ELSEVIER

Chemistry and Physics of Lipids
85 (1997) 157–174

CPL
CHEMISTRY AND PHYSICS OF LIPIDS

Synthesis of polyunsaturated constituents of phenolic lipids[1]

John H.P. Tyman*, N. Visani

Department of Chemistry, Brunel University, Uxbridge, Middlesex, UB8 3PH, UK

Received 22 October 1996; revised 10 December 1996; accepted 11 December 1996

Abstract

The diene, (*ZZ*)-[(8,11)-pentadecadienyl]salicylic acid, (or 2-hydroxy-6-[(*ZZ*)-pentadeca-8,11-dienyl]benzoic acid), has been synthesised by two routes. In the first, the key intermediate methyl or ethyl 2-hydroxy-6-(7-bromoheptyl)benzoate has been converted to methyl or ethyl 2-hydroxy-6-(10-hydroxydec-8-ynyl)benzoate and thence by reaction of the corresponding bromide with 1-pentynylmagnesium bromide to methyl or ethyl 2-hydroxy-6-(pentadeca-8,11-diynyl)benzoate. Selective reduction afforded methyl or ethyl 2-hydroxy-6-[(*ZZ*)-pentadeca-8,11-dienyl]benzoate. An attempt to employ the Grignard reagent from methyl 2-methoxy-6-(non-8-ynyl)benzoate and reaction with 1-bromohex-2-yne was ineffective because of a side reaction of the former with ethylmagnesium bromide to give a ketone. In the third approach ethyl 2-methoxy-6-methylbenzoate was alkylated with 1-iodotetradeca-7,10-diyne and the product selectively reduced as before to the O-methyl ether ethyl ester. A variety of C_{14} intermediates has been prepared for the derivation of the 8(*E*),11(*E*), 8(*E*),11(*Z*) and 8(*Z*),11(*E*) stereoisomers by the alkylation procedure. A similar methodology of alkylation can be adopted for obtaining corresponding trienes in which some progress has been made commencing with the synthesis of the 8(*Z*),11(*Z*),14 compound. © 1997 Elsevier Science Ireland Ltd.

Keywords: Phenolic lipid; Anacardic acid; Dienes; Trienes; Synthesis; Alkynes

1. Introduction

Phenolic lipids are widely distributed in many botanical and biological species most notably in the Anacardiaceae, for example *Anacardium occidentale*, the cashew tree, in which the principal component of the nut-shell is anacardic acid (**1**; $m = 15$, $n = 0,2,4,6$), a salicylic acid bearing a C_{15} alkyl, alkenyl, alkadienyl or alkatrienyl group in the 6-position (Tyman, 1979, 1991, 1996). Some other examples are the C_{13} and C_{15} compounds (**1**; $m = 13,15$, $n = 0,2$) in the pistachio nut, *Pistacia vera* (Yalpani and Tyman, 1983) and C_{17} members (**1**; $m = 17$, $n = 6$) in the African plum *Spondias mombin* (Coates et al., 1994; Arogba, 1987). Nut-

* Corresponding author. Tel.: 01895 274000.

[1] Long Chain Phenols, Part 34. Part 33, ref. 30.

PII S0009-3084(96)02654-0

meg, the liverwort, *Schistochila appendiculata* (Asakawa et al., 1987), and brown algae (Kazlauskas et al., 1980) are some other sources of saturated and unsaturated anacardic acids, although the unsaturated members are generally more prolific in a wide range of species including certain geraniums (Walters et al., 1989), mushrooms (Gianetti et al., 1978), and the Ginkgo biloba tree (Tyman, 1996; Itokawa et al., 1987).

Anacardium occidentale also contains 5-alkenylresorcinols, the cardols (**2**, $n = 0,2,4,6$) and 3-alkenylphenols, the cardanols (**3**, $n = 0,2,4,6$) and similar structures with C_{11} and C_{13} homologues are abundant in numerous species notably the Grevillea (Tyman, 1996) and with higher homologues in rye, *Cereale secale* (Kozubek and Tyman, 1995). Structures isomeric with the cardols are the 3-alkenylcatechols, the urushiols (**4**; $m = 15,17$, $n = 0,2,4,6$) of the Rhus genus such as *Rhus vernicifera* which contains not only the C_{15}, 8*Z*,11*Z*,14-triene (**4**, $n = 6$) but the isomeric 8*Z*,11*E*,13*E* and 8*Z*,11*Z*,13*Z* compounds (Miyakoshi et al., 1991). The thitsiols of Burmese lac, and other South Eastern Asian lacs, from *Melanorrhea usitata* are isomeric 4-alkenylcatechols (**5**; $m = 15,17$, $n = 0,2,4,6$) (Sargent and Wanachareontrajkul, 1989).

Many of these species are pest-resistant and indeed the properties particularly of anacardic acids in this respect are legendary (Tyman, 1979). In more recent work a wide variety of other properties have been revealed. Thus they have been found to be inhibitory towards methicillin-resistant *Staphylococcus aureus* (MSA) (Muroi and Kubo, 1996), to a number of enzymes such as prostaglandin synthase (Grazzini et al., 1991), glycerol-3-phosphate dehydrogenase (Irie et al., 1996), and β-lactamase (Coates et al., 1994). Furthermore they have proved useful molluscicides (Sullivan et al., 1982), thus of incidental interest for the control of schistosomiasis (Kubo et al., 1986), to have antitumour properties (Kubo et al., 1993a), and further applications for their long-established antimicrobial activity (Kubo et al., 1993b). Many potential technical uses (Tyman, 1996) have been discovered and the more unsaturated members such as the diene and triene appear to have greater interest in structure/property studies (Sullivan et al., 1982).

The isolation of mixed anacardic acids extracted (Tyman et al., 1989) from, for example, the cashew by ammoniated TLC (Tyman and Morris, 1967) or by a column chromatographic method (Nagabhushana and Ravindranath, 1995) is laborious and their subsequent separation into mono-, di- and triene constituents by argentation chromatography (Jacobs and Tyman, 1971) is expensive and time-consuming although preparative HPLC separations represent an advance in methodology (Tyman, 1991). Synthesis from readily available intermediates is nevertheless of interest particularly of the diene and triene constituents to obtain larger quantities and to aid stereochemical structure/property studies.

Saturated anacardic acids (**1**; $m = 15$, $n = 0$) were first synthesised by the thermolysis of basic copper salts of 2-alkylbenzoic acids (Durrani and Tyman, 1979a) and in improved yields by alkyllithium addition to the aryne from 2-fluoro or 3-fluoromethoxybenzene (Durrani and Tyman, 1979b), a method which was applied to the synthesis of (15:1)-anacardic acid, ginkgolic acid (Tyman, 1976). More recently saturated and monounsaturated anacardic acids have been prepared (Visani, 1988; Tyman and Visani, 1996) by the C-alkylation of the readily available methyl or ethyl 6-methyl-2-methoxybenzoates. The recently described synthesis of (15:2)-anacardic acid, anacardic acid diene (Zehnter and Gerlach, 1995), by the Diels-Alder addition of 1-methoxycyclohexa-1,3-diene (obtained from Birch reduction of methoxybenzene, followed by conjugation) with homologous propiolic esters, an extension of work in which methyl propiolate was employed (Kanakam et al., 1989) and with subsequent steps by strategies employed in our own work for the synthesis of (15:2)-cardol (Baylis et al., 1981) and (15:2)-cardanol (Caplin and Tyman, 1982), has prompted us to publish our results. This was completed some years ago (Visani, 1988) and referred to in a review but with no practical details (Tyman and Visani, 1986).

1.1. Synthesis of dienes

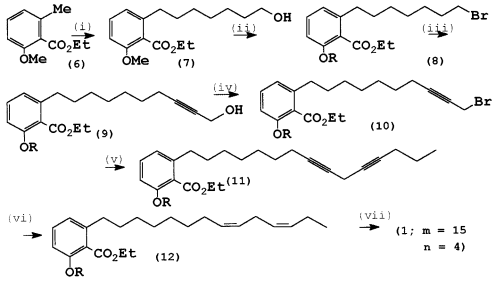
Synthetic work towards the dienes (and trienes) of cardanol, cardol, urushiol and thitsiol primar-

ily by acetylenic and Wittig reaction routes (Tyman, 1996) has been more extensive than with the anacardic acids where alkylation and acetylenic methods have been generally adopted. The ultimate objective in our work was to synthesise the four stereoisomers in the diene series, namely the 8(*Z*),11(*Z*), the 8(*E*),11(*E*), the 8(*Z*),11(*E*), and the 8(*E*),11(*Z*) compounds, commencing with the natural 8(*Z*),11(*Z*) isomer and to extend the work to the syntheses of stereoisomeric trienes.

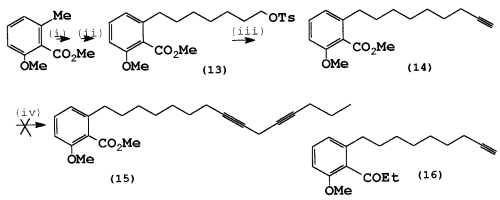
In the acetylenic approach (Scheme 1), an ArC_1 synthon (**6**), ethyl 2-methoxy-6-methylbenzoate was reacted with 6-chlorohexanol (HO-protected with ethyl vinyl ether) to afford an ArC_7 intermediate (**7**; R = Me) (ethyl 6-(7-hydroxyheptyl)-2-methoxybenzoate). From the derived bromide (**8**; R = Me), with lithioprop-2-ynol (HO-protected as the *t*-butyldimethylsilyl ether) an ArC_{10} hydroxy intermediate, ethyl 6-(10-hydroxy-8-decynyl)-2-methoxybenzoate (**9**; R = Me) was obtained and thence the ArC_{10} bromide (**10**; R = Me) which with a C_5 synthon (1-pentyne), afforded the ArC_{15} diyne (**11**; R = Me), ethyl 2-methoxy-6-(pentadeca-8,11-diynyl)benzoate. Catalytic reduction in ethanol containing quinoline with Pd-$BaSO_4$/hydrogen gave the corresponding diene, ethyl (*Z*,*Z*)-2-methoxy-6-(pentadeca-8,11-dienyl)benzoate (**12**; R = Me) and hydrolysis/demethylation with lithium *t*-butyl thiolate afforded (**1**; $m = 15$, $n = 4$).

