (5 mol%) in THF (10 ml) were sequentially added and the mixture was then heated to 60 °C until reaction was complete. After cooling, the mixture was added to dil. HCl and the product was extracted into ether. The extract was dried ($MgSO_4$), and concentrated under reduced pressure, and the residue was chromatographed on silica (hexane) to give the coupled product.

2-(*Oct-1-ynyl*)*benzaldehyde* (**8**).—(a) *By the Heck reaction.* 2-Bromobenzaldehyde (**7**) (7.4 g, 40 mmol) was treated with oct-1-yne (8 g, 1.8 mol equiv.), under the Heck conditions given above, to give 2-(*oct-1-ynyl*)*benzaldehyde* (**8**) (5.28 g, 62%) as an oil, $\nu_{max.}$ 2 220w, 1 700s, 1 595m, 1 485m, 1 190m, and 765m cm^{-1}; δ(90 MHz) 0.83 (3 H, distorted t, terminal Me), 1.20 (8 H, br, alkylene chain), 2.31 (2 H, t, *J* 6 Hz, $CH_2C{\equiv}C$), 7.15—7.90 (4 H, m, ArH), and 10.43 (1 H, s, CHO); *m/z* 214 (M^+, 20%), 157 (40), 144 (100), and 135 (55) (Found: M^+, 214.1356. $C_{15}H_{18}O$ requires *M*, 214.1358), characterized as the 2,4-*dinitrophenylhydrazone*, m.p. 143 °C (Found: C, 63.85; H, 5.55; N, 14.15. $C_{21}H_{22}N_4O_4$ requires C, 63.95; H, 5.6; N, 14.2%).

(b) *By the cross-coupling reaction.* 2-Bromobenzaldehyde (**7**)

(1.85 g, 10 mmol) was treated with oct-1-yne (1.1 mol equiv.), under the cross-coupling conditions given above; chromatography on silica (hexane) yielded 2-(oct-1-ynyl)benzaldehyde (**8**) (0.74 g, 37%) identical with the material obtained above, followed by 1-(2-*bromophenyl*)*oct*-2-*yn*-1-*ol* (**9**) (0.91 g, 31%), $\nu_{max.}$ 3 350br, 2 920s, 1 440m, 1 015s, and 745s cm^{-1}; δ(270 MHz) 0.88 (3 H, t, *J* 6.7 Hz, terminal Me), 1.27—1.59 (8 H, m, alkylene chain), 2.26 (2 H, t, *J* 7 Hz, $CH_2C{\equiv}C$), 2.38 (1 H, d, *J* 5.2 Hz, OH), 5.78 (1 H, d, *J* 5.2 Hz, C*H*OH), and 7.15—7.79 (4 H, m, ArH); *m*/*z* 296 (M^+, 8%), 215 (66), 185 (42), 183 (31), 145 (100), 131 (33), 115 (45), and 77 (40) (Found: M^+, 294.0621; C, 60.95; H, 6.35; Br, 26.55. $C_{15}H_{19}BrO$ requires *M*, 294.0619; C, 61.0; H, 6.5; Br, 27.1%).

(E)-6-[2-(*Oct*-1-*ynyl*)*phenyl*]*hex*-5-*enoic Acid* (**10**).—A solution of t-amyl alcohol (2-methylbutan-2-ol) (4.22 g, 48 mmol) in THF (25 ml) was added to sodium hydride (1.15 g, 48 mmol) at 25 °C. When the ensuing effervescence had ceased, the solvent was removed under reduced pressure and was replaced with benzene (25 ml). The resulting solution was added to a suspension of (4-carboxybutyl)triphenylphosphonium bromide (10.56 g, 24 mmol) and DMSO (0.72 ml) in benzene (48 ml) at 60 °C and after 15 min a solution of compound (**8**) (2.58 g, 12 mmol) was added to the orange suspension. The colour was immediately discharged and the suspension rapidly darkened. After 15 min the mixture was extracted into ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated to give an oil, which was chromatographed on argentated silica (dichloromethane–ether, 4:1) to give (E)-6-[2-(*oct*-1-*ynyl*)-*phenyl*]*hex*-5-*enoic acid* (**10**) (2.19 g, 64%) as an oil, $\nu_{max.}$ 2 940s, 2 220w, 1 710s, 970m, and 705m cm^{-1}; δ(90 MHz) 0.90 (3 H, t, *J* 5.4 Hz, terminal Me), 1.20—1.70 (8 H, m, alkylene chain), 1.84 (2 H, m, $CH_2CH_2CO_2H$), 2.31 (2 H, q, *J* 7.6 Hz, $CH_2CH_2CH_2$-CO_2H), 2.42 (2 H, t, *J* 7.4 Hz, CH_2CO_2H), 2.46 (2 H, t, *J* 7.1 Hz, $C{\equiv}CCH_2$), 6.22 (1 H, dt, *J* 7.1, 16.2 Hz, ArCH=C*H*), 6.90 (1 H, d, *J* 16.2 Hz, ArC*H*=CH), 7.05—7.50 (4 H, m, ArH), and 9.10—10.40 (1 H, br, CO_2H); *m*/*z* 298 (M^+, 14%), 167 (42), 155 (60), 141 (100), and 55 (57) (Found: M^+, 298.1926; C, 80.75; H, 8.75. $C_{20}H_{26}O_2$ requires *M*, 298.1933; C, 80.5; H, 8.8%).

