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Synthesis and Reactivity of Some 3,4-Dibromo-2*H*-[1]benzopyrans: The Generation and Reactions of 3,4-Didehydro-2*H*-[1]benzopyran

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Abstract: Reaction of 3,4-dibromo-2,2,6,8-tetramethyl-2*H*-[1]benzopyran with either organolithium reagents or magnesium generates the novel strained alkyne, 3,4-didehydro-2*H*-[1]benzopyran. Cycloaddition with furans gives access to the dibenzo[*b,d*]pyran system.

INTRODUCTION

The 2,2-disubstituted 2*H*-[1]benzopyran unit (2*H*-chromene) is ubiquitous in the plant kingdom[1] and the isolation of macrocyclic chromenes from sponges indicates an even wider natural occurrence.[2] The discovery of anti-juvenile hormone activity of the precocenes,[3] methoxy-substituted 2,2-dimethylchromenes, stimulated interest in the synthesis of benzopyrans, which was enhanced by the recognition of pharmacological properties of the 4-aminochroman-3-ols, Cromakalim and its analogues, accessible from chromenes *via* the 3,4-epoxychroman.[4] 2-Spiro-linked benzopyran derivatives and naphthopyrans exhibit photochromic[5] and thermochromic[6] properties, prompting further developments. Routes to 2*H*-[1]benzopyrans have been reviewed.[7]

In view of the synthetic utility of organolithium derivatives, we have described the synthesis and reaction with n-butyllithium of 4-bromo-2*H*-chromenes[8] and the 3-bromo analogues[9] and thence the preparation of a variety of 4-substituted 2*H*-[1]benzopyrans and the rotenoid skeleton from the former and 3-arylbuta-1,2-dienes by anionic cleavage of the latter.

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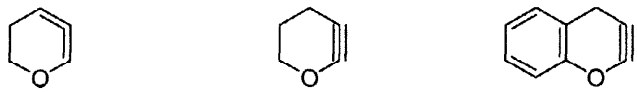
The generation and reactions of benzyne have been extensively studied[10] and analogous heteroarynes similarly confirmed.[11] 3-Halogenocoumarins yield mixtures of the 3- and 4- substituted coumarin on reaction with piperidine, implicating the intermediacy of 3,4-didehydrocoumarin.[12] The base promoted elimination of HBr from 5-bromo-3,4-dihydropyran is facile and leads to 3,4-didehydro-dihydropyran **1** rather than the strained alkyne **2**. The reaction of the strained allene **1** with a range of ketone enolates has been studied.[13] 2,3-Didehydro-2*H*-1-benzopyran **3** has been generated by the action of potassium t-butoxide on 3-bromo-2*H*-chromene and trapped with a range of furans to give cycloadducts.[14]

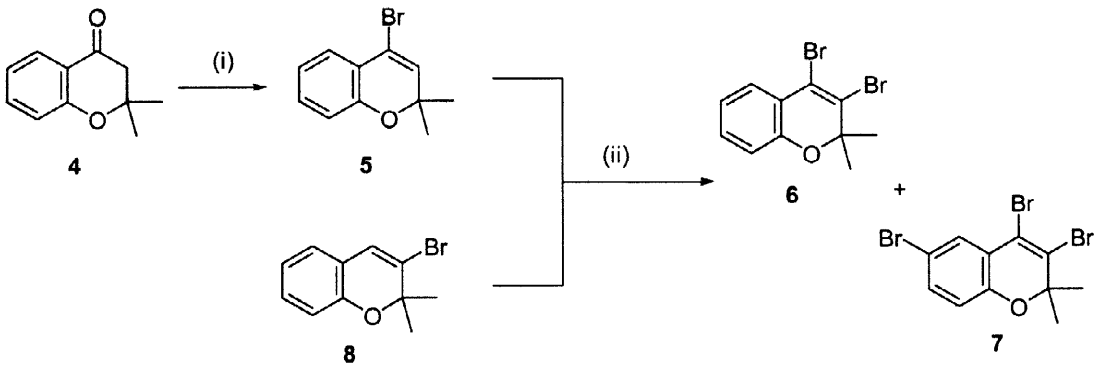


1 **2** **3**

The different behaviour of the 3-bromo-[9] and the 4-bromo- chromenes[8] towards n-butyllithium raised the question of the response of 3,4-dibromo-2*H*-chromenes towards organometallic reagents and we now report our full work on the generation and reactions of 3,4-didehydro-2*H*-[1]benzopyran, a highly strained alkyne, derived from a 2*H*-[1]benzopyran.[15]

DISCUSSION

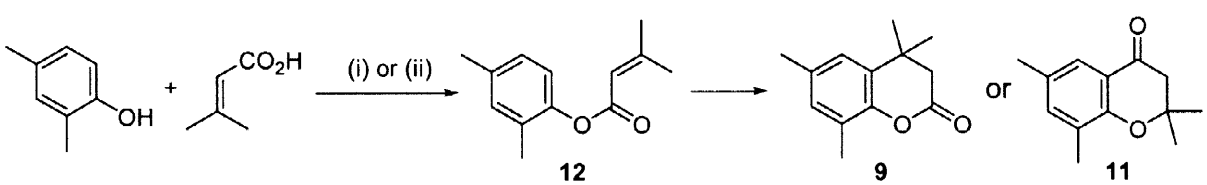
Whilst 3,4-dibromochromans are readily obtained by the addition of bromine to chromenes,[16] there are few examples of 3,4-dibromochromenes in the literature. 7,8-Diacetoxy-2,2-dimethylchroman, synthesised from pyrogallol and isoprene, yields the 3,4-dibromochromene on treatment with *N*-bromosuccinimide in the presence of benzoyl peroxide.[17] Reaction of 6-fluorocoumarin with bromine in chloroform and subsequent DIBALH reduction of the lactone unit led to 3,4-dibromo-6-fluoro-2*H*-chromen-2-ol.[18] On the other hand, monobromochromenes are more widely studied and these were considered to be convenient precursors of the 3,4-dibromochromenes. Thermal cyclisation of γ-bromopropargyl phenyl ethers affords mixtures of 3- and 4-bromochromenes by a Claisen rearrangement[19] and *o*-(3-hydroxy-3-methylbutynyl)phenols are cyclised to 4-bromo-2,2-dimethylchromenes by boron tribromide.[20] However, one of the most efficient and convenient routes to the benzopyran system relies upon the base catalysed condensation of *o*-hydroxyacetophenone with mesityl oxide to give 2,3-dihydro-2,2-dimethyl-4*H*-[1]benzopyran-4-one **4**,[21] from which the 4-bromo-2*H*-[1]benzopyran **5** is obtained directly by reaction with PBr_3.[22] Bromination gave the 3,4-dibromo compound **6** together with some unreacted **5** and a significant amount of a second new component which was characterised as 2,2-dimethyl-3,4,6-tribromo-2*H*-[1]benzopyran **7** which arises through facile bromination in the aromatic ring.[23] For comparison, a sample of 3-bromo-2,2-dimethyl-2*H*-[1]benzopyran[9] **8** was also subjected to bromination under identical conditions. However, the reaction required a considerably longer time for completion and still gave a mixture of the dibromo **6**, tribromo **7** and starting compounds. In the ^{1}H NMR spectrum, the *gem* dimethyl signal in the dibromo compound **6** appears at δ 1.61, similar to that in the 3-bromochromene **8** (δ 1.60) but different from that in the 4-bromo isomer **5** (δ 1.47).



