Total Synthesis of the Macrocyclic Diterpene (−)-Casbene, the Putative Biogenetic Precursor of Lathyrane, Tigliane, Ingenane, and Related Terpenoid Structures

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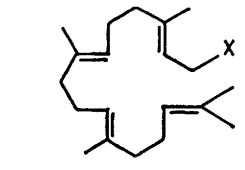
A total synthesis of the [12.1.0]bicyclic diterpene 1*S*,3*R*(−)-casbene (19), based on elaboration of 1*R*,3*S*(+)-*cis*-chrysanthemic acid (21) to the bis-allylic bromide (20), followed by closure of the 14-membered ring with tetracarbonylnickel, is described.

Synthetic casbene did not separate from natural casbene, isolated from *Ricinus communis*, in mixed chromatographic analysis, and their ^{1}H n.m.r. and mass spectral data were closely similar. ^{13}C N.m.r. data support the casbene structure (19), having a 1*S*,3*R*-*cis*-cyclopropane ring, and a 4,8,12-all-*E*-triene system.

SINCE the elucidation of the structure of the diterpene phorbol (14) some 12 years ago,[1] a considerable number of compounds bearing clear biogenetic relationships with it have been isolated from the Euphorbiaceae and the closely related Thymeliaceae. Like phorbol, the structures frequently occur in highly oxygenated form, esterified with various fatty or aromatic acid residues, and a series of carbon skeletons are involved. These are lathyrane (3) (*e.g.* lathyrol,[2] bertyadionol [3]), jatrophane A (4) (*e.g.* jatrophone,[4] the kansuinines [5]), jatrophane B (5) (*e.g.* jatrophatrione [6]), crotofolane (6) (*e.g.* crotofolin [7]), jatropholane (7),[8] tigliane (8) (*e.g.* phorbol and relatives [9]), rhamnifoliane (9),[10] daphnane (10) (*e.g.* daphnetoxin [11], huratoxin [12], gnidimacrin [13]), and ingenane (11) (*e.g.* ingenol, milliamines, and relatives [9]).



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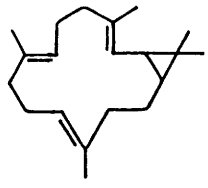

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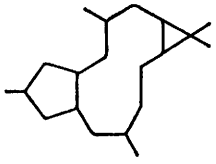

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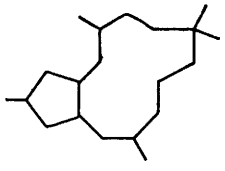

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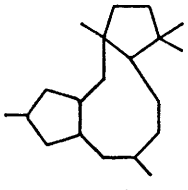

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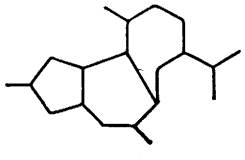
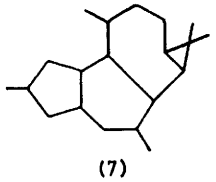


(6)

The co-occurrence of such structural types in two related families, sometimes together in one plant species, provides circumstantial evidence of a connected biosynthetic pattern.[9] Doubtless they are derived ultimately by cyclisation of a geranylgeraniol derivative (1), and the discovery by Robinson and West [14] of a bicyclic hydrocarbon casbene having the novel bicyclo[12.1.0]pentadecane [*i.e.* (2)] carbon skeleton



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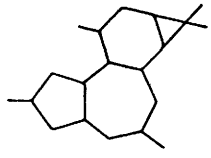

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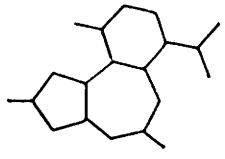

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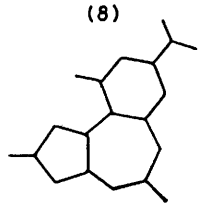

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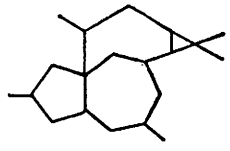
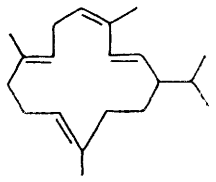


(11)

has aroused speculation [2a] that this may be the first distinct precursor of the group. In the elegant investigation of Robinson and West, only 3.2 mg of casbene was isolated from an enzyme preparation from 10 000 seedlings of *Ricinus communis* (Euphorbiaceae), and neither the structure nor the stereochemistry could be assigned with assurance. More recently casbene has been shown to be a phytoalexin, and amounts can be increased by the employment of fungal elicitors.[15] Because of the importance of the structure, we have undertaken a synthesis of casbene. Robinson and West have drawn attention to the relationship between casbene and cembrene (12),[16] which has three *E*- and one *Z*-double bonds. However, neocembrene (cembrene A) [17] (13) with three *E*-double bonds is perhaps a better analogue, and our first task was to define the structure and stereochemistry of the compound we were taking as our synthetic objective.