1.1.1. Reagents

(i) LiN^iPr_2, THF, HMPA; $Cl(CH_2)_6OCH(Me)OEt$, −70°C to 65°C, heat; H_3O^+, (ii)



Scheme 1. Synthesis of 8*Z*,11*Z*-diene by the route, $ArC_1 \rightarrow ArC_7ArC_{10} \rightarrow ArC_{15}$.



Scheme 2. Attempted synthesis of 8*Z*,11*Z*-diene by the route $ArC_1 \rightarrow ArC_7 \rightarrow ArC_9 \rightarrow ArC_{15}$.

4-TsCl, pyr.; DMSO, LiBr, (iii) BuLi, THF, $HC \equiv CCH_2OSiBu^tMe_2$, HMPA; H_3O^+, (iv) PBr_3, pyr., Et_2O, (v) $HC \equiv CC_3H_7$, EtMgBr, THF; CuI, heat, 50°C, (vi) Pd-$BaSO_4/H_2$, quinoline, EtOH, (vii) $LiSBu^t$, DMF.

In a variation of this method (shown in Scheme 1), (**7**) was demethylated and converted to the bromide with boron tribromide to give ethyl 6-(7-bromoheptyl)-2-hydroxybenzoate (**8**; R = OH). Reaction of this with lithioprop-2-ynol (HO-protected as before) afforded ethyl 6-(10-hydroxy-8-decynyl)-2-hydroxybenzoate (**9**; R = OH). The bromide (**10**; R = Br) formed with ethereal phosphorus tribromide containing pyridine, reacted with excess 1-pentynylmagnesium bromide in THF containing copper(I) iodide to give (**11**; R = OH), ethyl 2-hydroxy-6-(pentadeca-8,11-diynyl)benzoate. This was catalytically reduced to the diene (**12**; R = OH) as for the methyl ether and the product hydrolysed to afford (**1**; $m = 15$, $n = 4$).

1.1.2. Reagents

(ii) (**8**, R = OH), BBr_3, CH_2Cl_2, −70°C to 20°C, (iii) Excess, $LiC \equiv CCH_2OCH(Me)OEt$, THF, HMPA, (iv) PBr_3, pyr., Et_2O, (v) Excess, $BrMgC \equiv CC_3H_7$, CuI, THF, (vi) Pd-$BaSO_4/H_2$, quinoline, (vii) EtOH, KOH; H_3O^+.

In the second acetylenic approach (Scheme 2), a related ArC_7 intermediate (**13**), methyl 2-methoxy-6-(7-tosylheptyl)benzoate was converted with the lithium acetylide-diaminoethane complex to a terminal alkyne, ArC_9 (**14**), methyl 2-methoxy-6-(8-nonynyl)benzoate, but attempts to react this with the C_6 synthon, 1-bromo-2-hexyne, to form (**15**) did not succeed due to a side-reaction of the methoxycarbonyl group, resulting in a ketone (**16**).

1.1.3. Reagents

(i) $LiN^{I}Pr_2$, THF, HMPA, $Cl(CH_2)_6OCH(Me)OEt$, $-70°C$ to 65°C, heat; H_3O^+, (ii) 4-TsCl, pyr., heat, (iii) $LiC\equiv CH-H_2N(CH_2)_2NH_2$, DMSO, 10°C, (iv) THF, EtMgBr; CuCl, $BrCH_2C\equiv CC_3H_7$.

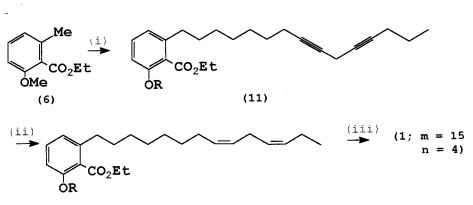
In the alkylation strategy in our work, ethyl 6-methyl-2-methoxybenzoate (**6**) was alkylated with a diunsaturated C_{14} component, 1-iodotetra-7,11-diyne (**18**), to afford the ArC_{15} diyne (**11**; R = Me) from which the ArC_{15} diene (**12**; R = Me) was obtained by catalytic reduction. The required product (**1**; $m = 15$, $n = 4$) was derived by hydrolysis and demethylation (Scheme 3).

1.1.4. Reagents

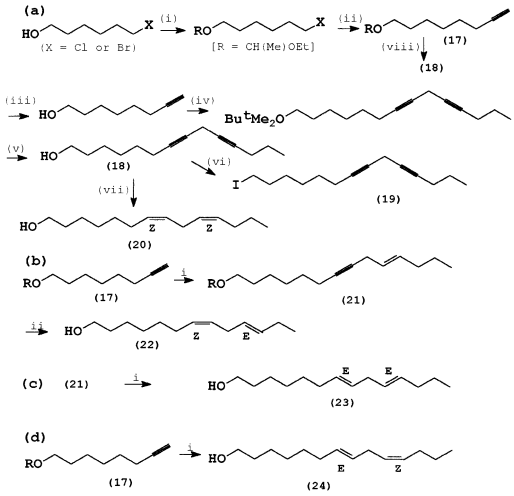
(i) $LiNPr^{i}_2$, THF, HMPA; $I(CH_2)_6C\equiv CCH_2C\equiv CC_3H_7$, $-70°C$ to 25°C, (ii) Pd-$BaSO_4/H_2$, EtOH, quinoline, (iii) $LiSBu^{t}$, DMF.

The alkylation of (**6**) is applicable to other intermediates for the synthesis of anacardic acids having the first double bond at other positions, at for example the 4-position. Thus, the reaction of (**6**) with HO-protected 3-chloropropanol led to ethyl 6-(4-hydroxybutyl)-2-methoxybenzoate.

The required C_{14} diyne reactant, 1-iodotetradeca-7,10-diyne (**19**), employed for Scheme 3 was synthesised by an acetylenic route (Scheme 4(a)). 6-Chloro or 6-bromohexan-1-ol protected as the 1-ethoxyethyl ether was reacted with lithium acetylide to form 8-(1-ethoxyethoxy)oct-1-yne (**17**). Its magnesiobromo derivative was reacted with 1-bromohex-2-yne in THF containing cuprous chloride and removal of the protective group afforded 1-hydroxytetradeca-7,10-diyne (**18**). Alternatively in a study of the relative effectiveness of protective groups, deprotected (**17**) was converted to the *t*-butyldimethylsilyl ether which was then reacted with 1-bromohex-2-yne as before, followed by removal of the protective group. Reaction of the trimethylsilyl (TMS) ether of (**18**) with sodium iodide in acetonitrile gave 1-iodotetradeca-7,10-diyne (**19**). Catalytic reduction of the diyne (**18**) with palladium-barium sulphate in the presence of quinoline resulted in 1-(*Z*,*Z*)-1-hydroxytetradeca-7,10-diene (**20**). These approaches are depicted in Scheme 4, which also shows the preparation by the routes (b), (c) and (d), from (**17**) of the three stereoisomeric tetradecadienols. In (b), the magnesiobromo derivative of (**17**) was reacted with (*E*)-1-bromohex-2-ene to afford the 7-yne-(*E*)10-ene (**21**) which upon catalytic hydrogenation with Pd-$BaSO_4$ gave 7(*Z*),10(*E*)-1-hydroxytetradeca-7,10-diene (**22**). By route (c), reduction of (**21**) with sodium in ammonia afforded after deprotection, (*E*,*E*)-1-hydroxytetradeca-7,10-diene (**23**). From route (d), (**17**) by reaction with (*Z*)-1-bromohex-2-ene in THF containing copper(I) chloride and deprotection, the 7(*E*),10(*Z*)-1-hydroxytetradeca-7,10-diene (**24**) was obtained.



Scheme 3. Synthesis of 8*Z*,11*Z*-diene by route $ArC_1 \rightarrow ArC_{15}$.



Scheme 4. Synthesis of stereoisomeric diene C_{14} alkylation reactants.

1.1.5. Reagents

(a) (i) CH_2=CHOEt, 4-TSA, (ii) $LiC\equiv CH$, NH_3, THF, HMPA, (iii) MeOH, HCl, (iv) $Bu^{t}Me_2Cl$, DMF, imidazole; EtMgBr, THF; CuCl, $BrCH_2C\equiv CC_3H_7$; (v) Bu_4NF, THF, (vi)

Me_3SiCl, pyr.; MeCN, NaI; (vii) Pd-$BaSO_4$, H_2, EtOAc, quinoline, (in step (ii), 6-halogenohexan-1-ol was alternatively treated with $LiC \equiv CH$–$H_2NCH_2CH_2NH_2$, THF, DMSO; MeOH, HCl.), (viii) EtMgBr, THF, CuCl, $BrCH_2C \equiv CC_3H_7$; MeOH, HCl. (b) (i) EtMgBr, THF; CuCl, THF, (*E*)–$BrCH_2CH{=}CHC_3H_7$, (ii) Pd-$BaSO_4$, H_2, EtOAc, quinoline; MeOH, HCl. (c) (i) Na/NH_3, THF, HMPA; MeOH, HCl. (d) (**17**) (i) EtMgBr, THF; CuCl, THF, (*Z*)–$BrCH_2CH{=}CHC_3H_7$; Na/NH_3, THF, HMPA; MeOH, HCl.