Scheme 1. Reagents: (i) PBr_3, heat; (ii) Br_2, $CHCl_3$, heat.

Although separation of the di- and tri-bromo compounds was achieved by flash chromatography, blocking the 6- and 8-positions to prevent tribromination was thought worthwhile and 4-bromo-2,2,6,8-tetramethyl-2*H*-[1]benzopyran **10** was selected for study. Our attempts to synthesise the precursor benzopyran-4-one **11** by the route advocated by Camps *et al.*[24] for the synthesis of alkoxy-substituted benzopyran-4-ones were unsuccessful. Heating 2,4-dimethylphenol and 3-methylbut-2-enoic acid in methanesulfonic acid (MSA) according to this procedure gave the isomeric dihydrobenzopyran-2-one (dihydrocoumarin) **9** in good yield together with a small amount of the ester **12**. However, when the reaction was repeated using polyphosphoric acid (PPA) as the cyclising medium, the desired ketone **11** and the ester **12** were isolated (Scheme 2). The synthesis of chroman-4-ones from phenols and acrylic acids using PPA as the cyclising medium has been reported though mixtures of chroman-4-ones and dihydrocoumarins were isolated.[25]

It is postulated that the ester **12** is intermediate in the formation of both **9** and **11**. Thus the ester **12** is cyclised in MSA to the dihydrocoumarin **9**, whereas heating the ester **12** in PPA effects a Fries rearrangement and subsequent cyclisation gives the chromanone **11** in excellent yield. The marked effect of the cyclising medium on the outcome of this type of reaction is currently under investigation.

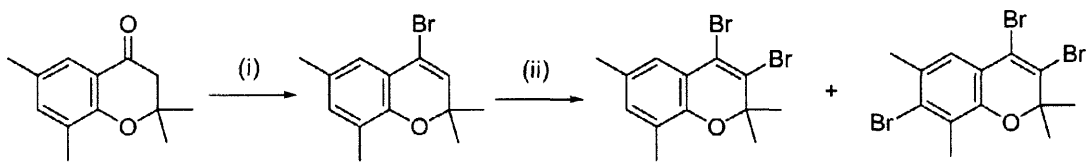


Scheme 2. Reagents: (i) $MeSO_3H$, 70 °C; (ii) polyphosphoric acid, 90 °C.

Distinction between the two isomeric compounds **9** and **11** was readily achieved by spectroscopic methods. The carbonyl ^{13}C resonance appears at δ 168.5 for the lactone **9** and at δ 193.2 for **11**, both values being typical of their respective classes of compound.[26] Their IR spectra show a vibration at 1761 cm^{-1}, typical of a lactone such as **9** and at 1695 cm^{-1} for **11** typical for aryl ketones.[27] The ^1H NMR spectra of these isomeric compounds are quite similar. However, a difference is noted in the chemical shift of 5-H which

resonates at δ 6.95 in **9**, but appears further downfield at δ 7.51 in **11** clearly affected by the anisotropic *peri* carbonyl function.

2,3-Dihydro-2,2,6,8-tetramethyl-4*H*-[1]benzopyran-4-one **11** was readily converted into 4-bromo-2,2,6,8-tetramethyl-2*H*-[1]benzopyran **10** on heating with PBr_3. Subsequent addition of bromine was accompanied by elimination of HBr, affording **13** in good yield. A minor amount of a tribromo compound, presumably 2,2,6,8-tetramethyl-3,4,7-tribromo-2*H*-[1]benzopyran **14**, was also isolated from the reaction mixture. This assignment follows from its ^{1}H NMR spectrum in which both of the aromatic methyl signals are deshielded by *ca.* 0.1 ppm relative to those in **13**. Bromination at the 5-position is considered unlikely because of the significant steric interaction between the incoming bromine molecule and the bromine atom at 4-C.

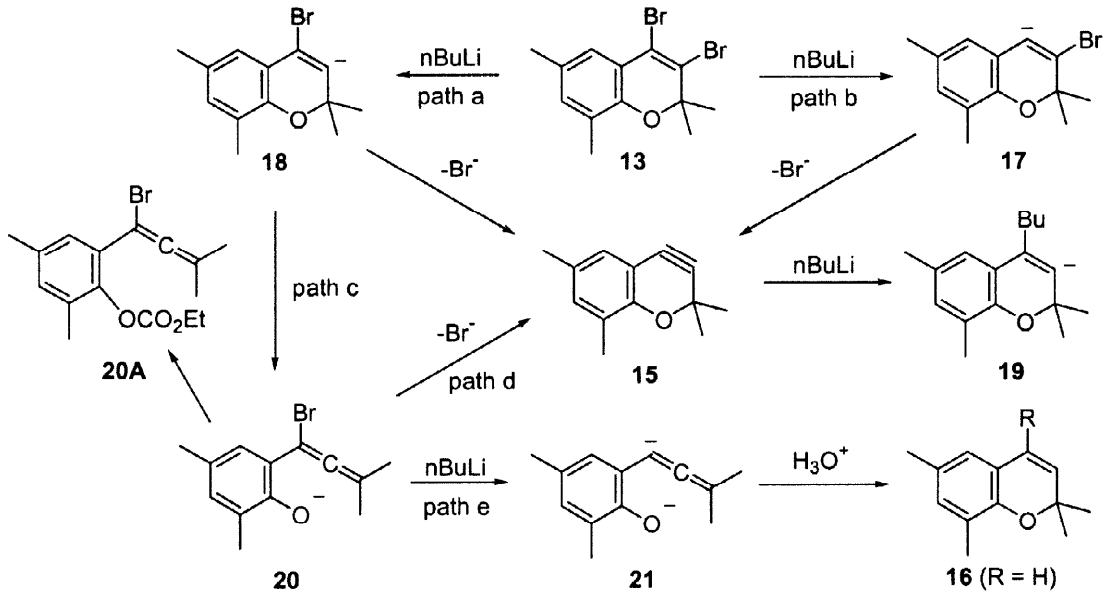


11 **10** **13** **14**

Scheme 3. Reagents: (i) PBr_3, heat; (ii) Br_2, $CHCl_3$, heat.