X-Ray structures of some 15 diterpenes belonging to the classes mentioned above, and occurring in the Euphorbiaceae and Thymeliaceae are available, some complete with absolute configurations.[18] Where the cyclopropane ring feature is present, it is clear that it is



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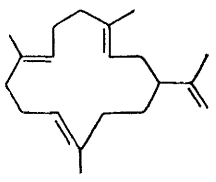
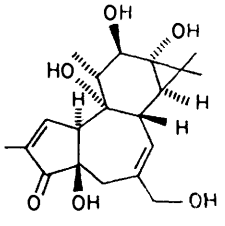


(13)

always *cis*- and related to the 1*S*,3*R*-chirality shown in (19). In the case of bertyadionol (15), (—)-*cis*-homocaronic acid (16) has been extracted by degradation, thus providing a chemical link.[3] Although jatrophone (17) has one *Z*- and one *E*-double bond, it is a rather distant model for casbene, containing a seco-cyclopropane feature and a new heterocyclic ring built within the confines of the 12-membered carbocycle.[4] Bertyadionol (15), represents the compound closest to casbene and this retains two *E*-double bonds.[3,18a] Although based on n.m.r. interpretations rather than direct *X*-ray work, the structure of jolkinol C (18) similarly has two *E*-double bonds.[19] Having regard to these facts, and to



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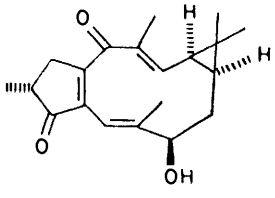

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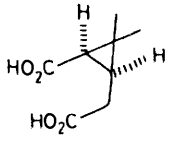

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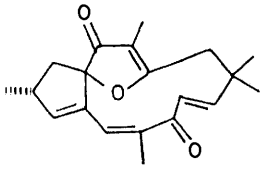

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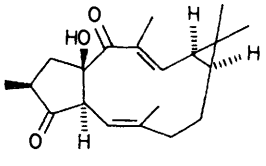
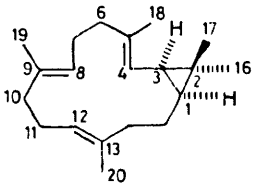


(18)

the structure of neocembrene, we have therefore made the assumption that our objective should be the casbene structure (19) having a 1*S*,3*R*-*cis*-cyclopropane and a 4,8,12-all-*E*-triene system.

Our approach to the synthesis of casbene was based on elaboration of the readily available cyclopropane *cis*-chrysanthemic acid (21) to the bis-allylic bromide (20) followed by closure of the 14-membered ring at C-10,C-11 with tetracarbonylnickel.* The synthesis of medium and large rings containing a 1,5-diene unit by tetracarbonylnickel-induced closure of terminal bis-allylic bromides has been investigated extensively by Corey and his co-workers,[21] and the method has been used by Dauben *et al.*,[16] as the key step in their synthesis of (+)-cembrene (12). Although the possibility of closing the 14-membered ring in casbene by coupling at either C-14, C-15 or at C-6, C-7 also existed, the propensity with which cyclopropylmethyl halides [*i.e.* (22)] and vinylogous cyclopropylmethyl halides [*i.e.* (24)] are



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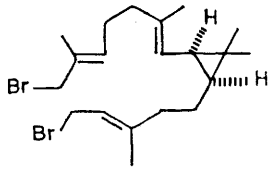

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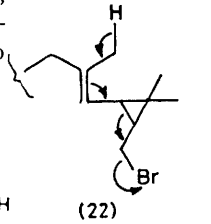

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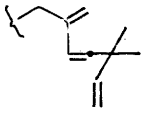

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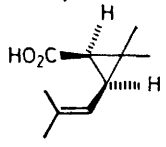

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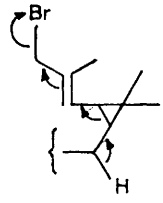

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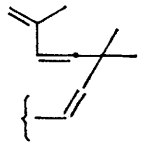


(25)

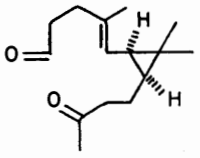
found to undergo carbocation-induced rearrangements, [*e.g.* (22) ⟶ (23) and (24) ⟶ 25)] discouraged the use of these precursors in corresponding coupling reactions.[22]

Corey and his co-workers [21] have shown that the tetracarbonylnickel-induced coupling of allylic halides leads to mixtures of geometrical isomers of 1,5-dienes, irrespective of the geometries of the starting allylic halides. The stereochemistries about the C-8, C-9 and C-12, C-13 double bonds in the immediate precursor (20) to casbene were not therefore important considerations in our synthesis design. Of much more importance was the availability of *cis*-chrysanthemic acid in both enantiomeric forms, of known absolute configuration.[23,24] This provided us with flexibility to elaborate the five-, or

* This approach was initially carried out in the (±)-series. For preliminary account see ref. 20.

alternatively the seven-, carbon side-chain in (20) from either the carboxylic acid or the isobutenyl group in (21), whilst still maintaining the correct absolute configuration for the final product. In the event, we selected that option involving elaboration of the isobutenyl group to the five-carbon side chain in (20), and elaboration of the carboxylic acid to the seven-carbon side chain.

