Pergamon

Tetrahedron Vol. 50, No. 29, pp. 8793-8808, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00475-7

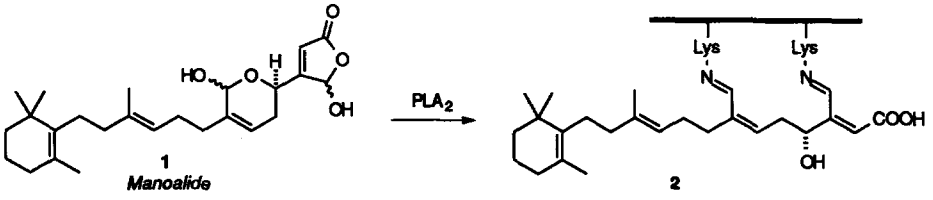
Two Syntheses of Manoalide *via* Heteroatom-Assisted Alkyne Carbometallation

Paul Bury, Georges Hareau, and Philip Kocieński*
Department of Chemistry, The University, Southampton, SO17 1BJ, U.K.

Dashyant Dhanak
SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn Garden City, AL6 9AR, U.K.

Abstract: Two approaches to the sesterterpenoid phospholipase A_2 inhibitors seco-manoalide (3) and manoalide (1) are described based on carbometallation of propargylic alcohols to generate the functionalised C6-C7 trisubstituted alkene. Both syntheses also deploy the photooxidation of a furan in order to generate a 4-substituted-5-hydroxy-2(5*H*)-furanone moiety.

The hydrolytic cleavage of arachidonic acid from membrane-bound phospholipids marks the launch of a complex cascade of biochemical reactions leading to the formation of pro-inflammatory mediators such as the leukotrienes and prostaglandins[1,2]. Therefore, the inhibition of phospholipase A_2 (PLA_2), the hydrolytic enzyme which catalyses arachidonic acid release, is a key therapeutic target for the suppression of inflammation and pain. In 1980 de Silva and Scheuer[3] reported the isolation and structure determination of manoalide (1), a sesterterpenoid metabolite from the Pacific sponge *Luffariella variablis*, which is a potent and irreversible inhibitor of PLA_2. Manoalide has been evaluated in phase II trials for the treatment of psoriasis[4] and a detailed structure-activity study revealed some of the dominant molecular features which contribute to its potency and efficacy[5]. Though its mechanism of action is only poorly understood, it would appear that the irreversible binding of manoalide to PLA_2 is the consequence of Schiff base formation between two lysine residues of the enzyme with the two aldehyde functions which result from ring-chain tautomerism of the two heterocyclic rings[6-9] giving rise to an inactive enzyme complex (2) (Scheme 1).



1
Manoalide

2

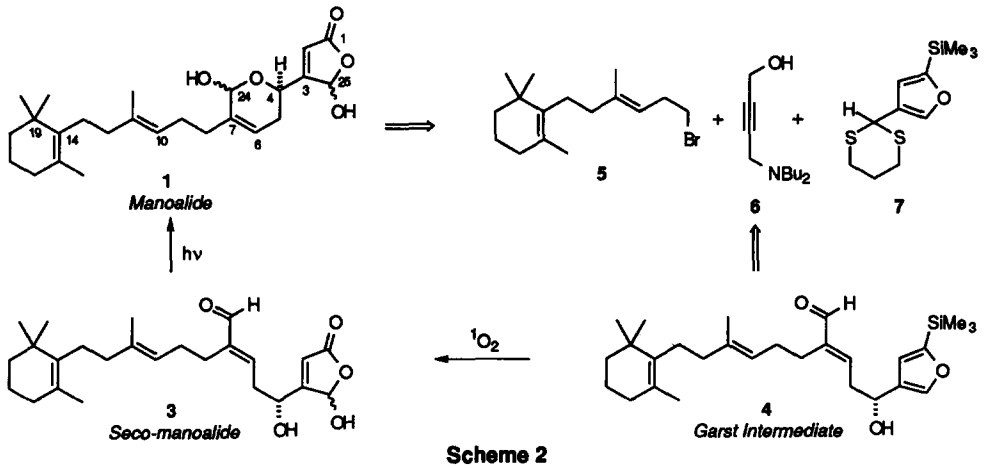
Scheme 1

A further search for biologically active metabolites from *Luffariella variabilis* and closely related sponges has uncovered other sesterterpenoids which are biogenetically related to manoalide. Seco-manoalide [10] and lufariellins A and B[10] approximate manoalide in their irreversible inhibition of PLA_2[5,11] whereas the simpler congener luffariellolide is a partially reversible inhibitor[12]. Luffolide[13] inhibits hydrolysis of phosphatidylcholine by bee venom PLA_2 and the neomanoalides[14] show significant *in vitro* antibiotic activity against *Streptomyces pyogenes* and *Staphylococcus aureus*. Luffariolides A–E reveal cytotoxicity against murine lymphoma L1210[15]. In addition, seco-manoalide inhibits aldose reductase whose unusual action causes diabetic cataracts resulting from abnormal accumulation of sorbitol by reduction of glucose[16].

Realisation of the medicinal potential of manoalide and seco-manoalide was initially hampered by the comparative difficulty of their isolation from natural sources and several groups[17-20] soon provided total syntheses. We now report two approaches to manoalide based on heteroatom-assisted alkyne carbomagnesiation reactions.

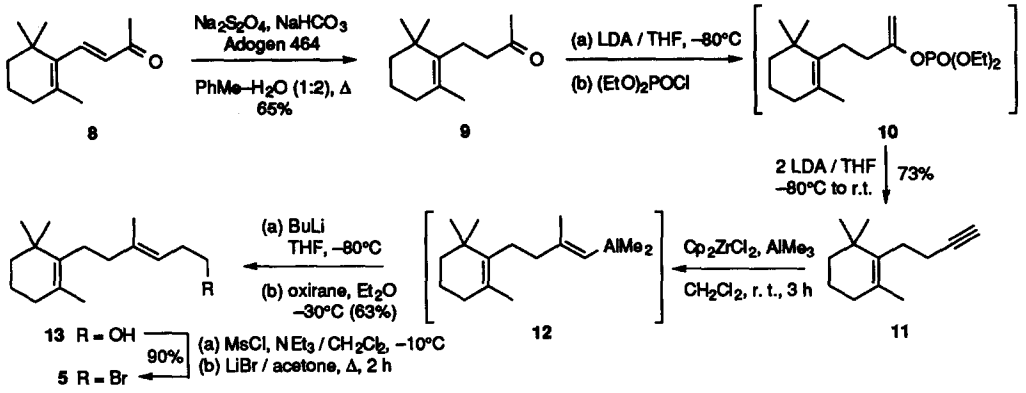
1. First Synthesis: Carbomagnesiation of 1-(Di-*n*-butylamino)but-2-yn-4-ol

Our synthetic plan (Scheme 2), like that of our predecessors, assumes that the two labile hemiacetal centres at C24 and C25 are best introduced at the end of the synthesis. Intermediate **4** is an especially attractive target because it harbours the entire carbon-skeleton of manoalide as well as both hemiacetals in latent form. Garst and coworkers[19] had already shown that the 5-hydroxy-2(5*H*)-furanone could be unravelled by photooxidation of the silylfuran to give seco-manoalide (**3**); an equally mild photoisomerisation of the C6-C7 alkene in seco-manoalide then furnished the pyran ring of manoalide. In order to prepare the Garst intermediate **4**, we used three fragments: homoallylic bromoalkane **5**, the known 1-(di-*n*-butylamino)but-2-yn-4-ol (**6**)[21], and dithiane **7** (Scheme 2).



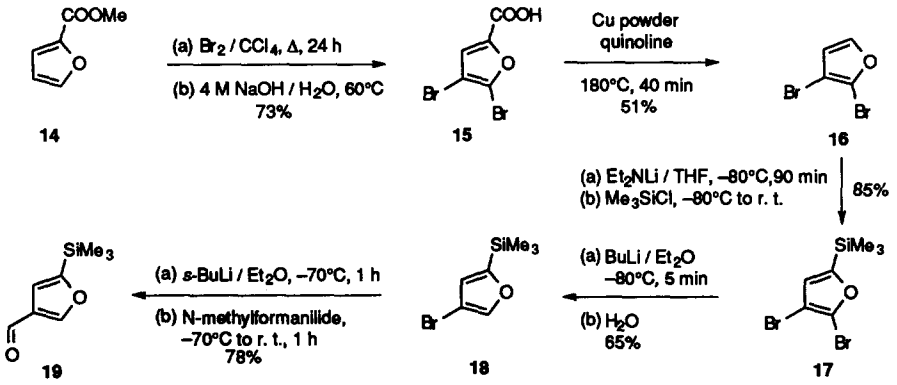
Scheme 2

Synthesis of Bromoalkane 5 (Scheme 3). The bromoalkane **5** was prepared in 6 steps from β-ionone (**8**). The sequence began with a modification of the conjugate reduction of β-ionone developed by Camps and coworkers[22] using sodium dithionite ($Na_2S_2O_4$) under phase transfer catalysis. Thus a vigorously stirred mixture of β-ionone, $NaHCO_3$, $Na_2S_2O_4$, and Adogen®464 in a ratio of 1: 5: 2.2: 0.3 in a refluxing mixture of water and toluene (2:1) gave the desired dihydro-β-ionone **9** in 65% yield along with 5-10% unreacted β-ionone which could be removed by column chromatography. Conversion of the methyl ketone **9** into the terminal alkyne **11** was achieved by a three-step, one-pot sequence involving treatment of **9** with LDA, followed by diethylchlorophosphate, to form an enol phosphate intermediate **10**; subsequent β-elimination using two further equivalents of LDA gave alkyne **11** in 70% yield[23]. Stereo- and regioselective zirconium-catalysed carboalumination of the alkyne produced alkenylalane intermediate **12** whose aluminate complex, prepared *in situ* by reaction with BuLi, reacted with oxirane affording homoallylic alcohol **13** (64% overall from **11**). Finally alcohol **13** was converted into the corresponding homoallylic bromide **5** by means of the standard mesylation/displacement sequence. In summary, bromide **5** was prepared from β-ionone in an overall yield of 27%.



