Tetrahedron Vol. 47, No. 3, pp. 481-496, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

RADICAL CYCLIZATION STRATEGIES TO TERPENOIDS: SYNTHESES OF (±)-β-CUPARENONE, (±)-LAURENE AND EPILAURENES

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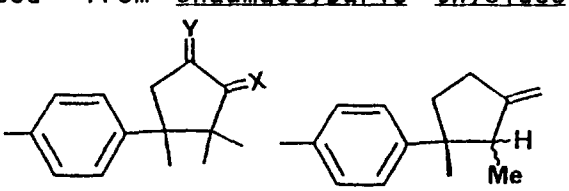
(*Received in UK 2 October* 1990)

ABSTRACT: Radical cyclization of the bromide 8, obtained in 5 steps from the ketone 9, furnished exclusively 14 via 6-endo trig cyclization with out any observable amount of 5-exo trig product 1. 5-Exo dig radical cyclization of the bromo acetate 23, prepared from 18 via the aldehyde 21, followed by routine transformations furnished the cyclopentenone 26, an immediate precursor to β-cuparenone (2). Similarly, total synthesis of laurenes 4 and 5 was achieved via the 5-exo dig radical cyclization of the xanthate 28, obtained from the aldehyde 21.

During the last decade, intramolecular addition of carbon centered free radicals to olefins, i.e. radical cyclizations, of predictable regio and stereo selectivity, provided a powerful technique for carbon- carbon bond formation in organic synthesis.[1] Five membered rings are readily prepared by this approach and the 5-exo cyclization is generally favoured. More over, the method is gentle and efficient for polyfunctional compounds under conditions in which the manipulation of the protecting groups may be minimized in multi step syntheses. The mildness of reaction conditions and the high levels of their chemo and regio selectivity allow radical reactions to serve as powerful synthetic tools whose applications often complement those of their ionic counterparts. The bicyclic sesquiterpenes, cuparenoids and their analogues, laurenes, present an interesting synthetic challenge owing to the steric congestion about the cyclopentane ring.[2] The parent hydrocarbon cuparene (1) was first isolated[3] from Chaamaecyparis thyoides and later from



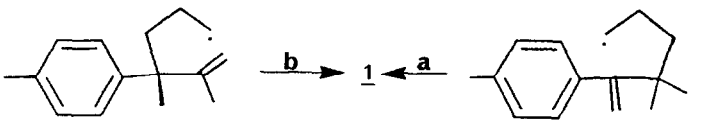
1. X = Y = H_2
2. X = H_2, Y = O
3. X = O, Y = H_2

4. α-Me
5. β-Me

Biota orientalis. Whereas the ketones a and ß- cuparenones (2) and (3) were first isolated[4] from the essential oil of Thuja orientalis and later on their presence was detected in a number of essential oils. Laurene (4) and isolaurene were first isolated from Laurentia glandulifera and more recently from the marine red algae Laurentia elata along with several oxygenated and brominated analogues.[5] In a continuation of our interest in the application of radical cyclization reactions to natural product synthesis,[6] in this account we now describe the approaches, based on radical cyclization reaction, to the hydrocarbon cuparene 1, along with successful routes to ß-cuparenone (2) and laurenes (4 & 5).

APPROACHES TO CUPARENE (1):

Our initial efforts were directed toward the cyclization of radicals 6 (path a) and 7 (path b) to assemble the molecule cuparene 1 (eq. 1).[7] The

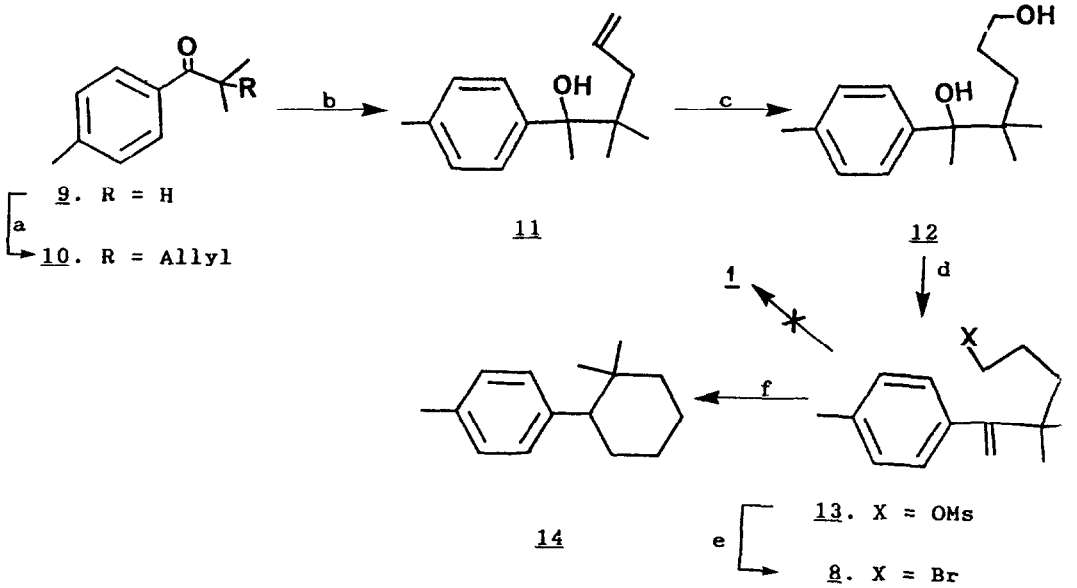


(eq. 1)

7 6

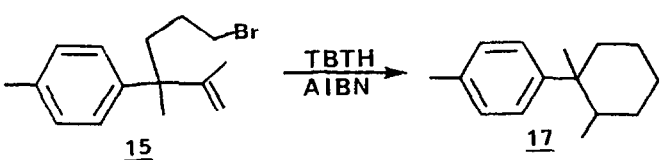
requisite radical precursor 8 (for path a) was prepared from the readily available (toluene, isobutyroyl chloride, $AlCl_3$) 4-methylisobutyrophenone (9) as depicted in the Scheme 1. Generation[8] of the enolate of 9 using freshly prepared $NaNH_2$ in dry toluene and quenching with allyl bromide furnished the allylated ketone 10 in 91% yield. Addition of methylmagnesium iodide in refluxing ether to 10 produced the tertiary alcohol 11 in over 90% yield. Hydroboration (BF_3-$NaBH_4$-THF) followed by oxidation (H_2O_2-NaOH) of 11 furnished, in 85% yield, the diol 12. Reaction of 12 with methanesulfonyl chloride and NEt_3 resulted 13 by simultaneous mesylation of the primary alcohol and dehydration of the tertiary alcohol. The enemesylate 13 was converted to the bromide, the key radical precursor, by treatment with NaBr in refluxing acetone. Refluxing a 0.02 M benzene solution of the bromide 8 with 1.1 equivalents of tri-n-butyltin hydride (TBTH) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) or alternately[9] refluxing a 0.2 M t-butanol solution of the bromide 8 with 0.1 equiv. of tri-n-butyltin chloride and sodium cyanoborohydride in the presence of AIBN resulted the 6-endo cyclized product 14 exclusively with out any detectable amount of cuparene 1 (characteristic methyl singlet at δ 0.53 ppm in the ^1H NMR spectrum of 1).[3] The exclusive formation of 14 can be rationalized based on the conjugation of the aromatic ring with the olefin and preferential attack of the radical at terminal carbon of the conjugated system instead of at C-2. The formation of 6-endo cyclized product 14 promted us to explore path b. The