With this general strategy in mind, we set the keto-aldehyde (26) as the key intermediate in our synthesis. It was envisaged that reaction between (26) and the phosphorane (29) would be largely regioselective producing the keto-ester (27), and that reaction between (27) and the phosphonate anion (30) would then lead to the bis-allylic ester (28). The synthesis of the keto-aldehyde (26) was achieved in eight steps starting from 1*R*,3*S*(+)-*cis*-chrysanthemic acid (21).[24] Oxidative cleavage of



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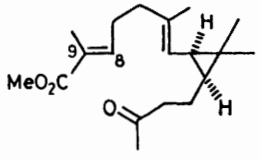

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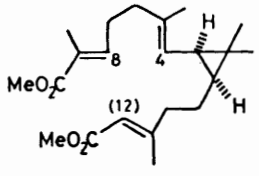

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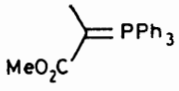

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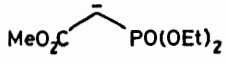
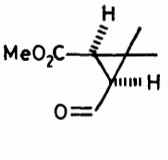


(30)

the double bond in the methyl ester derived from (21) using osmium tetraoxide–sodium metaperiodate first led to the (+)-*cis*-aldehyde-ester (31), which by reaction with 1-acetylmethylenetriphenylphosphorane [25] was smoothly converted into the *E*-enone (32). Hydrogenation of (32) in ethyl acetate in the presence of palladium on charcoal, then gave the keto-ester (33) which was protected as the corresponding dioxolan (36a).

Comparison of ^{13}C n.m.r. shift data for the *gem*-methyl carbon atoms in (32) and (33) (given in parentheses on formula) with those found in methyl *cis*-(34) and *trans*-(35) chrysanthemates fully supported a *cis*-geometry for the substituents about the cyclopropane rings in (32) and (33). In methyl *cis*-chrysanthemate (34), the *gem*-methyl carbon atom *cis*-to both the ester and methylpropenyl groups is considerably shielded by these substituents and resonates at δ 14.7 p.p.m. The corresponding methyl carbon *trans*- to the substituents is deshielded, and resonates at δ 28.7 p.p.m.[26] By contrast the *gem*-methyl carbon atoms in methyl *trans*-chrysanthemate resonate at similar chemical shift (δ 20.4 and 22.2 p.p.m.) [see formulae (34) and (35)]. The chemical shifts of the *gem*-methyl carbons atoms in the ^{13}C n.m.r. spectra of chrysanthemyl derivatives are thus highly diagnostic in assigning *cis*- and *trans*-geometries within this series of compounds.



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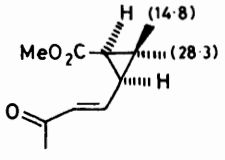

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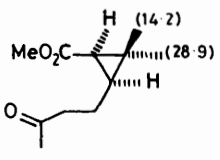

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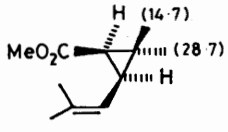

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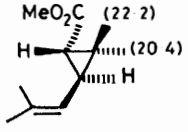
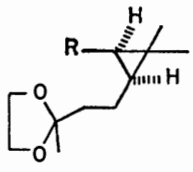


(35)

The conversion of the *cis*-ester (36a) into the *cis*-aldehyde (37) was accomplished in two stages, following reduction to the *cis*-carbinol (36b) and oxidation of the latter with Collins reagent. The *cis*-geometry of the carbinol (36b) was clearly revealed by double-resonance experiments on $Eu(fod)_3$-induced shift ^1H n.m.r. spectra. These experiments showed a coupling constant of 8.8 Hz between the vicinal hydrogens associated with the cyclopropane ring in (36b), which is closely similar to that found in *cis*-chrysanthemic acid [27] (J_{vic} 8.7 Hz; *cf.* J_{vic} 5.4 Hz for *trans*-isomer). ^1H N.m.r. data on the aldehyde (37), produced from (36b), suggested that a small amount (≯5%) of the corresponding *trans*-cyclopropane (τ 0.79, C*H*O) was produced during the Collins oxidation and work-up.



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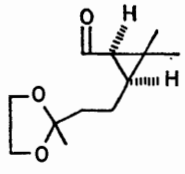

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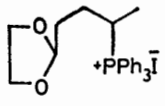
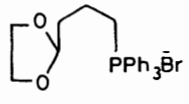


(38)

a R = CO_2Me
b R = CH_2OH



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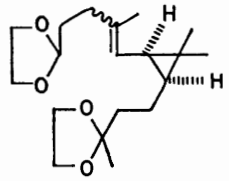
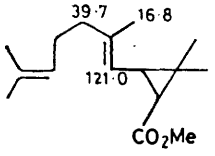


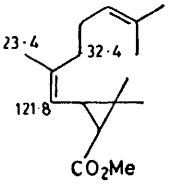
(40)