Scheme 3

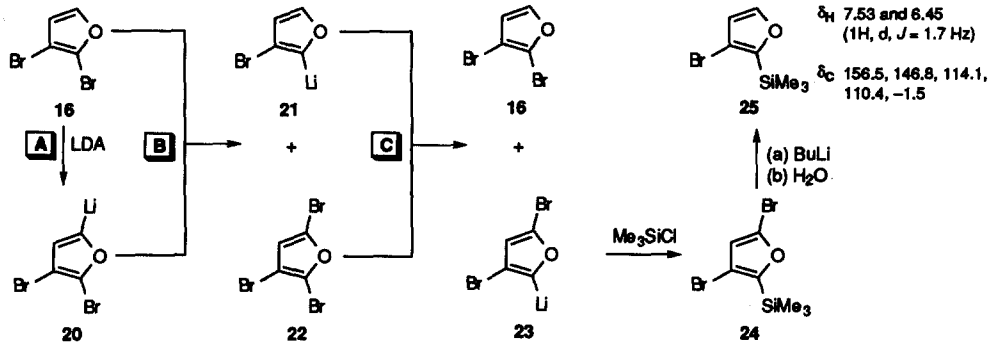
Synthesis of 2-Trimethylsilyl-4-(1,3-dithian-2-yl)furan (7) (Scheme 4). The starting point in the preparation of **7** was the inexpensive, commercially available methyl 2-furoate **14**, which was converted to 2,3-dibromofuran **16** using the method patented by Majoie[24]. The first step in the sequence was a dibromination reaction, achieved by adding a solution of bromine in CCl_4 to a *refluxing* solution of **14** in the same solvent. The resulting product was then saponified to give 4,5-dibromo-2-furoic acid (**15**) in 73% overall yield, with a small amount of the tribrominated acid as an impurity. Decarboxylation of the acid functionality was then achieved by heating a mixture of **15** and copper powder in quinoline at 180°C, giving **16** in 50% yield. Treatment of **16** with lithium diethylamide (*vide infra*) at low temperature followed by silylation gave 2-trimethylsilyl-4,5-dibromofuran (**17**) in 85% yield. Selective halogen-metal exchange occurred at the 5-position giving 2-trimethylsilyl-4-bromofuran (**18**) after protonation. To complete the sequence, halogen-metal exchange with *s*-BuLi followed by formylation returned 2-trimethylsilyl-4-furancarboxaldehyde (**19**) in 78% yield.



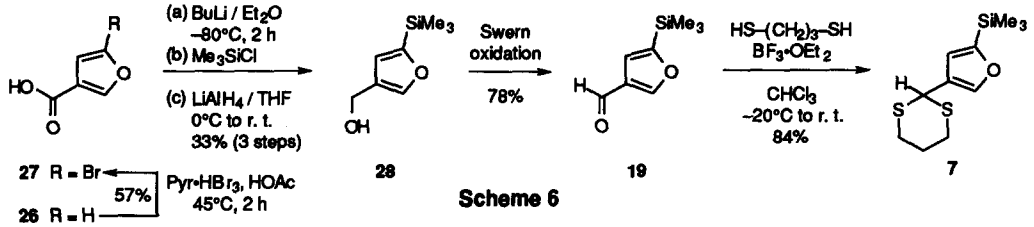
Scheme 4

The conditions required to accomplish the conversion of 2,3-dibromofuran (**16**) to the silyl derivative **17** required some effort to unravel. We had originally followed the procedure of Davies and Davies[25] who reported that treatment of **16** with LDA, followed by chlorotrimethylsilane, resulted in the formation of 2-trimethysilyl-4,5-dibromofuran (**17**). This observation was confirmed by Katsumura et al.[18]; however, in our hands, the product **17** was contaminated with variable amounts of a regioisomer tentatively assigned structure **24** (Scheme 5). The structure of **24** was confirmed by performing a

selective halogen-metal exchange of the bromine in the 2-position followed by protonation. The resultant 3-bromo-2-trimethylsilylfuran (**25**) revealed two adjacent protons with a coupling constant of 1.7 Hz. By contrast 3-bromo-5-trimethylsilylfuran (**18**) resulting from halogen-metal exchange and protonation of the desired regioisomer **17** revealed two aromatic protons with $J = 0$ Hz. The source of the isomerisation was the LDA deprotonation step; we found that the anion **20**, formed on treatment of **16** with LDA, underwent a rearrangement, which scrambled the positions of the bromine substitution. Assuming the rearrangement results from two sequential intermolecular halogen-metal exchange reactions (steps B and C in Scheme 5) competing with the initial deprotonation (step A), we reasoned that a more kinetically competent base could increase the rate of step A and remove **16** before step B occurred. Thus, treatment of **16** with lithium diethylamide, rather than LDA, gave exclusively the unisomerised product **20**. In view of the consistent difficulties which we encountered with the LDA reaction, we are surprised that the rearrangement was not recorded previously especially since analogous processes have been observed in the LDA deprotonations of 2,3-dibromothiophene[26,27], 2-bromo-3-methanethio-thiophene[28] and other halogenated heterocycles[29,30].



Scheme 5

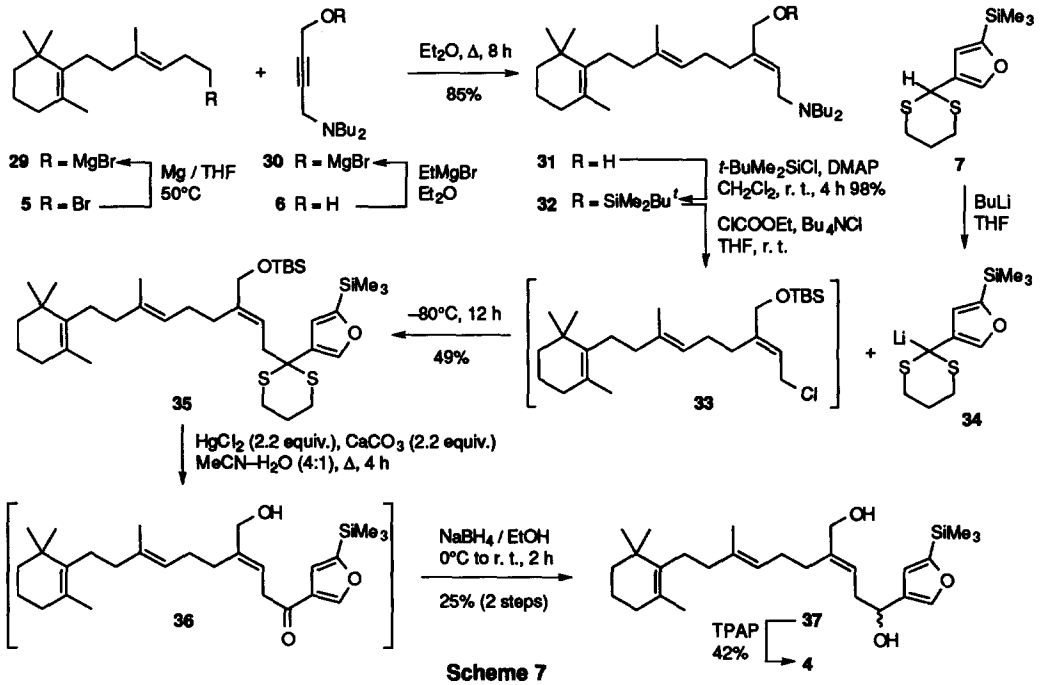


Scheme 6

Although the route outlined in Scheme 4 could be carried out on a large scale and benefited from cheap reagents, it was both long and time consuming. The initial bromination of the methyl 2-furoate (**14**) took a total of 72 h to complete, and this was followed by a further 24 h reaction for the saponification to prepare **15**. The high temperatures required for the decarboxylation of **15**, along with the rather unpleasant quinoline solvent, were also disadvantages of the route; albeit minor ones. We therefore developed a shorter route summarised in Scheme 6, which was based on the reaction sequence reported by Tanis and Head[31]. Commercial 3-furoic acid (**26**), was brominated by treatment with pyridinium bromide perbromide[32], to produce 2-bromo-4-furoic acid (**27**). Treatment of **27** with two equivalents of butyllithium formed a dianion, which was quenched with chlorotrimethylsilane to give a crude product, which was reduced to the alcohol **28** (33% overall from **27**). Subsequent oxidation of alcohol **28** gave aldehyde **19** identical with the sample prepared by the route depicted in Scheme 4.

Despite the similarity in yield for both routes (*ca* 15%), we prefer the shorter second route. After our work was complete, Garst and co-workers[33] reported an extremely short method for the preparation of **19** which is likely to be the method of choice.

A Formal Synthesis of Manoalide (Scheme 7). The key step in our first (formal) synthesis of manoalide (Scheme 7) involved the carbomagnesiation of 4-(di-*n*-butylamino)-2-butyn-1-oxymagnesium bromide (**30**) with the Grignard reagent **29** (derived from bromoalkane **5**)[21,34]. The desired trisubstituted alkene product **31** was obtained in an 85% yield, with greater than 97% of the (*E*)-configuration; none of the (*Z*)-geometrical isomer was visible in the high field ^1H and ^{13}C NMR spectra of the product. The TBS ether **32** of alcohol **31** reacted with ethyl chloroformate in THF in the presence of Bu_4NCl to give an inseparable mixture of the allylic chloride **33** and ethyl di-*n*-butylcarbamate. Owing to the instability of allylic chloride **33** it was neither purified nor stored; rather, it was immediately added to excess lithium reagent **34** (derived from metallation of dithiane **7**) to give the alkylated product **35** in 49% yield having the complete carbon skeleton of seco-manoalide.



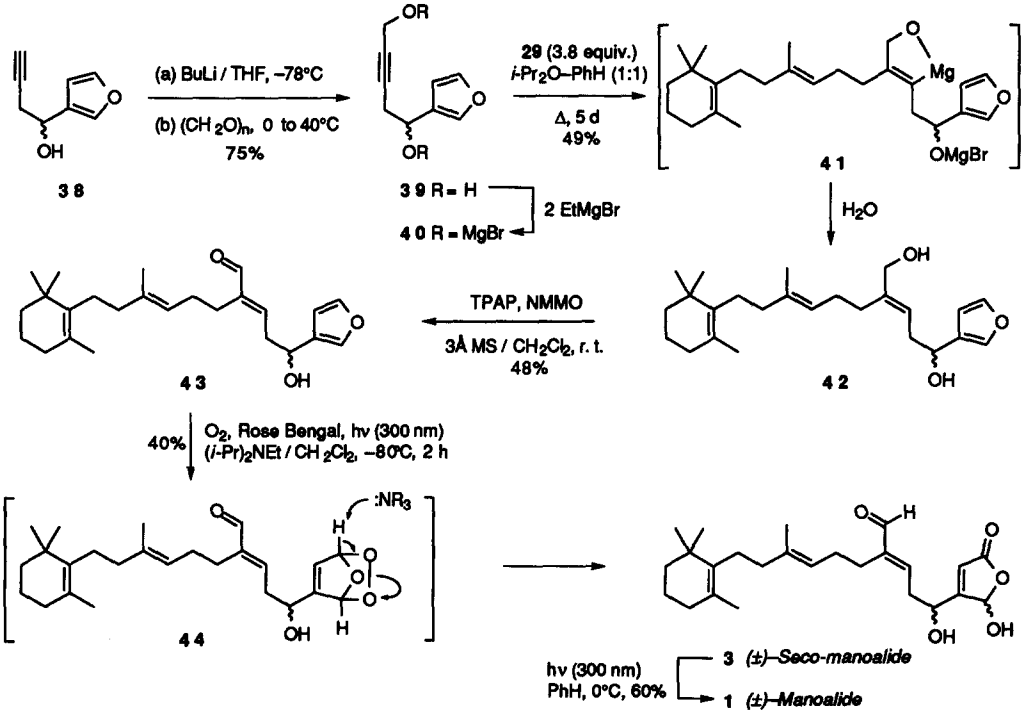
Scheme 7

Removal of the dithiane to reveal an unprotected carbonyl functionality proved to be extremely troublesome. A number of different reagent systems were tried, including treatment with methyl iodide[35], $CuCl_2/CuO$[36], $AgNO_3$/*N*-chlorosuccinimide[37], and h*ν*/methylene green[38]. The deprotection was finally achieved — and then in widely variable yields — by treating the dithiane with $HgCl_2$ and $CaCO_3$[37], resulting in the formation of the sensitive hydroxy-ketone **36** which was immediately reduced to diol **37**. Finally, the primary hydroxyl functionality of **37** was selectively oxidised using TPAP[39] to give an aldehyde which was spectroscopically identical to the seco-manoalide precursor **4** in the Garst synthesis of manoalide[19]. However, weighed in the balance, the ease and stereoselectivity of the carbometallaion was insufficient recompense for the instability of the intermediates **33** and **36** coupled with the capricious dithiane deprotection. A better route was sought and found.

