Synthesis of Casbene

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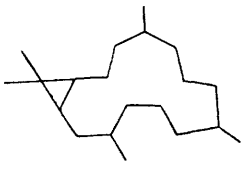
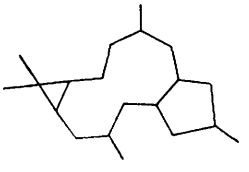
Summary A total synthesis of the [12.1.0] bicyclic diterpene casbene (**19**) is described.

MEMBERS of the Euphorbiaceae and Thymeleaceae contain oxygenated diterpenes having skeletal types (**2**), *e.g.* lathyrol, ingol, bertyadionol (*cf.* jatrophone, kansuinines), (**3**), *e.g.* phorbol, mancinellin (*cf.* daphnetoxin, mezerein, huratoxin, gnididin), and (**4**), *e.g.* ingenols, milliamines. The circumstantial evidence of stereochemistry and oxidation/unsaturation patterns, together with the familial

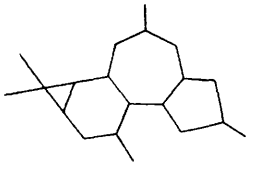
relations of the species concerned, suggest that the three types are biosynthetically connected and derive ultimately from a parent skeleton (**1**). The discovery of casbene,[1] a hydrocarbon considered to contain a novel bicyclo[12.1.0]-pentadecatrienyl system (**19**), has led to the suggestion that it may be biogenetically related to lathyrol and phorbol.[2] Unfortunately only 3·2 mg of casbene was isolated from an enzyme preparation derived from 10,000 seedlings of *Ricinus communis* (Euphorbiaceae) and neither the structure nor stereochemistry could be defined with complete assurance.[1] We now report a total synthesis of the casbene structure containing a *cis*-cyclopropane arrangement as found in the natural representatives of (**2**).



(1)



(2)



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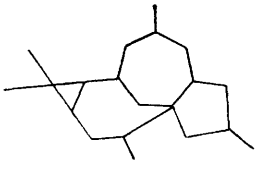
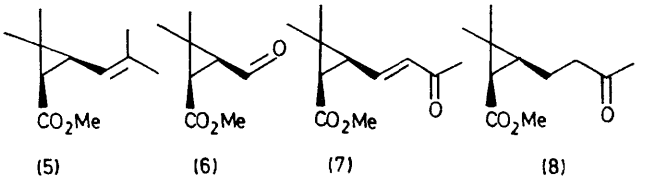


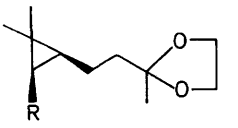
(4)

Oxidative cleavage (OsO_4–$NaIO_4$) of methyl (±)-*cis*-chrysanthemate (**5**) first produced the aldehyde (**6**) (65%) which with acetylmethylenetriphenylphosphorane gave the *E*-enone (**7**) (66%) ν_{max} 1730, 1673 cm^{-1} τ 2·8 (ddd, *J* 4·5, 10 and 16), 3·83 (d, *J* 16), m.p. 2,4-DNP derivative 157—158°C. Hydrogenation (5% Pd–C) of (**7**) in ethyl acetate then led to the ketoester (**8**) (93%), which was protected as the dioxolan (**9**). The ketoester (**8**) was also synthesised in three stages from car-3-ene, but this route was less adaptable to large-scale preparations. Reduction of (**9**) with lithium aluminium hydride led next to the *cis*-cyclopropanemethanol (**10**) (90%) whose geometry was established by double resonance experiments on $Eu(hfod)_3$ induced shift ^1H n.m.r. spectra (*J vic*-cyclopropyl-H's 8·8 Hz).