Condensation between the aldehyde (37) and the ylide produced from the phosphonium salt (38),[28] itself prepared from (39) by sequential treatment with n-butyllithium and iodomethane, led to a mixture of *E*- and *Z*-isomers (*ca.* 3 : 2) of the bis-dioxolan (40), in a combined

yield of 80%. Although the geometrical isomers of (40) were separated by column chromatography, this could not be accomplished without considerable loss of material, and the mixture of isomers was used in subsequent synthetic steps. Hydrolysis of the *Z,E*-bis-dioxolan (40), using 10% hydrochloric acid in tetrahydrofuran then afforded the key intermediate keto-aldehyde (26), which reacted in a regio-selective manner with the phosphorane (29) [29] producing the unsaturated ester (27). The ^{13}C n.m.r. spectrum of (27) exhibited only two resonances (at δ 29.0 and 15.3 p.p.m.), for the *gem*-methyl carbon atoms, showing that the cyclopropane ring had retained the *cis*-geometry; in addition, a single absorption, at δ 12.4 p.p.m. for the C-9-Me established that the configuration about the C-8, C-9 double bond in (27) was essentially *E*. Signals due to the sp^2-carbon atoms of the C-4, C-5 double bond however, were each duplicated [δ 120.8, 121.5 (C-4), δ 136.5, 136.3 (C-5)] in the ^{13}C n.m.r. spectrum suggesting that a mixture of geometrical isomers about the C-4, C-5 double bond had been produced in the Wittig reaction leading to (40). Comparison with ^{13}C n.m.r. data reported for the authentic *E*- and *Z*-isomers (41) and (42) [26] supported this supposition, and showed that the keto-ester was obtained as a 2 : 3-mixture of *Z*-4 and *E*-4 geometrical isomers.



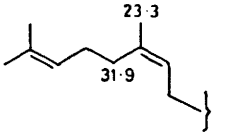
(41)



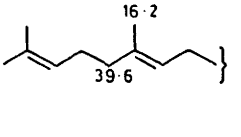
(42)

The Wadsworth-Emmons condensation between the keto-ester (27) and the phosphonate anion (30) [30] led to a mixture of geometrical isomers of the bis-allylic ester (28) in a combined yield of 68%. Repetitive continuous elution chromatography provided the all-*trans* di-ester contaminated with less than 20% of the *Z*-4 isomer. The stereochemical (*E*) homogeneities about the C-8 and C-12 double bonds in (28) were clearly revealed in both the proton and carbon magnetic resonance spectra (see Experimental section), whereas the isomerism about the C-4 double bond was indicated by duplication of the resonance due to C-4 (δ 121.0, 121.6) in the ^{13}C n.m.r. spectrum.

The elaboration of the bis-allylic ester (28) to casbene was accomplished by first reducing (28) to the corresponding bis-allylic alcohol using lithium aluminium hydride, followed by conversion into the dibromide (20) with phosphorus tri-bromide, and finally reaction of the latter with tetracarbonylnickel in dimethylformamide at 50 °C. Chromatography on Kieselgel impregnated with silver nitrate (with monitoring by capillary column g.l.c.) separated two major and one minor isomeric casbenes. The major isomer (eluted second) (*ca.* 60% of the mixture) did not separate from authentic natural casbene in mixed g.l.c. analysis, and its ^1H n.m.r. and mass spectral data were closely similar to those recorded for naturally derived casbene. The synthetic 1*S*,3*R*-casbene showed an optical rotation of −113° in $CHCl_3$ (natural −50°), and although a total interpretation of its ^{13}C n.m.r. spectrum was not possible, due largely to the superimposition of certain resonance lines, the data support the casbene structure (19) having a 1*S*,3*R*-*cis*-cyclopropane, and a 4,8,12- all-*E*-triene system.



Z−(43)



E−(44)

In particular, the ^{13}C n.m.r. spectrum of our synthetic casbene displayed six cleanly resolved sp^2 carbon resonances (three singlets and three doublets) expected of a single isomer, and showed characteristic resonances at δ 15.7 and 28.8 p.p.m. expected for the *gem*-methyl carbon atoms of a *cis*-cyclopropane ring. The vinyl methyl [C-18, C-19, C-20] and the vinyl methylene [C-6, C-10, C-14] carbon atoms making up the 14-membered ring in casbene each resonate at closely similarly chemical shifts [δ 15.7, 16.3, and 16.4 p.p.m. and δ 40.3, 39.5, and 39.3 p.p.m. respectively] in the ^{13}C n.m.r. spectrum, thereby suggesting that the double bonds have identical configurations.[31] Comparison with ^{13}C n.m.r. data for corresponding carbon atoms in *Z*- and *E*-acyclic 1,5-dienes, *e.g.* (43) and (44) [32] clearly supports an *E*-configuration for each of the double bonds in (19).

EXPERIMENTAL

For general experimental details see ref. 33.

