Total Synthesis of (±)-β-Bulnesene *via* Intramolecular Cycloaddition of a 2-Substituted 3-Oxidopyrylium

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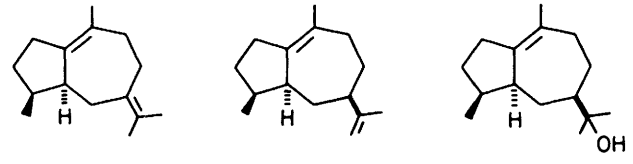
A route to the sesquiterpene (±)-β-bulnesene is described which starts with the substituted furan, 2-(1-hydroxy-4-methylhex-5-enyl)furan. Oxidation of the latter generates a precursor of a 2-substituted 3-oxidopyrylium, which undergoes smooth intramolecular cyclisation to generate a highly functionalised perhydroazulene intermediate. Further chemical manipulation of the latter readily generates the desired natural product. In order to control the relative geometry of the pendent 4-methyl group in the target molecule, a method involving the stereoselective reduction of an exocyclic methylene group is employed; the means for introducing such methylene groups are detailed.

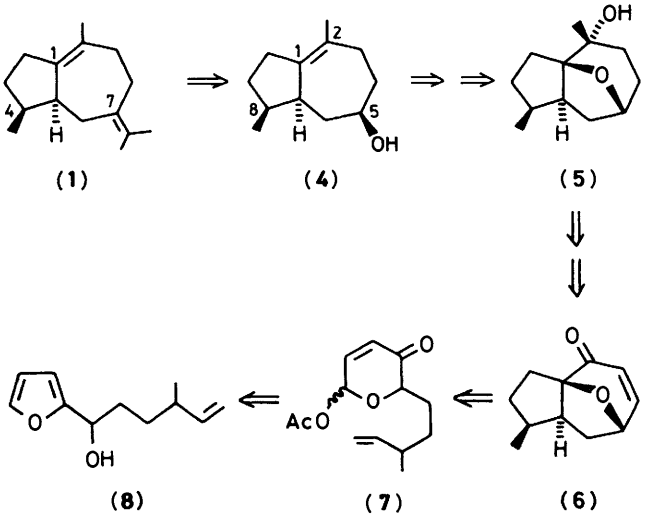
The perhydroazulenic sesquiterpene β-bulnesene (**1**) and the related compounds α-bulnesene (**2**) and bulnesol (**3**) have been selected as targets to illustrate several synthetic approaches to



(**1**) (**2**) (**3**)

the guaiane class of natural products.[1] Earlier approaches involved the solvolytic rearrangement of substituted bicyclo-[4.4.0]decanes[2] whilst, more recently, Oppolzer has employed a photochemical reaction to generate the appropriate precursor.[3] Herein we describe a route in which direct construction of the perhydroazulene system is achieved by means of an intramolecular cyclisation across a substituted 3-oxidopyrylium.[4]

A retrosynthetic analysis of (±)-β-bulnesene indicates that the epoxy-bridged perhydroazulene (**6**) (Scheme 1) could be



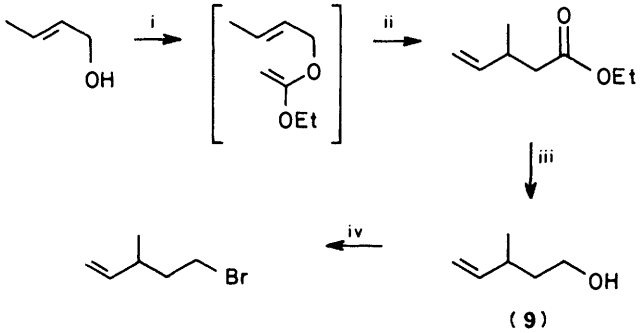
(**1**) (**4**) (**5**)

(**8**) (**7**) (**6**)

Scheme 1. (*Note* different numbering of intermediates compared with target)

a key intermediate, that can be prepared by intramolecular cycloaddition between an olefinic bond and a 3-oxidopyrylium betaine, such as that generated by heating the acetoxy-pyranulose (**7**).[4]

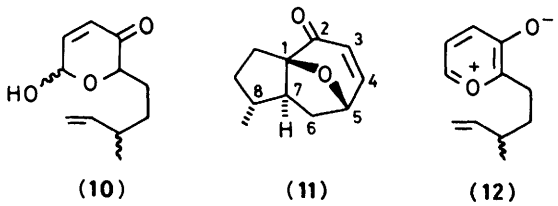
The starting material for the synthesis was the substituted furan (**8**). The side-chain bromide (**9**) was prepared by the sequence of reactions outlined in Scheme 2; a Grignard reaction between the bromide and 2-furaldehyde gave the desired alcohol (**8**).



(**9**)

Scheme 2. i, $MeC(OEt)_3$, catalyst; ii, heat; iii, $LiAlH_4$; iv, PBr_3, pyridine

Oxidation of the furfuryl alcohol (**8**) with *m*-chloroperbenzoic acid afforded, as a mixture of epimers, the substituted 6-hydroxypyranone (**10**), which was readily acetylated with acetic anhydride in pyridine to produce the acetate (**7**). The latter when heated in acetonitrile at 150 °C for 20 h was converted into a mixture of the perhydroazulene cycloadducts (**6**) and (**11**) in 75% yield. Presumably the reaction proceeds by intermediate generation of the 3-oxidopyrylium ylide (**12**), which undergoes

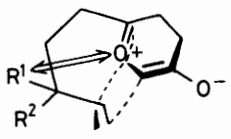


(**10**) (**11**) (**12**)

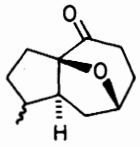
spontaneous intramolecular 1,3-dipolar cycloaddition across the olefinic bond. The 8-methyl epimers, (**6**) and (**11**) were shown to be formed in a ratio of 1:5, respectively, by examination of the 400 MHz ^1H n.m.r. spectrum of the mixture. For the minor, required epimer (**6**) the coupling constant between the 8-methyl group, at δ 0.76, and 8-H, at δ 2.10, is 7 Hz whereas for compound (**11**) the related coupling constant, between the 8-methyl at δ 0.79 and 8-H at δ 1.85, is 6 Hz. The related *J* values for β-bulnesene and 8-*epi*-bulnesene are 7 and 5 Hz respec-

tively.[5] Studies on model compounds have shown that the intramolecular cycloaddition of 2- and 6-alk-4-enyl-3-oxidopyrylium ylides occur stereoselectively in an *exo*-manner.[4] The formation of the unwanted adduct (**11**) as the major cycloaddition product can be explained by considering steric interactions in the transition state leading to the isomeric adducts. Steric repulsion between the methyl substituent and the aromatic ring in the 3-oxidopyrylium intermediate (**13**) leading to the adduct (**6**) would tend to disfavour this mode of addition with respect to its isomer (**14**).