SCHEME 1



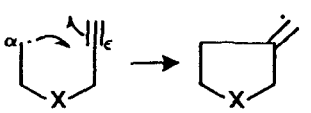
Reagents & Conditions: (a) (i) $NaNH_2$, dry Toluene, 50 °C, 3 h; (ii) Allyl bromide, 50 °C, 3 h, 91%; (b) MeMgI, Et_2O, RT - 16 h; reflux 1 h, 92%; (c) (i) $NaBH_4$, $BF_3.OEt_2$, THF, 0 °C, 1.5 h; (ii) H_2O_2, NaOH, RT, 2 h, 85%; (d) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C - RT, 16 h, 40%; (e) NaBr, Acetone, reflux, 16 h, 76%; (f) n-Bu_3SnCl, $NaCNBH_3$, AIBN, t-BuOH, reflux, 3 h, 70%.

necessary radical precursor 15 was synthesized from the ester 16 (vide infra) using the same sequence of reactions as above. However, even 15 on radical cyclization under standard conditions generated only the 6-endo product 17 with out any observable amount of cuparene (1). Failure of these two approaches led us to attempt the synthesis of ß-cuparenone (2).



SYNTHESIS OF ß-CUPARENONE (2):

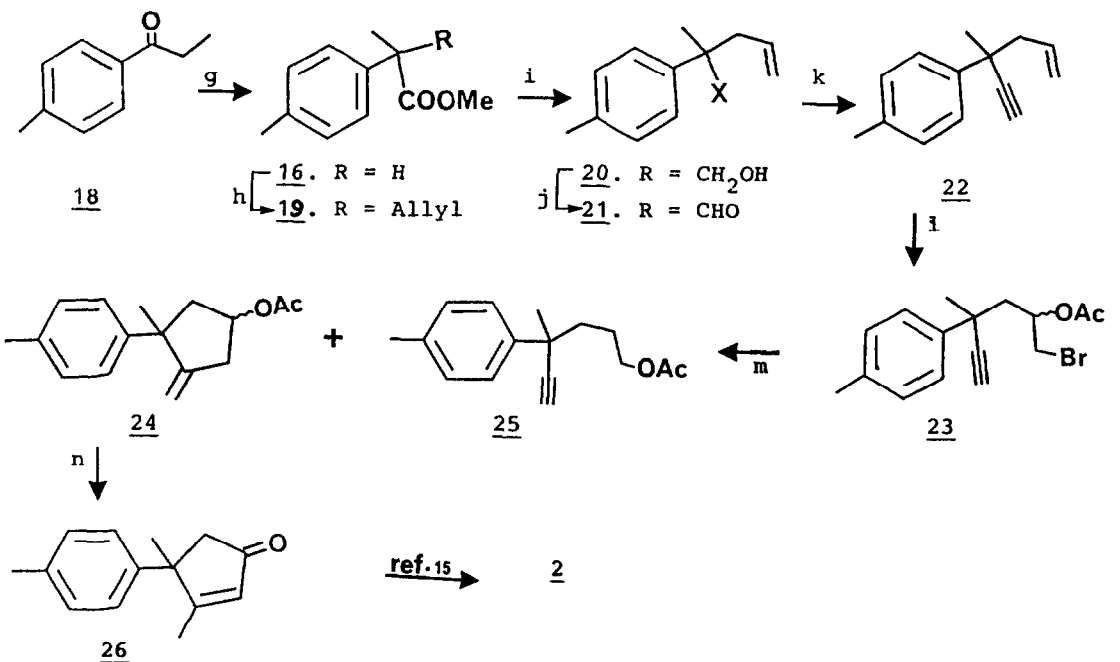
Cyclization of E-acetylenic radicals is a mild and very useful method for the construction of cyclopentanoids with an exo methylene moiety (eq. 2).[10]



(eq. 2)

Conversion of the exo methylene moiety into a variety of functional groups widens the synthetic potential of this reaction. This is the strategy used for the construction of β-cuparenone (2). The synthetic sequence starting from the readily available 4-methylpropiophenone (18) is depicted in the Scheme 2. Ketone 18 was converted into 2-aryl propionate 16, in 85% yield, using iodine in trimethyl orthoformate according to the one pot procedure, recently developed by Yamauchi et al.[11] Generation of the enolate (LDA, THF, -70 °C to RT) and quenching with allyl bromide transformed the propionate 16 into pentenoate 19. Aldehyde 21 was obtained from the ester 19 in a straight forward manner, namely reduction (LAH, Et_2O) to primary alcohol 20 followed by oxidation with buffered (NaOAc) PCC. Conversion of the aldehyde 21 into the enyne 22, key intermediate in the sequence, was most conveniently accomplished in 50% yield, through dibromomethylene Wittig reaction (PPh_3, CBr_4, CH_2Cl_2) followed by treatment with an excess n-BuLi.[12] The structure of 22 was

SCHEME 2

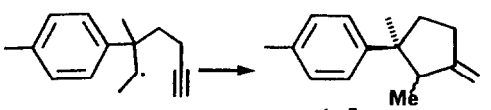


Reagents & Conditions: (g) I_2, $HC(OMe)_3$, RT, 24 h, 85%; (h) (i) LDA, THF, -70 °C, 1 h; (ii) ally bromide, -70 °C - RT, 2 h, 87%; (i) $LiAlH_4$, Et_2O, RT, 16 h, 90%; (j) PCC, NaOAc, CH_2Cl_2, RT, 4 h, 85%; (k) (i) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 1 h; (ii) n-BuLi, THF, -70 °C - RT, 2 h, 50%; (l) NBS, NaOAc, AcOH, CH_2Cl_2, RT, 16 h, 91%; (m) n-Bu_3SnCl, $NaCNBH_3$, AIBN, t-BuOH, reflux, 3 h, 60% (2:1); (n) (i) K_2CO_3, MeOH, RT, 1 h; (ii) PCC, CH_2Cl_2, RT, 3 h, 53%.