Methyl (+)-cis-2,2-*Dimethyl*-3-(3-*oxobut*-E-1-*enyl*)*cyclopropanecarboxylate* (32).—A solution of methyl 1*R*,3*S*-(+)-*cis*-chrysanthemate [23,24] (72 g) and osmium tetraoxide (4 g) in dioxan–water [1 680 ml; 33 : 9 (v/v)] was shaken at room temperature for 2 h. Sodium metaperiodate (324 g) was added during 2 h and the mixture was then shaken until it was colourless (*ca.* 2 days). Water (1 600 ml) was added to the mixture, and the resulting emulsion was then extracted with ether (4 × 200 ml). The organic layer was washed with 10% aqueous sodium hydrogen carbonate 2 × 25 ml), and then dried ($MgSO_4$). Removal of solvent afforded crude methyl *cis*-2-formyl-3,3-dimethylcyclopropanecarboxylate (31) (65 g), $\nu_{max.}$ (film) 2 743, 1 720, and 1 698 cm^{-1}; τ 0.37 (d, *J* 6, C*H*O), 6.37 (*Me*O_2C), 7.65—8.20m (C*H*·CHO), 8.47 (Me), and 8.73 (Me), which was used without further purification.

A solution of the aldehyde (31) (61.5 g) and 1-acetylmethylenetriphenylphosphorane [25] (129 g) in dry toluene (500 ml) was heated under reflux for 24 h. The solvent was removed *in vacuo* and the residue was then triturated with n-hexane (4 × 100 ml). Evaporation of the hexane and distillation of the residue through a 10 cm Vigreux column gave the *E*-enone (49.8 g, 62%), b.p. 78—81 °C/0.1 mmHg, n_D^{26} 1.473 9, $[\alpha]_D^{25}$ +28° (*c* 0.154 5; in $CHCl_3$), $\nu_{max.}$ (film) 1 715, 1 660, and 1 613 cm^{-1}; τ 2.73 (ddd, *J* 4.5, 10, 16, C*H*:CHCO), 3.77 (d, *J* 16, CH : C*H*CO), 6.25 (*Me*O_2C), 7.71

(*Me*CO), 8.61 (Me), 8.68 (Me); δ 197.2 (*C*OMe), 170.6 (*C*O_2Me), 144.0 (d, *C*H:), 132.7 (d, CH:), 51.4 (q, CO_2*Me*), 35.3 (d, *C*H), 33.7 (d, *C*H), 29.24 (cyclopropane), 28.30 (q, Me), 26.26 (q, Me), and 14.85 p.p.m. (q, Me); *m/e* 196.108; $C_{11}H_{16}O_3$ requires *M* 196.109.

Methyl (−)-cis-2,2-*Dimethyl*-3-(3-*oxobutyl*)*cyclopropanecarboxylate* (33).—A solution of the *E*-enone (32) (29.2 g) in ethyl acetate (234 ml), was shaken under hydrogen in the presence of 5% palladium on charcoal, until no further uptake of hydrogen was observed. The catalyst was filtered off, and the solution was then evaporated. Distillation of the residue afforded the keto-ester (33) (29.5 g, 95%), b.p. 70—72 °C/0.1 mmHg, n_D^{26} 1.447 5, $[\alpha]_D^{25}$ −27° (*c* 0.199 1; in $CHCl_3$) $\nu_{max.}$ (film) 1 715 and 1 700 cm^{-1}; τ 6.33 (*Me*O_2C), 7.5 (t, *J* 8, CH_2CH_2CO), 7.8 (*Me*CO), 8.77 (Me), and 8.83 (Me); δ 208.2 (*C*OMe), 171.9 (*C*O_2Me), 50.9 (q, *Me*O_2C), 43.3 (t, $CHCH_2$), 32.8 (d, CH), 29.7 (q, Me), 28.89 (d, CH), 28.24 (q, Me), 25.55 (cyclopropane), 17.95 (t, CH_2CO), and 14.15 p.p.m. (Me); *m/e* 198.124; $C_{11}H_{18}O_3$ requires *M* 198.125.

Dioxolan of Methyl (−)-cis-2,2-*Dimethyl*-3-(3-*oxobutyl*)-*cyclopropanecarboxylate* (36a).—A solution of the ester (32) (31.1 g) in ethylene glycol (13 g) and dry benzene (1 000 ml) containing toluene-*p*-sulphonic acid (2.5 g) was heated under reflux for 3 h with continuous removal of water (Dean and Stark). The cooled solution was washed with 10% aqueous sodium hydrogen carbonate (2 × 50 ml) and then dried ($MgSO_4$). The solvent was evaporated to leave a residue which on distillation through a 10 cm Vigreux column afforded the dioxolan (31.5 g, 83%), b.p. 80—83 °C/0.1 mmHg, n_D^{27} 1.449 5, $[\alpha]_D^{26}$ −26° (*c* 0.289 2; in $CHCl_3$), $\nu_{max.}$ (film) 1 713 and 920 cm^{-1}; τ 6.03 (OCH_2CH_2O), 6.35 (*Me*O_2C), 8.66 (Me), 8.75 (Me), and 8.84 (Me); δ 171.98 (*C*O_2Me), 109.82 (CO_2, dioxolan), 64.56 (t, CH_2, dioxolan), 50.88 (q, *Me*O_2C), 38.89 (t, $CHCH_2$), 33.74 (d, CH), 29.06 (d, CH), 2 836 (q, Me), 25.50 (cyclopropane), 23.68 (q, Me), and 14.15 p.p.m. (q, Me); *m/e* 242.153; $C_{13}H_{22}O_4$ requires *M* 242.151.