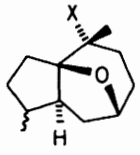
The 1:5 mixture of the cycloadducts (**6**) and (**11**) could not be readily separated by column chromatography and so the isomeric mixture was further processed.



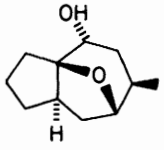
(**13**) $R^1 = Me, R^2 = H$
(**14**) $R^1 = H, R^2 = Me$



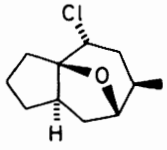
(**15**)



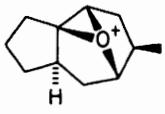
(**16**) X = OH
(**17**) X = Cl



(**18**)



(**19**)



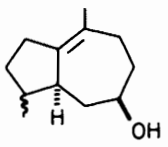
(**20**)

Hydrogenation of the double bond was effected by hydrogen over a palladium on charcoal catalyst and the saturated ketones (**15**) thus formed were treated with methylmagnesium iodide to give the alcohols (**16**). The stereoselective attack of the Grignard reagent probably reflects approach of the reagent from the least hindered side of the ketone, although some control by chelation to the bridged oxygen cannot be entirely ruled out. Treatment of the tertiary alcohols (**16**) with thionyl chloride in hexamethylphosphoric triamide (HMPA) gave, in very high yield, the chlorides (**17**). The stereospecific nature of this substitution had previously been noted for the secondary alcohol (**18**),[6] which gave only the chloride (**19**), with retention of configuration. Although thionyl chloride is quoted as the classical reagent for S_Ni reactions, such processes rarely occur selectively. In the present cases neighbouring-group participation of the bridged oxygen atom might also be occurring, possibly to the extent of forming a classical oxonium ion, of the type (**20**), which may then be opened by chloride attack from the opposite face of the molecule, leading to the observed retention of configuration about C-2.

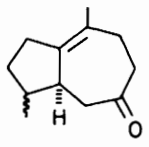
Two further pieces of information support the assignment of configuration at position C-2 in the alcohols (**16**) and (**18**). First, the epimeric alcohols are known to undergo a smooth rearrangement to a bicyclo[4.4.0]decane under the influence of reagents such as thionyl chloride in HMPA[7] and second, in a biological test system, the benzyl ethers of the epimeric alcohols are active as herbicides whereas the benzyl ethers of the isomers, for example of (**18**), are inactive.[6]

Cleavage of the epoxy bridge and introduction of the tetraalkyl substituted C(1)–C(2) olefinic bond, characteristic of the guaianes (**1**)—(**3**), was achieved by reduction of the chloro ethers (**17**) with sodium in ether.[8] Aqueous work-up afforded the 2,8-dimethyl-7α-bicyclo[5.3.0]dec-1-en-5-ols (**21**) in 76% yield. The ^1H and ^{13}C n.m.r. data on this mixture confirmed the original configurational assignments. The major component showed a methyl doublet at δ_H 1.00 (*J* 5 Hz) and δ_C 18.7 p.p.m. The corresponding methyl signals in the minor isomer occur at δ_H 0.85 (*J* 7 Hz) and δ_C 15.3 p.p.m. As mentioned above, in the ^1H n.m.r. spectra of several perhydro-2,8-dimethylazulene derivatives, the *trans*-relationship of the 8-methyl group and 7-H can be recognised by a doublet at 0.85 to 0.90 p.p.m. (*J* 8 Hz), whereas the corresponding *cis*-isomers show this doublet at δ 1.02 to 1.05 p.p.m. (*J* 5 Hz).[3,5,9]

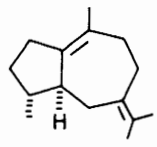
The alcohols (**21**) were oxidised with chromium trioxide in pyridine to give the ketones (**22**) in 70% yield. The required 5-isopropylidene group was introduced by reaction of the azulenones (**22**) with isopropylidenetriphenylphosphorane in dry dimethyl sulphoxide. The product (72%) was shown to be a 17:83 mixture of (±)-β-bulnesene (**1**) and (±)-4-*epi*-β-bulnesene (**23**) respectively.* The ^1H n.m.r. spectrum of the minor isomer showed a methyl doublet at δ 0.88, with a coupling constant of 7 Hz; the corresponding signal for the major isomer appeared at δ 1.05 and showed a coupling constant of 5 Hz. These data are in agreement with those reported for (±)-δ-bulnesene and (±)-4-*epi*-δ bulnesene respectively.[3] The isomers were separated by gas chromatography to afford (±)-δ-bulnesene (**1**) and (±)-4-*epi*-δ-bulnesene (**23**) in a ratio of 1:5 respectively.