1.2. Synthesis of trienes

Compared with the diene series the synthesis of trienes by acetylenic routes has met with greater difficulties. Thus in the cardanol series attempts to react the 3-methoxy analogue of the ArC_{10} bromide (**10**), namely 3-(10-bromo-8-decynyl)-methoxybenzene, with the mono Grignard reagent of either penta-1,4-diyne (Brandsma and Verkuijsse, 1981) or pent-1-yne-4-ene (Brandsma, 1971) followed by selective reduction of the triyne or diynene were unsuccessful. Model experiments on the selective catalytic hydrogenation of nona-4-yn-1-ene to produce nona-1,4-diene proved impractical.

By contrast greater success has been obtained in the urushiols (**4**), the thitsiols (**5**) and with the compound, 5-methoxy-3-[(*ZZ*)-pentadeca-8,11,14-trienyl]-1,2,4-trihydroxybenzene (**25**) by way of Wittig reaction methodology.

The experimental work (Sato, 1973) in which the synthesis of the dimethyl ether of 3-[(*ZZZ*)-pentadeca-8,11,13-trienyl]-catechol was reported has not been revealed but recently (Miyakoshi et al., 1991) full details of Wittig routes have been described by another group for the 8(*Z*),11(*Z*),14 and 8(*Z*),11(*E*),13(*E*) triene isomers of (**4**; $m = 15$, $n = 6$). Progress has also been made (Sargent and Wangchareontrakul, 1989) with the synthesis of thitsiols (**5**; $m = 15$, $n = 4{,}6$). A Wittig route (Sargent and Wangchareontrakul, 1989) which in theory could lead to the 8(*Z*),11(*Z*),14-triene in the cardol series (**2**; $n = 6$) was bypassed to give the trihydroxymethoxy compound (**25**). These syntheses involved the selective catalytic reduction of an internal triple bond in the presence of a terminal double bond, in the compound hept-6-ene-4-yn-1-ol, a procedure which was found impractical in our work carried out with catalysts available 10 years earlier.

Since the use of the acetylenic bromide (**10**) with a C_5 reactant appeared unpromising, experiments towards the triene (Visani, 1988) were directed to the alkylation route by reaction of a triunsaturated C_{14} iodide, from 1-hydroxytetra-13-ene-7,10-diyne, with the carbanion of ethyl 2-methoxy-6-methylbenzoate. 1-Ethoxyethyl 7-octynyl ether (**17**) was converted to the magnesiobromo derivative with ethyl magnesium bromide and reacted in THF containing copper(I) chloride with 1-bromohex-5-ene-2-yne to give the 7,10-diyn-13-ene (**26**). Removal of the protective group with 1% methanolic hydrochloric acid afforded the diynenol (**27**) which was converted to the iodide (**28**) by conversion to the trimethylsilyl ether in pyridine solution and reaction of the TMS ether with sodium iodide in acetonitrile solution. The carbanion of ethyl 2-methoxy-6-methylbenzoate reacted with the iodide to give ethyl 2-methoxy-6-pentadeca-8,11-diyn-14-enyl)-benzoate (**29**) which was purified by flash chromatography. Reduction with dibromoborane-dimethyl sulphide complex resulted in the 8(*Z*),11(*Z*),14-triene (**30**) as shown in Scheme 5.

1.2.1. Reagents

(i) 4-TSA, $CH_2{=}CHOEt$, (ii) EtMgBr, THF; CuCl, $BrCH_2C \equiv CCH_2CH{=}CH_2$, (iii) MeOH, HCl, (iv) Me_3SiCl, pyridine; MeCN, NaI, (v) $LNiPr^i_2$, THF, HMPA, $MeC_6H_3(OMe)CO_2Et$, (vi) (i-C_5H_{11})BH, THF.

2. Experimental procedures

2.1. Extraction of material

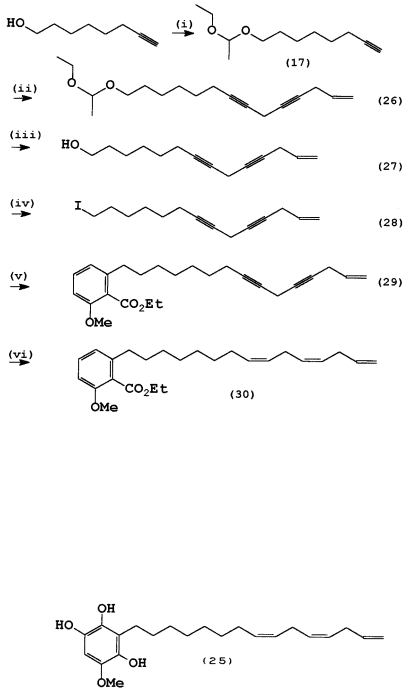
Natural cashew nut-shell liquid was extracted from raw nuts (*Anacardium occidentale*) as described (Tyman, 1973).

2.2. Chromatography

TLC was performed on silica gel GF254, column chromatography on silica gel (60–120 mesh) (BDH), flash chromatography with Kieselgel 60 (40–63 mμ) (Merck), dry flash chromatography with Kieselgel 60H and with 60GF (Merck) and with alumina (aluminiumoxid 60GF, neutral type E (Merck)). Argentation TLC was performed on HPTLC plates containing silica gel 60 incorporating 10% silver nitrate (Tyman and Morris, 1967; Jacobs and Tyman, 1971).

2.3. Spectroscopy

Infrared spectra were recorded on a Perkin Elmer 5100 instrument, liquids as neat films or as carbon tetrachloride solutions. ^{1}H-NMR spectra were obtained on a Varian CFT-20 (80 MHz) instrument. Mass spectra were determined on a modified AEI MS 902 instrument and accurate mass measurements by the SERC centre at the University of Swansea. Elemental analyses were carried out by Butterworth Laboratories.



Scheme 5. Synthesis of 8*Z*,11*Z*,14-triene.

2.4. Preparation of general intermediates

All reactions were effected in anhydrous conditions under nitrogen.

C_5 and C_6 alkenyl and alkynyl bromides were prepared by three methods, (1) by reaction of the alkenol or alkynol in diethyl ether containing pyridine, with phosphorus tribromide at -30°C, (2) by reaction of the trimethylsilyl ether in acetonitrile with lithium bromide (Moshidis, 1986) and (3) from the 4-toluenesulphonate by reaction in DMSO with lithium bromide (Kabalka et al., 1986; Brandsma and Verkuijsse, 1981). By method (1), 1-bromohex-5-ene, (*E*)-1-bromohex-2-ene, 1-bromohex-2-yne, 1-bromohex-2-yne-5-ene, and other bromides were obtained as given in Section 2.7. By method (2), 1-bromo-9-decene and methyl 6-(7-bromoheptyl)-2-methoxybenzoate were derived. Method (3) was employed for ethyl 6-(7-bromoheptyl)-2-methoxybenzoate and 1-bromooct-7-yne.

Alkyl iodides were obtained from the trimethylsilyl (TMS) derivative with sodium iodide in acetonitrile containing TMS chloride (Morita et al., 1979). 1-Iodooct-7-yne, 1-iodotetradeca-7-ene and 1-iodooctadeca-9-ene and other iodides as indicated in Section 2.7 were prepared by this method.

C_6 Alkynols and alkenols envisaged as necessary for the $ArC_9 + C_6$ route to the C_{15} diene were adapted from standard routes. Thus (*E*)-hex-2-en-1-ol was obtained from the dilithio derivative of prop-2-yn-1-ol and 1-bromopropane followed by Li/ammonia reduction. Hex-2-yn-1-ol was also isolated and catalytically hydrogenated in ethanol containing quinoline and Pd-$BaSO_4$ to (*Z*)-hex-2-en-1-ol. Hex-2-yn-1-ol was also derived from dilithio salt of prop-2-yn-1-ol by reaction with iodopropane and as described (Brandsma and Verkuijsse, 1981) by reaction of lithio 1-pentyne with paraformaldehyde in 81% yield.

Diunsaturated C_6 components were also prepared. Hex-5-en-2-yn-1-ol was synthesised from the magnesiobromo derivative of prop-2-ynyl 1-ethoxyethyl ether by reaction with 1-chloroprop-

2-ene in THF containing copper(I) chloride. Following removal of the ethoxyethyl group by acidic methanolysis, the product was obtained in 35% yield (required for C_6H_8O, m/z, 96.0575; found, 96.0576).

Hexa-2,5-diyn-1-ol (Brandsma, 1971) was prepared from the foregoing prop-2-ynyl 1-ethoxyethyl ether by reaction with 1-bromoprop-2-yne by reaction in THF containing copper(I) chloride.

Methyl and ethyl 2-methoxy-6-methyl benzoates were prepared as indicated (Hauser and Pogany, 1980) but with minor modifications.

The alkylation of these compounds to saturated, monoalkenyl and alkynyl compounds has been described (Visani, 1988; Tyman and Visani, 1996) by conversion of the respective alkyl 2-methoxy-6-methylbenzoate in THF at -70°C to the carbanion with lithium diisopropylamide, addition of HMPA and then of the alkyl, alkenyl or alkynyl halide.

2.5. Protective groups

A wide variety of protective groups were examined both for the aromatic component and the respective side-chain material.

2.5.1. The aromatic component

Ethyl 2-hydroxy-6-methylbenzoate (3.0 g, 16.7 mmol) was converted to the TMS ether with hexamethyldisilazane (4.02 g, 25.0 mmol) and a catalytic quantity (2 drops) of TMS chloride by refluxing for 9 h. Concentration and distillation of the residue afforded ethyl 6-methyl-2-trimethylsiloxybenzoate (3.50 g) in 83% yield, b.p. 104°C/0.9 mm and characterised from its ^{1}H-NMR and mass spectra.

Ethyl 2-hydroxy-6-methylbenzoate (1.0 g, 6.67 mmol) was converted to the *t*-butyldimethylsilyl ether (Corey and Venkateswalu, 1972) in DMF (6 cm^3) containing imidazole (0.94 g, 13.9 mmol) and reacted with dimethyl-*t*-butylsilyl chloride (1.0 g, 6.67 mmol) in DMF (2 cm^3) at 35°C during 48 h to give ethyl 2-dimethyl-*t*-butylsiloxy-6-methylbenzoate (1.55 g) after aqueous sodium bicarbonate work-up and ethereal extraction. It was characterised by TLC, and its ^{1}H-NMR and mass spectra.