The reaction of **13** with an excess of n-butyllithium afforded 4-n-butyl-2,2,6,8-tetramethyl-2*H*-[1]benzopyran **16** (R = n-Bu) in moderate yield together with some unreacted starting material **13** and a trace of the 4-unsubstituted 2*H*-[1]benzopyran **16** (R = H), which was characterised by low resolution GC/MS. Similar products resulted with methyllithium, phenyllithium and 2-furyllithium leading to the 2*H*-[1]benzopyrans **16** (R = Me, Ph, 2-furyl). Alkyl substitution in the 4-position is confirmed by reference to the chemical shift of 3-H (δ 5.39-5.61), similar to that of 3-H in 2,2-dimethyl-2*H*-[1]benzopyran (δ 5.46), whereas 4-H resonates at δ 6.21. These values are typical for a wide range of 2*H*-[1]benzopyrans.[22, 28] It appears that following halogen metal exchange, loss of LiBr occurred and nucleophilic addition to an intermediate alkyne **15** completed the reaction sequence. The generation of arynes from 1,2-dihalogenobenzenes is well established[10] and has been applied to 1,2-dihalogeno heterocycles.[11] The addition of n-butyllithium to 4-chloro-2,2-dimethyl-2*H*-chromene **5** (Cl replaces Br) to afford a mixture of 4-n-butyl-2,2-dimethyl-2*H*-chromene and 2,2-dimethyl-2*H*-chromene has been reported. It was suggested that the 4-butylchromene results from a coupling process with *in situ* generated BuCl.[29] However, our previous studies on the metallation of **5** failed to detect the formation of an analogous product.[8, 22] A mechanistic rationale proposed to account for the products from the reaction of 3,4-dibromo-2,2,6,8-tetramethylchromene with n-butyllithium is given in Scheme 4. The didehydrochromene **15** could be generated by Li-halogen exchange of either the 3- or 4-Br atom and subsequent elimination of LiBr (pathways a and b). Whilst neither of the anions **17** nor **18** could be directly intercepted with $ClCO_2Et$, the phenoxide ion **20**, derived from **18** *via* path c, was trapped as the carbonate **20A** (31%). However, this compound was particularly labile and decomposed on standing. Isolation of **20A**, albeit in modest yield, implicates the formation of **18** *via* path a. Loss of halide from **18** would lead to the highly strained alkyne **15** and thence to the 4-butylchromene *via* anion **19**. The regiospecificity of the addition of nBuLi to **15** is readily explained since the anion **19** will be stabilised by ring opening to the allenylphenoxide ion **20** (Bu replaces Br), ample evidence for this process exists.[8, 30] Alternatively, loss of Br^- from **20** may proceed by a

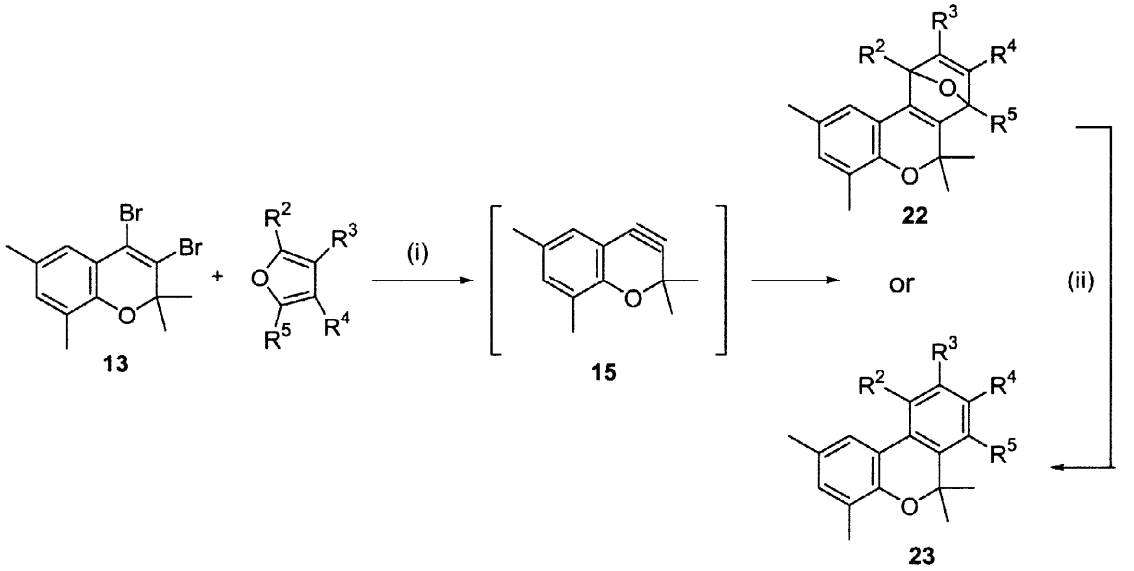
6-*endo-trig* ring closure leading to the didehydrochromene **15** (pathway d) or may proceed to the dianion **21** (pathway e) which cyclises on aqueous work-up to 2,2,6,8-tetramethyl-2*H*-chromene **16** (R = H).



Scheme 4

Cycloaddition reactions of arynes are well documented and in particular the use of furan to intercept any arynes generated during a reaction has become a standard technique.[31] Such a reaction features in the first total synthesis of the angucycline antibiotic C104,[32] whilst the introduction of a furyl side chain into a 2-halogenoaniline has allowed the synthesis of the tetrahydrobenzazepine skeleton through the intramolecular capture of an intermediate aryne.[33] Attempts to trap the didehydrochromene by incorporating furan into the reaction mixture failed despite operating at various temperatures in the range –15 °C to –90 °C and allowing the reaction mixture to warm up even to room temperature; only the 4-butylchromene **16** (R = n-Bu) and the parent tetramethylchromene **16** (R = H) could be detected.

An alternative approach to the *o*-halogenophenyl carbanion precursor of benzyne utilises the reaction of magnesium with a 1,2-halogenobenzene.[34] When **13** was treated with Mg in THF in the presence of furan, 2,5-disubstituted furans and 1,3-diphenylisobenzofuran, the cycloadducts **22** were obtained in good yields, confirming the intermediacy of the 3,4-didehydro-2*H*-[1]benzopyran species **15**. The ^{1}H NMR spectrum of **22** ($R^2 = R^3 = R^4 = R^5 = H$) displayed singlets at δ 1.22 and δ 1.64 assigned to the non-equivalent geminal methyl groups. No coupling was observed between 1-H (δ 5.39) and 3-H (δ 5.75) but the ethenyl bridge hydrogens gave rise to an AB system at *ca.* δ 7.1. The structure of the cycloadduct was corroborated by ^{13}C NMR spectroscopy. Of particular significance were the signals at δ 78.3 for a quaternary carbon (4-C) and at 81.6 and 82.5 which are tentatively assigned to 1-C and 3-C adjacent to the furan ring oxygen atom.



Scheme 5. Reagents: (i) Mg, anhyd. THF, heat; (ii) Zn, AcOH, heat.