β,β-*Dibromo*-2-(*oct*-1-*ynyl*)*styrene* (**12**).—To a solution of the aldehyde (**8**) (6.0 g, 28 mmol) in dichloromethane (60 ml), containing triphenylphosphine (14.1 g, 2 mol equiv.) at 5 °C was added tetrabromomethane (10.7 g, 1.15 mol equiv.) at a rate such that the temperature remained less than 5 °C. After 1 h at 5 °C, the mixture was warmed to 20 °C and stirred overnight. The solid formed was filtered off and the solvent removed under reduced pressure. Extraction of the residue with hexane followed by evaporation yielded an oil, which was chromatographed on silica (hexane) to yield β,β-*dibromo*-2-(*oct*-1-*ynyl*)*styrene* (**12**) (7.75 g, 77%) as an oil, $\nu_{max.}$ 2 940s, 2 225w, 1 600w, 1 470m, 885m, 860s, 785m, and 750s cm^{-1}; δ(90 MHz) 0.90 (3 H, distorted t, terminal Me), 1.15—1.80 (8 H, m, alkylene chain), 2.40 (2 H, t, *J* 7 Hz, $C{\equiv}CCH_2$), 7.15—7.75 (4 H, m, ArH), and 7.80 (1 H, s, $CH{=}CBr_2$); *m*/*z* 368 (M^+ < 1%), 221 (25), 219 (25), 145 (100), 139 (25), 113 (25), 89 (45), 82 (38), 80 (38), and 43 (85) (Found: M^+, 367.9793; C, 51.55; H, 4.85; Br, 43.2. $C_{16}H_{18}Br_2$ requires *M*, 367.9776; C, 51.9; H, 4.9; Br, 43.2%).

1-(2-*Bromoethynyl*)-2-(*oct*-1-*ynyl*)*benzene* (**14**).—To a solution of dibromide (**12**) (2.96 g, 8 mmol) in hexane (15 ml) at 0 °C was added potassium t-amylate (2.05 g, 16 mmol) suspended in hexane (2 ml). After 30 min the mixture was warmed to 20 °C and stirred overnight. After addition to ice–HCl, the mixture was extracted into ether. The extract was then washed with brine, dried ($MgSO_4$), and evaporated to give 1-(2-*bromo*-*ethynyl*)-2-(*oct*-1-*ynyl*)*benzene* (**14**) (1.58 g, 68%) as an oil, $\nu_{max.}$ 2 920s, 2 220w, 2 195w, 1 595w, 1 480m, 1 445m, and 755s cm^{-1}; δ(90 MHz) 0.90 (3 H, distorted t, terminal Me), 1.15—1.90 (8 H, m, alkylene chain), 2.43 (2 H, t, *J* 7 Hz, $C{\equiv}CCH_2$), and 7.10—7.60 (4 H, m, ArH) (Found: M^+, 288.0517; C, 66.65; H, 5.95; Br, 26.9. $C_{16}H_{17}Br$ requires *M*, 288.0514; C, 66.45; H, 5.95; Br, 27.65%).