2. Second Synthesis: Carbomagnesiation of a 2-Pentyn-1,5-diol

In a recent synthesis of the diterpene zoapatanol, we showed that carbomagnesiation of but-2-yn-1,4-diol was an effective means for generating functionalised trisubstituted alkenes[40,41]. We now show that a similar carbomagnesiation of a pent-2-yn-1,5-diol derivative is regioselective providing thereby an expeditious route to the manoalide skeleton. Furthermore, in our second synthesis (Scheme 8), we dispense with the services of the trimethylsilyl group without penalty to the penultimate furan photooxidation[42,43].

Allenylmagnesium bromide reacted with furan-3-carboxaldehyde (Aldrich) to give the racemic alcohol **38** in 98% yield. Alkyne metallation followed by reaction with paraformaldehyde then provided crystalline diol **39** in 75% yield. Conversion of diol **39** to its dimagnesium salt using two equiv. of ethylmagnesium bromide as a sacrificial Grignard reagent was followed by carbomagnesiation with 3.8 equiv. of **29**. The reaction was much slower than the corresponding carbomagnesiation of but-2-yn-1,4-diol but, by using a mixture of benzene and diisopropyl ether (1:1) at reflux, a 49% yield of the desired diol **42** was obtained after 5 days along with 20% recovered starting material **39**. It is noteworthy that the primary propargylic oxygen directed both the regiochemistry and stereochemistry of the addition providing magnesiocycle **41** as the only adduct. Protonolysis of **41** occurred with retention of double bond configuration to afford diol **42** as a single geometric isomer.



Scheme 8

Completion of the synthesis of manoalide followed along lines outlined in Scheme 7. Thus, selective oxidation of the primary hydroxyl function in **42** with TPAP furnished aldehyde **43** (48% yield) which was photooxidised in the presence of a hindered base [$(i\text{-Pr})_2$NEt][44] in order to control the decomposition of the peroxide intermediate **44**. Seco-manoalide (**3**), obtained in 40% yield, was then

photoisomerised (60% yield) to give manoalide which was identical with a ^{1}H NMR spectrum of an authentic sample. The signals were broadened and lacked distinction, in accord with a complex mixture of diastereoisomers and ring-chain tautomers; however, the more informative ^{13}C NMR spectrum was identical with data reported for natural manoalide.

In conclusion, we have shown that carbomagnesiation of propargylic alcohols is an effective and stereoselective means for creating the functionalised C6-C7 trisubstituted alkene of manoalide. In both examples, a propargylic alcohol function exerted its regio- and stereodirecting effect without competition from a proximate dialkylamine (first synthesis) or homopropargylic hydroxyl (second synthesis). A further desirable feature of our second synthesis is the total absence of protecting groups.

Experimental

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of dry oxygen-free nitrogen, or high purity argon where stated. Anhydrous solvents and reagents were prepared by distillation from the usual drying agent prior to use: THF from sodium and benzophenone; pyridine, diisopropylamine, triethylamine, benzene, toluene and dichloromethane from calcium hydride. Diethyl ether ('ether') was stored over calcium hydride. Commercial organometallic reagents were used as supplied by the Aldrich Chemical Company. All reactions were magnetically stirred unless otherwise stated.

Organic extracts were concentrated at aspirator pressure using a Büchi rotary evaporator. All reactions were monitored by TLC on Macherey-Nagel Duren Alugram Sil G/UV254 pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised with UV (254 nm), then I_2, followed by 2M H_2SO_4 in methanol and 0.2 M vanillin in ethanol or by 5% w/w phosphomolybdic acid in ethanol. Flash column chromatography was performed on May & Baker Colpak Sorbsil C60 (0.04-0.06 mm particle size) and run under low pressure. Light petroleum ether refers to distilled petroleum ether with a boiling point range of 40-60°C.

All IR spectra were recorded using a Perkin Elmer 1600 series FT-IR spectro-photometer, using a thin film supported on NaCl plates, or as solutions within sodium chloride cells where stated. Details are reported as ν_{max} in cm^{-1}, followed by an intensity descriptor: vs = very strong, s = strong, m = medium, w = weak or br = broad. ^{1}H NMR spectra were recorded in Fourier Transform mode on Jeol GX-270 (270 MHz), Bruker AM 360 (360 MHz) or Varian VXR 500 (500MHz) spectrometers. All spectra were obtained in $CDCl_3$ solution in 5 mm diameter tubes, and the chemical shift in p.p.m. relative to the residual signals of chloroform (δ = 7.27) as the internal standard. Multiplicities are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad. Coupling constants (J) are reported in parentheses in Hz. ^{13}C NMR spectra were recorded at 67.5 MHz or 90 MHz in $CDCl_3$ in 5 mm diameter tubes, and the chemical shift values are reported in p.p.m. relative to the signals of deuterochloroform (δ = 77.2) as the internal standard. Numbers in parenthesis following the chemical shift refer to the number of protons attached to that carbon as revealed by the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Low (LRMS) and high (HRMS) resolution mass spectra were run on a VG 70-250-SE spectrometer. Ion mass/charge (m/z) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%) and, where assigned, by the proposed identity of the peak. Signal patterns generated by compounds containing bromine or tin atoms, which have more than one isotope of significant natural abundance, are quoted as the signals derived from the ^{79}Br and ^{120}Sn isotopes. Mass spectra were recorded on samples judged to be ≥95% pure by ^{1}H and ^{13}C NMR spectroscopy unless otherwise stated.

4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-butanone (9): A mixture of β-ionone (12) (57.7 g, 0.30 mol), Adogen®464 (46.8 g) and $NaHCO_3$ (126 g, 1.5 mol) in a two-phase solvent system of toluene (600 mL) and water (1200 mL) was vigorously stirred under a nitrogen atmosphere. Sodium dithionite (67.6 g, 0.39 mol) was then added in one portion at room temperature, and the mixture heated to gentle reflux for 30 min, after which time the mixture was cooled and a further portion of sodium dithionite (67.6 g, 0.39 mol) added. The mixture was then heated under reflux for 3 h with vigorous stirring, cooled to room temperature, and the layers separated. The aqueous phase was extracted with ether (3 x 200 mL) and the combined organic layers washed with water (400 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. Unreacted β-ionone (*ca.* 5-10%) was removed from the residual pale yellow oil by column chromatography (SiO_2, 15:1

hexanes-ether) to give the *title compound* (37.8 g, 195 mmol, 65%) after short-path distillation: b.p. 47-49°C (0.01 mmHg). The compound crystallised at –20°C.
IR (film): ν = 2958s, 2928s, 2866s, 2830m, 1717s, 1474m, 1458m, 1434m, 1411m, 1360s, 1261m, and 1161s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.55-2.45 (m, 2H), 2.30-2.20 (m, 2H), 2.14 (s, 3H), 1.89 (t, 2H, J = 6Hz), 1.56 (s, 3H), 1.58-1.50 (m, 2H), 1.44-1.38 (m, 2H), 0.97 (s, 6H).
^{13}C NMR ($CDCl_3$, 90 MHz): δ = 208.9 (0), 136.0 (0), 127.8 (0), 44.6 (2), 39.8 (2), 35.1 (0), 32.8 (2), 29.8 (3), 28.5 (2C, 3), 22.3 (2), 19.7 (3), 19.5 (2).
LRMS (EI mode): *m/z* = 194 ($M^{+\bullet}$, 14%), 179 (23), 176 (29), 161 (40), 136 (45), 121 (100), 43 (55).

4-(2,6,6-Trimethyl-1-cyclohexenyl)-1-butyne (11): A solution of lithium diisopropylamide (LDA) was prepared by the dropwise addition of *n*-butyllithium (2.4 M in hexanes, 50.4 mL, 121 mmol) to a solution of diisopropylamine (16.9 mL, 121 mmol) in dry THF (220 mL), under a nitrogen atmosphere, at -78°C. The cooling bath was removed and the resulting solution was stirred at ambient temperature for 30 min and then cooled to –80°C. A solution of (**13**) (21.3 g, 110 mmol) in dry THF (40 mL) was added dropwise, and the mixture stirred for 1 h. Diethylchlorophosphate (19.1 mL, 132 mmol) was then added at -80°C over 15 min and the solution allowed to warm slowly over 1 h to r.t. and then stirred at r.t. for 2 h. The resulting crude enol phosphate was then cooled to –60°C and added *via* cannula to a solution of LDA (242 mmol prepared as described above) in THF (240 mL) at –80°C, and the dark orange solution so formed was then stirred at ambient temperature for 3 h. The reaction was quenched by the addition of water (60 mL) and any organic products extracted with light petroleum (4 x 150 mL). The extracts were combined, washed with 20% citric acid (100 mL), $NaHCO_3$ (100 mL), and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the crude product was purified by flash column chromatography (SiO_2, light petroleum eluant), followed by kugelrohr distillation to give the *title compound* (14.1 g, 80.1 mmol, 73%) as a colouress mobile oil: b.p. 70°C (bath)/0.1 mmHg. **IR** (film): ν = 3310s, 2120w, and 625s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 2.35-2.25 (2H, m), 2.25-2.15 (2H, m), 1.98 (1H, t, J 2.4 Hz), 1.90 (2H, bt, J 6.2 Hz), 1.62 (3H, s), 1.62-1.49 (2H, m), 1.49-1.37 (2H, m), 1.00 (6H, s).
^{13}C NMR ($CDCl_3$, 90 MHz): δ = 136.1 (0), 128.7 (0), 85.1 (0), 68.1 (1), 39.8 (2), 34.8 (2), 32.8 (2), 28.6 (2C, 3), 28.4 (2), 20.0 (3), 19.6 (3), 19.4 (2).
LRMS (EI mode): *m/z* = 176 ($M^{+\bullet}$, 25%), 161 (40), 137 (100), 123 (35), 119 (57), 105 (43), 95 (77), 91 (35), 81 (50), 69 (43), 67 (33), 55 (30).