Ethyl 2-hydroxy-6-methylbenzoate (1.00 g, 5.56 mmol) in dry THF (10 cm^3) was converted to the benzyl ether by treatment with sodium hydride (0.29 g, 6.16 mmol) and after the addition of tetrabutylammonium iodide (20 mg) benzyl chloride was introduced (0.70 g, 5.56 mmol). The reaction mixture was stirred at ambient temperature for 24 h and then, after TLC monitoring, addition of further catalyst and refluxing for 24 h, worked up to give (1.64 g) ethyl 2-benzyloxy-6-methylbenzoate which was substantially pure by TLC and was characterised chromatographically and spectroscopically.

Methyl 2-hydroxy-6-methylbenzoate (1.00 g, 6.02 mmol) was converted to the methoxymethyl ether (Corey and Venkateswalu, 1972; van Heerden et al., 1978), by stirring in dichloromethane (10 cm^3) containing the phase transfer catalyst Adogen 464 (0.02 mmol), and sodium hydroxide (0.36 g, 9.03 mmol) in water (3.5 cm^3) at ambient temperature for 20 min. Iodomethyl methyl ether (Yung et al., 1978) (3.12 g, 24.09 mmol) was then added and following reaction for 30 min, the mixture was worked up by dilution with water and dichloromethane extraction to give a red-coloured liquid (1.63 g) which was purified by dry flash chromatography to afford methyl 2-methoxymethyl-6-methylbenzoate (1.15 g) in 91% yield. It was characterised by its ^{1}H- NMR and its mass spectrum.

2.5.2. The side-chain component

The triphenylmethyl, the *t*-butyldimethyl and the 1-ethoxyethyl groups were examined.

1-Hydroxyoct-7-yne (1.00 g, 7.94 mmol) was converted to the trityl ether (Chaudhary and Hernandez, 1979) with trityl chloride (2.43 g, 8.73 mmol), 4-dimethylaminopyridine (0.05 g, 0.39 mmol) and triethylamine (2 cm^3) in DMF (25 cm^3) by stirring overnight at ambient temperature. After work-up by dichloromethane extraction and recovery and purification by dry flash chromatography, 1-triphenylmethoxy-oct-7-yne was derived as a yellow liquid (1.61 g) in 55% yield.

1-Dimethyl-*t*-butylsiloxyoct-7-yne was prepared (Corey and Venkateswalu, 1972) in 99% yield from 1-hydroxyoct-7-yne (2.0 g, 15.87 mmol) with *t*-butyldimethylsilyl chloride (2.87 g, 19.04 mmol)

and imidazole (2.70 g, 39.7 mmol) in DMF (4 cm^3) by reaction at 35°C during 12 h. Aqueous work-up, ethereal extraction followed by dry flash chromatography gave the pure derivative as a clear liquid (3.78 g).

1-Ethoxyethyl ethers were prepared as described (Tyman, 1979; Harwood, 1985). In the general method used the alcohol (1 M) was added dropwise to ethyl vinyl ether (2.8 M) cooled to 0°C and containing 4-toluenesulphonic acid (50 mg) while the temperature was maintained between 0–10°C. After 3 h the mixture was allowed to warm to below 20°C, then cooled prior to the addition of saturated potassium carbonate solution. After work-up by ethereal extraction, drying and concentration, an almost theoretical yield of the 1-ethoxyethyl ether of the respective alcohol was obtained. In this way 3-chloropropyl 1-ethoxyethyl ether, 7-chlorheptyl 1-ethoxyethyl ether, prop-2-ynyl 1-ethoxyethyl ether and 1-ethoxyethyl oct-7-ynyl ether were prepared.

2.6. General conditions for reduction of carbon-carbon triple bonds

2.6.1. Catalytic hydrogenation

To a suspension of 5% Pd-$BaSO_4$ (50% w/w) in ethyl acetate, a solution of quinoline (1 drop/g catalyst) in ethyl acetate was added and the mixture shaken with hydrogen in a glass vessel for 20 min. The alkyne in ethyl acetate was added through a septum and the mixture shaken at ambient temperature until the theoretical uptake of hydrogen had been achieved. The mixture was filtered through celite and the combined filtrate and washings, washed with dilute hydrochloric acid, dried and evaporated to give the crude product which was purified chromatographically. In this way, (*Z*)-hex-2-en-1-ol and (*Z*)-1-bromohex-2-ene and other compounds were derived as described in the experimental.

2.6.2. Alkali metal-ammonia reduction

To 100% ammonia small pieces of sodium (3 mol) were added. The alkyne in THF containing 10% HMPA was introduced to the solution and the mixture maintained under reflux for 2–3 h. The reaction mixture was quenched by the gradual addition of saturated ammonium chloride and stirred at ambient temperature to evaporate the ammonia. Ethereal extraction, washing and evaporation afforded the crude product which was purified by chromatography.

The combined alkynylation/reduction procedure (Patterson, 1985) was also used. To 100% ammonia containing ferric nitrate, lithium in small pieces was added, the blue colour being allowed to disappear between each addition. The alkyne in THF was then introduced and the mixture allowed to reflux for 1 h after which the halide was added over 20 min and the mixture allowed to reflux for 2 h. Lithium wire was then introduced until a persistent blue colour remained for 30 min. The reaction mixture was quenched with saturated ammonium chloride and the ammonia allowed to evaporate. The crude product was extracted with ether and purified after concentration by distillation or chromatography.

2.6.3. Hydroboration

Diisoamylborane was prepared (Dupont et al., 1954) by adding an equal volume of a 1 M solution of borane-THF complex to a 2 M solution of 2-methylbut-2-ene in THF kept at −5–0°C. The mixture was stirred at 0–5°C for 2 h, then transferred via a canula to the reaction flask containing the alkyne to be reduced.

Dicyclohexylborane was similarly prepared from cyclohexene (2 mols) and borane-THF complex in THF at −5–0°C. The resultant precipitate was stirred at the same temperature for 1 h. The alkyne in THF was added at 0°C and the reaction monitored by TLC.

The dibromoborane-dimethylsulphide complex (1 M) in dichloromethane was also used by addition to the alkynyl compound in 1,2-dichloroethane at 10–15°C during 1–2 h. The product was purified by chromatography.

2.7. Synthesis of dienes and trienes

All reactions were carried out in dry conditions under nitrogen.

*2.7.1. Ethyl 6-(7-hydroxyheptyl)-2-methoxybenzoate (**7**)*

n-Butylithium (38.9 mmol) was added to a solution of diisopropylamine (38.9 mmol) in dry THF (120 cm^3) under nitrogen and the mixture stirred at ambient temperature for 15 min. Ethyl 2-methoxy-6-methylbenzoate (5.0 g, 27.8 mmol) in dry THF (60 cm^3) was added to the mixture at −70°C and after 5–10 min HMPA (10 cm^3) was introduced into the orange-red solution followed by 1-ethoxyethyl 6-chloroethyl ether (8.69 g, 41.7 mmol). After the reaction mixture had been stirred at −70°C for 7 h it was heated at 90°C for 16 h, cooled and then worked up by pouring into dilute aqueous sulphuric acid which removed the protective group. Purification of the crude product isolated by ethereal extraction and concentration, by distillation, b.p. 165°C/0.125 mmHg, afforded the pure product as a pale orange oil (4.45 g) in 60% yield; ν_{max} 3600–3300 (OH), 1725 (C=O), 1600, 1580, 1465, 1265 (C–O) cm^{-1}; δ ($CDCl_3$) 7.3–6.5 (m, 3H, ArH), 4.3 (q, 7 Hz, 2H, OCH_2CH_3), 3.7 (s, 3H, OMe), 3.55 (t, 7 Hz, 2H, CH_2OH), 2.5 (t, 8 Hz, 2H, $ArCH_2$), 1.65 (s, 1H, D_2O exch., CH_2OH), 1.6–1.1 (m, 10H, $(CH_2)_5$). In a similar way the corresponding methyl ester was derived (required for $C_{16}H_{24}O_4$, C, 68.53, H, 8.63; found, C, 68.90, H, 8.86%).

2.7.2. Methyl 6-(4-hydroxybutyl)-2-methoxybenzoate

Methyl 2-methoxy-6-methylbenzoate (5.0 g, 27.78 mmol) was converted to the carbanion as in the preceding example and reacted with 1-ethoxyethyl 3-chloropropyl ether (6.95 g, 33.33 mmol) in THF containing HMPA and diglyme as cosolvents first at −70°C during 5–6 h and then at ambient temperature. Work-up as before gave a dark orange liquid (12.21 g) which was purified by flash chromatography with ethyl acetate/light petroleum to give, after substantial recovery of the starting material, the product as an orange liquid (1.13 g) in 23% yield; ν_{max} 3600–3300 (OH), 1730 (C=O), 1600, 1580, 1470, 1270 (C–O) cm^{-1}; δ ($CDCl_3$) 7.2–6.8 (m, 3H, ArH), 3.8–3.4 (m, 5H, $CO_2Me + CH_2OH$), 3.2 (s, 3H, OMe), 2.5 (m, H, $ArCH_2$), 2.05 (s, 1H, D_2O exch., OH), 1.8–1.3 (m, 4H, $2CH_2$).