1-*Ethynyl*-2-(*oct*-1-*ynyl*)*benzene* (**13**).—To a solution of bromide (**14**) (0.289 g, 1 mmol) in THF (10 ml) at −78 °C under nitrogen was added butyl-lithium (1.1 mol equiv.). After 2 h at −78 °C, the dark solution was added to dil. HCl and extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give 1-*ethynyl*-2-(*oct*-1-*ynyl*)*benzene* (**13**) (0.18 g, 86%) as an oil, $\nu_{max.}$ 3 290m, 2 920s, 2 220w, 1 595w, 1 480m, and 755s cm^{-1}; δ(90 MHz) 0.90 (3 H, distorted t, terminal Me), 1.15—1.80 (8 H, m, alkylene chain), 2.43 (2 H, t, *J* 7 Hz, $C{\equiv}CCH_2$), 3.25 (1 H, s, C≡CH), and 7.15—7.55 (4 H, m, ArH); *m*/*z* 210 (M^+, 34%), 167 (58), 165 (45), 141 (77), and 139 (100) (Found: M^+, 210.1414; C, 91.7; H, 8.5. $C_{16}H_{18}$ requires *M*, 210.1408; C, 91.4; H, 8.65%).

4-[2-(*Oct*-1-*ynyl*)*phenyl*]*but*-3-*yn*-1-*ol* (**17**) (*a*).—To a solution of the bromide (**14**) (2.3 g, 11 mmol) in THF (25 ml) at −78 °C was added butyl-lithium (1 mol equiv.). After the mixture had been stirred under nitrogen at −78 °C for 2 h, ethylene oxide (1.3 ml, 5 mol equiv.) was added. The mixture was stirred for 48 h, when the red solution was added to dil. HCl and extracted into ether. After drying ($MgSO_4$), the extract was evaporated to give an oil, which was chromatographed on silica (dichloromethane) to give 4-[2-(*oct*-1-*ynyl*)*phenyl*]*but*-3-*yn*-1-*ol* (**17**) (1.83 g, 65.5%) as an oil, $\nu_{max.}$ 3 375 m, br, 2 930s, 2 230w, 1 590w, 1 480s, 1 045s, and 755s cm^{-1}; δ(270 MHz) 0.91 (3 H, t, *J* 6.6 Hz, terminal Me), 1.26—1.53 (6 H, m, alkylene chain), 1.63 (2 H, m, $C{\equiv}CCH_2CH_2C_4H_9$), 2.40 (1 H, t, *J* 5.8 Hz, OH), 2.45 (2 H, t, *J* 7.1 Hz, $C{\equiv}CCH_2CH_2C_4H_9$), 2.73 (2 H, t, *J* 6 Hz, $C{\equiv}CCH_2CH_2OH$), 3.81 (2 H, t, *J* 5.9 Hz, CH_2OH), 7.20 (2 H, m, ArH), and 7.39 (2 H, m, ArH); *m*/*z* 254 (M^+, 100%), 178 (40), 167 (97), 165 (98), 153 (95), 152 (94), and 141 (70) (Found: M^+, 254.1668; C, 85.05; H, 8.85. $C_{18}H_{22}O$ requires *M*, 254.1671; C, 85.0; H, 8.7%).

(*b*) Tetrabutylammonium fluoride (6.15 g, 1.5 mol equiv.) was added to compound (**18**) (4.24 g, 13 mmol) in THF (50 ml) at 0 °C under nitrogen. After warming to 20 °C and being stirred for 1 h, the solution was evaporated under reduced pressure and the resulting oil was chromatographed on silica (dichloromethane) to yield 4-[2-(oct-1-ynyl)but-3-yn-1-ol (2.27 g, 69%), identical with that obtained above.

Dimethyl-t-*butylsilyl* 4-[2-(*Oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl Ether* (**18**).—Compound (**23**) (5.3 g, 20 mmol) was treated with dimethyl-t-butylsilyl but-3-ynyl ether (**20**) (5.53 g, 30 mmol) under the cross-coupling conditions given above to give *dimethyl*-t-*butylsilyl* 4-[2-(*oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl ether* (**18**) (4.58 g, 70%) as an oil, $\nu_{max.}$ 2 920s, 2 270w, 1 595w, 1 110s, and 835s cm^{-1}; δ(270 MHz, ref. MeCN) 0.00 (6 H, s, (Me_2Si), 0.83 (12 H, m, Bu^t + terminal Me), 1.20—1.80 (8 H, m, alkylene chain), 2.37 (2 H, t, *J* 6.6 Hz, $C{\equiv}CCH_2R$), 2.57 (2 H, t, *J* 7.5 Hz, $C{\equiv}CCH_2CH_2O$), 3.77 (2 H, t, *J* 7.5 Hz, CH_2O), and 7.25 (4 H, m, ArH); *m*/*z* 353 ($M^+ - CH_3$, 2%), 311 (100), 281 (15), 237 (35), and 73 (30) (Found: C, 78.2; H, 9.7. $C_{24}H_{36}OSi$ requires C, 78.2; H, 9.85%).