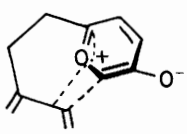
(**21**)



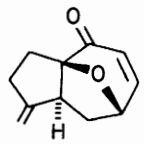
(**22**)



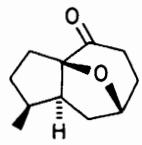
(**23**)



(**24**)



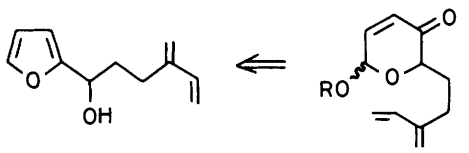
(**25**)



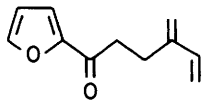
(**26**)

A major disadvantage of the above route is the predominance of the incorrect stereoisomer about position 8 in the cycloadducts. Further consideration of the transition state stereochemistry in the crucial cycloaddition step [*cf.* (**13**) *versus* (**14**)] suggested a method for circumventing this lack of stereocontrol; removal of the steric bulk of the sp^3 substituted carbon bearing the latent 8-methyl group would reduce the steric interference problem. Thus, replacement of the methyl group with a methylene group, as in intermediate (**24**), would produce one cycloadduct (**25**). Catalytic reduction of the group, at the same time as reduction of the enone formation, would be expected to occur from the least hindered face of the molecule, resulting in preferential formation of the desired epimer (**26**). A means for preparing the corresponding dienyl-substituted pyranulose acetate (**28**) was thus required. Reaction of 2-acetylfuran with isoprenyl bromide,[10] using lithium di-isopropylamide, as base, gave the ketone (**30**) which was reduced with sodium borohydride to give the required alcohol (**29**). Initially, protection of the dienyl function was employed in order to avoid complications during the oxidation of the furan ring to the pyranulose system. Trial reactions indicated that either bromine in methanol or *m*-chloroperbenzoic acid oxidised the dienyl

* The numbering of the guaiane sesquiterpenes differs from that of the formal bicyclo[4.3.0]decane system. Except for the natural products, the latter numbering system is adopted.

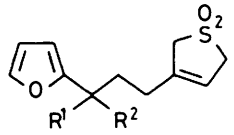


(29) (27) R = H
(28) R = OAc

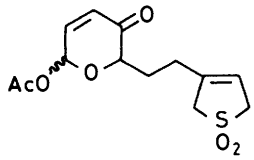


(30)

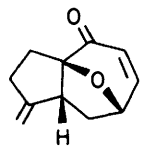
group at a rate similar to that of the furan ring. The ketone (**30**) was, therefore, treated with sulphur dioxide[11] to produce the sulpholene (**31**) before reduction to the alcohol (**32**). Oxidation of the alcohol (**33**) with *m*-chloroperbenzoic acid, followed by acetylation gave the pyranulose acetate mixture (**33**). Thermolysis of the acetate (**33**) in *o*-dichlorobenzene at 165 °C for 2 h was necessary to effect both elimination of sulphur dioxide and acetic acid with subsequent cycloaddition. However, the product was a three-component mixture (ratio 1:4:8 by h.p.l.c. analysis). The major isomer, being the desired cycloadduct (**25**), could only be isolated in 25% yield, whilst the second major isomer (isolated yield, 12%) was tentatively assigned as the *endo*-adduct (**34**).



(31) R^1, R^2 = O
(32) R^1 = H, R^2 = OH



(33)



(34)

In order to avoid the need for protection of the butadienyl group in the alcohol (**29**) a chemoselective oxidant was required. Singlet oxygen proved to be a satisfactory reagent. Thus, reaction of the alcohol (**29**) with singlet oxygen, in methanol, followed by reduction with triphenylphosphine afforded the pyranone (**27**) in excellent yield. After acetylation the ester (**28**) was heated in acetonitrile at 150 °C to give solely the intramolecular cycloadduct (**25**) (61%). The cycloadduct (**25**) was also prepared by treating the acetate (**28**) with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) at room temperature. Hydrogenation of the olefin (**25**) over palladium on charcoal in ethanol produced, as a single compound the desired epimer (**26**), which could be processed by the above described routes to the target, compound (**1**).

The outlined nine-step synthesis of (±)-β-bulnesene (**1**)[7] from the alcohol (**29**) proceeds with an overall yield of > 10%.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 297 or 1 420 spectrophotometer either on films or, for solids, as Nujol mulls. Unless otherwise stated, ^{1}H n.m.r. spectra were recorded on either a Perkin-Elmer R32 (90 MHz) instrument or a JEOL FX90Q spectrometer for solutions in deuteriochloroform using tetramethylsilane as internal reference. High-field (400 MHz) spectra were recorded at the University of Sheffield. Mass spectra were recorded on either a Kratos MS25 or MS9/50 instrument.

Thin layer chromatography (t.l.c.) and short column chromatography were carried out on Kieselgel GF_{254} (Merck) silica gel. Solvents were generally distilled and dried before use. Light petroleum refers to the fraction of boiling range 40—60 °C, THF to tetrahydrofuran, and ether refers to diethyl ether. Solvent ratios are described in ratios of volume before mixing. All apparatus was either flame-dried, under a stream of nitrogen, or oven-dried and cooled in a desiccator before use. Reactions were generally carried out under an atmosphere of oxygen-free nitrogen. Solutions were dried over anhydrous magnesium sulphate.

5-Bromo-3-methylpent-1-ene (**4**).—But-2-enyl alcohol (50 g, 0.69 mol) and triethyl orthoacetate (200 g, 1.24 mol) were heated for 4 h at 145 °C in the presence of a catalytic quantity of propionic acid (2 g). Ethyl alcohol was distilled out of the reaction vessel as it formed. The reaction mixture was cooled, ether (300 ml) added, and the organic phase washed with 2M-hydrochloric acid (4 × 75 ml) and then water (2 × 50 ml). The organic extract was dried, the solvent removed under reduced pressure, and the crude product distilled under reduced pressure (75—77 °C, 23 mmHg) to produce ethyl 3-methylpent-4-enoate (60 g, 61%), $\nu_{max.}$ 1 740 and 1 640 cm^{-1}. To a stirred solution of the latter ester (70 g, 0.5 mol) in THF (400 ml) at 0 °C was added lithium aluminium hydride (12 g, 0.3 mol), portionwise. After 1 h the reaction mixture was quenched with methanol, poured into dilute hydrochloric acid (150 ml), and extracted with ether. The combined ether extracts were washed with water, dried, and the solvent removed under reduced pressure. The crude alcohol was distilled (66 °C, 44 mmHg) to afford 3-methylpent-1-en-5-ol (40 g, 81%), $\nu_{max.}$ 3 360, 2 940, and 1 640 cm^{-1}; δ_H 1.00 (3 H, d, *J* 7 Hz, Me), 1.50 (2 H, m, CH_2), 2.25 (1 H, m, C*H*Me), 2.25 (1 H, s, OH), 3.60 (2 H, t, *J* 7 Hz, CH_2OH), 4.95 (2 H, m, C=CH_2), and 5.60 (1 H, m, CH=C).