clearly delineated from its IR, ^1H and ^{13}C NMR spectral data (see experimental section). Enyne 22 was converted, in 75% yield, to a 2:1 diastereomeric mixture of bromo acetate 23, the radical precursor, via a regiospecific NBS bromination in NaOAc-AcOH-CH_2Cl_2 medium.[13] Refluxing a 0.2 M t-butanol solution of 23 with tri-n-butyltin chloride (0.1 eq.), sodium cyanoborohydride (1.5 eq.) in the presence of AIBN [9] furnished a 2:1 mixture of 5-exo dig cyclized product 24 and acetate migrated[14] product 25 in 60% yield. Structures of 24 and 25 were derived from their spectral data (see experimental section). The cyclized acetate 24 was transformed in to the cyclopentenone 26 in a straight forward manner. Thus, hydrolysis of 24 with K_2CO_3 in methanol, and oxidation of the resultant alcohol with PCC followed by purification over silica gel column generated directly the cyclopentenone 26. Enone 26 exhibited spectral data (IR, ^1H and ^{13}C NMR) identical with that provided by Prof. Greene.[15] As this enone was already transformed to 2 via Ni catalyzed conjugate addition, our sequence constitutes a total synthesis of ß-cuparenone (2). The same methodology has been extended to the total synthesis of laurenes (4 & 5), which is described in the next section.

SYNTHESIS OF LAURENES (4 & 5):

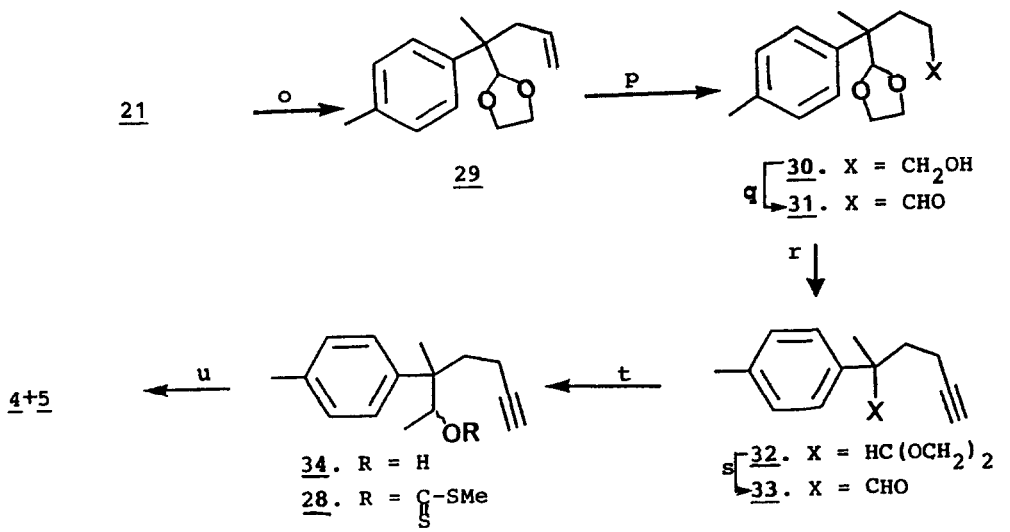
Synthesis of 4 and 5 was achieved by the 5-exo dig cyclization of the radical 27 (eq. 3).[16] The requisite radical precursor, xanthate 28 was



27 4,5 (eq. 3)

prepared (Scheme 3), starting from the aldehyde 21, an intermediate in the synthesis of 2. Protection of the aldehyde group with ethylene glycol in the presence of tolune-4-sulfonic acid transformed 21 into 29. Next step in the sequence is the conversion of the allyl to butynyl side chain. Towards this end, hydroboration ($NaBH_4$-BF_3.Et_2O-THF) of the terminal olefin in 29 followed by oxidation (NaOH-H_2O_2) furnished the primary alcohol 30, which was further oxidized to the aldehyde 31 with PCC-NaOAc in CH_2Cl_2. Conversion of the aldehyde 31 into one carbon extended terminal acetylene 32 was accomplished as described in the preveous section, i.e. via dibromomethylene Wittig reaction followed by treatment with excess n-BuLi.[12] Acid hydrolysis (3N aq. HCl - THF) of the acetylenic acetal 32 furnished the aldehyde 33. Addition of methylmagnesium iodide converted 33 into a 1:3 diastereomeric mixture of the alcohol 34. After several unsuccessful attempts to convert the alcohol into a halide, we resorted to xanthate 28 as the radical precursor. Thus, generation of the sodium salt of the alcohol 34 (NaH, THF, catalytic imidazole) and quenching with CS_2 followed by alkylation with methyl iodide provided[17] the xanthate 28. Radical cyclization of 28 under standard conditions (0.02 M in

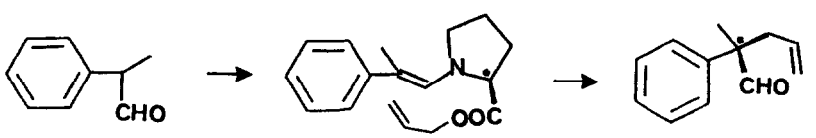
SCHEME 3



Reagents & Conditions: (o) $(CH_2OH)_2$, C_6H_6, p-TSA, reflux, 16 h, 93%; (p) (i) $NaBH_4$, $BF_3.OEt_2$, THF, 0 °C, 1.5 h; (ii) H_2O_2, NaOH, RT, 2 h, 95%; (q) PCC, NaOAc, CH_2Cl_2, RT, 2 h, 80%; (r) (i) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 1.5 h; (ii) n-BuLi, THF, -70 °C - RT, 2 h, 75%; (s) 3N aq. HCl, THF, RT, 14 h, 92%; (u) (i) NaH, imidazole, THF, 50 °C, 3 h; CS_2, 45 °C, 15 min; MeI, 50 °C, 0.5 h; (ii) TBTH, AIBN, C_6H_6, reflux, 3 h, 70%.

benzene, TBTH, AIBN) furnished, as expected,[18] a 1:1 mixture of laurene (4) and epilaurene (5), which exhibited spectral data identical to that reported in the literature.[5]

As is evident from the foregoing discussion, the aldehyde 21, if available in its chiral form, can serve as the starting material for the chiral synthesis of laurenes (4 & 5) and ß-cuparenone (2) and hence to cuparene (1). The recent report on the Pd catalyzed intramolecular chiral allylation of 2-phenyl propionaldehyde (eq. 4) via allyl prolinate enamine by Hiroi et al.[19] provides a convenient route to the chiral synthesis of the aldehyde 21.