1-*Bromo*-2-(*oct*-1-*ynyl*)*benzene* (**23**).—(*a*) 1,2-Dibromobenzene (**22**) (2.36 g, 10 mmol) was treated with oct-1-yne (1.1 g, 10 mmol) under the cross-coupling conditions given above; chromatography (hexane) gave 1-*bromo*-2-(*oct*-1-*ynyl*)*benzene* (**23**) (2.13 g, 80.4%), $\nu_{max.}$ 2 930s, 2 230w, 1 590w, 1 465m, 1 030m, and 750s cm^{-1}; δ(90 MHz) 0.73 (3 H, t, *J* 5.6 Hz, terminal Me), 1.10—1.80 (8 H, m, alkylene chain), 1.43 (2 H, t, *J* 6 Hz, $C{\equiv}CCH_2R$), and 6.90—7.70 (4 H, m, ArH); *m*/*z* 266 (M^+, 42%), 264 (M^+, 43), 223 (40), 221 (43), 195 (45), 156 (50), 142

(85), 129 (88), 116 (100), and 115 (70) (Found: M^+, 264.0516; C, 63.6; H, 6.2. $C_{14}H_{17}Br$ requires M, 264.0514; C, 63.4; H, 6.5%), followed by 1,2-*di*(*oct*-1-*ynyl*)*benzene* (**24**) (0.28 g, 10%), $\nu_{max.}$ 2 880s, 2 220w, 1 600w, and 755m cm^{-1}; δ(90 MHz) 0.93 (6 H, t, *J* 5.6 Hz, terminal Me), 1.10—1.90 (16 H, m, alkylene chain), 2.45 (4 H, t, *J* 6.5 Hz, C≡CCH_2R), and 7.05—7.50 (4 H, m, ArH); *m/z* 294 (M^+, 67%), 195 (33), 181 (86), 167 (100), 155 (56), and 141 (90) (Found: M^+, 294.2350; C, 90.05; H, 10.3. $C_{22}H_{30}$ requires M, 294.2347; C, 89.75; H, 10.3%).

(*b*) 1,2-Dibromobenzene (12.5 g, 53 mmol) was treated with oct-1-yne (10.5 g, 1.8 mol equiv.) under the Heck conditions given above to give 1-bromo-2-(oct-1-ynyl)benzene (5.61 g, 40%), identical with that obtained above.

(*c*) 1,2-Dibromobenzene (11.8 g, 50 mmol) was treated with oct-1-yne (10 g) under the Heck conditions given above [except that bis(triphenylphosphine)palladium dichloride (3.5 mol%) and copper(I) iodide (7 mol%) were used in place of palladium(II) acetate and triphenylphosphine] to give 1-bromo-2-(oct-1-ynyl)benzene (9.72 g, 73.1%), identical with that prepared above, and di(oct-1-ynyl)benzene (1.8 g, 12.2%), identical with that obtained above.

Methyl 6-[2-(*Oct*-1-*ynyl*)*phenyl*]*hex*-5-*ynoate* (**25**).—The bromide (**23**) (5.3 g, 20 mmol) was treated with methyl hex-5-ynoate (3.16 g, 25 mmol) under the cross-coupling conditions given above (except that butyl-lithium and zinc chloride were added at −60 °C and the remainder at −25 °C). Chromatography (hexane) gave the bromide (**23**) (1.22 g, 23%), followed by *methyl* 6-[2-(*oct*-1-*ynyl*)*phenyl*]*hex*-5-*ynoate* (**25**) (2.02 g, 32.6%) as an oil, $\nu_{max.}$ 2 975s, 2 220w, 1 740s, 1 595w, and 760m cm^{-1}; δ(270 MHz) 0.90 (3 H, t, *J* 6.8 Hz, terminal Me), 1.25—1.68 (8 H, m, alkylene chain), 1.95 (2 H, m, C≡CCH_2CH_2CH_2-CO_2Me), 2.46 (2H, t, *J* 7.15 Hz, C≡CC$H_2C_5H_{11}$), 2.55 (2 H, t, *J* 6.9 Hz, C≡CCH_2CH_2CH_2CH_2CO_2Me), 2.58 (2 H, t, *J* 7.4 Hz, CH_2CO_2Me), 3.68 (3 H, s, CO_2Me), 7.18 (2 H, m, ArH), and 7.36 (2 H, m, ArH); *m/z* 310 (M^+, 5%), 235 (15), 207 (18), 193 (28), 179 (80), 167 (87), 165 (100), 152 (53), and 115 (25) (Found: M^+, 310.1916; C, 81.65; H, 8.4. $C_{21}H_{26}O_2$ requires M, 310.1934; C, 81.25; H, 8.45%).