4-Methyl-6-(2,6,6-trimethyl-1-cyclohexenyl)-hex-3-en-1-ol (13): To a stirred slurry of zirconocene dichloride (1.46 g, 5.00 mmol) in dry CH_2Cl_2 (20 mL) at 0°C under argon, was added dropwise trimethylaluminium (3.5 M in hexanes, 2.9 mL, 10.0 mmol). Alkyne **11** (0.88 g, 5.00 mmol) in CH_2Cl_2 (5 mL) was added to the resulting lemon-coloured solution at r.t. After stirring for 3 h, volatile compounds were removed by evaporation at reduced pressure and the residue was extracted with dry pentane (4 x 20 mL). The combined extracts were transferred to a dry reaction vessel *via* a cannula and *n*-butyllithium (2.5 M in hexanes, 2.2 mL, 5.5 mmol) was added dropwise at –80°C under argon. The resultant white precipitate was dissolved by adding dry THF (5 mL). The reaction mixture was then warmed slowly to *ca* –30°C and oxirane (4 M solution in ether, 2.5 mL, 10 mmol) added. The reaction was allowed to warm gradually to r. t. and stirring continued for a total of 18 h whereupon water (40 mL) was added and the mixture acidified to pH 2 by adding 2 M HCl. The products were then extracted into ether (4 x 50 mL) and the combined extracts washed with $NaHCO_3$, dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was then purified by flash column chromatography (SiO_2, 10% light petroleum in CH_2Cl_2 eluant) to give the *title compound* (0.76 g, 3.21 mmol, 64%) as a colourless oil.
IR (film): ν = 3331bs, 2928s, 2866s, 1666w, 1473m, 1457m, 1382m, 1360m, 1048s, and 877w cm^{-1}.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 5.15 (1H, td, J = 7, 1 Hz), 3.61 (2H, t, J = 7 Hz), 2.29 (2H, dt, J = 7, 7 Hz), 2.05 (4H, A_2B_2 system appearing as a single major peak), 1.97 (1H, bs), 1.90 (2H, t, J = 6 Hz), 1.68 (3H, d, J = 1 Hz), 1.59 (3H, s), 1.60-1.50 (2H, m), 1.45-1.35 (2H, m), 0.98 (6H, s).
^{13}C NMR ($CDCl_3$, 90 MHz): δ = 139.7 (0), 137.1 (0), 127.1 (0), 119.3 (1), 62.55 (2), 40.45 (2), 40.0 (2), 35.1 (0), 32.9 (2), 31.6 (2), 28.7 (2C, 3), 28.0 (2), 19.9 (3), 19.65 (2), 16.35 (3).
LRMS (EI mode) m/z: 236 ($M^{+\bullet}$, 20%), 221 (5), 137 (100), 121 (20), 107 (15), 95 (35), 81 (40).

1-Bromo-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-hexene (5): To a dry 250 mL round bottom flask flushed with nitrogen was introduced triethylamine (5.65 mL, 1.5 eq) and alcohol **13** (6.39 g, 27.1 mmol) in dry CH_2Cl_2 (80 mL). The solution was cooled to –10°C and neat methanesulfonyl chloride (2.50 mL, 1.2 eq) was added *via* syringe over 5 min. A precipitate appeared rapidly. After 40 min of stirring at –10°C, the reaction was quenched with aqueous sodium

bicarbonate, worked-up with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated. The crude mesylate (8.5 g) was dissolved in acetone (100 mL) and dry LiBr (9.4 g, 4 eq) was added at room temperature in 3-4 portions. The mixture was then heated to a gentle reflux for 3 h whereupon the acetone was evaporated and the residue taken up into CH_2Cl_2 (75 mL) and washed sequentially with water, aqueous HCl, and aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (SiO_2; hexanes) to give the *title compound* (6.05 g, 20.3 mmol, 75%) as a colourless oil.
IR (film): ν = 3100-2800s, 1670m, 1385s, 1360s, 1270s, 1205s, 640s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 5.16 (1H, td, J = 7, 1 Hz), 3.36 (2H, t, J = 7 Hz), 2.58 (2H, dt, J = 7, 7 Hz), 2.06 (4H, A_2B_2 system appearing as a single major peak), 1.92 (2H, t, J = 6 Hz), 1.68 (3H, d, J = 1 Hz), 1.61 (3H, s), 1.58 (2H, m), 1.42 (2H, m), 1.00 (6H, s).
^{13}C NMR ($CDCl_3$, 90 MHz): δ = 139.8 (0); 137.1 (0); 127.3 (0); 120.3 (1); 40.4 (2); 40.0 (2), 35.1 (0); 33.0 (2); 32.9 (2); 31.9 (2); 28.8 (2C, 3); 27.9 (2); 20.0 (3); 19.7 (2); 16.5 (3).
LRMS (EI mode): *m/z* = 298 ($M^{+\cdot}$, 7%), 283 (2), 219 (2), 137 (100), 95 (50), 81 (20), 67 (12), 55 (20), 41 (20), 28 (33).
HRMS (CI mode, NH_3): Found: $(M+H)^+$, 299.1374. $C_{16}H_{28}Br$ requires M, 299.1374.

4,5-Dibromo-2-furoic acid (15): A solution of bromine (25.0 mL, 0.49 mol) in dry CCl_4 (20 mL) was added dropwise over 4 h to a mechanically stirred, gently refuxing CCl_4 (50 mL) solution of methyl 2-furoate (20.0 g, 0.16 mol). A vigorous evolution of gas was observed during the addition. After complete addition of the bromine, the mechanical stirrer was replaced with a magnetic stirrer and the mixture heated under gentle reflux for 24 h, and then at r.t. for a further 48 h. Nitrogen gas was then bubbled through the mixture to remove HBr and most of the excess bromine. The mixture was then poured into saturated aqueous Na_2CO_3 (100 mL) and the product extracted into CH_2Cl_2 (4 x 50 mL). The extracts were combined, washed with saturated aqueous sodium sulphite, a further portion of saturated aqueous Na_2CO_3, brine, and dried (Na_2SO_4). The solvent was then removed by rotary evaporation to give a yellow viscous oil which solidified to a solid mass when refrigerated. This mixture of methyl bromofuroates was hydrolysed by heating with mechanical stirring for 8 h at 60-65°C in 4 M aqueous sodium hydroxide (250 mL). The resulting mixture was then cooled and allowed to stand at room temperature for 16 h whereupon a thick white precipitate of water-insoluble sodium dibromofuroates formed. The precipitate was filtered off and washed with ether to remove any organic impurities. It was then recombined with the aqueous reaction liquors and ether (300 mL) added. The mixture was acidified by adding ice (90 g) and concentrated HCl (90 mL) with vigorous stirring. The ether layer was separated and the aqueous phase extracted with ether (5 x 200 mL). The combined ether phases were then washed with water until the aqueous phase was *ca* pH 4. The ether solution was dried ($MgSO_4$) and the solvent removed by rotary evaporation to give a waxy cream-coloured solid consisting mainly of the *title compound* along with minor amounts of a tribromo derivative (detected by LRMS) (31.9 g, *ca.* 63%).
IR (nujol mull): ν = 3000-2500bs, 1680vs, 1581s, 1418s, 1341s, 1299vs, 1191vs, 1089w, 985s, 952m, 852w, 761m, 618w, 570s cm^{-1}.
^{1}H NMR (CD_3OD, 270 MHz): δ = 7.47 (1H, s), 5.26 (1H, bs).
^{13}C NMR (CD_3OD, 67.5 MHz): δ = 159.9 (0), 148.5 (0), 129.5 (0), 123.0 (1) 104.9 (0).
LRMS (EI mode): *m/z* = 270 ($M^{+\cdot}$, 100%), 253 (15), 226 (14), 197 (18), 119 (16), 118 (17), 117 (18), 116 (17), 44 (22).

2,3-Dibromofuran (16): A stirred mixture of crude 4,5-dibromo-2-furoic acid (15) (20.2 g, 75 mmol) and copper bronze (8.60 g, 0.135 mol) in quinoline (100 mL) was heated to 180°C for 40 min during which time a vigorous evolution of gas was observed. The resulting dark coloured mixture was cooled and poured into a mixture of ice cold 6 M aqueous HCl (300 mL) and ether (200 mL). The mixture was stirred for 1 h and then filtered through celite in order to remove copper residues. The resulting heterogeneous mixture was separated and the aqueous phase extracted with ether (4 x 200 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and decolourised with activated charcoal. The solvent was then removed by distillation to give the crude product as a pale brown oil which was purified by short path distillation to give the *title compound* (8.6 g, 38.1 mmol, 51%) as a colourless oil: b.p. 58-59°C/13 mmHg.
IR (film): ν = 1684w, 1552m, 1484s, 1349m, 1192s, 1155s, 1039s, 956s, 881s, 728s, 612m, 592s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.43 (1H, d, J = 2.1Hz), 6.48 (1H, d, J = 2.1Hz).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 144.8 (1), 123.3 (0), 115.7 (1), 101.8 (0).
LRMS (EI mode): *m/z* = 226 ($M^{+\cdot}$, 100%), 197 (12), 145 (2), 117 (48), 38 (25), 37 (23), 28 (12). The mass spectrum also showed that a trace of a tribromofuran was present.

2-Trimethylsilyl-4,5-dibromofuran (17): *n*-Butyllithium (1.6 M in hexanes, 50 mL, 80 mmol) was added dropwise at –30°C under nitrogen to a stirred solution of diethylamine (8.80 mL, 6.22 g, 85.1 mmol) in dry THF (140 mL) and the mixture stirred for 20 min. The temperature was lowered to –80°C and a solution of 2,3-dibromofuran (**16**) (13.0 g, 57.6 mmol) in THF (150 mL) added dropwise. The solution was stirred for 90 min whereupon chlorotrimethylsilane (17.4 mL, 14.9 g, 137 mmol) was added and the mixture allowed to warm slowly to r.t. The mixture was then poured into saturated NH_4Cl solution and the product extracted into ether (4 x 100 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$) and concentrated by rotary evaporation to a dark yellow oil which was purified by short path distillation to give the *title compound* (14.6 g, 49 mmol, 85%) as a colourless oil: b.p. 134-140°C/12-15 mmHg.
IR (film): 2960s, 1537s, 1463s, 1317s, 1252s, 1164s, 1064m, 971s, 929s, 844s, 791m, 760s, 634m cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 6.34 (1H, s), 0.35 (9H, s).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 160.2 (0), 126.3 (0), 114.9 (1), 111.8 (0), –1.5 (3C, 3).
LRMS (EI mode): *m/z* = 300, 298, 296 ($M^{+\bullet}$, 24, 50, 23%), 285, 283, 281 (54, 100, 53), 257, 255, 253 (9, 16, 8), 229, 227, 225 (18, 36, 18), 205, 203, 201 (21, 41, 20), 139, 137 (62, 61), 73 (30), 43 (20).