(eq. 4)

EXPERIMENTAL SECTION

IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^1H NMR (60, 90 & 270 MHz) and ^{13}C NMR (22.5 MHz) spectra were recorded on a Varian T-60, JEOL FX-90Q and Brucker WH-270 spectrometers. chemical shifts and coupling constants are reported in standard fashion (δ) with reference to either internal tetramethylsilane (^1H NMR) or the central line (77.1 ppm) of

$CDCl_3$ (^{13}C NMR). In the ^{13}C NMR spectra, off-resonance multiplicities are given in parentheses. The standard abbreveations s, d, t, q, br and m refers to singlet, doublet, triplet, quartet, broad and multiplet respectively. Low and high resolution mass measurements were carried out on a Jeol JMS - DX 303 GC-Ms instrument using a direct inlet mode. Relative abundances of the fragments in LRMS are given in parentheses. Analytical thin layer chromatographies (TLC) were performed on (10 x 5 cm) glass plates coated with Acme's silica gel G (containing 13% calcium sulfate as binder) and various combinations of hexane and ethyl acetate (40:1 to 2:1) were used as eluents. All the reactions and column fractions were monitered by TLC. Visualization of the spots was accomplished by exposure to iodine vapor. Acme's silica gel (100 - 200 mesh) was used in the column chromatography. All solvent evaporations were done using either a Buchi rotovapor or steam bath. All the moisture sensitive reactions were conducted using standard syringe - septum technique in nitrogen atmosphere. All compounds were distilled bulb-to-bulb and the bp. refer to the bath temperature. Dry ether and benzene were prepared by distillation over sodium and stored over pressed sodium wire. THF was dried and distilled over sodium benzophenone ketyl prior to use. Dichloromethane was distilled over P_2O_5. All the commercial reagents were used as such with out further purification. AIBN was recrystallized from methanol and stored in dark. 4-Methyl isobutyrophenone and 4-methyl propiophenone were prepared according to the standard procedure.[20]

2,2-Dimethyl-1-(4-methylphenyl)-pent-4-en-1-one (10):

To a magnetically stirred, freshly distilled ammonia (200 ml), placed in a 3 necked flask equipped with a Dewar condenser, was added $FeCl_3$ (catalytic) and freshly cut sodium (0.8 g, 37.5 mmol) in small pieces over a period of 0.5 h. The mixture was stirred for 0.5 h, 175 ml of dry toluene was introduced slowly and ammonia was allowed to evaporate in 1 h. To the suspension of $NaNH_2$ thus formed, was added the ketone 9 (5.5 g, 34 mmol) and heated to 50 °C for 3 h. The reaction mixture was cooled to room temperature and 6.5 ml (73 mmol) of allyl bromide was introduced in one portion. The reaction mixture was heated to 50 °C for 3 h, cooled to room temperature and poured into 50 ml of 5% aqueous HCl. The organic layer was separated and the aqueous layer was extracted with benzene (3 x 50 ml). The combined organic extract was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue on 100 g of silica gel using 1:10 ethyl acetate - hexane as eluent furnished 10 (6.22 g, 91%) as an oil. IR (neat): 1670, 1605, 920, 830, 770 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 7.43 (2 H, d, J = 8 Hz), 7.05 (2 H, d, J = 8 Hz), 5.3 - 6.0 (1 H, m), 4.85 - 5.2 (2 H, m), 2.2 - 2.55 (5 H, m), 1.28 (6 H, s). Mass: 202 (35), 119 (100), 91 (100). HRMS: Calcd. for $C_{14}H_{18}O$ 202.1358; found 202.1356.

3,3-Dimethyl-2-(4-methylphenyl)-hex-5-en-2-ol (11):

To a cold (0 °C), magnetically stirred solution of methylmagnesium iodide [prepared from 2.4 g (0.1 g atom) of magnesium and 6.5 ml (0.105 mol) of methyl iodide in 45 mL of dry ether] was added a solution of the ketone 10 (2.02 g, 10 mmol) in 15 ml of dry ether. The reaction mixture was stirred at room temperature for 16 h and refluxed for 1 h. The reaction was quenched with 20 ml of pH-7 phosphate buffer solution and the organic layer was separated. The aqueous layer was extracted with ether (3 x 30 ml). The

combined organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over 50 g of silica gel with 1:10 ethyl acetate - hexane as eluent furnished the alcohol 11 (2.1 g, 92%) as an oil. IR (neat): 3480, 1380, 1100, 920, 830 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 7.2 (2 H, d, J = 8 Hz), 6.92 (2 H, d, J = 8 Hz), 5.4 - 6.1 (1 H, m), 4.65 - 5.1 (2 H, m), 2.3 (3 H, s), 1.96 (2 H, d, J = 7 Hz), 1.53 (3 H, s), 0.83 (6 H, s). Mass: 218 (5), 201 (40), 136 (80), 135 (100), 119 (70), 91 (80). HRMS: Calcd. for $C_{15}H_{21}$ (M^+-OH) 201.1643; found 201.1684.

4,4-Dimethyl-5-(4-methylphenyl)-hexan-1,5-diol (12):

To a magnetically stirred suspension of $NaBH_4$ (570 mg, 15 mmol) in 25 ml of dry THF was added a solution of $BF_3.OEt_2$ (2.25 ml, 13.7 mmol) in 5 ml of dry THF. The mixture was stirred at room temperature for 0.5 h, cooled to 0 °C and a solution of 11 (880 mg, 4 mmol) in 10 ml of dry THF was added dropwise. The reaction mixture was stirred for 1.5 h, 10 ml of cold water, 6 ml of 3N aqueous NaOH and 6 ml of 30% H_2O_2 were introduced sequentially and stirred for 2 h at room temperature. To the reaction mixture, 50 ml of ether was added, and the organic layer separated and washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on 10 g of silica gel with 1:5 ethyl acetate - hexane as eluent furnished the diol 12 (800 mg, 85%). IR (neat): 3400, 1510, 1380, 1110, 1070, 1040, 920, 830 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 7.21 (2 H, d, J = 8 Hz), 6.92 (2 H, d, J = 8 Hz), 3.1 - 3.8 (3 H, m), 2.28 (3 H, s), 1.1 - 2.15 (9 H, m), 0.83 (6 H, s). Mass: 236 (2), 219 (10), 136 (70), 135 (100), 119 (70), 91 (65). HRMS: Calcd. for $C_{15}H_{23}O$ (M^+-OH) 219.1749; found 219.1756.