4-[2-(*Oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl* *Toluene*-p-*sulphonate* (**19**).—Tosyl chloride (2.25 g, 2 mol equiv.) was added to a solution of compound (**17**) (1.5 g, 5.9 mmol) in dry pyridine (20 ml) at 0 °C. After 2 days at 0 °C the precipitated hydrochloride was removed by filtration and the solvent was removed under reduced pressure to give an oil. The oil was dissolved in ether, and the ethereal solution was washed with dil. HCl, dried ($MgSO_4$), and evaporated. The resulting oil was chromatographed on silica (dichloromethane–hexane, 1:3) to give 4-[2-(*oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl* *toluene*-p-*sulphonate* (**19**) (1.26 g, 52.5%), $\nu_{max.}$ 2 930s, 2 230w, 1 600m, 1 370s, 1 180s, 980s, 760s, and 665m cm^{-1}; δ(270 MHz) 0.90 (3 H, distorted t, terminal Me), 1.10—1.70 (8 H, m, alkylene chain), 2.40 (5 H, m, aromatic Me and C≡CC$H_2C_5H_{11}$), 2.81 (2 H, t, *J* 7 Hz, CH_2CH_2O), 4.20 (2 H, t, *J* 7 Hz, CH_2O), 7.10—7.50 (6 H, m, ArH), and 7.86 (2 H, d, *J* 8 Hz, part of tolyl ABq); *m/z* 253 (58), 236 (28), 193 (49), 183 (31), 179 (69), 178 (50), 165 (100), 152 (57), and 91 (87) (Found: M^+, 408.1738; C, 73.3; H, 6.8. $C_{25}H_{28}O_3S$ requires M, 408.1760; C, 73.50; H, 6.91%).

1-(4-*Bromobut*-1-*ynyl*)-2-(*oct*-1-*ynyl*)*benzene* (**28**).—Triphenylphosphine (2.63 g, 1.2 mol equiv.) was added during 30 min to a solution of compound (**17**) (1.72 g, 6.8 mmol) in dichloromethane (20 ml) containing tetrabromomethane (2.7 g, 1.2 mol equiv.) at 0 °C, under nitrogen. After the mixture had been stirred overnight at 0 °C, the solvent was removed under reduced pressure and the residue was extracted into hexane. The extract was filtered and evaporated, and the residue (2.63 g) was chromatographed on silica (dichloromethane–hexane, 2:3) to yield 1-(4-*bromobut*-1-*ynyl*)-2-(*oct*-1-*ynyl*)*benzene* (1.93 g, 89.5%) as an oil, $\nu_{max.}$ 2 930s, 2 225w, 1 595w, 1 480m, 1 440m, 1 270m, 1 210m, and 755s cm^{-1}; δ(270 MHz) 0.91 (3 H, t, *J* 6.9 Hz, terminal Me), 1.27—1.37 (4 H, m, CH_2CH_2Me), 1.48 (2 H, m, C≡CCH$_2$CH$_2$CH_2R), 1.62 (2 H, m, C≡CCH$_2$CH_2R), 2.46 (2 H, t, *J* 7 Hz, C≡CCH_2R), 3.01 (2 H, t, *J* 7.4 Hz, C≡CCH_2CH$_2$Br), 3.53 (2 H, t, *J* 7.4 Hz, CH_2Br), 7.14 (2 H, m, ArH), and 7.35—7.41 (2 H, m, ArH); *m/z* 318 (M^+, 28%), 316 (M^+, 28), 247 (12), 179 (25), 177 (25), 167 (75), 165 (100), and 152 (38) (Found: M^+, 316.0829; C, 68.3; H, 6.75; Br, 25.25. $C_{18}H_{21}Br$ requires M, 316.0827; C, 68.15; H, 6.65; Br, 25.2%).