In order to obtain unequivocal evidence for the formation of the cycloadducts **22**, the structure of **22** ($R^2 = R^5 = Ph$; R^3, R^4 = CH=CH-CH=CH) was determined by X-ray crystallography (Figure 1).[35]

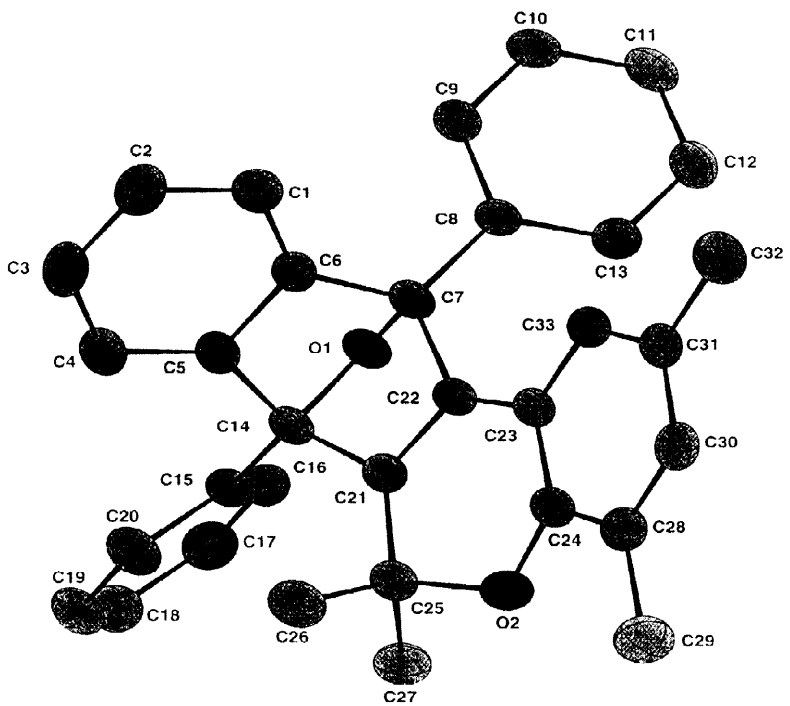
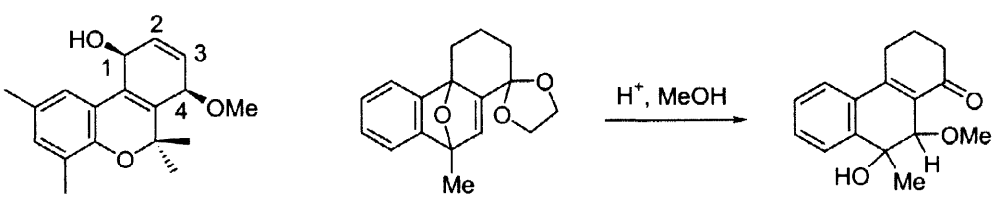


Figure 1. Perspective view and atom labelling of cycloadduct **22** ($R^2 = R^5 = Ph$; R^3, R^4 = CH=CH-CH=CH)

Of particular note is the formation of the fully aromatic hydroxydibenzo[*bd*]pyran **23** as a single regioisomer when 2-methylfuran was employed as the dienophilic component. The origins of this remarkable regiospecificity in the initial cycloaddition step are at present obscure. It is well known that cycloadditions of 2-methylfuran with unsymmetrical benzynes are completely non-regiospecific and are independent of steric and electronic effects in the aryne.[36] The direct aromatisation of cycloadducts resulting from arynes and 2-substituted furans has been documented.[37] In the present case it is likely that the dilute acid used in the work-up effected ring opening-aromatisation of the initial cycloadduct. The ^{1}H NMR spectrum of this compound shows the presence of an exchangeable signal at δ 4.69 and a signal assigned to the additional aromatic methyl group at δ 2.56. The key feature of the ^{13}C NMR spectrum is the absence of the signals associated with 1-C and 3-C at *ca.* δ 79, implying that the bridging oxygen atom is absent; a signal assigned to 4-C appears at δ 78. The use of NOE difference spectroscopy to unequivocally determine the regiochemistry of this product, *i.e.* either regioisomer **23** (R^2 = Me, R^3 = R^4 = H, R^5 = OH) or **23** (R^2 = OH, R^3 = R^4 = H, R^5 = Me), proved inconclusive.

The use of methanolic HCl has proved successful for the cleavage of the oxygen bridge of the benzyne – furan cycloadduct to form 1-naphthol.[38] Our attempts to cleave the oxygen bridge of adduct **22** (R^2 = R^3 = R^4 = R^5 = H) and obtain a hydroxydibenzo[*bd*]pyran using this reagent combination failed. The compound isolated from these reactions was characterised as the dihydrodibenzo[*bd*]pyran **24**. The formation of this compound is rationalised by protonation of the oxygen bridge followed by ring opening to give the more stable carbocation which is intercepted by methanol. In a NOE experiment, irradiation of the methoxy signal (δ 3.29) produced enhancement of the signal at δ 1.21 (5-Me) and the D_2O exchangeable signal at δ 2.50 (OH), indicating that these three functions must be in close proximity, further corroborating structure **24** and confirming the *cis* disposition of these substituents. The complexity of the signals in the ^{1}H NMR spectrum of the 1,4-dihydrocyclohexadiene unit in **24** merits some comment. The multiplicity of the signal for 1-H, which appears as a slightly broadened dt, arises through coupling to the hydroxyl proton (J = 4.4 Hz) and through *vicinal* coupling to 2-H (^3J = 1.4 Hz) and homoallylic coupling to 4-H (^5J = 1.3 Hz). The latter was confirmed by a ^{1}H-^{1}H COSY experiment. The similarity of the magnitudes of ^3J and ^5J account for the apparent multiplicity of the signal. Additional broadening arises through smaller allylic coupling to 3-H (^4J = 0.2 Hz). It is well documented that homoallylic couplings are frequently larger than allylic couplings in many cyclic systems.[39] The signal for 2-H appears at δ 6.45 as a dd through coupling to 1-H (^3J = 1.4 Hz) and to 3-H (J = 5.9 Hz). 3-H appears as a well resolved ddd at δ 5.68 with $J_{3,2}$ = 5.9 Hz, $J_{3,4}$ = 1.9 Hz and $J_{3,1}$ = 0.2 Hz. The magnitude of the coupling constants between the alkenic protons ($J_{2,3}$ = 5.9 Hz) and those between 1-H and 2-H ($J_{1,2}$ = 1.4 Hz) and 3-H and 4-H ($J_{3,4}$ = 1.9 Hz) are comparable with literature values for *cis*-1,4-disubstituted 1,4-dihydrocyclohexadienes.[39, 40] 4-H resonates at δ 4.75 and appears as a dd, $J_{4,3}$ = 1.9 Hz and $J_{4,1}$ = 1.3 Hz.



24 **25** **26**

The failure of furan – aryne cycloadducts to aromatise under acid catalysed methanolysis is rare and we are aware of only one literature precedent for this, whereby adduct **26** results from cleavage of the oxabicycle unit in **25**.[41]

Aromatisation of the cycloadduct **22** (R^2 = R^5 = Ph; R^3, R^4 = CH=CH-CH=CH) using zinc in acetic acid according to the procedure described by Wittig *et al.*[42] gave the benzo[*e*]naphtho[2,3-*c*]pyran **23** (R^2 = R^5 = Ph; R^3, R^4 = CH=CH-CH=CH) in 87% yield.