Phosphorus tribromide (50 g) was added to a vigorously stirred mixture of 3-methylpent-1-en-5-ol (40 g, 0.4 mol) and pyridine (15 g) held at −35 °C. After all the phosphorus tribromide had been added (45 min) the mixture was allowed to warm to room temperature and then stirred at that temperature for a further 1 h. The mixture was carefully poured into an ice–water slurry and extracted with ether (3 × 250 ml). The combined ether extracts were washed with water, 1M-sodium hydroxide solution, and then water before being dried. The solvent was removed under reduced pressure and the crude product distilled and redistilled under nitrogen (130—140 °C, atmospheric pressure) to afford 5-bromo-3-methylpent-1-ene (**4**) (25 g, 38%) as a colourless liquid, $\nu_{max.}$ 2 940 and 1 640 cm^{-1}; δ_H 1.00 (3 H, d, *J* 7 Hz, Me), 1.70 (2 H, m, CH_2), 2.30 (1 H, m, C*H*Me), 3.32 (2 H, t, *J* 7 Hz, CH_2Br), 4.95 (2 H, m, C=CH_2), and 5.60 (1 H, m, CH=C).

2-(1-Hydroxy-4-methylhex-5-enyl)furan (**8**).—To a solution of the Grignard reagent, prepared from the bromide (**4**) (18 g, 0.11 mol) and magnesium (3.5 g, 0.15 g-atom), in ether (250 ml) at 0 °C was added a solution of 2-furaldehyde (10 g, 0.10 mol) in ether (40 ml). The reaction mixture was warmed to room temperature and stirred for 0.5 h before being quenched with

saturated aqueous NH_4Cl and extracted with ether. The combined organic extracts were washed with brine and water, dried, and the solvent removed under reduced pressure to afford the title compound as a mixture of epimers (15 g, 80%), $\nu_{max.}$ 3 380, 3 080, 2 940, and 1 640 cm^{-1}; δ_H (3 H, d, *J* 7 Hz, Me), 1.05—2.70 (5 H, m), 2.31 (1 H, br s, OH), 4.60 (1 H, m, C*H*OH), 4.85 (2 H, m, C=CH_2), 5.60 (1 H, m, CH=C), 6.21 (2 H, m, ArH), and 7.32 (1 H, m, ArH) (Found: *M*, *m/z* 180.115 29. $C_{11}H_{16}O_2$ requires M^+, 180.115 02).

6-*Hydroxy*-2-(3-*methylpent*-4-*enyl*)*pyran*-3(6H)-*one* (**10**).—A solution of the substituted furan (**9**) (12 g, 67 mmol) in dichloromethane (20 ml) was added, in a single portion, to a stirred solution of *m*-chloroperbenzoic acid (17.7 g, 82 mmol) in dichloromethane (250 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and, after 3 h, the precipitate was filtered off. The organic solution was washed with dilute aqueous sodium hydrogen carbonate (5 × 100 ml) and water, dried, and the solvent removed under reduced pressure. The crude product was subjected to column chromatography through silica gel (300 g), with ether–light petroleum (1:3) as eluant, to afford the *title pyranones* (**10**) (7.5 g, 57%) as a colourless oil, $\nu_{max.}$ 3 400, 3 080, 2 940, 1 690, and 1 640 cm^{-1}; δ_H 1.05 (3 H, d, *J* 6.5 Hz, Me), 1.05—2.35 (5 H, m), 4.00 (1 H, br s, OH), 4.10 and 4.60 (1 H, m, 2-H), 5.00 (2 H, m, C=CH_2), 5.72 (1 H, m, CH=C), 5.75 (1 H, br d, *J* 5 Hz, 6-H), 6.15 (1 H, d, *J* 10 Hz, 4-H), and 6.90 (1 H, dd, *J* 5, 10 Hz, 5-H) (Found: C, 67.6; H, 8.3. $C_{11}H_{16}O_3$ requires C, 67.4; H, 8.2%).

6-*Acetoxy*-2-(3-*methylpent*-4-*enyl*)-2H-*pyran*-3(6H)-*one* (**8**).—The alcohol (**10**) (6.5 g, 33 mmol) was acetylated with acetic anhydride (20 ml) and pyridine (4.5 ml) at 0 °C for 3 h after which the solvent was removed under reduced pressure (below 30 °C). The residue was taken up in benzene and chromatographed through a column of silica gel (300 g), with ether–light petroleum (1:3) as eluant to give the title *acetate* (7.6 g, 96%) as a pale yellow oil, $\nu_{max.}$ 3 080, 2 940, 1 760, 1 700, and 1 640 cm^{-1}; δ_H 1.00 (3 H, d, *J* 7.5 Hz, Me), 1.05—2.1 (5 H, m), 2.15 (3 H, s, OAc), 4.2 and 4.5 (1 H, m, 2-H), 4.95 (2 H, m, C=CH_2), 5.65 (1 H, m, CH=C), 6.15 (1 H, d, *J* 11 Hz, 4-H), 6.55 (1 H, d, *J* 4 Hz, 6-H), and 6.90 (1 H, dd, *J* 4, 11, Hz, 5-H) (Found: *M*, *m/z* 238.119 98. $C_{13}H_{18}O_4$ requires M^+, 238.120 50).