Diethyl 2-{4-[2-(*Oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl*}*malonate* (**30**).—Diethyl malonate (1.28 g, 2 mol equiv.) was slowly added to a stirred suspension of potassium hydride (0.32 g, 2 mol equiv.) in THF (5 ml) at 0 °C. After 5 min the effervescence had ceased and the solvent was removed under reduced pressure and replaced with DME (15 ml). To this mixture was added 18-crown-6 (0.2 g) followed by a solution of the tosyl ester (**19**) (1.63 g, 4 mmol) in DME (5 ml). The resulting mixture was stirred overnight at 80 °C after which it was added to dil. HCl and was extracted into ether. The extract was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica (dichloromethane) to give 1-(*but*-3-*en*-1-*ynyl*)-2-(*oct*-1-*ynyl*)-*benzene* (**29**) (0.26 g, 27.5%), $\nu_{max.}$ 2 920s, 2 220w, 1 605w, 1 585w, 1 475m, 915m, and 765s cm^{-1}; δ(90 MHz) 0.90 (3 H, t, *J* 6.6 Hz, terminal Me), 1.28—1.54 (6 H, m, alkylene chain), 1.63 (2 H, m, C≡CCH$_2$CH_2R), 2.46 (2 H, t, *J* 7.1 Hz, C≡CCH$_2$), 5.55 (1 H, dd, J_a 11, J_c 2.3 Hz, C≡C–H$_a$=CH_bH$_c$), 5.74 (1 H, dd, J_a 17.6, J_b 2.3 Hz, C≡CH$_a$=CH$_b$H$_c$), 6.06 (1 H, dd, J_b 11, J_c 17.6 Hz, C≡C–CH_a=CH$_2$), 7.16—7.21 (2 H, m, ArH), and 7.36—7.43 (2 H, m, ArH); *m/z* 236 (M^+, 37%) 178 (50), 165 (100), 152 (55), 139 (33), 115 (30) (Found: M^+, 236.1578; C, 91.25; H, 8.6. $C_{18}H_{20}$ requires M, 236.1564; C, 91.45; H, 8.6%).

Further elution afforded *diethyl* 2-{4-[2-(*oct*-1-*ynyl*)*phenyl*]-*but*-3-*ynyl*}*malonate* (**30**) (0.99 g, 62.5%) as an oil, $\nu_{max.}$ 2 925s, 2 210w, 1 750s, 1 735s, 1 245m, 1 150m, and 755 m cm^{-1}; δ(270 MHz) 0.90 (3 H, t, *J* 6.6 Hz, terminal Me), 1.23—1.5 (12 H, m, ester Me and alkylene chain), 1.62 (2 H, m, C≡CCH$_2$CH_2R), 2.24 [2 H, q, *J* 7.1 Hz, CH_2CH(CO_2Et)$_2$], 2.47 (2 H, t, *J* 7.1 Hz, C≡CCH_2R), 2.57 [2 H, t, *J* 6.9 Hz, C≡CCH_2CH$_2$CH(CO_2Et)$_2$], 3.71 [1 H, t, *J* 7.4 Hz, CH(CO_2Et)$_2$], 4.20 (2 H, t, *J* 7.1 Hz, ester CH$_2$), 4.22 (2 H, t, *J* 7.1 Hz, ester CH$_2$), 7.18 (2 H, m, ArH), and 7.33 (2 H, m, ArH) (Found: C, 75.5; H, 8.15. $C_{25}H_{32}O_4$ requires C, 75.75; H, 8.1%).

Reaction of the bromide (**28**) (1.74 g, 5.5 mol) with diethyl malonate (1.06 g, 1.5 mol equiv.) gave 1-(but-3-en-1-ynyl)oct-1-ynyl)benzene (0.25 g, 19%), identical with that obtained above.