2-Trimethylsilyl-4-bromofuran (18): To a magnetically stirred solution of 2-trimethylsilyl-4,5-dibromofuran (**17**) (12.5 g, 42.0 mmol) in dry ether (150 mL) at –80°C under nitrogen was added dropwise a solution of *n*-butyllithium (1.7 M in hexanes, 26.0 mL, 44.2 mmol). After addition was complete, the mixture was stirred for 5 min and then poured into saturated aqueous NH_4Cl. The product was extracted into ether (4 x 100 mL) and the combined extracts were washed with brine, dried ($MgSO_4$), and the solvent removed by rotary evaporation. The residue was purified by Kugelrohr distillation to give the *title compound* (6.01 g, 27.4 mmol, 65%) as a colourless oil: b.p. 140°C(bath)/10 mmHg.
IR (film): ν = 2960m, 1321m, 1252s, 1204s, 1110s, 1062s, 923m, 904m, 843s, 759m, 588s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.62 (1H, d, J = 0.6 Hz), 6.63 (1H, d, J = 0.6 Hz), 0.28 (9H, s).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 162.3 (0), 145.0 (1), 122.7 (1), 99.7 (0), –1.7 (3C, 3).
LRMS (EI mode): *m/z* = 218 ($M^{+\bullet}$, 42%), 203 (98), 173 (2), 147 (12), 137 (73), 123 (5), 109 (6), 95 (6), 73 (14), 43 (15).

2-Trimethylsilyl-4-furaldehyde (19): To a solution of 2-trimethylsilyl-4-bromofuran (**18**) (1.03 g, 4.7 mmol) in dry ether (25 mL) was added at –70°C *s*-butyllithium (1.3 M solution in cyclohexane, 4.3 mL, 5.6 mmol) and the solution stirred for 1 h. To the resultant solution was added freshly distilled *N*-methylformanilide (1.2 mL, 1.3 g, 9.7 mmol) and stirring continued at –70°C for 20 min followed by 1 h at r.t. The mixture was poured into 0.5 M citric acid solution and the organic products extracted into ether. The organic layer was washed with 0.5 M citric acid, brine and then dried ($MgSO_4$) and concentrated. The product was purified by column chromatography (SiO_2, 2% ether in hexanes) to give the *title compound* (0.62 g, 3.68 mmol, 78%) as a colourless oil.
IR (film): ν = 2961s, 2901m, 2823m, 1692s, 1568s, 1398m, 1372m, 1253s, 1137s, 1061s, 898s, 843s, 759s, 701m, 632m, 600s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 9.91 (1H, d, J = 0.4 Hz), 8.22 (1H, d, J = 0.7 Hz), 6.94 (1H, apparent t, J = 0.5 Hz), 0.24 (9H, s).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 184.6 (1), 164.1 (0), 155.6 (1), 129.0 (0), 116.2 (1), –1.9 (3C, 3).
LRMS (EI mode): *m/z* = 168 ($M^{+\bullet}$, 32%), 153 (100), 125 (39), 97 (24), 59 (10), 43 (14).

The title compound (2.05 g, 12.2 mmol, 79%) was also obtained by Swern oxidation of 2-trimethylsilyl-4-furanmethanol (**28**) (2.63 g, 15.4 mmol) using the normal procedure.

2-Bromo-4-furoic acid (27): The *title compound* (15.21 g, 0.086 mol, 69%) was prepared from 3-furoic acid (14.10 g, 0.125 mol) and pyridinium hydrobromide perbromide (42.1 g, 0.132 mol) in glacial HOAc (60 mL) by the method of Ferraz and do Amaral[32].

2-Trimethylsilyl-4-furanmethanol (28): The crude 2-bromo-4-furoic acid (**27**) (5.07 g, 26.5 mmol) in dry ether (200 mL) was cooled to –80°C. With mechanical stirring, BuLi (1.6 M in hexanes, 42 mL, 67 mmol) was added dropwise and after addition was complete, the temperature was allowed to rise to –60°C and stirring continued for a further 40 min whereupon chlorotrimethylsilane (9.4 g, 11.0 mL, 87 mmol) was added. The cooling bath was removed and the mixture allowed to warm to r.t. over 2 h and stirring continued at r.t. for a further 30 min. The mixture was poured into saturated NH_4Cl (200 mL) and the the product extracted into EtOAc (4 x 200 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The residue obtained on concentration *in vacuo*, was then added to a stirred suspension of $LiAlH_4$ (2.0 g, 53 mmol) in dry THF (30 mL) at 0°C. After addition was complete the

mixture was allowed to warm to r.t. and stirred for a further 2 h. The mixture was poured into iced water (200 mL) and acidified to pH 1 by adding conc. HCl. The products were extracted into EtOAc (4 x 100 mL) and the combined extracts washed with brine and dried over $MgSO_4$. The residue obtained on evaporation *in vacuo* was purified by column chromatography (SiO_2, 20% EtOAc in light petroleum) to give the *title alcohol* (1.50 g, 8.82 mmol, 33% overall) as a colourless oil.
IR (film): ν = 3331bs, 2958s, 2899s, 1409m, 1251s, 1121m, 1077s, 1019s, 980s, 911s, 844s, 757s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.59 (1H, m, J = 0.8 Hz), 6.66 (1H, broadened s), 4.53 (2H, d, J = 1 Hz), 2.33 (1H, broad s), 0.26 (9H, d, J = 0.8 Hz).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 161.8 (0), 144.2 (1), 125.2 (0), 119.9 (1), 56.5 (2), –1.6 (3C, 3).
LRMS (CI mode, NH_3): *m/z* = 171 [$(M+H)^{+\bullet}$, 37%], 153 (16), 132 (100), 115 (15), 98 (14), 90 (14), 81 (17), 35 (44).

2-Trimethylsilyl-4-(1,3-dithian-2-yl)-furan (7): To a magnetically stirred solution of 2-trimethylsilyl-4-furancarboxaldehyde (**19**) (0.84 g, 5.0 mmol) and 1,3-propanedithiol (0.50 mL, 0.53 g, 5.0 mmol) in $CHCl_3$ at –20°C was added BF_3•Et_2O (0.05 mL, 0.06 g, 0.4 mmol, 8 mol%). The cooling bath was removed and the mixture allowed to stir at ambient temperature for 7 h. The mixture was extracted with water (20 mL), 10% KOH (20 mL), water (20 mL) and the organic layer dried over K_2CO_3. The residue obtained on evaporation of the solvent was chromatographed (SiO_2, 2% Et_2O in light petroleum eluant) to give the *title compound* (1.09 g, 4.22 mmol, 84%) as a white solid. A sample recrystallised from EtOH gave m.p. 92-93°C.
IR ($CHCl_3$): ν = 1960s, 2902s, 1423m, 1252s, 1216s, 1171m, 1125s, 1076s, 987m, 911s, 841s cm^{-1}.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.70 (1H, apparent t, J = 0.6 Hz), 6.70 (1H, apparent d, J = 0.6 Hz), 5.14 (1H, m), 2.99 (2H, ddd, J = 14.5, 11.5, 2.7 Hz), 2.88 (2H, ddd, J = 14.5, 5, 3.2 Hz), 2.15 (1H, dtt, J = 14.1, 4.2, 2.6 Hz), 1.92 (1H, m), 0.25 (9H, s).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 161.5 (0), 144.5 (1), 124.0 (0), 119.6 (1), 41.5 (1), 31.3 (2), 25.3 (2), –1.6 (3C, 3).
LRMS (EI mode): *m/z* = 258 ($M^{+\bullet}$, 97%), 243 (7), 225 (8), 211 (9), 193 (19), 184 (73), 169 (100), 73 (64), 45 (17).
Found: C, 50.97; H, 6.92%. $C_{11}H_{18}OS_2Si$ requires C, 51.12; H, 7.02%.

4-Di-*n*-butylamino-2-butyn-1-ol (6): The *title compound*, prepared on a 0.45 mole scale (90% yield) by the method of Salvador and Simon[45], gave b.p. 100-108°C/0.05 mmHg (Lit.[21] b.p. 125-126°C/0.5 mm Hg).
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 4.21 (3H, overlapping bs and t, J = 1.7 Hz), 3.38 (2H, t, J = 1.7 Hz), 2.41 (4H, m), 1.40 (4H, m), 1.27 (4H, m), 0.88 (6H, t, J = 7.1 Hz).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 83.9 (0), 79.1 (0), 53.5 (2), 50.5 (2), 42.1 (2), 29.4 (2), 20.8 (2), 14.1 (3).

(2*E*,6*E*)-9-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-7-methyl-3-hydroxymethyl-1-(*N*,*N*-di-*n*-butylamino)-2,6-nonadiene (31): Into a dry 250 mL 3 necked round bottom flask, under nitrogen, equipped with a mechanical stirrer, an effective condenser and a dropping funnel, was introduced 2 g of magnesium (4 eq). The system was flame dried and allowed to cool before the addition of freshly distilled ether (10 mL). One drop of dibromoethane was then added and the suspension heated to gentle reflux. About 5% of the solution of bromoalkane **5** in ether (100 mL) was added *via* dropping funnel and the remaining solution was added dropwise over a period of 6-7 h. The solution was then refluxed for one further hour. The supernatant solution was transferred *via* cannula into an organometallic bottle and stored overnight at –20°C. Titration (I_2/$Na_2S_2O_3$) gave 0.25 M.

To a magnetically stirred solution of 4-di-*n*-butylamino-2-butyn-1-ol (**6**) (0.90 g, 4.6 mmol) in ether (5 mL) was added dropwise, at r.t., EtMgBr (1.5 M solution in ether, 3.1 mL, 4.6 mmol). Vigorous gas evolution was accompanied by the formation of a gelatinous white precipitate. After stirring for 5 min, Grignard reagent (**29**) (0.22 M, 22.8 mL, 5.01 mmol) was added. The precipitate dissolved and the resulting solution was refluxed for 8 h and then poured into cold saturated aqueous NH_4Cl with vigorous stirring. The organic layer was separated and the aqueous layer extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 10% EtOAc in hexanes) to give the *title compound* (1.63 g, 3.9 mmol, 85%) as a colourless oil.
IR (film): ν = 3348bs, 2957s, 2931s, 2864s, 1664w, 1458m, 1379m, 1360m, 1088m, 1068m, 1015m, 787m, 764m cm^{-1}.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 5.56 (1H, t, J = 6.6 Hz), 5.14 (1H, apparent t, J = 6.0 Hz), 4.06 (2H, d, J = 0.7 Hz), 3.14 (2H, d, J = 6.6 Hz), 2.7 (1H, bs), 2.43 (4H, m), 2.12 (4H, m), 2.02 (4H, m), 1.89 (2H, t, J = 6.2 Hz), 1.64 (3H, d, J = 1.5 Hz), 1.60 (3H, s), 1.56 (2H, m), 1.42 (6H, m), 1.29 (4H, sextet, J = 7.3 Hz), 0.99 (6H, s), 0.90 (6H, distorted t, J = 7.3 Hz).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 141.6 (0), 137.2 (0), 136.7 (0), 127.1 (0), 123.4 (1), 123.3 (1), 66.6 (2), 53.8 (2), 51.3

(2), 40.4 (2), 40.0 (2), 35.1 (0), 32.9 (2), 29.0 (2), 28.7 (3), 28.6 (2), 27.9 (2), 27.05 (2), 21.0 (2), 19.9 (3), 19.7 (2), 16.2 (3), 14.2 (3).
LRMS (EI mode): *m/z* = 417 ($M^{+\bullet}$, 47%), 386 (32), 374 (18), 280 (100), 224 (5), 210 (11), 137 (40), 95 (24), 86 (38), 81 (19), 55 (11), 41 (14).
HRMS (EI mode): Found, $M^{+\bullet}$ 417.3965. $C_{28}H_{51}NO$ requires M, 417.3971.