*2.7.3. Ethyl 6-(7-bromoheptyl)-2-hydroxybenzoate (**8**; R = OH)*

Ethyl 6-(7-hydroxyheptyl)-2-methoxybenzoate (4.0 g, 13.6 mmol) in dichloromethane (50 cm^3) and boron tribromide (19.0 g) in dichloromethane (30 cm^3) were separately cooled to −75°C and then slowly mixed at that temperature. After 5 days at that temperature during which the mixture was monitored by TLC, it was poured into diethyl ether (300 cm^3), and water (400 cm^3) containing hydrobromic acid (10 cm^3). The recovered organic material was purified by column chromatography to give the product as the major fraction (2.58 g) in 53% yield as a yellow liquid; ν_{max} 3060, 1720 (C=O, ester), 1670, (C=O, H-bonded), 1600, 1575, 1450 cm^{-1}; δ ($CDCl_3$) 12.0 (s, 1H, D_2O exch., HOAr), 7.3–6.5 (m, 3H, HAr), 4.35 (q, 2H, 7 Hz, OCH_2CH_3), 3.35 (t, 2H, 6 Hz, CH_2Br), 3.1–2.7 (m, 2H, CH_2Ar), 2.2–1.2 (m, 13H, $(CH_2)_5 + OCH_2CH_3$); *m/e*, 344 (M^+, 5%), 298, 296, ($M^+ - OEt$, 16%).

Some 2-hydroxy-6-(7-bromoheptyl)benzoic acid (0.5 g) was also formed.

*2.7.4. Methyl and ethyl 6-(7-bromoheptyl)-2-methoxybenzoate (**8**; R = Me)*

Two methods were used for this compound. The first from the methyl ester and the second from the 4-tosyl derivative of the ethyl ester.

(1) Methyl 6-(7-hydroxyheptyl)-2-methoxybenzoate (0.5 g, 1.79 mmol), chlorotrimethylsilane (0.49 g, 4.47 mmol) and lithium bromide (0.31 g, 3.57 mmol) were reacted in dry acetonitrile (4 cm^3) by refluxing for 48 h to give a crude product which after isolation was purified by preparative TLC (30% ethyl acetate/light petroleum) to afford a pale yellow liquid (0.23 g) in 37% yield; ν_{max} 3060, 3000, 1730 (C=O), 1600, 1580, 1470, 1265 cm^{-1}; δ ($CDCl_3$) 7.0–6.3 (m, 3H, HAr), 3.6 (s, 3H, CO_2CH_3), 3.5 (s, 3H, OCH_3), 2.95 (t, 6 Hz, 2H, CH_2Br), 2.35 (t, 5 Hz, CH_2Ar), 1.5–1.1 (m, 10H, $(CH_2)_5$); *m/e*, 344, 342 (M^+, 2%). Found, 342.0821; $C_{16}H_{23}O_3^{79}Br$ requires 342.0831.

(2) Ethyl 2-methoxy-6-(7-tosyloxyheptyl)benzoate was prepared from the alcohol (**7**) in pyridine

solution with 4-toluenesulphonyl chloride. The tosyl ester (0.62 g, 1.43 mmol) in DMSO (5 cm^3) was treated with lithium bromide (0.19 g, 2.14 mmol) and the mixture heated at 70°C for 1.5 h. Following dilution in ice-cold water and ethereal extraction the product, ethyl 2-methoxy-6-(7-bromoheptyl) benzoate, (0.49 g) formed in 99% yield was found to be substantially pure.

2.7.5. Methyl 6-(7-iodoheptyl)-2-methoxybenzoate

Methyl 6-(7-hydroxyheptyl)-2-methoxybenzoate (0.5 g, 1.78 mmol) was converted to the TMS ether with chlorotrimethylsilane (0.23 g, 2.14 mmol) in the presence of pyridine (0.34 g, 4.28 mmol). After removal of excess pyridine, reaction of the crude TMS ether with sodium iodide (0.40 g, 2.67 mmol) in refluxing acetonitrile (15 cm^3) containing chloromethylsilane (0.29 g, 2.67 mmol) during 1 h gave after work-up and purification the iodide as a pale yellow liquid (0.50 g) in 72% yield; ν_{max} 3080, 3010, 1735 (C=O, ester), 1600, 1580, 1475, 1275 (C–O) cm^{-1}; δ ($CDCl_3$) 7.0–6.3 (m, 3H, HAr), 3.6 (s, 3H, $CO_2\underline{CH_3}$), 3.5 (s, 3H, $O\underline{CH_3}$), 2.95 (t, 6 Hz, 2H, $\underline{CH_2}I$), 2.35 (t, 5 Hz, 2H, $\underline{CH_2}Ar$), 1.5–1.1 (m, 10H, $(CH_2)_5$). *m/e*, 390, (M^+, 19%).

*2.7.6. Ethyl 6-(10-hydroxy-8-decynyl)-2-hydroxybenzoate (**9**; R = H)*

1-Ethoxyethyl 2-propynyl ether (prepared from prop-2-ynol and ethyl vinyl ether) (0.56 g, 4.37 mmol) under nitrogen in THF (10 cm^3) at 0°C was slowly treated with *n*-butyl-lithium (3.45 ml, 1.27 M). After the mixture had been stirred for 1 h at 5–10°C, ethyl 6-(7-bromoheptyl)-2-hydroxybenzoate (0.5 g, 1.46 mmol) in THF (10 cm^3) was introduced followed by HMPA (2 cm^3). The mixture was stirred for 19 h and was monitored by TLC. When reaction was complete the mixture was poured into iced water containing dilute sulphuric acid. Ethereal extraction afforded the crude product which was purified by preparative TLC to give a viscous orange oil (0.26 g), in 56% yield; ν_{max} 3600–3200 (OH), 2240, 2210 (C ≡ C), 1720, 1650, (phenolic OH), 1600, 1580, 1450 cm^{-1}; δ ($CDCl_3$) 10.2 (s, 1H, D_2O exch. HOAr), 7.3–6.7 (m, 3H, HAr), 4.6 (q, 2H, $O\underline{CH_2}CH_3$), 4.4 (t, 2H, $\underline{CH_2}OH$), 3.3–2.9 (m, 2H, $\underline{CH_2}C \equiv C$), 2.5–2.1 (m, 3H, (1H D_2O exch.), $\underline{CH_2}Ar + CH_2\underline{OH}$), 2.0–1.9 (m, 13H, $(CH_2)_5 + CH_3$); *m/e* 273 ($M^+ - OEt$, 6%). Found: C, 72.5; H, 8.7. $C_{24}H_{28}O_4$ requires C, 72.2; H, 8.5%.

*2.7.7. Ethyl 6-(10-hydroxy-8-decynyl)-2-methoxybenzoate (**9**, R = Me)*

The preceding method was superior to the use of lithamide to generate the acetylide ion from the 1-ethoxyethyl 2-propynyl ether which gave a 41% yield of the product. Variations such as employing the 4-toluenesulphonyl ester of prop-2-ynol and its *t*-butylsilyldimethyl ether were not useful alternatives. The latter experiment, with *t*-butyldimethylsiloxy 2-propynyl ether (1.98 g, 10.9 mmol) and ethyl 6-(7-bromoheptyl)-2-methoxybenzoate (1.30 g, 3.64 mmol) gave ethyl 6-(10-*t*-butyldimethylsiloxy-8-decynyl)-2-methoxybenzoate (0.48 g). The alcohol protective group was removed by stirring the compound with tetrabutylammonium fluoride (3 moles) in THF (50 cm^3) to give ethyl 6-(10-hydroxy-8-decynyl)-2-methoxybenzoate.

The acetylenic alcohol was accompanied by 0.51 g of the propynyl ether, ethyl 2-methoxy-6-(7-prop-2-ynoxyheptyl)benzoate; ν_{max} 3300, 2930, 2860, 2100 (C ≡ C), 1725 (C=O), 1600, 1580, 1470 cm^{-1}; δ ($CDCl_3$) 7.3–6.6 (m, 3H, HAr), 4.4 (q, 8 Hz, 2H, $O\underline{CH_2}CH_3$), 4.1 (d, 5 Hz, 2H, $O\underline{CH_2}C \equiv C$), 3.8 (s, 3H, $O\underline{CH_3}$), 3.5 (t, 3H, 2H, $(CH_2)_5\underline{CH_2}O$), 2.4 (t, 1H, C ≡ CH), 1.6–1.3 (m, 10H, $(CH_2)_5$), 1.0 (t, 3H, $CH_2\underline{CH_3}$); *m/e* 332 (M^+). Found 332.1987. $C_{20}H_{28}O_4$ requires 332.1981.

*2.7.8. Methyl 6-(10-bromo-8-decynyl)-2-methoxybenzoate (methyl ester corresponding to **10**)*

Methyl 6-(10-hydroxy-8-decynyl)-2-methoxy benzoate (0.3 g, 0.94 mmol), and phosphorus tribromide (0.085 g, 0.31 mmol) were reacted in diethyl ether containing pyridine in catalytic amount to give after column chromatography (20% diethyl ether in light petroleum) the product

as a yellow liquid (0.28 g) in 78% yield; ν_{max} 3070, 2240 (C ≡ C), 1730, (C=O), 1665, 1605, 1580, 1470 cm^{-1}; δ ($CDCl_3$) 7.5–6.6 (m, 3H, HAr), 3.8–3.9 (m, 4H, $O\underline{CH_2}CH_3 + CH_2Br$), 3.6 (s, 3H, OCH_3), 3.1–2.7 (m, 2H, CH_2Ar), 2.5–2.0 (m, 2H, $CH_2C \equiv C$), 1.8–1.1 (m, 10H, $(CH_2)_5$), 0.9 (t, 6 Hz, 3H, $O\underline{CH_2}CH_3$); *m/e*, found 380.0996. $C_{19}H_{25}O_3^{79}Br$ requires 380.0988.

The ethyl ester (**10**, R = Me) was prepared similarly.

*2.7.9. Ethyl 2-methoxy-6-(pentadeca-8,11-diynyl)benzoate (**11**; R = Me)*

This compound was prepared by two methods. In Method A, ethyl 2-methoxy-6-methylbenzoate was alkylated with 1-iodotetradeca-7,10-diyne and in Method B, the preceding ArC_{10} bromide was alkylated with 1-pentynyl bromide.