Ethyl *t-Butyl* 2-{4-[2-(*Oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl*}-*malonate* (**32**).—Ethyl t-butyl malonate (2.36 g, 10 mmol) was treated with compound (**19**) (2.04 g, 5 mmol) in the manner described above to give 1-(but-3-en-1-ynyl)-2-(oct-1-ynyl)-benzene (**29**) (0.6 g, 51%), identical with that obtained above, and *ethyl* *t-butyl* 2-{4-[2-(*oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl*}-*malonate* (**32**) (0.52 g, 26%) as an oil, $\nu_{max.}$ 2 925s, 2 220w, 1 750s, 1 730s, 1 595w, and 750 m cm^{-1}; δ(270 MHz) 0.90 (3 H, t, *J* 6.6 Hz, terminal Me), 1.25—1.35 (9 H, m, alkylene chain and ethyl ester Me), 1.47 (9 H, s, Bu^t), 1.61 (2 H, m, C≡CCH$_2$CH_2R), 2.18 [2 H, m, CH_2CH(CO_2R)$_2$], 2.47 (2 H, t, *J* 7.0 Hz, C≡CCH_2R), 2.56 [2 H, t, *J* 7.0 Hz, CH_2CH$_2$CH(CO_2R)$_2$], 3.60 [1 H, t, *J* 7.7 Hz, CH(CO_2R)$_2$], 4.20 (2 H, m, ester CH$_2$), 7.18 (2 H, m, ArH), and 7.37 (2 H, m, ArH); *m/z* 368 (10%), 322 (8), 236 (40), 207 (27), 193 (30), 179 (40), 165 (38), 152 (30), and 57 (100) (Found: M^+, 424.2623; C, 76.2; H, 8.55. $C_{27}H_{36}O_4$ requires M, 424.2613; C, 76.4; H, 8.55%).

(Z)-6-{2-[(Z)-*Oct*-1-*enyl*]*phenyl*}*hex*-5-*enoic Acid* (**5**).—A mixture of acid (**26**) (1.08 g, 3.6 mmol), pyridine (25 ml), and 5% palladium on barium sulphate (0.06 g) was hydrogenated at atmospheric pressure until 2 equiv. of hydrogen had been absorbed. Filtration through Celite and evaporation of the filtrate at reduced pressure gave an oil, which was chromatographed on 10% argentated silica (dichloromethane) to give (Z)-6-{2-[(Z)-*oct*-1-*enyl*]*phenyl*}*hex*-5-*enoic acid* (**5**) (0.53 g, 49%) as an oil, $\nu_{max.}$ 2 920s, 1 710s, 965m, and 750m cm^{-1}; δ(90 MHz) 0.85 (3 H, t, *J* 7.1 Hz, terminal Me), 1.10—1.70 (8 H, m, alkylene chain), 1.83 (2 H, m, $CH_2CH_2CO_2H$), 2.09 (2 H, q, *J* 7.5 Hz, $CH{=}CHCH_2[CH_2]_2CO_2H$), 2.41 (2 H, t, *J* 7.6 Hz, CH_2CO_2H), 5.73 (1 H, dt, *J* 11.5, 7.3 Hz, CH=CHR), 6.08 (1 H, dt, *J* 15.7, 6.9 Hz, $CH{=}CH[CH_2]_3CO_2H$), 6.46 (1 H, d, *J* 11.5 Hz, ArCH=CHR), 6.56 (1 H, d, *J* 15.7 Hz, $ArCH{=}CH[CH_2]_3CO_2H$), and 7.05—7.50 (4 H, m, ArH); *m/z* 300 (M^+, 14%), 213 (20), 197 (100), 143 (38), 141 (50), 129 (87), 128 (40), 115 (35), and 55 (32) (Found: M^+, 300.2080; C, 80.0; H, 9.5. $C_{20}H_{28}O_2$ requires *M*, 300.2089; C, 79.95; H, 9.4%).

(Z)-*Methyl* 6-{2-[(Z)-*Oct*-1-*enyl*]*phenyl*}*hex*-5-*enoate* (**27**).—The diyne (**25**) (1.09 g, 3.5 mmol) was hydrognated in the manner described above to give (Z)-*methyl* 6-{2-(Z)-*oct*-1-*enyl*]*phenyl*}*hex*-5-*enoate* (0.85 g, 77.3%) as an oil, $\nu_{max.}$ 2 925s, 1 740s, 1 640w, 1 595w, and 765m cm^{-1}; δ(270 MHz) 0.86 (3 H, t, *J* 7.2 Hz, terminal Me), 1.25—1.64 (10 H, m, alkylene chain + $CH_2CH_2CO_2Me$), 1.73 (2 H, m, $C{\equiv}CCH_2R$), 2.10—2.23 (4 H, m, $C{\equiv}CCH_2CH_2CH_2CO_2Me$), 3.62 (3 H, s, ester Me), 5.64 (1 H, dt, *J* 11.5, 7.4 Hz, ArCH=CHR), 5.68 (1 H, dt, *J* 11.5, 7.4 Hz, $ArCH{=}CH[CH_2]_3CO_2Me$), 6.36 (1 H, d, *J* 11.3 Hz, CH=CHR), 6.44 (1 H, d, *J* 11.6, $CH{=}CH[CH_2]_3CO_2Me$), and 7.11—7.26 (4 H, m, ArH); *m/z* 314 (M^+, 5%), 197 (70), 169 (20), 155 (35), 141 (50), 129 (100), 128 (55), 105 (22), and 91 (24) (Found: M^+, 314.2250; C, 80.2; H, 9.8. $C_{21}H_{30}O_2$ requires *M*, 314.2246; C, 80.2; H, 9.6%).