8-*Methyl*-1β,5β-*epoxy*-1β,7α-*bicyclo*[5.3.0]*dec*-3-*en*-2-*one** (**11**) *and* (**26**).—A solution of the acetate (**8**) (7.0 g, 29 mmol) in acetonitrile (30 ml) was heated at 150 °C for 20 h in a Carius tube. Evaporation of the solvent under reduced pressure and chromatography of the residue on silica gel (100 g), with ether–light petroleum (1:3) as eluant, yielded the title intramolecular *cycloadduct* (3.9 g, 75%) as a 1:5 mixture of C-8 epimers. The oily mixture showed $\nu_{max.}$ 2 940 and 1 690 cm^{-1}; δ_H (400 MHz; C_6D_6; 8β-epimer) 0.76 (3 H, d, *J* 7 Hz, 8-Me), 1.10—1.85 (16 H, m, CH_2), 2.10 (1 H, m, 8-H), 2.35 (1 H, m, 7-H), 4.28 (1 H, m, *J* 1.5, 4.5, 7 Hz, 5-H), 5.82 (1 H, d, *J* 10 Hz, 3-H), and 6.27 (1 H, dd, *J* 4.5, 10 Hz, 4-H); (8α-epimer) 0.79 (3 H, d, *J* 6 Hz, 8-Me), 1.10—1.85 (6 H, m, CH_2), 1.85 (1 H, m, 8-H), 2.84 (1 H, m, 7-H), 4.36 (1 H, m, *J* 1.5, 4.5, 7 Hz, 5-H), 5.78 (1 H, d, *J* 10 Hz, 3-H), and 6.32 (1 H, dd, *J* 4.5, 10 Hz, 4-H) (Found: C, 73.8; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%). This mixture could not be separated under a range of t.l.c. and h.p.l.c. conditions.

Hydrogenation of the Cycloadducts (**11**) *and* (**12**).—The adducts (3.0 g) in ethanol (100 ml) were hydrogenated over 5% Pd on carbon catalyst (0.3 g) at atmospheric pressure and room temperature. After the uptake of 1 equivalent of hydrogen the suspension was filtered through a pad of Celite and the solvent removed under reduced pressure. The residual oil was purified through silica gel (100 g) using ether–light petroleum (1:3) as eluant, to afford a mixture of 8-methyl-1β,5β-epoxy-1β,7α-bicyclo[5.3.0]decan-2-ones (**15**) (2.2 g, 73%) as a colourless oil, $\nu_{max.}$ 3 460 and 1 725 cm^{-1}; δ_H 1.00 (3 H, d, *J* 6.5 Hz, Me), 1.0—2.7 (12 H, m, OH and CH_2), 4.70 (1 H, m, 5-H) (Found: *M*, *m/z* 180.115 49. $C_{11}H_{16}O_2$ requires M^+, 180.115 02).

Methylation of the Perhydroazulenones (**15**).—To a freshly prepared solution of methylmagnesium iodide [from methyl iodide (3.1 g, 22 mol) and magnesium (0.5 g, 21 mmol)] in ether (150 ml), at 0 °C was added a solution of the epimeric ketones (**15**) (2.2 g, 12 mmol) in ether (30 ml). The reaction mixture was allowed to warm to ambient temperature and was then stirred for 30 min before work-up. The organic extract was subjected to column chromatography through silica gel (150 g), using ether–light petroleum (1:2) as eluant, to yield 2β,8-dimethyl-1β,5β-epoxy-1β,7α-bicyclo[5.3.0]decan-2α-ols (**16**) (1.85 g, 77%) as a colourless solid, m.p. (from hexane) 97 °C, $\nu_{max.}$ 3 420 and 2 900 cm^{-1}; δ_H 0.95 (3 H, d, *J* 5 Hz, 8-Me), 1.32 (3 H, s, 2-Me), 0.95—2.30 (13 H, m, CH, CH_2, and OH), 4.50 (1 H, m, 5-H) (Found: C, 73.3; H, 10.2. $C_{12}H_{20}O_2$ requires C, 73.4; H, 10.2%).

Chlorination of the Alcohols (**16**).—Thionyl chloride (0.4 g, 3.4 mmol) was added dropwise to a solution of the alcohols (0.5 g, 2.5 mmol) in HMPA (3 ml) at 0 °C. The reaction mixture was then stirred at room temperature for 16 h before being quenched with water (5 ml) and extracted with ether. The organic extract was washed with water (3 × 30 ml), dried, and the solvent removed under reduced pressure. The residue was chromatographed through silica gel (20 g), with ether–light petroleum (1:4) as eluant to afford the 2α-*chloro*-2β,8-*dimethyl*-1β,5β-*epoxy*-1β,7α-*bicyclo*[5.3.0]*decanes* (**17**) (0.53 g, 97%) as a colourless oil, $\nu_{max.}$ 2 940, 1 470, 1 375, and 710 cm^{-1}; δ_H 1.00 (3 H, d, *J* 5 Hz, 8-Me), 1.71 (3 H, s, 2-Me), 0.9—2.8 (12 H, m, CH and CH_2), 4.50 (1 H, m, 5-H) (Found: C, 67.3; H, 9.0; Cl, 16.7. $C_{12}H_{19}ClO$ requires C, 67.1; H, 8.9; Cl, 16.6%).

Reductive Cleavage of the Chloro Epoxides (**17**).—Finely cut pieces of sodium (0.4 g, 17 mmol) were added to a stirred solution of the chlorides (0.5 g, 2.3 mmol) in ether (25 ml). The reaction mixture was then heated to reflux for 15 min before being stirred at room temperature for 16 h. The excess of sodium was carefully quenched with ethanol, and the mixture diluted with water and extracted with ether. The ether extract was dried, the solvent removed under reduced pressure, and crude product chromatographed through silica gel (20 g), with ether–light petroleum as eluant (1:1), to produce 2,8-*dimethyl*-7α-*bicyclo*-[5.3.0]*dec*-2-*en*-5β-*ols* (**21**) (1.85 g, 77%) as a colourless solid, m.p. 45 °C, $\nu_{max.}$ 3 340 and 2 900 cm^{-1}; δ_H 0.85 (0.1 H, d, *J* 7 Hz, 8-Me), 1.00 (0.83 H, d, *J* 5 Hz, 8-Me), 1.62 (3 H, br s, 2-Me), 0.9—2.7 (13 H, m, CH, CH_2, and OH), 3.65 (1 H, m, 5-H); δ_C (8α-epimer) 17.7 (p, 8-Me), 22.3 (2-Me), 30.4 (C-9), 30.9 (C-4), 34.1 (C-6), 35.3 (C-10), 41.4 (C-3), 42.7 (C-7), 46.8 (C-8), 74.0 (C-5), 127.5 (vinyl, C-2), and 141.7 (vinyl, C-1); (8β-epimer) 15.3 (8-Me), 22.0 (2-Me), 30.3 (C-9), 32.8 (C-6), 35.5 (C-10), 36.4 (C-3), 38.5 (C-7), 41.8 (C-8), 74.4 (C-5), 128.2 (vinyl, C-2), and 141.2 (vinyl, C-4); *m/z* 180 (M^+, 14%), 162 ($M^+ - H_2O$, 20), 147 (41), 133 (12), 121 (21), and 105 (40) (Found: C, 80.0; H, 11.2. $C_{12}H_{20}O$ requires C, 79.9; H, 11.2%).