In conclusion, 3,4-dibromo-2,2-dimethylchromenes react with either magnesium or organolithium reagents to generate the highly strained alkyne or heteroaryne 3,4-didehydro-2*H*-chromene which has been trapped by nucleophiles and with dienes. The cycloadducts from the latter give access to the dibenzo[*b,d*]pyran system.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Distillations were performed using a kugelrohr (Buchi GKR-50 Glass Tube Oven) and all boiling points quoted relate to the oven temperature at which the distillation commenced. Fourier transform infrared spectra were recorded on a Mattson Polaris spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on either a Bruker Advance DPX 250 or a Jeol 400 MHz lambda instrument for solutions in $CDCl_3$; *J* values are given in Hz. Flash chromatographic separations were performed on Crossfields Sorbsil C60 silica gel (M.P.D. 60Å, 40 - 60μ, activated) according to the general procedure.[41]

Preparation of 2,2,6,8-Tetramethylchroman-4-one 11.

2,4-Dimethylphenol (0.33 mol) and 3-methylbut-2-enoic acid (0.33 mol) were added to polyphosphoric acid (400 g) and the viscous solution was maintained at 90 °C for 4 h with occasional stirring. The cooled reaction mixture was diluted with ice/water (1000 cm^3), stirred for 2 h and extracted with ethyl acetate (3 x 150 cm^3). The organic layer was washed well with water (3 x 200 cm^3) and then with aqueous NaOH (2M, 3 x 50 cm^3). The organic layer was dried (Na_2SO_4) and evaporated to give the crude product, which was eluted from silica with 20% ethyl acetate in hexane to give two fractions:

Fraction 1: **2,4-Dimethylphenyl 3-methylbut-2-enoate 12** (13%) as a pale yellow oil after distillation, b.p. 110 °C at 0.06 mbar; υ_{max} /(neat) 2920, 1736, 1649, 1500 cm^{-1}; δ_H 1.98 (3H, s, Me), 2.16 (3H, s, Me), 2.25 (3H, s, Me), 2.32 (3H, s, Me), 5.97 (1H, s, C=CH), 6.89 (1H, d, *J* 8.0, Ar-H), 7.01-7.06 (2H, m, Ar-H) (Found: C, 76.3; H, 7.9. $C_{13}H_{16}O_2$ requires C, 76.5; H, 7.8%).

Fraction 2: **2,2,6,8-Tetramethylchroman-4-one 11** (49%) as colourless micro-crystals after recrystallisation from light petroleum (b.p. 30-40 °C), m.p. 70 - 71 °C; υ_{max} /(Nujol) 1695 cm^{-1}; δ_H 1.45 (6H, s, 2-Me), 2.19 (3H, s, 6-Me), 2.27 (3H, s, 8-Me), 2.69 (2H, s, 3-H), 7.17 (1H, s, 7-H), 7.51 (1H, s, 5-H); δ_C 48.7, 78.5, 119.4, 123.3, 123.7, 127.2, 129.1, 137.5, 137.9, 138.3, 156.2, 193.2 (Found: C, 76.4; H, 8.1. $C_{13}H_{16}O_2$ requires C, 76.5; H, 7.8%).

Preparation of 4,4,6,8-Tetramethyldihydrocoumarin 9.

A stirred solution of 2,4-dimethylphenol (0.2 mol) and 3-methylbut-2-enoic acid (0.2 mol) in methanesulfonic acid (300 cm^3) was maintained at 70 °C for 3 h. The cooled solution was cautiously poured into ice/water (1500 cm^3), stirred for 2 h and extracted with ethyl acetate (3 x 100 cm^3). The organic layer was washed well with water (3 x 100

cm^3) and then with aqueous NaOH (2M, 2 x 50 cm^3). The organic layer was dried (Na_2SO_4) and evaporated to give the crude product, which was eluted from silica with 20% ethyl acetate in hexane to give two fractions:

Fraction 1: **2,4-Dimethylphenyl 3-methylbut-2-enoate 12** (9%).

Fraction 2: **4,4,6,8-Tetramethyldihydrocoumarin 9** (79%) as colourless crystals after recrystallisation from hexane containing a trace of ethyl acetate, m.p. 104 - 105 °C; υ_{max} /(Nujol) 1761 cm^{-1}; δ_H 1.35 (6H, s, 4-Me), 2.30 (3H, s, 6-Me), 2.32 (3H, s, 8-Me), 2.61 (2H, s, 3-H), 6.94 (1H, s, 7-H), 6.95 (1H, s, 5-H); δ_C 33.2, 43.6, 122.1, 122.4, 122.9, 125.9, 130.1, 130.5, 130.8, 131.2, 133.6, 146.8, 168.5 (Found: C, 76.5; H, 8.0. $C_{13}H_{16}O_2$ requires C, 76.5; H, 7.8%).

Preparation of 4-Bromo-2,2,6,8-tetramethyl-*2H*-chromene 10.

A solution of the 2,2,6,8-tetramethylchroman-4-one (30 mmol) in phosphorus tribromide (130 mmol) was refluxed for 45 min. The solution was cooled and cautiously poured onto crushed ice (400 g). The resulting aqueous suspension was extracted with ethyl acetate (5 x 50 cm^3) and the combined extracts were washed with water (2 x 50 cm^3), $NaHCO_3$ solution (2 x 50 cm^3), dried (Na_2SO_4) and evaporated to afford the crude product as a mobile yellow oil which was eluted from silica with 7.5% ethyl acetate in hexane to afford **10** (71%) as a pale yellow solid, m. p. 34 –36 °C; δ_H 1.44 (6H, s, 2-Me), 2.16 (3H, s, 6-Me), 2.28 (3H, s, 8-Me), 5.99 (1H, s, 3-H), 6.89 (1H, s, 7-H), 7.07 (1H, s, 5-H) (Found: C, 58.4; H, 5.7; Br, 29.5. $C_{13}H_{15}BrO$ requires C, 58.7; H, 5.7; Br, 29.7%).

Bromination of Bromo-2*H*-chromenes.