Diethyl 2-[(Z)-4-{2-[(Z)-*Oct*-1-*enyl*]*phenyl*}*but*-3-*enyl*]-*malonate* (**34**).—Diyne (**30**) (0.99 g, 2.5 mmol) was hydrogenated in the manner described above to give diethyl 2-[(Z)-4-{2-[(Z)-*oct*-1-*enyl*]*phenyl*}*but*-3-*enyl*]*malonate* (**34**) (0.84 g, 83.5%) as an oil, $\nu_{max.}$ 2 930s, 2 890m, 1 750s, 1 635w, 1 590w, and 770s cm^{-1}; δ(270 MHz) 0.86 (3 H, t, *J* 7 Hz, terminal Me), 1.10—1.40 (14 H, m, alkylene chain + ester Me), 2.0 [2 H, q, *J* 7.7 Hz, $CH_2CH(CO_2Et)_2$], 2.18 [4 H, m, $CH{=}CHCH_2CH_2CH(CO_2Et)_2$ + $CH{=}CHCH_2R$], 3.30 [1 H, t, *J* 7.4 Hz, $CH(CO_2Et)_2$], 4.70 (4 H, m, ester CH_2), 5.66 {2 H, m, $CH{=}CH[CH_2]_2CH(CO_2Et)_2$ + CH=CHR}, 6.36 (1 H, d, *J* 11.5 Hz, CH=CHR), 6.46 {1 H, d, *J* 11.5 Hz, $CH{=}CH[CH_2]_2CH(CO_2Et)_2$}, and 7.20 (4 H, m, ArH); *m/z* 400 (M^+, 3%), 269 (5), 240 (47), 167 (30), 165 (27), 155 (100), 141 (50), 129 (80), 128 (55), and 115 (32) (Found: M^+, 400.2615; C, 74.75; H, 9.15. $C_{25}H_{36}O_4$ requires *M*, 400.2613; C, 74.95; H, 9.05%).

General Hydrolysis Procedure.—Lithium hydroxide monohydrate (1.5 mol equiv.) was added to a solution of an ester (2.5 mmol) in aqueous THF (1:1; 40 ml) and the resulting solution was heated to reflux overnight. After cooling and acidification with dil. HCl, the product was extracted into ether, and the extract was dried ($MgSO_4$) and evaporated. Chromatography on C_{18} reverse-phase silica (95% MeOH–water) yielded the corresponding acid. In this manner the following compounds were prepared:

6-[2-(*Oct*-1-*ynyl*)*phenyl*]*hex*-5-*ynoic acid* (**26**), yield 95%, oil (Found: C, 81.2; H, 8.05. $C_{20}H_{24}O_4$ requires C, 81.05; H, 8.15%).

(Z)-6-{2-[(Z)-*Oct*-1-*enyl*]*phenyl*}*hex*-5-*enoic acid* (**5**), yield 93%, oil (Found: C, 80.1; H, 9.5. $C_{20}H_{28}O_2$ requires C, 79.95; H, 9.4%).

2-{4-[2-(*Oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl*}*malonic acid* (**31**), yield 88%, m.p. 52—53.5 °C (Found: C, 71.8; H, 7.0. $C_{21}H_{24}O_4{\cdot}0.5H_2O$ requires C, 72.2; H, 7.2%).

2-[(Z)-4-{2-[(Z)-*Oct*-1-*enyl*]*phenyl*}*but*-3-*enyl*]*malonic acid* (**6**), yield 80%, oil (Found: C, 69.65; H, 8.15. $C_{21}H_{28}O_4{\cdot}H_2O$ requires C, 69.6; H, 8.35%).

t-Butyl hydrogen 2-{4-[2-(*oct*-1-*ynyl*)*phenyl*]*but*-3-*ynyl*}-*malonate* (**33**), yield 62%, oil (Found: C, 75.9; H, 8.35. $C_{25}H_{32}O_4$ requires C, 75.7; H, 8.15%).

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