Oxidation of the Alcohols (**21**).—A solution of the alcohols (0.3 g, 1.6 mmol) in pyridine (2 ml) was added to a solution of chromium trioxide (0.7 g) in pyridine (3.5 ml) at room temperature and the reaction mixture stirred for 7 h. The bulk of

* All cycloadducts were isolated as racemates. The relative orientation of substituents are referred to the plane of the perhydroazulene skeleton. Those above the plane of the carbon skeleton, as drawn, are denoted as β-oriented, those below this plane as α-oriented.

the pyridine was removed under reduced pressure and the residue extracted with ether. The extract was washed with water, dried, and the solvent evaporated off to give a residue which was chromatographed through silica gel (20 g), with ether–light petroleum (1:1.5) as eluant, to afford the 2,8-*dimethyl*-7α-*bicyclo*[5.3.0]*dec*-1-*en*-5-*ones* (**22**) (0.175 g, 70%) as a colourless oil, $\nu_{max.}$ 2 900 and 1 705 cm^{-1}; δ_H (8β-epimer) 0.86 (3 H, d, *J* 7 Hz, 8-Me), 1.68 (3 H, br s, 2-Me), 0.9—3.2 (12 H, m, CH and CH_2); (8α-epimer) 1.05 (3 H, d, *J* 5 Hz, 8-Me), 1.68 (3 H, br s, 2-Me), 0.9—3.2 (12 H, m, CH and CH_2); δ_C (8α-epimer) 18.2 (8-Me), 21.5 (2-Me), 31.2, 31.8, 33.7, 41.8, 42.7, 46.4, 47.4, 125.9, 140.3, and 212.6 (CO); (8β-epimer) 14.7 (8-Me), 21.7 (2-Me), 30.3, 31.9, 33.6, 38.4, 42.7, 44.9, 47.4, 126.9, 139.6, and 213.0 (CO) (Found: C, 80.7; H, 10.1. $C_{12}H_{18}O$ requires C, 80.9; H, 10.2%).

(±)-β-*Bulnesene* (**1**) *and* (±)-4-epi-β-*Bulnesene* (**23**).—A solution of isopropylidenetriphenylphosphorane [freshly prepared from isopropyltriphenylphosphonium iodide (4.1 g, 9.5 mmol) and sublimed potassium t-butoxide (1.1 g, 9.5 mmol) in dry dimethyl sulphoxide (12 ml)] was added to a solution of the ketones (**22**) (0.17 g, 1 mmol) in benzene (4 ml) at −5 °C. The reaction mixture was heated at 60 °C for 2.5 h, quenched with saturated aqueous NH_4Cl, and extracted with pentane; the extract was dried and the solvent carefully distilled off. Chromatography of the product through silica gel (15 g) containing 5% (w/w) silver nitrate, with pentane as eluant, afforded a 1:5 mixture of (±)-β-bulnesene and its epimer, respectively (0.14 g, 70%). A sample (0.10 g) of the product was separated by preparative g.l.c. (column: 13 mm ID × 2 m, 10% Carbowax on Chromosorb W, flow rate 100 ml N_2/min, 170 °C), to give (±)-8-*epi*-β-bulnesene (**23**) as the major isomer (73 mg; R_b time, 12.7 min) and (±)-β-bulnesene (**1**) (15 mg; R_b 14.1 min). The minor isomer showed δ_H 0.88 (3 H, d, *J* 7 Hz, 8-Me), 1.62 (3 H, s, 2-Me), 1.67 (6 H, s, Me_2C), and 1.6—2.8 (12 H, m, Ch and CH_2); δ_C 14.9 (8-Me), 20.2 (Me), 22.1 (Me), 22.6 (Me), 29.6 (CH_2), 30.8 (CH_2), 32.1 (CH_2), 33.3 (CH_2), 36.2 (CH_2), 38.7 (CH), 44.3 (CH), 122.0 (vinyl), 126.9 (vinyl), and 139.2 (vinyl) (Found: *m/z* 204.188 51. Calc. for $C_{15}H_{24}$: M^+, 204.187 79). The major isomer showed δ_H 1.05 (3 H, d, *J* 5 Hz, 8-Me), 1.62 (3 H, s, 2-Me), 1.69 (6 H, s, Me_2C), and 1.2—2.9 (12 H, m, CH and CH_2); δ_C 18.6 (8-Me), 20.1 (Me), 21.9 (Me), 22.7 (Me), 29.6 (CH_2), 31.5 (CH_2), 33.9 (CH_2), 36.8 (CH_2), 37.1 (CH_2), 42.8 (CH), 49.5 (CH), 121.8 (vinyl), 126.3 (vinyl), 133.2 (vinyl), and 140.3 (vinyl).