*2.7.9.1. Method A, 1-iodotetradeca-7,10-diyne (**19**).* 6-Chlorohexan-1-ol or the bromo compound was converted to the 1-ethoxyethyl derivative by reaction with ethyl vinyl ether as described and thence to 1-ethoxyethyl 7-octynyl ether with lithium acetylide or the lithium acetylide-diaminoethane complex. After removal of the protective group, 1-hydroxy-7-octyne was converted to the *t*-butyldimethyl derivative. This C_8 material was then converted to the magnesiobromo derivative with ethylmagnesium bromide which was reacted with 1-bromo-2-hexyne to give the *t*-butyldimethyl silyl ether of 1-hydroxy-7,10-tetradecadiyne in 81% yield. After removal of the protective group with ammonium fluoride, 1-iodotetradeca-7,10-diyne was obtained from the trimethylsilyl derivative in pyridine by treatment with sodium iodide.

2.7.9.2. 1-t-Butyldimethylsiloxy-7-octyne. 1-(1-Ethoxy)ethoxy-6-bromohexane (10.0 g, 39.5 mmol) and lithium acetylide-diaminoethane complex (4.0 g, 43.5 mol) were reacted in DMSO (22 cm^3) under nitrogen at 8–10°C during 2 h after which the mixture was poured into ice water. Extraction with light petroleum and recovery afforded the crude product which was purified by dry flash chromatography to give a pale yellow oil (5.97 g) in 72% yield. Acidic methanolysis gave 1-hydroxy-7-octyne.

This alcohol (2.0 g, 15.9 mmol) with *t*-butyldimethylsilyl chloride (2.87 g, 19.0 mmol) in DMF (4 cm^3) containing imidazole (2.70 g, 29.7 mmol) was reacted at 35°C for 12 h. Work-up by dilution with diethyl ether, water washing and purification by dry flash chromatography afforded the product as a clear liquid (3.78g) in 99% yield.

*2.7.9.3. 1-Hydroxytetradeca-7,10-diyne (**18**)*

2.7.9.3.1. Method 1. 1-*t*-Butyldimethylsiloxy-7-octyne (3.50 g, 14.6 mmol) was treated with ethylmagnesium bromide (2.91 g, 21.9 mmol) in THF at 40°C. To the magnesiobromo derivative copper(I) chloride (100 mg) and 1-bromo-2-hexyne (2.81 g, 17.5 mmol) were added and the reaction mixture heated for 2 h at 50–55°C. After cooling and work-up with aqueous ammonium chloride, ethereal extraction and purification of the recovered crude product by dry flash chromatography 1-*t*-butyldimethylsiloxytetradeca-8,11-diyne was obtained as a pale yellow liquid (3.80 g) in 81% yield; *m/e*, found 320.2539. $C_{20}H_{36}OSi$, requires 320.2535. 1-Hydroxytetradeca-8,11-diyne was obtained as a pale yellow liquid (0.27 g) in 52% yield from the silyl ether (0.8 g, 2.50 mmol) with tetrabutylammonium fluoride (1.96 g, 7.50 mmol) in THF (20 cm^3) by reaction over 12 h, aqueous dilution, ethereal extraction, and recovery of the crude product which was purified by dry flash chromatography (20% ethyl acetate and light petroleum); ν_{max} 3300–3100 (O–H), 2980, 2240 (C ≡ C) cm^{-1}; δ ($CDCl_3$) 3.6–3.4 (m, 5H, $\underline{CH_2}OH + C \equiv C\underline{CH_2}C \equiv C$, 1H D_2O exch.), 2.3–2.0 (m, 4H, 2, $CH_2C \equiv C$), 1.9–1.2 (m, 2, $CH_2C \equiv C + (CH_2)_4 + CH_2CH_3$); *m/e*, found 206.1681. $C_{14}H_{22}O$ requires 206.1671.

2.7.9.3.2. Method 2. 1-(1-Ethoxy)ethoxy-7-octyne (3.0 g, 16.5 mmol) in dry THF (30 cm^3) was reacted with ethylmagnesium bromide (12.4 cm^3 from a pre-prepared solution containing (0.23 g/cm^3)), during 1 h at 50–60°C under nitrogen. After the addition of copper(I) chloride (0.5 g), the mixture was cooled to 30°C, treated with 1-bromohex-2-yne (2.92 g, 18.1 mmol) and then reacted for 1 h at 60°C. Work-up with saturated

ammonium chloride solution, ethereal extraction and purification of the crude product by dry flash chromatography afforded a pale yellow liquid (3.29 g) in 72% yield consisting of the ethoxyethyl derivative of 1-hydroxy-7,10-diyne; ν_{max} 3300, 2100 (C ≡ C), 1450, 1440 cm^{-1}; δ ($CDCl_3$) 4.5 (q, 5 Hz, 1H, O<u>CH</u>O), 3.7–3.1 (m, 4H, 2, O<u>CH_2</u>), 2.3–1.8 (m, 6H, 3, C ≡ C<u>CH_2</u>), 1.8–1.0 (m, 11H, $(CH_2)_4 + CH_2$<u>CH_3</u>); *m/e*, 183 ($M^+ - CH_3$, 16%). Removal of the protective group by acidic methanolysis gave 1-hydroxy-7,10-diyne (**18**); *m/e*, found 206.1681. $C_{14}H_{22}O$ requires 206.1671.

1-Hydroxytetradeca-7,10-diyne (0.25 g, 1.21 mmol), chlorotrimethylsilane (0.16 g, 1.46 mmol) and pyridine (0.23 g, 2.90 mmol) afforded the TMS ether which by stirring with chlorotrimethylsilane (0.2 g, 2.05 mmol) and sodium iodide (0.51 g, 2.05 mmol) in dry acetonitrile (15 cm^3), work-up and purification by dry flash chromatography gave the iodo compound, 1-iodotetradeca-8,11-diyne (**19**), as an orange liquid (0.65 g).

Ethyl 2-methoxy-6-methylbenzoate (0.28 g, 1.44 mmol) was converted in THF solution under nitrogen to the carbanion with lithium diisopropylamide (from *n*-butyl-lithium and diisopropylamine both in 2.02 mmol). Following the addition of HMPA, the mixture was cooled to − 70°C and 1-iodotetradeca-7,10-diyne (0.55 g, 1.74 mmol) then added. After reaction over 10 h the crude product was isolated by ethereal extraction. Purification by dry flash chromatography with diethyl ether and light petroleum afforded a pale yellow liquid (0.48 g) comprising ethyl 2-methoxy-6-(pentadeca-8,11-diynyl)benzoate (**11**, R = Me), in 78% yield; ν_{max} 3310, 3100, 2960, 2860, 1750 cm^{-1} (C=O); δ ($CDCl_3$) 7.2–6.6 (m, 3H, HAr), 4.36 (q, 7 Hz, 2H, O<u>CH_2</u>CH_3), 3.8 (s, 3H, OCH_3), 3.5 (t, 2H, C ≡ CCH_2C ≡ C), 2.5 (t, 2H, CH_2Ar), 2.3–1.3 (m, 19H, 2<u>CH_2</u>C ≡ C, $(CH_2)_5$, CH_2CH_3).

*2.7.9.4. Method B (for ethyl 2-methoxy-6-(pentadeca-8,11-diynyl)benzoate (**11**, R = Me).* To 1-pentyne (1.00 g, 14.7 mmol) in THF (7 cm^3), ethylmagnesium bromide (2.54 g, 1.1 mmol) was added and after complete reaction at 40°C during 30 min, half of the solution was treated under nitrogen with copper(I) iodide (100 mg) and THF (10 cm^3). After 10 min ethyl 6-(10-bromo-8-decynyl)-2-methoxy-benzoate (0.31 g, 0.785 mmol) in THF (10 cm^3) was added, the reaction mixture was kept at 50°C for 3 h and following continued reaction at ambient temperature overnight, worked up by dilution with ammonium chloride solution. Ethereal extraction gave the crude product which was purified by dry flash chromatography to afford a viscous yellow liquid, ethyl 2-methoxy-6-(pentadeca-8,11-diynyl)-benzoate; ν_{max} 3070, 2940, 2870, 2120 (C ≡ C), 1700 (C=O), 1600, 1470 cm^{-1}; δ ($CDCl_3$), 7.3–6.7 (m, 3H, Ar<u>H</u>), 3.8 (q, 2H, 6 Hz, O<u>CH_2</u>CH_3), 3.7 (s, 3H, OMe), 2.7 (q, 2H, 2 Hz, C ≡ CCH_2C ≡ C), 2.5 (t, 2H, Ar<u>CH_2</u>), 2.4 (t, 4H, 2 × CH_2C ≡ C), 2.1 (m, 12H, $(CH_2)_5 + CH_2$<u>CH_2</u>CH_3), 1.7 (t, 7 Hz, 3H, OCH_2<u>CH_3</u>), 1.3 (t, 3H, 8 Hz, CH_2<u>CH_3</u>).

*2.7.10. Methyl 2-methoxy-6-(8-nonynyl)benzoate (**14**)*

For this preparation methyl 2-methoxy-6-(7-tosylheptyl)benzoate was first obtained from methyl 6-(7-hydroxyheptyl)-2-methoxybenzoate (9.81 g, 18.9 mmol), 4-toluenesulphonyl chloride (8.25 g, 43.3 mmol), and pyridine (4.56 g, 57.7 mmol) at 0°C with monitoring of the reaction mixture by TLC. After 5 h, work-up with water (10 cm^3), and extraction with diethyl ether (90 cm^3), the crude product (14.3 g) obtained was purified by flash chromatography (ethyl acetate and light petroleum). A yellow liquid (5.37 g) was obtained in 43% yield together with a by-product which appeared spectroscopically to be ethyl 4-toluenesulphonate (5.2 g).

The preparation of the nonynyl compound from the foregoing tosyl derivative with lithium acetylide in THF/HMPA was not successful whereas with the lithium acetylide-diaminoethane complex, reaction proceeded well.