A solution of bromine (1.2 g, 7.5 mmol) in dry chloroform (25 cm^3) was added dropwise over 1 h to a cold (~ 5 °C) stirred solution of 4-bromo-2,2,6,8-tetramethyl-2*H*-chromene (2.0 g, 7.5 mmol) in dry chloroform (25 cm^3). The resulting orange reaction mixture was stirred at room temperature for 22 h. Removal of the chloroform gave a pale yellow oil which was eluted from silica with light petroleum (b.p. 30 - 40 °C) to give:

Fraction 1: **3,4,7-Tribromo-2,2,6,8-tetramethyl-*2H*-chromene 14** (7%) as a colourless oil after distillation, m.p. 48.0 - 49.5 °C, b.p. 140 °C at 0.08 mbar; υ_{max} /(neat) 2995, 1577, 1469 and 1248 cm^{-1}; δ_H 1.59 (6H, s, 2-Me), 2.31 (3H, s, 6-Me), 2.39 (3H, s, 8-Me), 7.21 (1H, s, 5-H); δ_C 16.0, 23.4, 26.8, 82.8, 119.9, 120.5, 126.1, 126.5, 127.4, 129.2, 131.0, 147.4 (Found: C, 36.9; H, 2.9; Br, 56.3. $C_{13}H_{13}Br_3O$ requires C, 36.7; H, 3.1; Br, 56.4%) and

Fraction 2: **3,4-Dibromo-2,2,6,8-tetramethyl-*2H*-chromene 13** (78%) as a colourless oil after distillation, b.p. 130 °C at 0.08 mbar; υ_{max} /(neat) 2997, 1577, 1470, 1250 cm^{-1}; δ_H 1.58 (6H, s, 2-Me), 2.17 (3H, s, 6-Me), 2.29 (3H, s, 8-Me), 6.92 (1H, s, 7-H), 7.12 (1H, s, 5-H); δ_C 15.3 (2 x C), 20.6, 26.8, 81.6, 120.7, 121.4, 125.6, 125.7, 127.0, 130.3, 132.6, 147.2 (Found: C, 45.1; H, 4.2; Br, 46.1. $C_{13}H_{14}Br_2O$ requires C, 45.1; H, 4.1; Br, 46.2%). (Found M^+, 343.9411. $C_{13}H_{14}{}^{79}Br_2O$ requires M^+, 343.9411).

Using an identical procedure, **4-bromo-2,2-dimethyl-*2H*-chromene 4** gave:

Fraction 1: **3,4,6-Tribromo-2,2-dimethyl-*2H*-chromene 7** (37%) as colourless crystals from light petroleum (b.p. 30 - 40 °C), m.p. 71-72 °C; υ_{max} /(Nujol) 1593, 1487 cm^{-1}; δ_H 1.59 (6H, s, 2-Me), 6.71 (1H, d, *J* 8.6, 8-H), 7.32 (1H, m, 7-H), 7.60 (1H, d, *J* 2.1, 5-H) (Found: C, 33.4; H, 2.1; Br, 60.4. $C_{11}H_9Br_3O$ requires C, 33.3; H, 2.3; Br, 60.4%) and

Fraction 2: **3,4-Dibromo-2,2-dimethyl-*2H*-chromene 6** (52%) as a colourless oil after distillation, b.p. 110 °C at 0.4 mbar; υ_{max} /(neat) 1607, 1522 cm^{-1}; δ_H 1.61 (6H, s, 2-Me), 6.83 (1H, d, *J* 7.8, 8-H), 6.98 (1H, m, 7-H), 7.23 (1H, m, 6-H), 7.47 (1H, d, *J* 7.8, 5-H) (Found: C, 41.5; H, 3.4; Br, 50.1. $C_{11}H_{10}Br_2O$ requires C, 41.5; H, 3.2; Br, 50.3%).

Similarly, **3-Bromo-2,2-dimethyl-2*H*-chromene 8** with bromine gave:

Fraction 1: **3,4,6-Tribromo-2,2-dimethyl-*2H*-chromene 7** (38%).

Fraction 2: **3,4-Dibromo-2,2-dimethyl-*2H*-chromene 6** (49%).

Reaction of 3,4-Dibromo-2,2,6,8-tetramethyl-*2H*-chromene 13 with Alkyl/Aryl Lithium Reagents.

The commercial alkyl/aryl lithium solution (6.0 mmol) was added *via* syringe to a cold (-15 °C) stirred solution of 3,4-dibromo-2,2,6,8-tetramethyl-2*H*-chromene (5.8 mmol) in dry ether (40 cm^3) under N_2. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was then diluted with water (100 cm^3) and aqueous saturated ammonium chloride solution (20 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford the crude product. The following compounds were obtained in this fashion after elution of the crude product from silica with light petroleum (b.p. 30 – 40 °C) which removed unchanged starting material (17 – 30%) as the first fraction.

1. Reaction with n-butyllithium gave **4-n-butyl-2,2,6,8-tetramethyl-*2H*-chromene 16 (R = Bu)** (47%) as a colourless oil, b.p. 125 °C at 0.08 mbar, υ_{max}/(neat) 1624, 1573 cm^{-1}; δ_H 0.96 (3H, t, *J* 7.2, $(CH_2)_3C\underline{H}_3$), 1.39 (6H, s, 2-Me), 1.43-1.53 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 2.17 (3H, s, 6-Me), 2.27 (3H, s, 8-Me), 2.36 (2H, t, *J* 7.7, $C\underline{H}_2CH_2CH_2CH_3$), 5.39 (1H, s, 3-H), 6.83 (1H, s, 7-H), 6.85 (1H, s, 5-H) (Found: MH^+, 245.1905; C, 83.4; H, 9.8. $C_{17}H_{24}O$ requires MH^+, 245.1905; C, 83.5; H, 9.9%).

2. Reaction with n-butyllithium followed by addition of ethyl chloroformate (12 mmol) at –10 °C gave **1-bromo-(3,5-dimethyl-2-ethoxycarbonyloxyphenyl)-3-methylbuta-1,2-diene 20A** (31%) as a yellow oil υ_{max}/(neat) 1955, 1761 cm^{-1}; δ_H 1.40 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.82 (6H, s, CH_3), 2.18 (3H, s, Ar-Me), 2.30 (3H, s, Ar-Me), 4.30 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 6.91 (1H, s, Ar-H), 6.94 (1H, s, Ar-H). This compound exhibits a marked instability and consequently we were unable to obtain satisfactory elemental analysis even though it was chromatographically homogeneous (TLC). However, the similarity of its spectra with those of related allenes[9] firmly established its constitution.

3. Reaction with phenyllithium gave **2,2,6,8-tetramethyl-4-phenyl-*2H*-chromene 16 (R = Ph)** (64%) as a colourless oil, b.p. 130 °C at 0.1 mbar; υ_{max}/(neat) 1637, 1601, 1485 cm^{-1}; δ_H 1.49 (6H, s, 2-Me), 2.18 (3H, s, 6-Me), 2.23 (3H, s, 8-Me), 5.61 (1H, s, 3-H), 6.66 (1H, s, 7-H), 6.88 (1H, s, 5-H), 7.39 (5H, m, phenyl) (Found: M^+, 264.1514; C, 86.3; H, 7.7. $C_{19}H_{20}O$ requires M^+, 264.1514; C, 86.3; H, 7.6%).

4. Reaction with methyllithium gave **2,2,4,6,8-pentamethyl-*2H*-chromene 16 (R = Me)** (50%) as a colourless oil, b.p. 60 °C at 0.2 mbar; υ_{max}/(neat) 1655, 1607, 1465 cm^{-1}; δ_H 1.39 (6H, s, 2-Me), 2.00 (3H, s, 4-Me), 2.17 (3H, s, 6-Me), 2.26 (3H, s, 8-Me), 5.41 (1H, s, 3-H), 6.83 (2H, s, Ar-H) (Found: M^+, 202.1358; C, 83.1; H, 8.7. $C_{14}H_{18}O$ requires M^+, 202.1358; C, 83.1; H, 9.0%).