(2*E*,6*E*)-9-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-7-methyl-3-[(*tert*-butyldimethylsilyloxy)methyl]-1-(*N*,*N*-di-*n*-butylamino)-2,6-nonadiene (32): A solution of alcohol **31** (1.41 g, 3.37 mmol), DMAP (20 mg), imidazole (0.57 g, 8.37 mmol), and *tert*-butyldimethylchlorosilane (0.76 g, 5.04 mmol) in dry CH_2Cl_2 (40 mL), was stirred at r.t. for 4 h. The mixture was then poured into water (50 mL) and the product extracted into CH_2Cl_2 (4 x 40 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* and the product purified by flash column chromatography (SiO_2, 10-20% EtOAc in light petroleum graduated eluant) to give the *title compound* (1.76 g, 3.30 mmol, 98%) as a colourless oil.
IR (film): ν = 2929s, 2859s, 1666w, 1462m, 1380m, 1360m, 1254m, 1099m, 1062m, 837s, 775m cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.53 (1H, tt, J = 6.6, 1.5 Hz), 5.14 (1H, m), 4.08 (2H, apparent q, J = 1.5 Hz), 3.14 (2H, d, J = 6.6 Hz), 2.40 (4H, m), 2.08 (4H, A_2B_2 system appearing as a single broad peak), 2.02 (4H, m), 1.90 (2H, t, J = 6.4 Hz), 1.64 (3H, d, J = 1.5 Hz), 1.60 (3H, s), 1.56 (2H, m), 1.42 (6H, m), 1.28 (4H, sextet, J = 7.3 Hz), 0.99 (6H, s), 0.90 (9H, s), 0.895 (6H, t, 7.3 Hz), 0.06 (6H, s).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 140.6 (0), 137.2 (0), 136.5 (0), 127.1 (0), 123.5 (1), 122.6 (1), 67.0 (2), 53.95 (2), 51.3 (2), 40.4 (2), 40.0 (2), 35.1 (0), 32.9 (2), 29.5 (2), 28.8 (3), 28.5 (2), 28.0 (2), 27.2 (2), 26.1 (3), 21.0 (2), 20.0 (3), 19.7 (2), 18.6 (0), 16.2 (3), 14.3 (3), –5.1 (3).
LRMS (CI mode, NH_3): *m/z* = 532 [$(M+H)^{+\bullet}$, 100%], 394 (11), 387 (9), 312 (3), 142 (4), 137 (5), 130 (5), 129 (4), 86 (3), 35 (31).
HRMS (EI mode): Found, $M^{+\bullet}$, 531.4843. $C_{34}H_{65}NOSi$ requires M, 531.4835.

2-[(2*E*,6*E*)-9-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-7-methyl-3-[(*tert*-butyldimethylsilyloxy)methyl]-2,6-nonadienyl]-2-[2-trimethylsilylfuran-4-yl]-1,3-dithian (35): To a magnetically stirred mixture of tetra-*n*-butylammonium chloride (2.98 g, 10.7 mmol), K_2CO_3 (0.14 g, 1.01 mmol), and ethyl chloroformate (1.13 g, 1.0 mL, 10.5 mmol) in THF (20 mL), was added a solution of the allylic amine **32** (0.57 g, 1.07 mmol) in THF (30 mL) and the mixture stirred at r.t. for 20 min. The mixture was then poured into water (100 mL), the organic layer separated, and the aqueous layer extracted with ether (4 x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue, containing allylic chloride **33** and ethyl di-*n*-butylcarbamate could not be separated by flash column chromatography owing to decomposition of the allylic chloride **33** and so the crude product was used immediately in the next step.

To a magnetically stirred solution of dithian **7** (1.39 g, 5.4 mmol) in THF (20 mL) at –40°C was added *n*-BuLi (1.6 M in hexanes, 3.6 mL, 5.8 mmol), and the resultant yellow solution was stirred for 1 h. The temperature was then reduced to –80°C and a solution of the crude allylic chloride **33** in THF (50 mL) added over 10 min. After stirring for a further 12 h at –80°C, the mixture was poured into saturated aqueous NH_4Cl and the organic layer separated. The aqueous layer was extracted with ether (4 x 100 mL) and the combined organic phases washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 2% ether in light petroleum eluant) to give the *title compound* (0.35 g, 0.53 mmol, 49% overall from the allylic amine) along with recovered dithiane (**7**) (0.18 g, 0.69 mmol).
IR (film): ν = 2954s, 2982s, 2857s, 1664w, 1472m, 1462m, 1423m, 1382m, 1360m, 1250s, 1124m, 1074s, 1006m, 911m, 842s, 776s, 758s, 735m, 631m cm^{-1}.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.65 (1H, d, J = 0.7 Hz), 6.65 (1H, d, J = 0.7 Hz), 5.41 (1H, tm, J = 7.1 Hz), 5.14 (1H, m), 4.06 (2H, d, J = 1.3 Hz), 2.87 (2H, ddd, J = 14.4, 11.4, 2.9 Hz), 2.77 (2H, d, J = 7.1 Hz), 2.69 (2H, ddd, J = 14.4, 5.0, 3.3 Hz), 2.1-1.96 (10H, m), 1.91 (2H, t, J = 6.3 Hz), 1.64 (3H, d, J = 1.3 Hz), 1.61 (3H, s), 1.58 (2H, m), 1.42 (2H, m), 1.00 (6H, s), 0.89 (9H, s), 0.26 (9H, s), 0.04 (6H, s).
^{13}C NMR ($CDCl_3$, 90 MHz): δ= 161.7 (0), 146.8 (1), 141.6 (0), 137.3 (0), 136.4 (0), 128.7 (0), 127.0 (0), 123.5 (1), 120.6 (1), 117.9 (1), 66.6 (2), 51.3 (0), 41.7 (2), 40.3 (2), 40.0 (2), 35.1 (0), 32.9 (2), 28.8 (3), 28.6 (2), 27.9 (2), 27.7 (2), 27.0 (2), 26.1 (3), 25.4 (2), 20.0 (3), 19.7 (2), 18.5 (0), 16.2 (3), –1.5 (3), –5.2 (3).
LRMS (70eV, EI mode): *m/z* = 660 ($M^{+\bullet}$, 5%), 257 (100), 185 (3), 137 (6), 95 (6), 73 (21), 55 (2), 45(2).
HRMS (EI mode): Found, $M^{+\bullet}$, 660.3887, $C_{37}H_{64}O_2S_2Si_2$ requires M, 660.3886.

2-Trimethylsilyl-4-[(2*E*,6*E*)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-7-methyl-4-hydroxymethyl-1-hydroxy-2,6-nonadien-1-yl]-furan (37): A mixture of dithian **35** (0.35 g, 0.53 mmol), $HgCl_2$ (0.31 g, 1.14 mmol), and $CaCO_3$ (0.115 g, 1.15 mmol) in 80% aqueous acetonitrile (70 mL) was heated under gentle reflux, under argon, for 4 h. After cooling to r.t., the mixture was filtered through Celite and the filter cake washed with 1:1 CH_2Cl_2 / light petroleum (200 mL). The filtrate was then washed successively with saturated aqueous NH_4OAc and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude unstable ketone product (0.28 g) as a colourless oil. This ketone was then dissolved in EtOH, cooled to 0°C and $NaBH_4$ (0.05 g, 1. 3 mmol) added. The mixture was allowed to warm to r.t. and then stirred for 2 h. The reaction mixture was then diluted with water (100 mL) and the product extracted into CH_2Cl_2 (2 x 100 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The product was then purified by flash column chromatography (SiO_2, 25% EtOAc in light petroleum eluant) to give the *title compound* (0.060 g, 0.13 mmol, 25%) as a colourless, viscous oil:
IR ($CHCl_3$): ν = 3607bs, 3027m, 2960s, 2931s, 2867s, 1252s, 1077s, 1050m, 1005m, 912m, 845s cm^{-1}.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 7.57 (1H, tm J = 0.7 Hz), 6.63 (1H, d, J = 0.7 Hz), 5.51 (1H, t, J = 7 Hz), 5.18 (1H, tm, J = 7 Hz), 4.69 (1H, dd, J = 7.9, 5 Hz), 4.06 (2H, s), 2.62-2.38 (2H, m), 2.40 (2H, bs), 2.24-2.04 (4H, m), 2.02 (4H, A_2B_2 system apearing as a doublet, J = 1.9 Hz), 1.91 (2H, t, J = 6.2 Hz), 1.64 (3H, d, J = 1.2 Hz), 1.60 (3H, s), 1.58-1.54 (2H, m), 1.44-1.39 (2H, m), 0.99 (6H, s), 0.26 (9H, s).
^{13}C NMR ($CDCl_3$, 90 MHz): δ = 161.6 (0), 143.3 (1), 142.2 (0), 137.2 (0), 136.9 (0), 128.7 (0), 127.1 (0), 123.2 (1), 122.2 (1), 118.5 (1), 66.9 (2), 66.9 (1), 40.4 (2), 40.0 (2), 36.4 (2), 35.1 (0), 32.9 (2), 28.8 (3), 28.5 (2), 28.0 (2), 27.0 (2), 20.0 (3), 19.7 (2), 16.2 (3), –1.5 (3).
LRMS (70eV, EI mode): *m/z* = 458 ($M^{+\bullet}$, 8%), 440 (4), 272 (10), 169 (46), 153 (8), 137 (100), 123 (15), 121 (16), 120 (11), 109 (10), 107 (10), 95 (40), 81 (29), 73 (51), 55 (23), 41 (23).
HRMS (EI mode): Found, $M^{+\bullet}$, 458.3216. $C_{28}H_{46}O_3Si$ requires M, 458.3220.