Lithium acetylide-diaminoethane complex (0.22 g, 2.42 mmol) under nitrogen in DMSO (1.5 cm^3) was treated at 10°C with methyl 2-methoxy-6-(7-tosylheptyl)benzoate (1.05 g, 2.30 mmol) in dry THF (10 cm^3) and after stirring for 3 h, the reaction mixture was diluted with water and extracted with light petroleum to give the crude product which was purified by dry flash chromatography to give a pale yellow liquid (0.49 g) in

74% yield; ν_{max} 3300 (C≡CH), 2130 (C≡C), 1735 (C=O), 1270 cm^{-1} (C–O); δ ($CDCl_3$) 6.9–6.2 (m, 3H, HAr), 3.5 (s, 3H, CO_2CH_3), 3.4 (s, 3H, OCH_3), 2.2 (t, 7 Hz, 2H, CH_2Ar), 2.1–1.7 (m, 2H, $CH_2C\equiv C$), 1.6 (t, 2 Hz, 1H, C≡CH), 1.5–0.8 (m, 10H, $(CH_2)_5$). *m/e*, 289 ($M^+ + 1$), 5%, 288, (M^+, 23%). Found, 288.1718. $C_{18}H_{24}O_4$ requires 288.1725. Found, C, 75.20; H, 8.60. Required, C, 75.0; H, 8.4%. Similar results were obtained in the alkylation procedure of lithium acetylide-diaminoethane complex with methyl or ethyl 2-methoxy-6-(7-bromoheptyl)benzoate prepared from the 7-tosyl derivative by reaction in DMSO with lithium bromide.

*2.7.11. 2-Methoxy-6-(pentadeca-8,11-diynyl)-phenyl ethyl ketone (**16**)*

Methyl 2-methoxy-6-(8-nonynyl)benzoate (0.60 g, 2.08 mmol) in THF (15 cm^3) was treated with ethylmagnesium bromide (0.36 g, 2.70 mmol) and the mixture heated at 40°C during 1 h. After cooling to 25°C, copper(I) chloride (100 mg) was added followed by 1-bromo-2-hexyne (0.37 g, 2.29 mmol) in THF (10 cm^3). The reaction mixture was heated at 60°C for 2 h and after cooling was then worked up by pouring into saturated ammonium chloride solution and ethereal extraction to give a crude product (1.05 g) which upon dry flash chromatography afforded a yellow liquid (0.63 g). The spectral data on this material indicated it to be ketonic due to reaction of EtMgBr at both the ester and acetylenic groups.

This was confirmed by treatment of methyl 2-methoxy-6-(8-nonynyl)benzoate with ethylmagnesium bromide at 30–40°C whereby a ketonic product 2-methoxy-6-(8-nonynyl)phenyl ethyl ketone was derived; ν_{max} 3300, 3360, 2920, 2850, 2120, 1700 (C=O, ester), 1600, 1580, 1465 cm^{-1}; *m/e*, 286 (M^+, 18%). Found, 286.1931. $C_{19}H_{26}O_2$ requires 286.1932.

*2.7.12. (Z,Z) Ethyl 2-methoxy-6-(pentadeca-8,11-dienyl)benzoate (**12**, R = Me)*

Total catalytic reduction of the 8,11-diyne gave ethyl 2-methoxy-6-pentadecylbenzoate; *m/z* (M^+, 390, (25%)). Partial reduction in ethyl acetate containing quinoline gave (*Z*,*Z*) ethyl 2-methoxy-6-(pentadeca-8,11-dienyl)benzoate; $C_{25}H_{38}O_3$ requires *m/z*, M^+ 386. Found, (M^+, 386).

This was identical by argentation chromatography (Tyman, 1977) and spectroscopically with the O-methyl ether methyl ester of anacardic acid diene obtained from the acid by methylation with dimethyl sulphate in acetone or xylene containing potassium carbonate.

Demethylation of ethyl 6-methoxy-2-pentadecylbenzoate with lithium *t*-butylthiolate has been described (Visani, 1988; Tyman and Visani, 1996) and the hydrolysis of methyl ginkgolate effected with methanolic potassium hydroxide.

In the hydrolysis no change of the double bond positions appears to take place. For example in the hydrolysis of ethyl 6-(11-dodecenyl)-2-methoxybenzoate the corresponding acid was formed.

Ethyl 6-(11-dodecenyl)-2-methoxybenzoate (0.86 g, 2.48 mmol) in ethanol (3 cm^3) was added to ethanol (5 cm^3) containing sodium hydroxide (0.20 g, 4.97 mmol) dissolved in water (3 cm^3) at 60°C and the mixture refluxed for 48 h and monitored by TLC. Upon work-up by acidification and ethereal extraction followed by flash chromatography, 6-(11-dodecenyl)-2-methoxybenzoic acid was obtained as a viscous oil (0.31 g, 39%); ν_{max} 3600–3300, 3080, 3010, 1700 (C=O, acid), 1600, 1580, 1470, 1290, 1270 cm^{-1}; δ ($CDCl_3$) 10.6 (s, 1H, COO<u>H</u>, D_2O exch.), 7.4–6.6 (m, 3H, <u>H</u>Ar), 5.6–4.8 (m, 3H, CH=CH_2), 3.9 (s, 3H, OMe), 2.7 (t, 7 Hz, 2H, <u>CH_2</u>Ar), 2.2–1.2 (m, 18H, $(CH_2)_9$); *m/z*, 319 ($M^+ + 1$, 13%), 318 (M^+, 5%). Found, C, 75.3; H, 8.60. $C_{20}H_{30}O_3$ requires C, 75.40; H, 9.40.

2.7.13. Preparation of stereoisomeric 1-hydroxytetradeca-7,10-dienes

*2.7.13.1. (7E,10E)-1-Hydroxytetradeca-7,10-diene (**23**).* 1-(1-Ethoxy)-ethoxy-7-octyne (3.0 g, 16.5 mmol) was lithiated with lithamide (prepared from lithium (0.22 g, 32.97 mmol) and liquid ammonia (220 cm^3)). (*E*)-1-Bromohex-2-ene (3.49 g, 21.43 mmol) was added and the mixture then refluxed for 2 h to give (**21**). After reductive treatment by the addition of lithium wire (0.2 g),

the mixture after 1 h was quenched with saturated ammonium chloride solution, the excess ammonia evaporated, and the extracted product purified by dry flash chromatography to give, after removal of the protective group by acidic methanolysis, and purification, (*E*,*E*)-1-hydroxytetradeca-7,10-diene, (1.48 g, 48%).

*2.7.13.2. (10E)-1-Hydroxytetradeca-10-ene-7-yne (**21**).* 1-(1-Ethoxy)-ethoxy-7-octyne (3.0 g, 16.5 mmol) was treated with ethylmagnesium bromide (2.85 g, 21.42 mmol) at ambient temperature then at 40°C and copper(I) chloride (100 mg) added, followed by (*E*)-1-bromohex-2-ene (2.95 g, 18.1 mmol). The reaction mixture was heated at 50–60°C for 2 h, cooled and then poured into saturated ammonium chloride solution. After work-up by ethereal extraction and removal of the protective group by acidic methanolysis the product was obtained containing some 1-hydroxy-7-octyne.

*2.7.13.3. (7Z,10E)-1-Hydroxytetradeca-7,10-diene (**22**).* Reduction of 1-hydroxytetradeca-10(*E*)-ene-7-yne with diisoamylborane at 0°C gave 1-hydroxy-tetradeca-7(*Z*),10(*E*)-diene.

*2.7.13.4. (7Z,10Z)-1-Hydroxytetradeca-7,10-diene (**20**).* 1-Hydroxytetradeca-7,10-diyne upon catalytic hydrogenation in ethyl acetate containing Pd-$BaSO_4$ and quinoline afforded (*Z*,*Z*)-1-hydroxytetradeca-7,10-diene.

*2.7.13.5. (7E,10Z)-1-Hydroxytetradeca-7,10-diene (**24**).* (*Z*)-Hex-2-en-1-ol was similarly prepared from hex-2-yn-1-ol and converted to the bromide. Reaction with 1-(1-ethoxy)-ethoxy-7-octynylmagnesium bromide in the presence of copper(I) chloride afforded after removal of the protective group, the compound 1-hydroxytetradeca-7-yne-10(*Z*)-ene, lithium reduction of which in situ gave 1-hydroxytetradeca-7(*E*),10(*Z*)-diene.

2.7.13.6. 1-Iodotetradeca-7(E),10(E)-diene. 1-Hydroxytetradeca-7(*E*),10(*E*)-diene (1.68 g, 8.00 mmol), chlorotrimethylsilane (1.04 g, 9.60 mmol), with pyridine (1.52 g, 9.20 mmol) formed the TMS ether which was then refluxed in acetonitrile (30 cm^3) containing sodium iodide (1.80 g, 12 mmol) and chlorotrimethylsilane (1.3 g, 12.0 mmol). The pure product was obtained by dry flash chromatography as a yellow liquid (1.29 g, 50% yield).

This diene compound was also prepared by reduction of 1-iodo-10(*E*)-tetradecen-7-yne with diisoamylborane.

1-Iodo-10(*E*)-tetradecen-7-yne (3.25 g, 10.22 mmol) was treated with freshly-prepared diisoamylborane (1.59 g, 10.32 mmol) in dry THF at 0°C. The reaction mixture was quenched with glacial acetic acid and then neutralised with sodium hydroxide solution. Prep TLC showed two bands the lower of which was the required product (0.53 g); ν_{max} 3100, 2980, 1650, 1470 cm^{-1}; δ ($CDCl_3$) 5.8–5.0 (m, 4H, 2 × $\underline{CH}$=$\underline{CH}$), 3.2 (t, 6 Hz, 2H, O$\underline{CH_2}$), 2.3–2.0 (CH=CH$\underline{CH_2}$CH=CH + OH, D_2O exch.), 1.9–1.2 (m, 14H, ($\underline{CH_2}$)$_5$ + 2$\underline{CH_2}$), 0.8 (t, 6 Hz, $\underline{CH_3}$).