Dioxolan of (−)-cis-2,2-*Dimethyl*-3-(3-*oxobutyl*)*cyclopropylmethanol* (36b).—A solution of the ester (36a) (5 g) in dry ether (175 ml) was added to a suspension of lithium aluminium hydride (1.0 g) in dry ether (40 ml) at 25 °C. The mixture was heated under reflux for 0.5 h and then cooled and treated successively with water (1 ml), 15% aqueous sodium hydroxide solution (1 ml), and then water (3 ml). The solution was filtered, dried ($MgSO_4$), and evaporated *in vacuo* to afford the crude carbinol (4.4 g). A sample had b.p. 91—92 °C/0.3 mmHg, $[\alpha]_D^{27}$ −25° (*c*, 0.136 0; in $CHCl_3$); $\nu_{max.}$ (film) 3 300 cm^{-1}; τ 6.03 (OCH_2CH_2O), 6.35 (d, *J* 8, CH_2OH), 7.44br (OH), 8.66 (Me), 8.90 (Me), and 8.96 (Me); *m/e* 214.155; $C_{12}H_{22}O_3$ requires *M* 214.156.

Bis-dioxolan of (−)-cis-1,1-(*Dimethyl*-2-(2-*methyl*-5-*oxopent*-1-*enyl*-3-(3-*oxobutyl*)*cyclopropane* (40).—A solution of the carbinol (36b) (5 g) in dichloromethane (5 ml) was added to a solution of chromium trioxide (14 g) in pyridine (22 g) and dichloromethane (450 ml), and the resulting solution was stirred at 25 °C for 0.5 h and then poured into ether (500 ml). The organic layer was separated and washed successively with ice-cold 5% aqueous sodium hydroxide (2 × 25 ml), ice-cold 5% dilute hydrochloric acid (2 × 25 ml), ice-cold saturated sodium chloride solution; it was then dried ($MgSO_4$). Evaporation of the solvent *in vacuo* afforded the aldehyde (37) (3.75 g, 76%), $[\alpha]_D^{23}$ −24° (*c* 0.187 4; in $CHCl_3$); $\nu_{max.}$ (film) 1 690 cm^{-1}; τ 0.56 (d, *J* 6, *CH*O), 6.03 (OCH_2CH_2O), 8.60 (Me), 8.63 (Me), 8.75 (Me), and 8.0—9.0 (m, 6 H); *m/e* 212.140; $C_{12}H_{20}O_3$ requires *M* 212.141.

A solution of n-butyl-lithium (10.9 mmol) in hexane was added by syringe to a suspension of the phosphonium salt (39) [28] (3.7 g) in dry tetrahydrofuran (25 ml), under nitrogen, at room temperature with external cooling (ice-bath). The red solution was stirred at room temperature for 0.25 h before freshly distilled anhydrous iodomethane (1.55 g) was added whilst the reaction temperature was maintained at 25 °C until a precipitate of the methylated phosphonium salt (38) was formed. A solution of n-butyl-lithium (7.17 mmol) in hexane was added by syringe, and the solution was stirred for 0.25 h. A solution of the aldehyde (37) (1.52 g) in dry tetrahydrofuran (2 ml) was then added, and the solution was stirred at 25 °C for 0.5 h before the addition of potassium t-butoxide (250 mg, freshly sublimed). The solution was stirred at room temperature for 16 h under nitrogen. Warm water was then added, and the mixture was extracted with ether (3 × 25 ml). The combined organic extracts were washed with warm water and then dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave an oily residue which on trituration with hexane afforded the crude bis-dioxolan (40) (2.26 g, 80%), as a mixture of *Z*- and *E*-isomers. Chromatography of a sample (0.45 g) on silica gel with benzene–ether (10%) as eluant yielded two isomers: (*a*) high R_F isomer (30 mg) τ 5.2 (m, 2 H, :C*H* and *CH*O_2), 6.13 (2 × OCH_2CH_2O), 8.72 (:CMe), 8.96 (Me), and 9.1 (Me); (*b*) low R_F isomer (50 mg) τ 5.15 (m, 2 H, :C*H* and *CH*O_2), 6.12 (2 × OCH_2CH_2O), 8.71 (:C*Me*), 8.94 (Me), and 9.09 (Me).