2-*Furyl* 3-*Methylenepent*-4-*enyl Ketone* (**30**).—2-Acetylfuran (3.74 g, 34 mmol) in THF (30 ml) was added to a freshly prepared solution of lithium di-isopropylamide [from di-isopropylamine (3.4 g, 34 mmol) and n-butyl-lithium (2.4M hexane solution; 13.5 ml, 34 mmol) in THF (25 ml)] at −78 °C over 10 min. The solution was stirred for a further 1 h at −70 °C before 2-bromomethylbuta-1,3-diene[9] (2 g, 13.6 mmol) and HMPA (4 ml) in THF (20 ml) were added. The stirred reaction mixture was allowed to warm to room temperature overnight before it was quenched with brine (100 ml), acidified with 2M-hydrochloric acid, and extracted with ether (4 × 100 ml). The combined extracts were washed with 2M-hydrochloric acid (100 ml) followed by 2M-aqueous hydrogen carbonate (100 ml), dried, and evaporated under reduced pressure. The crude product was chromatographed through silica gel (50 g), with ethyl acetate–light petroleum (1:9) as eluant, to afford the *title ketone* (1.1 g, 46%); $\nu_{max.}$ 1 678 and 1 470 cm^{-1}; δ_H 2.65 (2 H, m, CH_2), 3.0 (2 H, m, CH_2CO), 5.0—5.4 (4 H, m, vinylic H), 6.40 (1 H, dd, *J* 11, 17 Hz, C*H*=CH_2), 6.53 (1 H, m, ArH), 7.2 (1 H, d, *J* 3.6 Hz, ArH), and 7.6 (1 H, m, ArH) (Found: M^+, *m/z* 176.083 48. $C_{11}H_{12}O_2$ requires M^+, 176.083 72).

3-[3-(2-*Furyl*)-3-*oxopropyl*]-2,5-*dihydrothiophene* 1,1-*Dioxide* (**31**).—The substituted butadiene (**30**) (1.58 g, 9 mmol) in methanol (10 ml) and liquified sulphur dioxide (1.7 g, 25 mmol), together with a few crystals of hydroquinone, were sealed into a Carius tube and heated to 85 °C overnight. The solvent and excess of sulphur dioxide were removed under reduced pressure to afford the *title compound* as a colourless crystalline solid (1.34 g, 62%). Recrystallisation of this from methanol afforded material, m.p. 130—131 °C (decomp.); $\nu_{max.}$ 1 650, 1 287, 1 270, and 1 090 cm^{-1}; δ_H 2.6 (2 H, m, CH_2C=C), 3.04 (2 H, m, CH_2CO), 3.75 (4 H, s, CH_2SO_2), 5.70 (1 H, m, CH=C), 6.56 (1 H, dd, *J* 1.7, 3.6 Hz, ArH), 7.22 (1 H, dd, *J* 0.7, 3.6 Hz, ArH), and 7.60 (1 H, dd, *J* 0.7, 1.7 Hz, ArH) (Found: C, 55.0; H, 5.0; S, 13.3. $C_{11}H_{12}O_4S$ requires C, 55.0; H, 5.0; S, 13.3%).

Reduction of the Ketones (**30**) *and* (**31**).—These reductions were separately carried out in the following manner. The ketone (**30**) (0.2 g, 1.2 mmol) in methanol (10 ml) was treated at 0 °C with sodium borohydride (65 mg, 1.7 mmol). After 1 h the reaction mixture was poured into water (30 ml) and extracted with ether (5 × 30 ml). The combined extracts were washed with water, dried, and the solvent removed under reduced pressure. Chromatography of the residue through silica gel (10 g) with ether–light petroleum (1:3) as eluant afforded 1-(2-*furyl*)-4-*methylenehex*-5-*enol* (**29**) (0.18 g, 89%) as a colourless oil; $\nu_{max.}$ 3 380, 1 595, 1 005, and 900 cm^{-1}; δ_H 1.9—2.5 (5 H, m), 4.70 (1 H, m, C*H*OH), 5.0—5.3 (4 H, m, CH_2=C), 6.2—6.55 (3 H, m), and 7.36 (1 H, s, ArH) (Found: C, 74.3; H, 8.00. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%).

The ketone (**31**) (0.66 g, 2.7 mmol) in methanol (20 ml) and THF (20 ml) at 0 °C was treated with sodium borohydride (0.12 g, 3.1 mmol). After 1 h the reaction was quenched with water and worked up in the manner described above to yield 3-[3-(2-*furyl*)-3-*hydroxypropyl*]-2,5-*dihydrothiophene* 1,1-*dioxide* (**32**) (0.55 g, 84%) as a colourless oil; $\nu_{max.}$ 3 380, 1 290, and 1 230 cm^{-1}; δ_H 2.1—3.3 (5 H, m), 3.67 (4 H, s, CH_2SO_2), 4.64 (1 H, t, *J* 7 Hz, C*H*OH), 5.78 (1 H, br s, CH=C), 6.26 (2 H, m, ArH), 7.32 (1 H, m, ArH) (Found: M^+, *m/z* 242.061 25. $C_{11}H_{14}O_4S$ requires M^+, 242.061 27).

2-(6-*Acetoxy*-3,6-*dihydro*-3-*oxopyran*-2-*yl*)-2,5-*dihydrothiophene* 1,1-*Dioxide* (**33**).—A solution of the alcohol (**32**) (0.54 g, 2.2 mmol) in dichloromethane (3 ml) was added to a stirred solution of *m*-chloroperbenzoic acid (0.50 g, 2.9 mmol) in dichloromethane (30 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and, after 7 h, the precipitate was filtered off. The solution was washed with dilute sodium aqueous hydrogen carbonate (5 × 50 ml), dried, and the solvent removed under reduced pressure. The residue was purified by chromatography through silica gel, using ethyl acetate–light petroleum (2:1) as eluant to afford the hydroxypyranone (0.28 g, 50%) as a colourless oil. The oil (from the reactions, 0.44 g) was immediately acetylated with acetyl chloride (0.15 g) in pyridine (0.2 ml) and dichloromethane (10 ml) at 0 °C. Work-up in the normal manner afforded the *title compound* (0.38 g, 75%) as a pale yellow oil; $\nu_{max.}$ 1 740, 1 690, 1 300, 1 230, 1 120, 1 080, 1 040, and 930 cm^{-1}; δ_H 1.7—2.5 (4 H, m), 2.20 (3 H, s, Ac), 3.75 (4 H, s, CH_2SO_2), 4.2 and 4.5 (1 H, m, 2-H), 5.76 (1 H, br s, CH=C), 6.2 (1 H, d, *J* 11 Hz, 4-H), 6.5 (1 H, d, *J* 4 Hz, 6-H), and 6.92 (1 H, dd, *J* 4, 11 Hz, 5-H) (Found: C, 51.7; H, 5.4; S, 11.0. $C_{13}H_{16}O_6S$ requires C, 52.0; H, 5.4; S, 10.7%).