4,4-Dimethyl-5-(4-methylphenyl)-hex-5-enyl-1-methanesulfonate (13):

To a cold (-10 °C), magnetically stirred solution of 12 (236 mg, 1 mmol) and dry Et_3N (2.4 ml, 18 mmol) in 10 ml of dry CH_2Cl_2 was added methanesulfonyl chloride (0.68 ml, 9 mmol) dropwise, and stirred at 0 °C for 1 h and at room temperature for 16 h. The reaction mixture was poured into 10 ml of water and extracted with CH_2Cl_2 (3 x 15 ml). The CH_2Cl_2 extract was washed with 2N aqueous HCl (15 ml), aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on 5 g of silica gel with 1:10 ethyl acetate - hexane as eluent furnished 13 (130 mg, 40%). IR (neat): 1360, 1180, 1100, 830, 750 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 6.65 - 7.2 (4 H, m, aromatic), 5.03 (1 H, d, J = 2 Hz) & 4.8 (1 H, d, J = 2 Hz) (olefinic), 4.0 (2 H, t, J = 7 Hz, -CH_2-OMs), 2.8 (3 H, s, -SO_2Me), 2.3 (3 H, s, Ar-Me), 1.1 - 1.85 (4 H, m), 1.07 (6 H, s, gem dimethyl). Mass: 296 (25), 160 (100), 159 (60), 117 (40), 105 (40). HRMS: Calcd. for $C_{16}H_{24}O_3S$ 296.1446; found 296.1463.

6-Bromo-3,3-dimethyl-2-(4-methylphenyl)-hex-1-ene (8):

A solution of 13 (100 mg, 0.34 mmol) and NaBr (175 mg, 1.7 mmol) in 10 ml of dry acetone was refluxed for 16 h. Acetone was removed under reduced pressure and the residue taken in water and extracted with ether (3 x 10 ml).

The ether extract was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on 5 g of silica gel with hexane as eluent furnished the bromide 8 (55 mg, 76%). IR (neat); 1510, 830, 740 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 6.9 - 7.04 (4 H, m), 5.1 (1 H, d, J = 2 Hz), 4.9 (1 H, d, J = 2 Hz), 3.36 (2 H, t, J = 7 Hz), 2.36 (3 H, s), 1.2 - 2.16 (4 H, m), 1.0 (6 H, s).

2,2-Dimethyl-1-(4-methylphenyl)-cyclohexane (14):

To a magnetically stirred solution of the bromide 8 (54 mg, 0.2 mmol) and n-Bu_3SnCl (0.01 ml, 0.025 mmol) in 3 ml of t-BuOH was added $NaCNBH_3$ (30 mg, 0.5 mmol) and AIBN (catalytic), and refluxed for 3 h. The solvent was removed under reduced pressure, the residue taken in water and extracted with ether (2 x 5 ml). The ether extract was washed with 1% aqueous NH_4OH and brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on 5 g of silica gel with hexane as eluent furnished 14 (26 mg, 70%). ^1H NMR (270 MHz, $CDCl_3$):δ7.06 (2 H, d, J = 7 Hz) & 7.02 (2 H, d, J = 7 Hz) (aromatic), 2.34 (1 H, m, benzylic CH), 2.32 (3 H, s, Ar-Me), 1.7 - 2.0 (2 H, m), 1.4 - 1.6 (4 H, m), 1.2 - 1.4 (2 H, m), 0.79 (3 H, s), 0.75 (3 H, s). HRMS: Calcd. for $C_{15}H_{22}$ 202.1721; found 202.1712.

Methyl-2-(4-methylphenyl)-propionate (16):

To a magnetically stirred solution of the ketone 18 (7.45 mL, 50 mmol) in 27 ml of trimethyl orthoformate, iodine (25 g, 0.1 mol) was added and the resulting dark reaction mixture was stirred at room temperature for 24 h in dark. The reaction mixture was poured in to 100 ml of 10% aqueous sodium thiosulfate and extracted with hexane (3 x 50 ml). The hexane extract was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue over 100 g of silica gel using 1:40 ethyl acetate - hexane as eluent furnished the ester 16 (7.6 g, 85%) as an oil.[21] IR (neat): 1740, 1520, 1210, 1170, 820 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 7.0 (4 H, s), 3.55 (3 H, s), 3.5 (1 H, q, J = 7 Hz), 2.25 (3 H, s), 1.4 (3 H, d, J = 7 Hz).

Methyl-2-methyl-2-(4-methylphenyl)-pent-4-enoate (19):

To a magnetically stirred solution of 8.6 ml (60 mmol) of diisopropylamine in 30 ml of dry THF at 0 °C was added 27.3 ml of n-BuLi (2.2 M in hexane, 60 mmol), dropwise, over a period of 20 min. The solution was maintained at 0 °C for 1 h and cooled to -70 °C (EtOH-liq N_2 bath). To the LDA solution thus formed, was added a solution of the ester 16 (3.6 g, 20 mmol) in 20 ml of dry THF dropwise and stirred at the same temperature for 1 h. 6 ml (70 mmol) of allyl bromide was added in one portion, the reaction mixture was slowly warmed to room temperature, quenched with saturated aqueous NH_4Cl solution (10 ml) and extracted with ether (3 x 50 ml). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on 50 g of silica gel with 1:40 ethyl acetate - hexane as eluent furnished 19 (3.8 g, 87%). bp. 110-115 °C

(bath)/5 torr). IR (neat): 1730, 1640, 1520, 1240, 1150, 930, 825 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.2 (2 H, d, J = 8.2 Hz), 7.13 (2 H, d, J = 8.2 Hz), 5.6 (1 H, t of d of d, J = 18, 10, 7 Hz), 5.06 (1 H, d, J = 18 Hz), 5.04 (1 H, d, J = 10 Hz), 3.64 (3 H, s), 2.81 (1 H, d of d, J = 13.6, 7.1 Hz), 2.63 (1 H, d of d, J = 13.6, 7.1 Hz), 2.32 (3 H, s), 1.51 (3 H, s). Mass: 177 ($M^+-C_3H_5$, 90), 159 (100), 149 (80), 117 (80), 91 (25). HRMS: Calcd. for $C_{11}H_{13}O_2$ ($M^+-C_3H_5$) 177.0916; found 177.0921.

2-Methyl-2-(4-methylphenyl)-pent-4-en-1-ol (20):

To a cold (-15 °C), magnetically stirred suspension of 1.15 g (30 mmol) of LAH in 25 ml of dry ether was added a solution of the ester 19 (2.05 g, 10 mmol) in 20 ml of dry ether. The reation mixture was stirred at room temperature for 16 h, 5 ml of ethyl acetate was introduced to consume excess LAH and quenched with 10 ml of ice cold water. The reaction mixture was acidified with 10% aquous H_2SO_4, and extracted with ether (3 x 30 ml). The ether extract was washed with water (2 x 20 ml) followed by brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished the alcohol 20 (1.6 g, 90%) as an oil. bp. 125 - 30 °C (bath)/5 torr. IR (neat): 3400, 1640, 1520, 1040, 920, 825 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.25 (2 H, d, J = 7.5 Hz), 7.12 (2 H, d, J = 7.5 Hz), 5.5 (1 H, t of d of d, J = 18, 10, 7 Hz), 5.0 (1 H, d, J = 18 Hz), 4.96 (1 H, d, J = 10 Hz), 3.76 & 3.45 (2 H, AB q, J = 11 Hz), 2.4 (2 H, m), 2.36 (3 H, s), 1.32 (3 H, s). Mass: 173 (M^+-17, 10), 159 (100), 149 (98), 131 (75), 105 (55), 91 (50). HRMS: Calcd. for $C_{12}H_{15}$ (M^+-CH_2OH) 159.1174; found 159.1182.