(−)-cis-1,1-*Dimethyl*-2-(2-*methyl*-5-*oxopent*-1-*enyl*)-3-(3-*oxobutyl*)*cyclopropane* (26).—A solution of the crude bis-dioxolan (40) (10.5 g) in tetrahydrofuran (75 ml) was shaken with 10% dilute hydrochloric acid (75 ml) for 24 h. The mixture was extracted with ether (2 × 20 ml) and then saturated with sodium chloride and re-extracted with ether (3 × 10 ml). The combined organic extracts were washed with water (10 ml) and then dried ($MgSO_4$). Evaporation of solvent *in vacuo* yielded the crude keto-aldehyde (26) (8.21 g), $\nu_{max.}$ (film) 1 718 cm^{-1}; τ 0.18 (m, *CH*O), 5.05 (d, *J* 7.5; :CH), 7.83 (*Me*CO), 8.28 (*Me*C:), 8.90 (Me), and 9.05 (Me).

(−)-cis-1,1-*Dimethyl*-2-(6-*methoxycarbonyl*-2-*methylhepta*-1,5-*dienyl*)-3-(3-*oxobutyl*)*cyclopropane* (27).—A solution of the keto-aldehyde (26) (8.21 g) and 1-methoxycarbonylethylidenetriphenylphosphorane (7.5 g) [29] in dry dichloromethane (75 ml) was stirred at room temperature for 16 h. Evaporation of the solvent *in vacuo*, followed by trituration with hexane afforded the crude keto-ester (5.26 g). Kieselgel chromatography [eluting with benzene–ether (10%)] gave the keto-ester as a 2 : 3 mixture of *Z*- and *E*- (at C-4) isomers [2 g, 17% based on aldehyde (26)], n_D^{24} 1.482 2, $[\alpha]_D^{25}$ −13° (*c* 1.47; in $CHCl_3$); $\nu_{max.}$ (film) 1 710 and 1 649 cm^{-1}; τ 3.26br (CH_2CH:CMe), 5.09 (d, *J* 9, CH C*H*:C), 6.25 (*Me*O_2C), 7.84 (*Me*CO), 8.15 (:C*Me*. CO_2Me), 8.30 (*Me*C:), 8.90 (Me), and 9.05 (Me); δ 208.65 (*C*OMe), 168.42 (*C*O_2Me), 142.10 (d, *C*H:), 136.49 (*C*H:), 127.48 (CH:*C*Me), 121.46 (d, *C*H, *Z*-isomer), 120.82 (d, *C*H, *E*-isomer), 51.52 (q, CO *Me*), 43.74 (t, CH_2), 29.88 (q, Me), 29.01 (d, ·CH), 28.54 (q, Me), 27.25 (t, CH_2), 25.67 (d, CH), 20.17 (cyclopropane), 19.65 (t, CH_2), 16.61 (q, Me), 15.32 (q, Me), and 12.40 p.p.m. (q, Me); *m/e* 306.223; $C_{19}H_{30}O_3$ requires *M* 306.219.

(−)-cis-1,1-*Dimethyl*-2-(4-*methoxycarbonyl*-3-*methylbut*-3-

enyl)-3-(6-*methoxycarbonyl*-2-*methylhepta*-1,5-*dienyl*)*cyclopropane* (28).—Methyl diethylphosphonoacetate [30] (1.92 g) was added by syringe to a suspension of sodium hydride (0.219 g) in dry dimethylformamide (30 ml) under an atmosphere of nitrogen at 25 °C, and the solution was then stirred for 0.75 h. A solution of the keto-ester (27) (1.4 g) in dry dimethylformamide (2 ml) was introduced by syringe, and the mixture was then stirred at 60 °C under nitrogen for 17 h. The mixture was cooled and poured into ether (100 ml). The organic layer was separated and washed with dilute hydrochloric acid (2 × 5 ml) and water (2 × 5 ml) and then dried ($MgSO_4$). Removal of the solvent *in vacuo* left the crude di-ester (2.14 g) which on silica gel chromatography, with benzene–ether (5%) as eluant, afforded a sample displaying predominantly the all-*E*-configuration (0.77 g, 28%), $[\alpha]_D^{26}$ −10.3° (*c*, 0.54; in $CHCl_3$) $\nu_{max.}$ (film) 3 062, 1 711, and 1 647 cm^{-1}; τ 3.39 (t, *J* 6, $CH_2CH{:}CMe$), 4.44 ($C{:}CH$ CO_2Me), 5.20 (d, *J* 9, $CHCH{:}C$), 6.33 (CO_2Me), 6.36 (CO_2Me), 7.88 ($MeC{:}CHCO_2Me$), 8.20 ($C{:}CMe$ CO_2Me), 8.34 ($MeC{:}C$), 8.93 (Me), and 9.06 (Me, cyclopropyl); δ 168.24 (CO_2Me), 166.90 (CO_2Me), 160.11 ($C{:}C{\cdot}CO_2Me$), 142.04 (d, $CH{:}C{\cdot}CO_2Me$), 136.49 ($CH{:}C{\cdot}CO_2Me$), 127.54 ($CH{:}CMe$), 120.99 (d, $CH{:}CMe$), 115.38 (d, $C{:}CH$ CO_2Me), 51.46 (q, CO_2Me), 50.58 (q, CO_2Me), 41.17 (t, CH_2), 38.42 (t, CH_2), 29.06 (d, CH), 29.06 (q, Me), 26.31 (t, CH_2), 20.12 (cyclopropane), 16.67 (q, Me), 15.44 (q, Me), 14.39 (q, Me), and 12.46 p.p.m. (q, Me); *m/e* 362.244 7; $C_{22}H_{34}O_4$ requires *M* 362.245 7.