5. Reaction with 2-lithiofuran gave **4-(2-furyl)-2,2,6,8-tetramethyl-*2H*-chromene 16 (R = 2-furyl)** (41%) as a colourless oil, b.p. 100 °C at 0.4 mbar, υ_{max}/(neat) 1659, 1608 cm^{-1}; δ_H 1.51(6H, s, 2-Me), 2.20 (3H, s, 6-Me), 2.30 (3H, s, 8-Me), 6.49 (1H, s, 3-H), 6.62 (1H, d, *J* 3.4, furyl-H), 6.93 (2H, s, Ar-H), 7.26 (1H, s, furyl-H), 7.47 (1H, d, *J* 1.0, furyl-H) (Found: M^+, 254.1306. $C_{17}H_{18}O_2$ requires M^+, 254.1307). Satisfactory elemental analysis could not be obtained for this compound.

Reaction of 3,4-Dibromo-2,2,6,8-tetramethyl-*2H*-chromene 13 with Magnesium in the Presence of a Furan.

3,4-Dibromo-2,2,6,8-tetramethyl-2*H*-chromene (5.8 mmol) in dry tetrahydrofuran (30 cm^3) was added dropwise to a suspension of magnesium (6.58 mmol) and freshly distilled furan (46.4 mmol) in tetrahydrofuran (5 cm^3) under N_2. A crystal of iodine was added to the reaction mixture which was then warmed gently to initiate the reaction, whereupon the remaining 3,4-dibromo-2,2,6,8-tetramethyl-2*H*-chromene was added at a rate sufficient to maintain a steady reflux. On completion of the addition, the mixture was refluxed for a further 2 h. The cooled reaction mixture diluted with water (50 cm^3) and dilute HCl (3M aq., 100 cm^3) and extracted with ethyl acetate (3 x 50 cm^3). The combined organic extracts were washed successively with water (100 cm^3), saturated $NaHCO_3$ solution (100 cm^3) and water (100 cm^3). The organic layer was dried (Na_2SO_4) and evaporated to give a brown oil, which was eluted from silica with 5% ethyl acetate in hexane to afford the product together with some unreacted starting material. The following compounds were obtained in this manner.

1. The reaction of of 3,4-dibromo-2,2,6,8-tetramethyl-*2H*-chromene **13** with magnesium and furan gave **1,3-etheno-1,3-dihydro-4,4,6,8-tetramethyl-4*H*-furo[3,4-*c*][1]benzopyran 22 (R^2 = R^3 = R^4 = R^5 = H)** (48%) as pale yellow needles after recrystallisation from light petroleum (b.p. 60 - 80 °C), m.p. 110.5 - 111.5 °C; υ_{max}/(Nujol) 1605, 1251, 1190, 1155, 935 cm^{-1}; δ_H 1.22 (3H, s, 4-Me), 1.64 (3H, s, 4-Me), 2.14 (3H, s, 6-Me), 2.25 (3H, s, 8-Me), 5.39 (1H, s, 1-H†), 5.75 (1H, s, 3-H†), 6.67 (1H, d, *J* 1.4, Ar-H), 6.80 (1H, d, *J* 1.4, Ar-H), 7.10 and 7.12 (each 1H, d, *J* 5, CH=CH); δ_C 15.8, 20.5, 24.3, 28.1, 78.3, 81.6, 82.5, 118.2, 119.7, 125.0, 129.1, 131.1, 142.6, 143.4, 144.1, 146.7, 149.9, 193.3 (Found: C, 80.1; H, 7.2. $C_{17}H_{18}O_2$ requires C, 80.3; H, 7.1%). † assignments may be reversed.

2. The reaction of **13** with magnesium and 2-methylfuran gave either **1-hydroxy-4,5,5,7,9-pentamethyl-5*H*-dibenzo[*bd*]pyran 23 (R^2 = OH; R^3 = R^4 = H; R^5 = Me)** or **4-hydroxy-1,5,5,7,9-pentamethyl-5*H*-dibenzo[*bd*]pyran 23 (R^2 = Me; R^3 = R^4 = H; R^5 = OH)** (32%) as brown crystals from ethyl acetate and hexane, m.p. 162 - 164 °C; υ_{max}/(Nujol) 3354, 1606, 1561, 1462 cm^{-1}; δ_H 1.69 (6H, m, 5-Me), 2.26 (3H, s, 7-Me), 2.33 (3H, s, 9-Me), 2.58 (3H, s, 4-Me), 4.67 (1H, s, OH), 6.55 (1H, d, *J* 8.1, Ar-H), 6.93 (1H, d, *J* 1.4, Ar-H), 7.02 (1H, d, *J* 8.1, Ar-H), 7.28 (1H, d, *J* 1.4, Ar-H); δ_C 15.7, 21.1, 22.8, 26.4, 78.3, 114.9, 123.5, 125.7, 126.3, 126.9, 129.1, 129.6, 130.5, 131.3, 131.5, 149.0, 149.6 (Found: C, 80.6; H, 7.3. $C_{18}H_{20}O_2$ requires C, 80.6; H, 7.5%).

3. The reaction of **13** with magnesium and 2,5-dimethylfuran gave **1,3-etheno-1,3-dihydro-1,3,4,4,6,8-hexamethyl-4*H*-furo[3,4-*c*][1]benzopyran 22 (R^2 = R^5 = Me; R^3 = R^4 = H)** (65%) as a brown oil υ_{max}/(Nujol) 2854, 1604, 1496 cm^{-1}; δ_H 1.23 (3H, s, 4-Me), 1.64 (3H, s, 4-Me), 1.78 (3H, s, 1-Me), 2.03 (3H, s, 3-Me), 2.13 (3H, s, 6-Me), 2.25 (3H, s, 8-Me), 6.80 - 6.88 (4H, m, Ar-H and CH=CH) (Found: M^+, 282.1620; C, 80.7; H, 7.9. $C_{19}H_{22}O_2$ requires M^+, 282.1620; C, 80.9; H, 7.8%).

4. The reaction of **13** with magnesium and 2,5-diphenylfuran gave **1,3-etheno-1,3-dihydro-4,4,6,8-tetramethyl-1,3-diphenyl-4*H*-furo[3,4-*c*][1]benzopyran 22 (R^2 = R^5 = Ph; R^3 = R^4 = H)** (31%) as pale yellow crystals after recrystallisation from ethyl acetate and hexane, m.p. 171.5 - 172.5 °C; υ_{max}/(Nujol) 1558, 1496, 1307 cm^{-1}; δ_H 1.13 (3H, s, 4-Me), 1.16 (3H, s, 4-Me), 1.98 (3H, s, 6-Me), 2.11 (3H, s, 8-Me), 6.02 (1H, s, Ar-H), 6.72 (1H, s, Ar-H), 7.42-7.50 (6H, m, Ar-H), 7.60-7.67 (2H, m, Ar-H), 7.69-7.76 (4H, m, Ar-H) (Found: C, 85.5; H, 6.7. $C_{29}H_{26}O_2$ requires C, 85.7; H, 6.4%).