2-Methyl-2-(4-methylphenyl)-pent-4-en-1-al (21):

To a magnetically stirred suspension of PCC (3.2 g, 15 mmol) and NaOAc (1.65 g, 20 mmol) in 20 ml of dry CH_2Cl_2 was added a CH_2Cl_2 solution (15 ml) of the alcohol 20 (1.8 g, 10 mmol) in one portion. The reaction mixture was stirred vigorously at room temperature for 4 h. The reaction mixture was charged on a silica gel (50 g) column and eluted with CH_2Cl_2. Evaporation of the solvent furnished the aldehyde 21 (1.5 g, 85%) as an oil. bp. 105 - 110 °C (bath)/5 torr. IR (neat): 2700, 1730, 1645, 1520, 815 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 9.7 (1 H, s), 7.08 (4 H, s), 4.7 - 6.1 (3 H, m), 2.56 (2 H, d, J = 7 Hz), 2.32 (3 H, s), 1.36 (3 H, s). Mass: 188 (6), 163 (15), 159 (70), 145 (25), 135 (50), 131 (20), 119 (100), 105 (25), 91 (60). HRMS: Calcd. for $C_{12}H_{15}$ (M^+-CHO) 159.1174; found 159.1159.

4-Methyl-4-(4-methylphenyl)-hex-1-en-5-yne (22):

To a cold (-15 °C), magnetically stirred solution of Ph_3P (7.85 g, 30 mmol) in 20 ml of dry CH_2Cl_2 was added a solution of 5 g (15 mmol) of CBr_4 in 20 ml of dry CH_2Cl_2 and the deep orange mixture was kept at 0 °C for 0.5 h. A solution of the aldehyde 21 (0.95 g, 5 mmol) in 10 ml of dry CH_2Cl_2 was added. The reaction mixture was stirred at 0 °C for 1 h and filtered through 20 g of silica gel with hexane as eluent. Evaporation of the solvent furnished the dibromomethylene compound.

To a cold (-70 °C), magnetically stirred solution of above dibromide in 5 ml of dry THF was added 2 ml of n-BuLi (2.2 M in hexane, 4.4 mmol) dropwise. The reaction mixture was stirred at the same temperature for 1 h and at room temperature for 0.5 h. The reaction mixture was quenched with 5 ml of saturated aqueous NH_4Cl and extracted with ether (3 x 15 ml). Evaporation of the solvent and purification of the residue over 5 g of silica gel with hexane as eluent furnished the enyne 22 (0.46 g, 50%) as an oil. IR (neat): 3320, 2150, 1520, 920, 820 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.41 (2 H, d, J = 8.3 Hz) & 7.14 (2 H, d, J = 8.3 Hz) (aromatic), 5.69 - 5.85 (1 H, m, $-C\underline{H}=CH_2$), 5.0 - 5.06 (2 H, m, $-CH=C\underline{H}_2$), 2.56 & 2.54 (2 H, d of AB q, J = 13.7, 7.5 Hz, allylic), 2.4 (1 H, s, $-C\equiv C-\underline{H}$), 2.33 (3 H, s, Ar-Me), 1.57 (3 H, s, Me). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 141.8 (s), 136.1 (s), 129.0 (2 C, d) & 126.1 (2 C, d) (aromatic), 134.7 (d, $-\underline{C}H=CH_2$), 117.9 (t, $-CH=\underline{C}H_2$), 89.3 (s, $-\underline{C}\equiv CH$), 71.7 (d, $-C\equiv\underline{C}H$), 48.5 (t, $-\underline{C}H_2-CH=CH_2$), 39.7 (s, C-4), 29.2 (q, Me), 21.1 (q, Me). Mass: 184 (20), 144 (55), 143 (98), 128 (100), 115 (40), 91 (25). HRMS: Calcd. for $C_{14}H_{16}$, 184.1252; found, 184.1255.

1-Bromo-4-methyl-4-(4-methylphenyl)-hex-5-yn-2-ol acetate (23):

To a magnetically stirred suspension of enyne 22 (160 mg, 0.86 mmol), acetic acid (0.5 ml) and NaOAc (150 mg, 2.2 ml) in 3 ml of dry CH_2Cl_2 was added 180 mg (1 mmol) of NBS in small batches and stirred at room temperature for 16 h. The reaction mixture was diluted with 25 ml of CH_2Cl_2, washed with water (10 ml), saturated aqueous $NaHCO_3$ (10 ml) and brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on 5 g of silica gel with 1:10 ethyl acetate - hexane as eluent furnished the bromo acetate 23 (255 mg, 91%) as a 1:2 mixture of diastereomers. IR (neat): 3300, 1740, 1525, 1230, 1020, 820 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.42 (2 H, m), 7.16 (2 H, m), 4.38 & 3.97 (2 H, d, J = 5.3 Hz), 3.15 - 3.47 (1 H, m), 2.47 - 2.58 (2 H, m), 2.35 & 2.33 (3 H, s), 2.08 & 2.01 (3 H, s), 2.02 (1 H, s), 1.66 & 1.62 (3 H, s). Mass: 322 (15) & 324 (15), 243 (16), 183 (20), 144 (100), 143 (100), 128 (80), 115 (40), 91 (25). HRMS: Calcd. for $C_{16}H_{19}BrO_2$ 322.0569 and 324.0550; found 322.0582 and 324.0547.

4-Methyl-4-(4-methylphenyl)-3-methylenecyclopentanol acetate (24) and 4-methyl-4-(4-methylphenyl)-hex-5-yn-1-ol-acetate (25):

A magnetically stirred suspension of the bromo acetate 23 (160 mg, 0.5 mmol), tri-n-butyltin chloride (0.01 ml, 0.038 mmol), sodium cyanoborohydride (63 mg, 1 mmol) and AIBN (catalytic) in 4 ml of t-butanol was refluxed for 3 h. Solvent was evaporated under reduced pressure and residue was taken in water and extracted with ether (3 x 20 ml). The ether extract was washed with 1% aqueous NH_4OH followed by brine and dried over Na_2SO_4. Solvent was removed and the residue was chromatographed on 5 g of silica gel. Elution with hexane to remove tin byproducts followed by elution with 1:10 ethyl acetate - hexane and careful pooling of fractions furnished the cyclized 24 (48 mg, 41%) and rearranged 25 (22 mg, 19%) products.