1S,3R-(−)-cis-2,2,5,9,13-*Pentamethylbicyclo*[12.1.10]*pentadeca*-E-4,E-8,E-12-*triene* (*Casbene*) (19).—A solution of the bis-ester (28) (0.8 g) in dry ether (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.2 g) in dry ether (7 ml) under an atmosphere of nitrogen. The mixture was stirred for 0.5 h at room temperature and then water (5 ml) was added, followed by 15% NaOH solution (0.5 ml). The mixture was extracted with ether (2 × 5 ml) and the organic extracts were then dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded the corresponding bis-diol (0.61 g, 89%), an oil, $[\alpha]_D^{26}$ −17° (*c* 0.9; in $CHCl_3$); $\nu_{max.}$ (film) 3 359 cm^{-1}; τ 4.62 (overlapping t, *J ca.* 6, $C{:}CH{\cdot}CH_2OH$ and $CH_2CH{:}CMe$), 5.11 (d, *J* 8, $CHCH{:}CMe$), 5.90 (d, *J* 6, $C{:}CHCH_2OH$), 6.16 ($C{:}C(CH_2OH)$, 7.30 (2 × *OH*), 8.33 (3 × $:CMe$), 8.91 (Me), and 9.05 (Me); δ 139.53 ($:CMe$), 136.96 ($:CMe$), 134.67 ($:CMe$), 125.84 (d, $:CH$), 123.39 (d, $:CH$), 120.52 (d, $:CH$), 68.65 (t,, CH_2OH), and 59.14 p.p.m. (t, CH_2OH); *m/e* 306.253 6; $C_{20}H_{34}O_2$ requires *M* 306.255 9.

A solution of phosphorus tribromide (1.36 g) in dry ether (6 ml) was added to a stirred solution of the bis-diol (1.5 g) and pyridine (1 ml) in ether (30 ml) under argon at 0—5 °C. The mixture was allowed to warm to 25 °C during 1 h and then poured onto ice-cold 2M-hydrochloric acid and extracted with dichloromethane (4 × 100 ml). The combined organic extracts were washed with 5% aqueous sodium hydrogen carbonate (50 ml) and then water; they were then dried. Evaporation of the solvent, *in vacuo*, gave the crude bis-allylic bromide (20) (1.32 g) as a labile viscous oil, which was used without further purification.

The bromide (0.9 g) in dry dimethylformamide (3.5 ml) was added during 15 h *via* an automatic syringe to a stirred solution of tetracarbonylnickel (1.1 g) in dry dimethylformamide (75 ml) at 50 °C under argon. The mixture was heated at 50 °C for a further 12 h and then cooled, diluted with water (75 ml), and extracted with light petroleum (b.p. 60—80 °C) (3 × 100 ml). The combined extracts were washed with water and then dried and evaporated to leave crude casbene (0.21 g) as a mixture of geometrical isomers. Chromatography on Kieselgel impregnated with 25% silver nitrate, using 10% ethyl acetate in benzene as eluant, and monitoring each fraction by gas chromatography (SCOT capillary column, OV 225 at 175 °C) gave the following: (−)-1,3-*cis*-*E*-4,*E*-8,*E*-12 casbene (19) (33 mg) (eluted second) $[\alpha]^{24.5}$ −113° (*c*, 0.3 in $CHCl_3$), τ 5.1 (m, 3 H), 7.5—9.6 m [29 H including τ 8.36 ($:CMe$), 8.44 (2×$:CMe$), 8.97 (·CMe), 9.1 (·CMe)]; δ 136.05 (s), 135.3 (s), 133.2 (s), 125.5 (d), 123.4 (d), 121.2 (d), 40.3, 39.5, 28.8, 16.4, 16.3, and 15.7 p.p.m.; *m/e* 272.250 3; $C_{20}H_{32}$ requires *M*, 272.250 4; *m/e* 272 (50%), 257 (13%) 229 (10%), 221 (5%), 136 (78%), 121 (100%), 107 (74%), 93 (86%), 91 (45%), 81 (50%), 79 (45%), and 67 (55%). A second major isomer was eluted before natural casbene (15 mg), τ 4.98 (m, 3 H), 5.2 (d, *J* 9, 1 H), 7.6—9.7 [29 H, including τ 8.30 (2 × $:CMe$), 8.41 ($:CMe$), 8.92 (·CMe), 9.05 (·CMe)]; *m/e* 272.251 4, and a minor isomer was eluted after natural casbene (3 mg), *m/e* 272.252 0.

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