5. The reaction of **13** with magnesium and 2,5-diphenylisobenzofuran gave **7,12-dihydro-2,4,6,6-tetramethyl-7,12-diphenylbenzo[*c*]furano[1,3-*c*][1]benzopyran 22 (R^2 = R^5 = Ph; R^3, R^4 = CH=CH-CH=CH)** (59%) as pale green crystals after recrystallisation from ethyl acetate and hexane, m.p. 222 - 223 °C; υ_{max}/(Nujol) 1255, 1116, 937, 752 cm^{-1}; δ_H 1.06 (3H, s, 6-Me), 1.34 (3H, s, 6-Me), 2.08 (3H, s, 4-Me), 2.12 (3H, s, 2-Me), 6.41 (1H, d, *J* 1.7, Ar-H), 6.77 (1H, d, *J* 1.7, Ar-H), 7.09 (2H, m, Ar-H), 7.44-7.57 (7H, m, Ar-H), 7.69 (2H, m, Ar-H), 7.80 (1H, m, Ar-H), 7.90 - 7.99 (2H, dd, *J* 7.5, 1.4, Ar-H); δ_C 15.7, 20.7, 23.9, 27.7, 80.1, 92.2, 120.8, 121.1, 121.6, 125.1, 125.5, 127.6, 128.5, 129.3, 130.4, 131.0, 133.9, 147.4, 149.5 (Found: M^+, 456.2120; C, 86.6; H, 6.0. $C_{33}H_{28}O_2$ requires M^+, 456.2089; C, 86.8; H, 6.1%).

Reaction of 1,3-Etheno-1,3-dihydro-4,4,6,8-tetramethyl-*4H*-furo[3,4-*c*][1]benzopyran benzopyran 22 (R^2 = R^3 = R^4 = R^5 = H) with Methanolic Hydrogen Chloride.

A solution of 1,3-etheno-1,3-dihydro-4,4,6,8-tetramethyl-*4H*-furo[3,4-*c*][1]benzopyran (3.54 mmol) in methanol (20 cm^3) containing 4 drops of conc. hydrochloric acid was refluxed for 25 min. Removal of the solvent from the cooled reaction mixture gave a brown solid which was recrystallised from hexane to give **1-hydroxy-4-methoxy-1,4-dihydro-5,5,7,9-tetramethyl-*5H*-dibenzo[*bd*]pyran 24** (98%) as pale brown crystals, m.p. 133 - 134 °C; υ_{max}/(Nujol) 1251, 1192, 1155, 1097 cm^{-1}; δ_H 1.21 (3H, s, 5-Me), 1.45 (3H, s, 5-Me), 2.07 (3H, s, 9-Me), 2.27 (3H, s, 7-Me), 2.50 (1H, d, *J* 4.4, 1-OH), 3.29 (3H, s, 4-OMe), 4.75 (1H, dd, *J* 1.9, 1.3, 4-H), 5.06 (1H, dt, *J* 4.4, 1.4, 1-H), 5.68 (1H, ddd, *J* 5.9, 1.9, 0.2, 3-H), 6.45 (1H, dd, *J* 5.9, 1.4, 2-H), 6.85 (1H, m, 8-H), 7.05 (1H, m, 10-H); δ_C 15.9, 20.7, 26.5, 28.2, 52.3, 53.4, 73.5, 81.1, 81.6, 88.7, 95.5, 123.7, 127.0, 129.5, 130.7, 132.5, 134.7, 149.1 (Found: C, 75.2; H, 8.0. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.7%).

Reduction of 7,12-Dihydro-2,4,6,6-tetramethyl-7,12-diphenylbenzo[*e*]furano[1,3-*c*][1]benzopyran 22 (R^2 = R^5 = Ph; R^3, R^4 = CH=CH-CH=CH) using Zinc and Acetic Acid.

7,12-Dihydro-7,12-diphenyl-2,4,6,6-tetramethylbenzo[*e*]furano[1,3-*c*][1]benzopyran (0.53 mmol) was dissolved in glacial acetic acid (10 cm^3) at room temperature and then zinc powder (34.4 mmol) was added in portions over 5 min. The mixture was refluxed for 1 h, cooled and filtered to remove the unreacted zinc which was washed with acetic acid (5 cm^3). The filtrate and washings were poured into water (100 cm^3) and the resulting precipitate was collected and air-dried. Recrystallisation from ethyl acetate and hexane gave **2,4,6,6-tetramethyl-7,12-diphenyl-*6H*-benzo[*e*]naphtho[2,3-*c*]pyran 23 (R^2 = R^5 = Ph; R^3, R^4 = CH=CH-CH=CH)** (87%) as pale yellow crystals, m.p. 225 - 226 °C; υ_{max}/(Nujol) 1599, 1248, 1153 cm^{-1}; δ_H 1.13 (3H, s, 6-Me), 1.38 (3H, s, 6-Me), 1.95 (3H, s, Ar-Me), 2.24 (3H, s, Ar-Me), 6.43 (1H, d, *J* 1.6, Ar-H), 6.77 (1H, d, *J* 1.6, Ar-H), 6.95 (1H, d, *J* 7.7, Ar-H), 7.18 (1H, m, Ar-H), 7.34-7.56 (8H, m, Ar-H), 7.69 (2H, d, *J* 7.7, Ar-H), 7.82 (2H, m, Ar-H) (Found: M^+. 440.2140; C 89.9; H, 6.4. $C_{33}H_{28}O$ requires M^+. 440.2140; C, 90.0; H, 6.4%).

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35. Crystal data for **22** (R^2 = R^5 = Ph; R^3, R^4 = CH=CH-CH=CH) ($C_{33}H_{28}O_2$) M_r = 456.55, monoclinic, a = 11.2190(10), b = 14.307(4), c = 15.4990(10) Å, β = 103.140(10)°, V = 2422.6(7) Å^3, space group $P2_1/n$, Z = 4, D_c = 1.252 mg m^{-3}, $F(000)$ = 968, μ = 0.076 mm^{-1}, crystal size = 0.85 x 0.35 x 0.2 mm, T = 293(2), θ = 1.96 to 25.11°, index ranges -12<=h<=13, -10<=k<=16, -16<=l<=16, reflections collected 9022, independent reflections 3464 (full-matrix least squares on F^2), R_{int} = 0.0922, direct methods solution, R_1 (all data) 0.0673 and (I>2σ(I) 0.0425, wR_2 (all data) 0.1040 and (I>2 σ(I) 0.0858, l_{max}/l_{min} = 0.175 and –0.249 eA^{-3}, hydrogen atoms riding model. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC113992.
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