6-*Acetoxy*-2-(3-*methylenepent*-4-*enyl*)*pyran*-3(6H)-*one* (**28**).—The butadiene (**29**) (0.1 g, 0.6 mmol) and Methylene Blue (1 mg) in methanol (30 ml) were irradiated with light from fluorescent lamps (2 × 100 W) at −35 °C whilst a slow stream of oxygen was bubbled through the solution. After 0.5 h, when all starting material had disappeared, a solution of triphenylphosphine (0.15 g, 0.6 mmol) in ether (10 ml) was added and the

mixture stirred at 0 °C for 0.5 h. The solvent was removed under reduced pressure and the residue chromatographed through silica gel, using ether–light petroleum (1:1) as eluant, to afford the alcohol (**27**) (90 mg, 83%) as a colourless oil.

The alcohol (0.25 g, 1.3 mmol) was acetylated with acetyl chloride (0.14 g, 1.7 mmol) in pyridine (0.16 g, 2.0 mmol) and dichloromethane (10 ml) at 0 °C. Work-up afforded the title acetate (0.26 g, 86%) as a mixture of epimers; $\nu_{max.}$ 1 760, 1 690, 1 220, and 930 cm^{-1}; δ_H 1.8—2.6 (4 H, m), 2.1 (3 H, s, Ac), 4.25 and 4.5 (1 H, m), 5.0—5.4 (4 H, m, CH_2=C), 6.1—6.4 (3 H, m), and 6.8 and 6.9 (1 H, m) (Found: C, 66.2; H, 6.4. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%).

8-*Methylene*-1,5-*epoxybicyclo*[5.3.0]*dec*-3-*en*-2-*one* (**25**).—(a) *Pyrolysis of the acetate* (**28**). The pyranulose acetate (130 mg, 0.55 mmol) in acetonitrile (20 ml) was heated in a sealed tube at 150 °C for 20 h. Evaporation of the solvent and chromatography of the residue through silica gel, with ether–light petroleum (1:2) as eluant, afforded the *title cycloadduct* (59 mg, 61%) as an oil; $\nu_{max.}$ 2 940 and 1 690 cm^{-1}; δ_H 1.7—3.0 (7 H, m, CH and CH_2), 4.8—5.0 (3 H, m, CH_2=C and CHO), 5.98 (1 H, d, *J* 9.8 Hz, 3-H), and 7.17 (1 H, dd, *J* 4.3, 9.8 Hz, 4-H) (Found: C, 75.1; H, 7.0. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.9%; *M*, *m/z* 176.083 35. $C_{11}H_{12}O_2$ requires M^+, *m/z* 176.083 72).

(b) *Treatment of the acetate* (**28**) *with base*. 1,5-Diazabicyclo-[4.3.0]non-5-ene (0.6 mmol) in dichloromethane (3 ml) was added dropwise to a stirred solution of the pyranulose acetate (90 mg, 0.4 mmol) in dichloromethane (15 ml) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 8 h before being worked up to give the cycloadduct (**25**) (44 mg, 65%) the spectral characteristics of which were identical with those described above.

(c) *Pyrolysis of the acetate* (**33**). A solution of the acetate (**33**) (0.20 g, 0.67 mmol) in dry *o*-dichlorobenzene (75 ml) was heated to 165 °C for 2 h. Most of the solvent was distilled off under reduced pressure and the residue chromatographed through silica gel, with ether–light petroleum (1:3) as eluant to give a mixture of 3 compounds (105 mg), ratio 1:4:8 (h.p.l.c.). After h.p.l.c. separation, on silica gel, the major compound possessed spectroscopic properties identical with those of the authentic cycloadduct (**25**). The second major product had similar, but not identical, spectroscopic properties and has been tentatively assigned as the 7-epimer (**34**).

Reduction of the Cycloadduct (**25**).—The adduct (50 mg, 0.3 mmol) in ethanol (15 ml) was hydrogenated over 5% palladium on charcoal (15 mg) at atmospheric pressure and room temperature for 5 h when hydrogen uptake ceased. The resulting suspension was filtered through Celite, the ethanol removed under reduced pressure, and the residue filtered through silica gel, with ether–light petroleum (1:2) as eluant, to afford the desired 8β-*methyl*-1β,5β-*epoxy*-1β,7α-*bicyclo*[5.3.0]*decan*-2-*one* (**26**) (39 mg, 78%) as a colourless oil; $\nu_{max.}$ 3 460 and 1 725 cm^{-1}; δ_H 0.95 (3 H, d, *J* 7 Hz, Me), 1.1—2.7 (12 H, m, CH and CH_2), 4.70 (1 H, m, 5-H) (Found M^+, *m/z* 180.115 49. $C_{11}H_{16}O_2$ requires *M*, 180.115 02).

Chlorination of the Alcohol (**18**).—The alcohol (**18**)[6] (0.2 g, 1.1 mmol) in HMPA (25 ml) was treated, dropwise, with thionyl chloride (0.3 g, 2.5 mmol) at room temperature. After addition, the solution was stirred for a further 16 h, poured into water, and worked up to give, as the major product, 2α-*chloro*-4α-*methyl*-1β,5β-*epoxy*-1β,7α-*bicyclo*[5.3.0]*decane* (**19**) (0.15 g, 68%); $\nu_{max.}$ 2 960 cm^{-1}; δ_H 1.10 (3 H, d, *J* 7 Hz, Me), 1.2—2.7 (12 H, m, CH and CH_2), 3.90 (1 H, m, 2-H), 4.30 (1 H, m, *J* 1.5, 2.8 Hz, 5-H) (Found: $M,^+$, 200.096 92. $C_{11}H_{17}ClO$ requires *M*, 200.096 79).

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