Compound 24 (mixture of 3:2 diastereomers): IR (neat): 1735, 1515, 1375,

1245, 1045, 905, 825 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 6.77 - 7.33 (4 H, m, aromatic), 4.7 - 5.2 (3 H, m, =CH_2 & C$\underline{H}$-OAc), 2.38 - 2.97 (2 H, m, allylic), 2.3 (3 H, s, Ar-Me), 2.0 - 2.23 (2 H, m), 1.93 (3 H, s, OAc), 1.46 & 1.41 (3 H, s, Me). Mass: 244 (7), 185 (90), 184 (100), 169 (90), 145 (60), 105 (20). HRMS: Calcd. for $C_{14}H_{16}$ (M^+-AcOH) 184.1252; found 184.1230.

Compound 25: IR (neat): 3280, 1740, 1510, 1240, 825 cm^{-1}. ^1H NMR (60 MHz, CCl_4): δ 7.34 (2 H, d, J = 8 Hz), 7.0 (2 H, d, J = 8 Hz), 3.85 (2 H, t, J = 7 Hz), 2.3 (3 H, s), 1.95 (3 H, s), 1.4 - 1.9 (4 H, m), 1.6 (3 H, s). Mass: 244 (25), 184 (30), 169 (35), 144 (75), 143 (100), 128 (75), 115 (30), 101 (70), 91 (25). HRMS: Calcd. for $C_{14}H_{16}$ (M^+-AcOH) 184.1252; found 184.1248.

3,4-Dimethyl-4-(4-methylphenyl)-cyclopent-2-en-1-one (26):

To a cold (ice bath), magnetically stirred solution of 24 (45 mg, 0.19 mmol) in 2 ml of MeOH was added 150 mg (1.14 mmol) of K_2CO_3 and stirred at room temperature for 1 h. The reaction mixture was diluted with 15 ml of ether, washed with water (2 x 10 ml) followed by brine and dried over Na_2SO_4. Evaporation of the solvent furnished the crude alcohol which was oxidized without further purification. IR (neat): 3400, 1520, 825 cm^{-1}.

To a magnetically stirred solution of the above alcohol and NaOAc (82 mg, 1 mmol) in 2 ml of dry CH_2Cl_2 was added PCC (105 mg, 0.5 mmol) in one portion. The reaction mixture was stirred vigorously at room temperature for 3 h and filtered through 5 g of silica gel using CH_2Cl_2 as eluent. Evaporation of the solvent furnished the enone 26 (17 mg, 53%).[15] IR (neat): 1700, 1620, 1515, 825 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.15 (2 H, d, J = 8.5 Hz), 7.13 (2 H, d, J = 8.5 Hz), 6.03 (1 H, q, J = 1.02 Hz), 2.67 & 2.54 (2 H, AB q, J = 18.9 Hz), 2.3 (3 H, s), 1.83 (3 H, d, J = 1.02 Hz), 1.63 (3 H, s). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 208.5, 184.6, 141.3, 136.7, 130.2, 129.5 (2 C), 125.7 (2 C), 54.4, 49.8, 23.8, 20.9, 15.0.

5,5-Ethylenedioxy-4-methyl-4-(4-methylphenyl)-pent-4-ene (29):

A solution of the aldehyde 21 (6 g, 32 mmol), ethylene glycol (5.2 ml, 100 mmol) and toluene-p-sulfonic acid (catalytic) in 75 ml of dry benzene was refluxed for 16 h with a Dean-Stark water separator. The reaction mixture was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over 75 g of silica gel with 1:10 ethyl acetate - hexane as eluent furnished the acetal 29 (7.4 g, 93%) as an oil. bp. 120-125 °C (bath)/5 torr. IR (neat): 1650, 1530, 1100, 920, 820 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.29 (2 H, d, J = 8 Hz), 7.13 (2 H, d, J = 8 Hz), 5.5 (1 H, m), 4.9 - 5.5 (2 H, m), 4.9 (1 H, s), 3.8 (4 H, m), 2.8 (1 H, d of d, J = 14, 6 Hz), 2.39 (1 H, d of d, J = 14, 8 Hz), 2.31 (3 H, s), 1.32 (3 H, s). Mass: 232 (20), 207 (45), 159 (100), 143 (55), 128 (40), 119 (75), 117 (90), 115 (45), 105 (40), 91 (70). HRMS: Calcd. for $C_{15}H_{20}O_2$ 232.1463; found 232.1464.

5,5-Ethylenedioxy-4-methyl-4-(4-methylphenyl)-pentan-1-ol (30):

To a magnetically stirred suspension of $NaBH_4$ (1.3 g, 34 mmol) in 40 ml

of dry THF was added a solution of $BF_3.Et_2O$ (5.2 ml, 42 mmol) in 20 ml of dry THF drop wise at room temperature. The reaction mixture was stirred for 0.5 h, cooled to 0 °C and a solution of the eneacetal 29 (2.0 g, 8.6 mmol) in 15 ml of dry THF was added dropwise. The reaction mixture was stirred for 1.5 h and treated with 10 ml of cold water, 20 ml of 3N aqueous NaOH and 20 ml of 30% H_2O_2 successively and stirred at room temperature for 2 h. The mixture was extracted with ether and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over 35 g of silica gel with 1:5 ethyl acetate - hexane as eluent furnished the alcohol 30 (2.04 g, 95%) as an oil. bp. 160 °C (bath)/ 5 torr. IR (neat): 3400, 1510, 1100, 1060, 815 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.24 (2 H, d, J = 7.2 Hz), 7.08 (2 H, d, J = 7.2 Hz), 4.84 (1 H, s), 3.76 (4 H, s), 3.48 (2 H, t, J = 7 Hz), 2.28 (3 H, s), 1.0 - 2.1 (5 H, m), 1.28 (3 H, s). Mass: 250 (22), 189 (100), 177 (30), 159 (98), 145 (55), 131 (45), 117 (70), 105 (65), 91 (70). HRMS: Calcd. for $C_{15}H_{22}O_3$ 250.1569; found 250.1554.

5,5-Ethylenedioxy-4-methyl-4-(4-methylphenyl)-pentan-1-al (31):

To a magnetically stirred suspension of PCC (2.6 g, 12 mmol) and NaOAc (1.25 g, 16 mmol) in 30 ml of dry CH_2Cl_2 was added a solution of the alcohol 30 (2 g, 8 mmol) in 15 ml of CH_2Cl_2 in one portion. The reaction mixture was stirred for 2 h at room temperature and filtered through 30 g of silica gel with CH_2Cl_2 as eluent. Evaporation of the solvent furnished the aldehyde 31 (1.58 g, 80%) as an oil which was used immediately in the next reaction. IR (neat): 2720, 1730, 1520, 1110, 820 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 9.75 (1 H, s), 7.25 (2 H, d, J = 8 Hz), 7.1 (2 H, d, J = 8 Hz), 4.9 (1 H, s), 3.83 (4 H, s), 2.3 (3 H, s), 2.0 - 2.4 (4 H, m), 1.35 (3 H, s).