2-Trimethylsilyl-4-[(3*E*,7*E*)-10-(2,6,6-trimethyl-1-cyclohexen-1-yl)-8-methyl-4-formyl-1-hydroxy-3,7-decadien-1-yl]-furan (4): A solution of tetra-*n*-propylammonium perruthenate (TPAP, 1.6 mg, 4.56 μmol) in CH_2Cl_2 (1 mL) was added to a mixture of crushed 4Å molecular sieves (80 mg), *N*-methylmorpholine *N*-oxide (12.0 mg, 102 μmol) and diol **37** (38 mg, 73.7 μmol) in 10% acetonitrile in CH_2Cl_2 (10 mL) at r.t. under argon. The mixture was stirred for 1.5 h; then further amounts of *N*-methyl morpholine *N*-oxide (6 mg, 51 μmol) and TPAP (0.8 mg, 0.28 μmol) were added and stirring continued for a further 1.5 h. The mixture was then passed through a plug of silica gel, the products being eluted with ethyl acetate (100 mL) to remove the molecular sieves and the TPAP residues. The products were concentrated *in vacuo* and then purified by flash column chromatography (SiO_2, 10-20% EtOAc in light petroleum graduated eluant) to give in order of elution, unreacted starting diol **37** (11 mg, 24 μmol, 28%) and the title compound (16 mg, 35 μmol, 42%) as a colourless oil.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 9.40 (1H, s), 7.61 (1H, apparent t, J = 0.7 Hz), 6.64 (1H, d, J = 0.7 Hz), 6.57 (1H, t, J = 7.2 Hz), 5.14 (1H, tm, J = 7.2, 1.2 Hz), 4.87 (1H, dd, J = 7.3, 5.6 Hz), 2.85 (1H, dt, J = 15.4, 7.3 Hz), 2.79 (1H, ddd, J = 15.4, 7.2, 5.6 Hz), 2.31 (2H, t, J = 7.7 Hz), 2.10-1.94 (6H, m), 1.91 (2H, t, J = 6.3 Hz), 1.62-1.53 (2H, m), 1.61 (3H, d, J = 1.2 Hz), 1.60 (3H, s), 1.42 (2H, m), 1.27 (1H, bs), 1.0 (6H, s), 0.27 (9H, s).
^{13}C NMR ($CDCl_3$, 90 MHz): δ = 195.1 (1), 162.3 (0), 150.0 (1), 145.1 (0), 143.4 (1), 137.3 (0), 137.2 (0), 128.3 (0), 127.1 (0), 122.8 (1), 118.0 (1), 66.1 (1), 40.4 (2), 40.0 (2), 37.5 (2), 35.1 (0), 32.9 (2), 28.8 (3), 27.9 (2), 26.9 (2), 24.6 (2), 19.9 (3), 19.7 (2), 16.2 (3), –1.6 (3).
LRMS (70eV, EI mode): *m/z* = 456 ($M^{+\bullet}$, 5%), 438 (4), 302 (5), 169 (40), 153 (21), 137 (100), 136 (42), 123 (10), 121 (12), 95 (40), 81 (30), 73 (36), 55 (16), 41(15).
HRMS (EI mode): Found, $M^{+\bullet}$, 456.3055. $C_{28}H_{44}O_3Si$ requires M, 456.3060.

3-(1-Hydroxybut-3-ynyl)furan (38): To an ethereal solution of allenylmagnesium bromide (1.3 eq; 0.85M; 45 mL) prepared according to Brandsma's procedure[46], was added dropwise, over 20 min, at –40°C under nitrogen, freshly distilled 3-furfural (2.5 mL, 29 mmol) in ether (10 mL). The resultant white suspension was allowed to warm to r.t. and stirred for 1 h before the addition of ammonium chloride (5 mL of saturated solution). The solution was taken up in CH_2Cl_2 (20 mL); the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexanes-ether gradient) and Kugelrohr distillation (b.p. 140°C/15 mmHg) to give compound the *title compound* (3.87 g, 28.5 mmol, 98%) as a colourless oil that crystallised at –20°C.

IR (film): ν = 3400s, 3294s, 2914m, 2120w, 1503m, 1158m, 1030s, 875s, 798m cm^{-1}.
^{1}H NMR ($CDCl_3$, 270MHz): δ = 7.46 (1H, m), 7.39 (1H, m), 6.45 (1H, m), 4.84 (1H, t, J = 6 Hz), 2.66 (1H, dd, J = 1, 0.5 Hz), 2.64 (1H, dd, J = 1.5, 0.5 Hz), 2.29 (1H, br s), 2.09 (1H, t, J = 2.5 Hz).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 143.3 (1), 139.3 (1), 127.4 (0), 108.5 (1), 82.6 (1), 71.2 (0), 65.2 (1), 28.1 (2).
LRMS (EI mode): *m/z* = 136 ($M^{+\cdot}$, 7), 118 (5), 107 (21), 97 (100), 69 (34), 41 (66), 39 (58).

3-(1,5-Dihydroxypent-3-ynyl)furan (39): To a solution of alcohol **38** (3.87 g, 28.45 mmol) in THF (120 mL) at –80°C was added dropwise, under nitrogen, BuLi (2.2 eq; 2.4 M; 26 mL). The resulting pale yellow solution was stirred 30 min at –80°C before allowing the temperature to rise to 0°C. Paraformaldehyde (15 g, excess) was then added slowly in 4 portions. The cooling bath was removed and the mixture heated to 40-50°C for 2 h. The reaction was hydrolysed at 0°C with an ammonium chloride solution (10 mL). The THF was evaporated and the residue taken up in CH_2Cl_2 (50 mL) and washed with brine (10 mL) and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by flash chromatography (SiO_2, hexanes-ether gradient) and then by recrystallisation from toluene giving 3.54 g (21.3 mmol, 75%) of diol **39** as white crystals (m.p. 75.5-76.5°C).
IR (film): ν = 3250s, 2921w, 1591w, 1504m, 1420m, 1154m, 1022s cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.44 (1H, apparent s), 7.39 (1H, apparent s), 6.43 (1H, apparent s), 4.82 (1H, t, J = 6 Hz), 4.22 (2H, s), 3.21 (2H, br s), 2.65 (2H, m).
^{13}C NMR ($CDCl_3$, 67.5 MHz): δ = 143.5 (1), 139.4 (1), 127.6 (0), 108.7 (1), 82.5 (0), 81.2 (0), 65.6 (1), 51.1 (2), 28.7 (2).
LRMS (EI mode): *m/z* = 166 ($M^{+\cdot}$, 3), 148 (2), 137 (5), 120 (8), 97 (100), 69 (25), 52 (22), 41 (39), 39 (25).
Found: C, 64.88; H, 6.09. $C_9H_{10}O_3$ requires C, 65.05; H, 6.07%.

3-[(1*R,S*)-[(3*E*,7*E*)-10-(2,6,6-trimethyl-1-cyclohexen-1-yl)]-8-methyl-4-hydroxymethyl-1-hydroxy]-3,7-decadien-1-yl]furan (42): To a solution of diol **39** (4.00 mmol, 664 mg) in benzene (10 mL) and freshly distilled diisopropyl ether (10 mL) at 10-15°C was added dropwise ethylmagnesium bromide (5.1 mL, 1.6 M in ether, 2.0 equiv.) After 10 min of stirring at r.t., the Grignard reagent **29** (15.2 mmol, 0.25 M solution in ether, 61 mL, 3.8 equiv.) was added and bulk of the ether removed by distillation. The remaining mixture (*ca* 30 mL) was refluxed for 5 days under nitrogen. The reaction was then quenched at 0°C with aq. ammonium chloride (5 mL) and the organic layers separated and washed with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue purified by flash chromatography (SiO_2, gradient hexanes : ether) to give *the title compound* (760 mg; 1.97 mmol; 49%) as a colourless oil.
IR (film): 3345s, 2927s, 2864s, 1455m, 1026s, 874s cm^{-1}.
^{1}H NMR ($CDCl_3$, 360MHz): δ = 7.41 (2H, m, C1H, C25H), 6.41 (1H, s, C2H), 5.49 (1H, t, J = 7.2 Hz, C6H), 5.15 (1H, tq, J = 6.5, 0.5 Hz, C10H), 4.70 (1H, dd, J = 7.6, 5.3 Hz, C4H), 4.05 (2H, s, $C24H_2$), 2.61-2.43 (2H, m, $C5H_2$), 2.29 (1H, br s), 2.22-1.95 (9H, m), 1.90 (2H, t, J = 6.3 Hz, $C12H_2$), 1.64 (3H, d, J = 0.5 Hz, $C23H_3$), 1.59 (3H, s, $C22H_3$), 1.59-1.52 (2H, m, $C18H_2$), 1.45-1.36 (2H, m, $C17H_2$), 0.99 (6H, s, $C20H_3$ and $C21H_3$).
^{13}C NMR ($CDCl_3$, 90 MHz): δ = 143.4 (1), 142.2 (0), 139.1 (1), 137.2 (0), 136.9 (0), 128.8 (0), 127.1 (0), 123.1 (1), 121.8 (1), 108.7 (1), 67.85 (1), 67.8 (2), 40.3 (2), 40.0 (2), 36.2 (2), 35.1 (0), 32.9 (2), 28.7 (2C, 3), 28.5 (2), 27.9 (2), 26.9 (2), 19.9 (3), 19.6 (2), 16.2 (3).
LRMS (EI mode): *m/z* = 386 ($M^{+\cdot}$, 5%), 368 (5), 272 (5), 163 (7), 137 (100), 121 (17), 95 (46), 81 (34).
HRMS (EI mode): Found $M^{+\cdot}$, 386.2808. $C_{25}H_{38}O_3$ requires M, 386.2821.

3-[(1*R,S*)-(3*E*,7*E*)-[10-(2,6,6-trimethyl-1-cyclohexen-1-yl)-8-methyl-4-formyl-1-hydroxy]-3,7-decadien-1-yl]furan (43): The diol **42** (269 mg; 0.697 mmol), *N*-methylmorpholine *N*-oxide (245mg; 2.1 mmol) and crushed 3Å molecular sieves (550 mg) were stirred under argon in dry CH_2Cl_2 (8 mL) for 30 min before adding at r.t. TPAP (40 mg) in one portion. After 3 h the mixture was filtered through a cotton pad, evaporated, and the black residue purified by flash chromatography (SiO_2; gradient petrol-ether) to give *the title compound* (128 mg, 0.33 mmol, 48%) as a colourless oil along with unreacted starting material (54 mg, 0.14 mmol, 20%).
IR ($CHCl_3$): 3605m, 3015m, 2931s, 2866m, 2725w, 1684s, 1642m, 734s cm^{-1}.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 9.37 (1H, s, CHO), 7.47-7.40 (2H, m, C2H and C25-H), 6.54 (1H, t, J = 7.1 Hz, C6H), 6.43 (1H, s with fine coupling, C3H), 5.12 (1H, tq, J = 7.2, 1 Hz, C10H), 4.86 (1H, dd, 6.9, 5.9 Hz, C4H), 2.85 (1H, dd, J = 15.6, 8 Hz, $C5H_A$), 2.79 (1H, ddd, J = 15.6, 7.3, 5.6 Hz, $C5H_B$), 2.29 (2H, t, J = 7.7 Hz, $C8H_2$), 2.08-1.94 (6H, m,

$C9H_2$, $C13H_2$, $C17H_2$), 1.90 (2H, t, J = 6.3 Hz, $C12H_2$), 1.60 (3H, d, J = 1 Hz, $C23H_3$), 1.58 (3H, s, $C22H_3$), 1.58-1.52 (2H, m, $C17H_2$), 1.43-1.37 (2H, m, $C18H_2$), 0.99 (6H, s, $C20H_3$ and $C21H_3$).
^{13}C NMR ($CDCl_3$, 90.5 MHz): δ = 195.1 (1, C24), 149.9 (1, C6), 145.1 (0, C7), 143.8 (1, C1), 139.2 (1, C25), 137.3 (0), 137.1 (0), 128.4 (0), 127.1 (0), 122.7 (1, C10), 108.3 (1, C2), 65.7 (1, C4), 40.3 (2), 40.0 (2), 37.4 (2), 37.1 (0), 32.9 (2), 28.7 (2C, 3), 27.9 (2), 26.9 (2), 24.5 (2), 19.9 (3), 19.6 (2), 16.1 (3).
LRMS (EI mode): m/z = 384 ($M^{+\bullet}$, 18), 366 (39), 288 (30), 270 (17), 247 (20), 230 (65), 216 (25), 203 (33), 191 (28), 177 (35), 161 (50), 137 (100), 95 (41), 81 (32).
HRMS (EI mode): Found $M^{+\bullet}$, 384.2664. $C_{25}H_{36}O_3$ requires M, 384.2677.