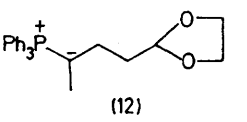
Collins oxidation of (**10**) gave (**11**) (76%) which in a Wittig reaction with (**12**)[3] produced (**13**) and the corresponding *E*-isomer (*ca.* 3:7 ratio). The two isomers were separated by preparative layer chromatography [τ 8·26 and 8·32 (=C*Me*)] but with considerable loss of material; a mixture of isomers of (**13**) was used in the subsequent synthetic steps, and these were separated at a later stage. Hydrolysis of *Z*-*E*- (**13**) with 10% HCl in tetrahydrofuran afforded the *Z*-*E*-ketoaldehyde (**14**) (80%) which reacted both regio- and stereo-selectively with α-methoxycarbonylethylidenetriphenylphosphorane to produce the *E*-α-unsaturated ester (**15**). Wadsworth–Emmons condensation between (**15**) and methyl diethylphosphonoacetate then led to a mixture of C(2) and C(9) geometrical isomers of the diester (**16**).



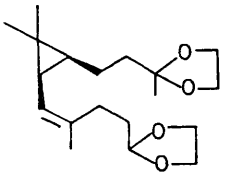
(5) (6) (7) (8)



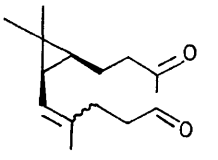
(9); R = CO_2Me
(10); R = CH_2OH
(11); R = CHO



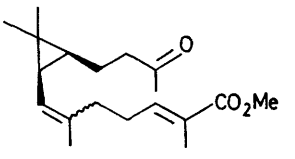
(12)



(13)



(14)



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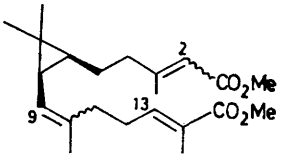
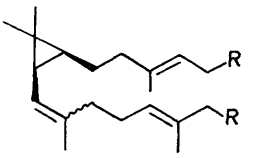
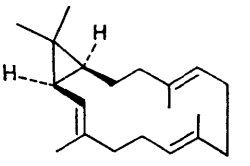


(16)



(17); R = OH
(18); R = Br



(19)

The isomers were separated by chromatography giving (a) a mixture of *E*-2, *E*-9,*E*-13 and *E*-2, *Z*-9, *E*-13 isomers of (**16**), τ 3·28 [C(13)-H], 4·36[C(2)-H], 5·09 [C(9)-H], 6·34, 6·36, (OMe), 7·6—8·0 (6H), 7·85 [C(3)-Me], 8·16 [C(14)-Me], 8·26/8·30 [C(10)-Me], 8·3—8·9 (*ca.* 4H, m), 8·9 (Me), 9·05 (Me), and (b) a mixture of *Z*-2, *E*-9, *E*-13 and *Z*-2, *Z*-9, *E*-13 isomers of (**16**) τ 8·16 (=C*Me*), 8·18 (=C*Me*), 8·26/8·30 (C*Me*). Reduction of the former mixture of isomers with lithium aluminium hydride afforded the diol (**17**) which was then converted (PBr_3–C_5H_5N) into the dibromide (**18**). Treatment of (**18**) with nickel tetracarbonyl in dimethylformamide[4] produced two major isomers of casbene (**19**) [*ca.* 15% from the diol (**17**)] which were separated by chromatography on silver nitrate. The isomer eluted second in $AgNO_3$ chromatography (>95% isomerically homogenous by g.l.c.; SCOT column OV 225, 175 °C) [*m/e* 272·250, $C_{20}H_{32}$; τ 4·9—5·3 (3H, m), 7·7—8·2 (*ca.* 11H, m),

8·36 (=C*Me*), 8·42(=C*Me*), 8·44 (=C*Me*), 8·6—8·75 (2H, m), 8·97 (-C*Me*), 9·1 (-C*Me*), 9·2—9·5 (1H, m)] showed closely similar spectral data to those recorded for natural casbene. From the method of synthesis and ^{1}H n.m.r. shift parameters this isomer is tentatively assigned the geometry (**19**).

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[4] *cf.* E. J. Corey and E. K. W. Wat, *J. Amer. Chem. Soc.*, 1967, **89**, 2757; E. J. Corey and E. Hamanaka, *ibid.*, 1967, **89**, 2758; E. J. Corey and H. A. Kirst, *ibid.*, 1972, **94**, 667; W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, and S. Suter, *ibid.*, 1975, **97**, 4973; E. J. Corey and P. Helquist, *Tetrahedron Letters*, 1975, 4091.