The trimethylsilyl ether of 1-hydroxytetradeca-7(*Z*),10(*E*)-diene was converted with sodium iodide in acetonitrile to the corresponding iodide. Found: *m*/*z*, M^+, 320.1008. $C_{14}H_{25}OI$ requires 320.1003.

2.7.13.7. Methyl 2-methoxy-6-[pentadeca-8(Z),11(E)-dienyl]benzoate. Methyl 2-methoxy-6-methylbenzoate was converted to the anion with lithium diisopropylamide and reacted in THF containing HMPA with 1-iodotetradeca-7(*Z*),10(*E*)-diene to afford the product after chromatographic purification in 21% yield.

Similar alkylations were carried out with 1-iodotetradeca-7(*E*),10(*E*)-diene and with the 7(*Z*),10(*E*) isomer.

*2.7.14. Experiments in the synthesis of the triene, ethyl (ZZ) 2-methoxy-6-(pentadeca-8,11,14-trienyl)benzoate (**30**)*

1-(1-Ethoxy)ethoxyoct-7-yne (**17**) (3.0 g, 16.5 mmol) was treated with ethyl magnesium bromide (2.89 g, 21.4 mmol) in THF at 40°C followed by copper(I) bromide (100 mg) and then 1-bromohex-5-ene-2-yne (2.88 g, 18.1 mmol). The reaction mixture was heated at 50–60°C during 2 h, cooled and poured into saturated ammonium chloride

solution. After ethereal extraction and recovery the crude yellow product was purified by dry flash chromatography to give 1-ethoxyethyl-13-tetradec-13-ene-7,10-dienyl ether (**26**) as a pale yellow liquid in 79% yield; ν_{max} 3070, 2980, 2910, 2860, 2200 (C≡C) cm^{-1}; δ ($CDCl_3$) 5.3–4.8 (m, 3H, CH=CH_2), 4.7 (q, 1H, 7 Hz, OCH_2), 3.7–3.1 (m, 4H, $2OCH_2$) 3.0 (t, 2 Hz, C≡CCH_2C≡C), 2.8–2.7 (m, 2H, C≡CCH_2 CH=CH_2), 2.1–2.0 (m, 14H, $2CH_3 + (CH_2)_4$); *m/e*, 216 ($M^+ - CH_3 + OEt$).

1-Hydroxytetradec-13-ene-7,10-diyne (**27**) was derived by treatment with methanolic hydrochloric acid.

Upon reaction of this alcohol with dibromoborane-dimethyl sulphide complex, and conversion to the iodide, partial reduction occurred of one unsaturated bond, probably resulting in a dieneyne. Found: *m/z*, M^+, 316.0680. $C_{14}H_{21}I$ requires 316.0689.

Treatment of the 7,10-diyn-13-en-1-ol (0.40 g, 1.92 mmol), with chlorotrimethylsilane (0.25 g, 2.3 mmol), and pyridine (0.37 g, 4.6 mmol) afforded the TMS ether which with sodium iodide (0.43 g, 2.88 mmol) in acetonitrile (10 cm^3) containing chlorotrimethylsilane (0.31 g, 2.88 mmol) and work-up by flash chromatography gave an orange liquid (0.20 g), 1-iodotetradeca-13-ene-7,10-diyne (**28**) in 33% yield; ν_{max} 3295, 3050, 2920, 2850, 2110 (C≡C), 1730, 1640 cm^{-1}; 6.0–5.3 (m, 3H, CH=CH_2), 3.4 (t, 7 Hz, 2H, C≡C$\underline{CH_2}$C≡C), 3.2 (t, 7 Hz, 2H, $\underline{CH_2}$I), 3.0 (t, 3 Hz, 2H, $\underline{CH_2}$C≡C), 2.8–1.8 (m, 8H, $(CH_2)_4$).

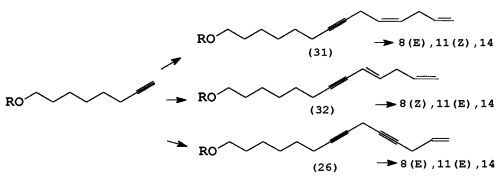
Alkylation of the carbanion of ethyl 2-methoxy-6-methylbenzoate with the preceding iodide was effected in THF containing HMPA and the product ethyl 2-methoxy-6-(pentadeca-8,11-diynyl-14-enyl)-benzoate (**29**) purified by flash chromatography. Reduction with dibromoborane-dimethyl sulphide complex afforded the triene, (*Z*,*Z*)-ethyl 2-methoxy-6-(pentadeca-8,11,14-trienyl)benzoate (**30**). Argentation chromatographic comparison with the methylation product of (15:3)-anacardic acid indicated the required product had been formed.

3. Results and discussion

In the present synthetic work in the anacardic series for 8,11-dienes and 8,11,14-trienes acetylenic routes were adopted primarily because an ArC_7 intermediate can readily be obtained from an ArC_1 starting material (methyl 2-methoxy-6-methylbenzoate) by the use of the readily available HO-protected 6-chlorohexan-1-ol. In Wittig reactions the use of an ArC_8 is required involving preparations with the less available 7-halogenoheptan-1-ols. Although steric control of the stereochemistry of the Wittig reaction is now possible the availability of selective catalytic and chemical reduction together with advances in boration methodology (Brown and Campbell, 1981) have greatly enhanced the utility of acetylenic syntheses.

The choice of protective group for the aromatic and for the side-chain components was studied in our approach. The benzyl, methoxymethyl and trimethysilyl groups were found to be less beneficial than the methyl group in alkyl-2-methoxy-6-methylbenzoates particularly in the alkylation of the carbanion. For the side-chain component the ethoxyethyl group (readily introduced by reaction of the hydroxy compound with ethyl vinyl ether) was superior to the trityl and *t*-butyldimethylsilyl groups, a feature confirmed from earlier work with the phenolic lipids of the cardanol (Caplin and Tyman, 1982) and cardol (Baylis et al., 1981) series.

Demethylation of polyunsaturated phenolic lipids is subject to side reactions and this problem is increased where hydrolysis is a concomitant reaction. Wherever possible phenolic intermediates were employed as in Scheme 1 to avoid demethylation as the terminal step. For the hydrolysis of the model compound ethyl 6-(dodec-11-enyl)-2-methoxybenzoate, potassium *t*-butoxide under mild ambient conditions (Gassman and Schenk, 1977) was less effective than warm sodium hydroxide. Finally it was found that with the model compound ethyl 2-methoxy-6-pentadecylbenzoate, lithium *t*-butyl thiolate (Bartlett and Johnson, 1970; Wolfe et al., 1975) effected simultaneous demethylation and hydrolysis. Unsaturated compounds also re-



Scheme 6. Synthesis of stereoisomeric triene C_{14} alkylation reactants.

sponded with retention of unsaturation. The alternative reagents for demethylation, namely trimethylsilyl iodide (Yung and Lyster, 1977) and trimethylsilyl chloride-sodium iodide (Olah et al., 1979) resulted also in some side reaction of the unsaturation.

The strategy of Scheme 1 for the diene, involving the reaction of the ArC_{10} bromide with pentynyl magnesium bromide was successful whereas that of Scheme 2 failed through side reaction of ethyl magnesium bromide with the ester group of the ArC_9 as well as the alkyne group, resulting in non-selectivity and formation of the ketone (**16**). This difficulty might be overcome by the use of an alternative to the ethyl as protecting group for the ester, although this was not examined at the time. However another aspect of this proposed route was that it required a C_6 component which was necessary in the C_{14} alkylation methodology of Scheme 3, because in this strategy the synthesis of isomeric C_{14} reactants involved the use of the two isomeric (*Z*) and (*E*) monounsaturated C_6 compounds as depicted in Scheme 4. The bromides of the two diunsaturated C_6 alcohols, hexa-2,5-diyn-1-ol and hexa-5-ene-2-yn-1-ol and those of (*E*,*E*)-hexa-2,5-dien-1-ol and (*E*)-hexa-2,5-diene-1-ol were to be used for the preparation of isomeric C_{14} reactants required for the stereoisomeric triene series by reaction with (**17**) as shown in Scheme 6.

In the first place, the use of (**17**) had led to the diynol (**26**) which was employed as shown in Scheme 5 for the synthesis of (**30**) and only partial progress was made towards the preparations of analogues, (**31**) required for the 8(*E*),11(*Z*)-14-triene, and (**32**) for the 8(*Z*),11(*E*),14-triene. Reduction of (**26**) to (*E*,*E*)-tetradeca-7,10,13-triene-1-ol would give access to the fourth stereoisomer, the 8(*E*),11(*E*),14-triene.

Greatly expanded boration methodology has enabled selective reduction of alkyne bonds in the presence of alkenes possible by the use of modified boranes (Brown and Campbell, 1980) although in our experience chromatographic and spectroscopic monitoring of reaction progress is essential in their usage.

Their selectivity is probably superior to catalytic and chemical reductions where both double and triple bonds are present. Although selective catalytic reduction of the triple bond in $CH_2{=}CHCH_2C \equiv CCH_2CH_2OH$ has been apparently achieved (Miyakoshi et al., 1991; Sargent and Wanachareontrajkul, 1989) our own model experiments were much less selective indicating that a terminal vinyl group is more susceptible than an internal alkyne. Other experiments (Tyman, 1991; Tyman and Visani, 1996) have indicated that a terminal alkyne protected by the trimethylsilyl group enables an internal alkyne to be preferentially reduced as found by others (Schmidt and Arens, 1967).

An attempt to adapt a route to 5,6-dehydroarachidonic acid (Corey and Kang, 1982), based upon the employment of an allenic intermediate with the organotin reactant 1,1-di-*n*-butyl-1-stannacyclohexadiene, for the synthesis of the triene (**30**) was partially successful but will be described elsewhere.

Acknowledgements

We thank the Dow Chemical Co., Smith Kline and French Ltd. and the Society of Chemical Industry for financial support.

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