(5*R,S*)-5-Hydroxy-4-[(1*R,S*)-[(3*E*,7*E*)-10-(2,6,6-trimethyl-1-cyclohexen-1-yl]-8-methyl-4-formyl-1-hydroxydeca-3,7-dien-1-yl]-2(5*H*)furanone (seco-manoalide) (3): Dry oxygen gas was bubbled through a solution of aldehyde **11** (58 mg, 0.151 mmol), Rose Bengal (1 mg), and $(i\text{-Pr})_2NEt$ (100 μL, 0.6 mmol, 4 equiv.) in dry CH_2Cl_2 (5 mL) at –80°C whilst being irradiated by a mercury lamp (300 nm, 150 W) for 2 h. Evaporation of the solvent gave a pink residue that was purified by flash chromatography (SiO_2, gradient hexanes : ether : acetone) to give *the title compound* (25 mg, 40%) as a pale pink oil.
IR (film): 3384br, 2927s, 2864s, 1748br, 1672 cm^{-1}.
^{1}H NMR ($CDCl_3$, 270 MHz) : δ = 9.38 (1H, s), 6.61 (1H, br t, J = 6.5 Hz), 6.28 (1H, s), 6.10 (1H, s), 5.11 (1H, br t, J = 6.5 Hz), 4.80 (1H, br s), 2.81 (2H, m), 2.25 (2H, m), 2.20-1.80 (8H, m), 1.65-1.35 (7H, m), 1.30 (3H, s), 0.98 (6H, s).
^{13}C NMR ($CDCl_3$, 90.5 MHz): δ = 195.2 (1), 171.1 (0), 169.0 (0), 148.0 (0), 146.0 (1), 137.7 (0), 137.1 (0), 127.2 (0), 122.4 (1), 118.6 (1), 98.0 (1), 67.0 (1), 40.3 (2), 40.0 (2), 35.1 (0), 34.9 (2), 32.9 (2), 28.8 (2C, 3), 27.9 (2), 26.9 (2), 24.6 (2), 20.0 (3), 19.7 (2), 16.2 (3).
LRMS (CI mode): 398 [$(M\text{-}H_2O)^{+\bullet}$, 3%], 149 (66), 137 (100).

(5*R,S*)-5-Hydroxy-4-[(2*R,S*,6*R,S*)2,3-dihydro-6-hydroxy-5-[(3*E*)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-hexenyl]-(5*H*)-pyran-2-yl]-2(5*H*)-furanone (Manoalide) (1): Seco-manoalide (**3**) (21.8 mg, 52.4 μmol) in dry benzene (90 mL) at 0°C was irradiated with a mercury lamp (300 nm, 150 W) for 3 h. The reaction mixture was then evaporated *in vacuo* to give an oil that was purified by flash chromatography (SiO_2, gradient hexanes : ether) to give *the title compound* (13.0 mg, 31.2 μmol, 60%) as a colourless oil.
IR ($CHCl_3$): 3587w, 3377m, 2928s, 1790w, 1762s, 1655w, 783s cm^{-1}.
^{1}H NMR ($CDCl_3$, 360 MHz): δ = 6.25 and 6.10 (1H, s, C25H), 6.12 and 6.05 (1H, s with fine coupling, C2H), 5.76-5.69 (2H, m, C6H), 5.37 and 5.34 (1H, s, C24H), 5.18-5.11 (2H, m, C10H and C4H), 4.96 (1H, apparent t, J = 7.5 Hz, C10H), 4.87 (1H, apparent dd, J = 10.7, 4 Hz, C4H), 4.40 (1H, br s, OH), 2.39-2.22 (2H, m, $C5H_2$), 2.22-1.96 (m, 8H), 1.91 (2H, t, J = 5.8 Hz, $C12H_2$), 1.66 (3H, s, $C23H_3$), 1.61 (3H, s, $C15H_3$), 1.56-1.51 (2H, m), 1.47-1.38 (2H, m), 1.00 (6H, s).
^{13}C NMR ($CDCl_3$, 90.5 MHz): δ = 171.2 (0), 168.5(0, broad), 137.5 (0), 137.3 (0), 137.2 (0), 127.1 (0), 122.9 (1), 121.1 (1), 117.7 (1, broad), 98.0 (1), 91.6 (1), 63.2 (1, broad), 40.4 (2), 40.0 (2C, 2), 35.1 (0), 32.9 (2), 32.9 (2), 28.8 (2C, 3), 28.1 (2), 26.1 (2), 20.0 (3), 19.7 (2), 16.2 (3).
LRMS (FAB, NaI): m/z = 439 [$(M+Na)^{+\bullet}$, 33%], 137 (73).

Acknowledgements. We thank SmithKline Beecham Pharmaceuticals for a CASE studentship (P. B.) and Glaxo Group Research for additional support. We also thank Dr. Michael Garst for copies of NMR spectra for manoalide and seco-manoalide.

References

(1) Flower, R. J.; Blackwell, G. J. *Biochem. Pharmacol.* **1976**, *25*, 285.
(2) Dennis, E. A. *Biotechnology* **1987**, *5*, 1294.
(3) de Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611.
(4) De Vries, G. W.; Lee, G.; Amdahl, L.; Wenzel, M.; Harcourt, D.; Holmes, J.; Syage, E.; Garst, M.; Wheeler, L. A. *Drugs of the Future* **1990**, *15*, 460.
(5) Glaser, K. B.; Jacobs, R. S. *Biochem. Pharmacol.* **1987**, *36*, 2079.
(6) Wheeler, L. A.; Sachs, G.; De Vries, G.; Goodrum, D.; Woldemussie, E.; Muallem, S. *J. Biol. Chem.* **1987**, *262*, 6531.
(7) Reynolds, L. J.; Morgon, B. P.; Hite, G. A.; Mihelich, E. D.; Dennis, E. A. *J. Am. Chem. Soc.* **1988**, *110*, 5172.
(8) Potts, B. C. M.; Faulkner, D. J.; De Carvalho, M. S.; Jacobs, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 5093.

(9) Katsumura, S.; Han, Q.; Fujiwara, S.; Isoe, S.; Nishimura, H.; Inoue, S.; Ikeda, K. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1267.
(10) de Silva, E. D.; Scheuer, P. J. *Tetrahedron Lett.* **1981**, *22*, 3147.
(11) Deems, R. A.; Lombardo, D.; Morgan, B. P.; Mihelich, E. D.; Dennis, E. A. *Biochim. Biophys. Acta* **1987**, *917*, 258.
(12) Albizati, K. F.; Holman, T.; Faulkner, D. J.; Glaser, K. B.; Jacobs, R. S. *Experientia* **1987**, *43*, 949.
(13) Kernan, M. R.; Faulkner, D. J.; Parkanyi, L.; Clardy, J.; de Carvalho, M. S.; Jacobs, R. S. *Experientia* **1989**, *45*, 388.
(14) Kernan, M. R.; Faulkner, D. J.; Jacobs, R. S. *J. Org. Chem.* **1987**, *52*, 3081.
(15) Tsuda, M.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 3503.
(16) Nakagawa, M.; Ishihama, M.; Hamamoto, Y.; Endo, M. In *Symposium on the Chemistry of Natural Products*; Sendai, Japan, 1986; pp 200.
(17) Katsumura, S.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 5827.
(18) Katsumura, S.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1988**, *29*, 1173.
(19) Garst, M. E.; Tallman, E. A.; Bonfiglio, J. N.; Harcourt, D.; Ljungwe, E. B.; Tran, A. *Tetrahedron Lett.* **1986**, *27*, 4533.
(20) Ekow Amoo, V.; De Bernardo, S.; Weigele, M. *Tetrahedron Lett.* **1988**, *29*, 2401.
(21) Mornet, R.; Gouin, L. *Bull. Soc. Chim. Fr.* **1977**, 737.
(22) Camps, F.; Coll, J.; Guitart, J. *Tetrahedron* **1986**, *42*, 4603.
(23) Negishi, E.; King, A. O.; Klima, W. L. *J. Org. Chem.* **1980**, *45*, 2526.
(24) Majoie, B. German Patent 2,030,625, 1971. Chem. Abstr. **1971**, *74*, 76318h.
(25) Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 3507.
(26) Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* **1989**, 771.
(27) Fröhlich, H.; Kalt, W. J. *J. Org. Chem.* **1990**, *55*, 2993.
(28) Taylor, E. C.; Vogel, D. E. *J. Org. Chem.* **1985**, *50*, 1002.
(29) Bunnet, J. F. *Acc. Chem. Res.* **1972**, *5*, 139.
(30) Guildford, A.; Tometzki, M. A.; Turner, R. W. *Synthesis* **1983**, 987.
(31) Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, *25*, 4451.
(32) Ferraz, J. P.; do Ameral, L. *J. Org. Chem.* **1976**, *41*, 2350.
(33) Lee, G. C. M.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Org. Chem.* **1992**, *57*, 3126.
(34) Mornet, R.; Gouin, L. *Synthesis* **1977**, 786.
(35) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68.
(36) Stütz, P.; Stadler, P. A. *Org. Synth. Coll. Vol. VI* **1988**, 109.
(37) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(38) Epling, G. A.; Wang, Q. *Synlett* **1992**, 335.
(39) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 12.
(40) Kocieński, P. J.; Love, C. J.; Whitby, R. J.; Costello, G.; Roberts, D. A. *Tetrahedron* **1989**, *45*, 3839.
(41) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1.
(42) Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3505.
(43) Lee, G. C. M.; Syage, E. T.; Harcourt, D. A.; Holmes, J. M.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 7007.
(44) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773.
(45) Salvador, R. L.; Simon, D. *Can. J. Chem.* **1966**, *44*, 2570.
(46) Brandsma, L. *Preparative Acetylenic Chemistry;* 2nd ed.; Elsevier: Amsterdam, 1988, p 95.

(*Received in UK* 6 *May* 1994; *revised* 24 *May* 1994; *accepted* 27 *May* 1994)