6,6-Ethylenedioxy-5-methyl-5-(4-methylphenyl)-hex-1-yne (32):

To a cold (-15 °C), magnetically stirred solution of Ph_3P (7.8 g, 28.7 mmol) in 20 ml of dry CH_2Cl_2 was added a solution of 5 g (15 mmol) of CBr_4 in 20 ml of dry CH_2Cl_2 and the deep orange mixture was kept at 0 °C for 0.5 h. A solution of the aldehyde 31 (1.84 g, 7.42 mmol) in 10 ml of dry CH_2Cl_2 was added. The reaction mixture was stirred at 0 °C for 1 h and filtered through 20 g of silica gel with hexane as eluent. Evaporation of the solvent furnished the dibromomethylene compound.

To a cold (-80 °C), magnetically stirred solution of the above dibromide in 20 ml of dry THF was added 5 ml of n-BuLi (2.2 M, 11 mmol) drop wise and stirred for 1 h at the same temperature and for one more hour at room temperature. The reaction was quenched with 10 ml of saturated aqueous NH_4Cl and extracted with ether. The ether extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over 20 g of silica gel with 1:20 ethyl acetate - hexane as eluent furnished 32 (1.38 g, 75%) as an oil. IR (neat): 3300, 2140, 1520, 1100, 820 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.25 (2 H, d, J = 8 Hz) & 7.12 (2 H, d, J = 8 Hz) (aromatic), 4.86 (1 H, s, O-C<u>H</u>-O), 3.79 (4 H, br s, O-C<u>H</u>$_2$C<u>H</u>$_2$-O), 2.31 (3 H, s, Ar-Me), 1.6 - 2.3 (5 H, m), 1.33 (3 H, s, Me). ^{13}C NMR (22.5 MHz, $CDCl_3$):

δ 139.1 (s), 135.8 (s), 128.9 (2 C, d) & 127.2 (2 C, d) (aromatic), 109.5 (d, O-CH-O), 85.0 (s, -C≡CH), 68.0 (d, -C≡CH), 65.3 (2 C, t, O-CH_2CH_2-O), 44.8 (s, C-5), 35.6 (t, C-4), 20.9 (q, Me), 18.2 (q, Me), 13.4 (t, C-3). Mass: 244 (20), 171 (45), 143 (40), 132 (45), 117 (55), 105 (55), 91 (50), 73 (98). HRMS: Calcd. for $C_{16}H_{20}O_2$ 244.1463; found, 244.1441.

2-Methyl-2-(4-methylphenyl)-hex-5-yn-1-al (33):

A solution of the acetal **32** (1 g, 4.1 mmol) in 40 ml of a 1:1 mixture of THF and 3N aqueous HCl was stirred at room temperature for 14 h and extracted with ether (3 x 30 ml). The organic phase was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on 10 g of silica gel with 1:10 ethyl acetate - hexane furnished **33** (0.75 g, 92%) as an oil. IR (neat): 3300, 2720, 2130, 1725, 1520, 820 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 9.46 (1 H, s), 7.2 (2 H, d, J = 8.2 Hz), 7.12 (2 H, d, J = 8.2 Hz), 2.34 (3 H, s), 1.9 - 2.3 (5 H, m), 1.5 (3 H, s). Mass: 185 (M^+-Me, 5), 171 (M^+-CHO, 100), 143 (20), 135 (70), 119 (65), 105 (30), 91 (45). HRMS: Calcd. for $C_{13}H_{15}$ (M^+-CHO) 171.1174; found, 171.1164.

3-Methyl-3-(4-methylphenyl)-hept-6-yn-2-ol (34):

To a magnetically stirred suspension of methylmagnesium iodide [prepared from 200 mg (8.3 mmol) of Mg and 0.65 ml (10 mmol) of MeI in 10 ml of dry ether at ice temperature] was added a solution of the aldehyde **33** (200 mg, 1 mmol), in 2 ml of dry ether and stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous NH_4Cl and the ether layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent furnished a 1:3 diastereomeric mixture of the alcohol **34** (205 mg, 95%). IR (neat): 3450, 3300, 2140, 1520, 1075, 815 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.15 (4 H, s), 3.83 & 3.74 (1 H, q, J = 6 Hz), 2.32 (3 H, s), 1.8 - 2.19 (6 H, m), 1.27 & 1.28 (3 H, s), 0.95 & 1.12 (3 H, d, J = 6 Hz). Mass: 216 (1), 199 (10), 172 (95), 157 (95), 143 (65), 132 (100), 119 (80), 105 (80), 91 (80).

Laurene and epilaurene (4 and 5):

To a magnetically stirred solution of the alcohol **34** (110 mg, 0.5 mmol) and imidazole (catalytic) in 5 ml of THF was added NaH (95 mg, 50% suspension, 2 mmol) and heated to 60 °C under nitrogen atmosphere for 2 h. The reaction mixture was cooled to room temperature and dry CS_2 (0.3 ml, 5 mmol) was added and heated to 45 °C for 15 min. The reaction mixture was recooled to room temperature and 0.3 ml (5 mmol) of MeI was added and heated to 50 °C for 0.5 h. The reaction mixture was cooled to room temperature, quenched with 2 ml of AcOH, diluted with 10 ml of water and extracted with ether (3 x 20 ml). Evaporation of the solvent and filtration of the residue through 5 g of silica gel furnished the xanthate **28**, which was immediately used in the next reaction.

A solution of the xanthate **28**, TBTH (0.15 ml, 0.55 mmol) and AIBN (catalytic) in 30 ml of benzene was refluxed for 3 h. The reaction mixture was cooled, washed with 1% aqueous NH_4OH, brine and dried over Na_2SO_4.

Evaporation of the solvent and purification of the residue over 5 g of neutral alumina using hexane as eluent furnished 70 mg (70%) of a 1:1 mixture of laurene (4) and epilaurene (5). IR (neat): 1510, 1455, 1375, 875, 810 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.1 (s) and 7.14 (d, J = 8 Hz) & 7.14 (d, J = 8 Hz) (4 H, aromatic), 4.9 (2 H, m, $=CH_2$), 2.41 - 2.6 (2 H, m, allylic), 2.35 and 2.37 (3 H, s, Ar-Me), 1.66 - 1.89 (2 H, m), 1.32 and 1.12 (3 H, s), 0.67 and 0.96 (3 H, d, J = 7 Hz).

ACKNOWLEDGEMENTS: We thank Prof. A.E. Greene for providing the authentic spectra of 26, and one of us (GS) wishes to thank the Council of Scientific and Industrial Research, New Delhi for the award of a research fellowship.

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