

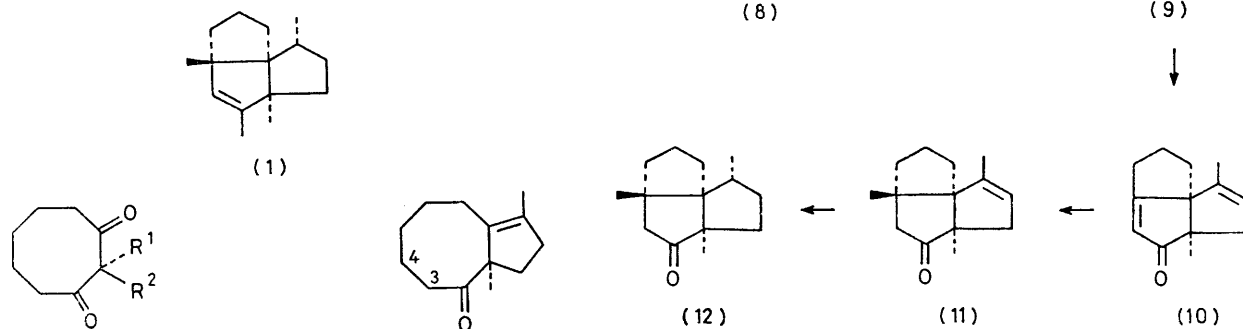
**Transannular Cyclization. A Simple Stereospecific Total Synthesis of
a Novel Sesquiterpene, Isocomene**

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Summary A simple stereospecific total synthesis of the novel sesquiterpene, isocomene (**1**) is described involving acid-catalysed transannular cyclization of (**8**) as the key step.

ISOCOMENE (1),¹ a recently discovered sesquiterpene contains an unusual tricyclo[6.3.0.0^{1,5}]undecane skeleton which has no close structural correlation with sesquiterpenes hitherto known. A simple stereospecific total synthesis of (1) is described. The synthesis was designed on the assumption that acid-catalysed cyclization of the epoxide [(8) → (9); Scheme] through participation of the remote double bond would proceed in the regio- and stereo-specific manner indicated for both steric and electronic reasons. It is noteworthy that this synthetic sequence could be a useful guideline for exploration towards the sesterterpene, retrigeranic acid.²



SCHEME

	R ¹	R ²	
(2);	Me	H	(6)
(3);	Me	[CH ₂] ₂ CH(OAc)Me	(7); Δ ³⁽⁴⁾ -dehydro
(4);	Me	[CH ₂] ₂ CH(OH)Me	
(5);	Me	[CH ₂] ₂ CH(Br)Me	

Hydroboration-oxidation of 2-methylcyclo-oct-2-ene produced the diketone (2) (83%) which was condensed with 1-bromo-3-acetoxybutane in the presence of potassium *t*-butoxide to furnish (3)† in excellent yield. A brief treatment with 5% methanolic KOH solution converted (3) into (4) which was treated without isolation with PBr₃ and pyridine to give (5) (81%), b.p. 137 °C at 0.3 mmHg; δ (CDCl₃) 4.09 (1H, m), 1.73 (3H, s), and 1.57 (3H, d, *J* 5 Hz). The phosphonium salt of (5) (obtained by reaction with triphenylphosphine) was treated with *n*-butyl-lithium at -10 °C (2 h) followed by gentle reflux (5 h) to give (6), b.p. 115 °C at 3 mmHg; δ (CDCl₃) 1.84 (3H, t, *J* 0.5 Hz) and 1.37 (3H, s); ν_{max} 1710 and 1620 cm⁻¹. Selective bromination³ of (6) with 2-pyrrolidone hydrotribromide followed by dehydrobromination⁴ of the resulting α-bromoketone with hexamethylphosphoric triamide at 120 °C gave (7) (81% overall), b.p. 108–110 °C at 3 mmHg; ν_{max} 1685, 1628, and 1620 cm⁻¹. Epoxidation⁵ of the enone (7) with *t*-butyl hydroperoxide in tetrahydrofuran containing Triton B gave the crystalline β-epoxy ketone (8) (91%) as the sole product (g.l.c.), m.p. 70–71 °C; δ (CDCl₃) 4.93 (1H, br d, *J* 4.5 Hz, C-3-H) and 4.09 (1H, m, C-4-H). It was anticipated that the bulky *t*-butyl hydroperoxide anion would approach the

enone system from the side opposite the angular methyl group. When treated with trifluoroacetic acid (TFA) in CH₂Cl₂‡ at -78 °C (4 h), (8) gave a homogeneous ketol (89%), m.p. 79 °C, which was assigned the structure (9) on the basis of physical data (Scheme): ν_{max} 3560, 1740, and

1620 cm⁻¹, δ [(CD₃)₂SO] 4.93 (1H, m), 4.34 (1H, d, *J* 5 Hz), 1.69 (3H, d, *J* 1.5 Hz), and 1.08 (3H, s); *m/e* 206 (*M*⁺), 188. The formation of (9) is explicable from a transannular ring closure at C-4 as indicated earlier and this cyclization is found to be stereospecific from the product analysis. On treatment with POCl₃ in pyridine, the ketol (9) underwent smooth dehydration to give (10), b.p. 145–148 °C at 0.9 mmHg; δ (CDCl₃) 5.79 (1H, s) and 4.93 (1H, m). Addition of lithium dimethylcopper solution in ether at -78 °C to (10) resulted in the formation of (11) (73%) which solidified on standing, m.p. 43 °C (single peak in g.l.c.). From well appreciated grounds of steric interactions,⁶ the methyl group is expected to have been transferred from the β-face. Catalytic hydrogenation of (11) over Pd-C (5%) at atmospheric pressure yielded only the isomer (12) (97% in g.l.c.), m.p. 49 °C, which would be expected considering the stereochemistry at both C-1 and C-5 in (11). Addition of methylmagnesium iodide to (12) and subsequent dehydration of the crude product by treatment with MeC₆H₄-SO₃H-*p* furnished the oily hydrocarbon (1) which was homogeneous and had spectroscopic data identical with those reported in the literature. The authenticity of this synthetic specimen was further supported by its conversion, by the published procedure,¹ into the corresponding *cis*-diol, m.p. 135 °C.

(Received, 24th April 1979; Com. 429.)

† Satisfactory C and H combustion analyses and spectral data were obtained for all new compounds.

‡ 0.1 Equiv. of TFA (5% in CH₂Cl₂ solution) was employed.

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