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BIOMIMETIC SHORT-STEP SYNTHESIS OF (±)-CASBENE FROM GERANYLGERANIOL

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(±)-Casbene was synthesized from all-*trans* geranylgeraniol by a route involving intramolecular carbene-olefin cyclization.

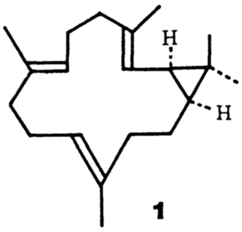
Casbene (**1**), an anti-fungal diterpene produced in cell-free extracts of castor bean,1) has been suggested to be a key intermediate in the biosynthesis of lathyrane, tigliane, ligenane, and related diterpenes from geranylgeraniol.2) A total synthesis of (-)-casbene (**1**) from (+)-*cis*-chrysanthemic acid has been achieved in connection with the structure determination of **1**.2) However, no efficient synthesis of casbene (**1**) has yet been described. We wish to report a biomimetic short-step synthesis of (±)-casbene (**1**) from all-*trans* geranylgeraniol (**2**).

Successful intramolecular cyclization by diazo decomposition has been reported for the synthesis of (±)-thujopsene (**3**),3) (±)-sesquicarene (**4**),4) and (±)-sirenin.5) Similar reaction has now been applied to the synthesis of macrocyclic compound containing a cyclopropane ring; an intramolecular carbene-olefin cyclization of a C_{20}-carbene (**A**) derived from all-*trans* geranylgeraniol (**2**) resulted in a formation of both fourteen-membered and three-membered rings at a time to afford (±)-casbene (**1**). A preferential attack of the carbene center of **A** must have occurred to the C-14(15) double bond rather than those at C-6(7) and C-10(11); this can be well interpreted by a folded conformation of **A**.

Transformation of geranylgeraniol (**2**) into the carbene (**A**) was carried out according to the procedures described in the literature.4b) All-*trans* geranylgeraniol (**2**)6) was oxidized with excess activated manganese dioxide in hexane at 0 °C for 2 h to give geranylgeranial (**5**) in *ca*. 80% yield. The aldehyde (**5**) was converted into a hydrazone (**6**) on treatment with anhydrous hydrazine and triethylamine (each 6 equivalent moles) in absolute ethanol at room temperature for 1 h. When **6** was oxidized with activated manganese dioxide in dichloromethane at 0 °C for 2 h, an orange diazo compound (**7**)7) was formed. An intramolecular cyclization of **7** *via* **A** proceeded by slow addition of **7** in tetrahydrofuran (THF) to a suspension of copper(I) iodide (2 equivalent moles) in THF at 0 °C followed by stirring at 0 °C for 30 min and then at room temperature for 30 min to give a mixture of products.8) From this mixture pure (±)-casbene (**1**) was isolated as a main product by column chromatography using silica gel impregnated with silver nitrate. Without purification in each step (±)-casbene (**1**) was obtained in *ca*. 14% yield based on geranylgeraniol (**2**). The mass, ^{1}H-NMR, and

^{13}C-NMR spectral data[9] were identical with those reported for (-)-casbene by Crombie *et al.*[2b]

Further studies including cyclization of casbene (**1**) so obtained and its derivatives are under way.



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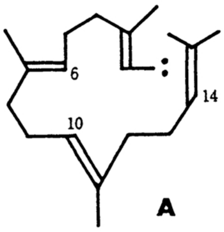
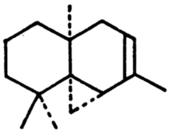


A



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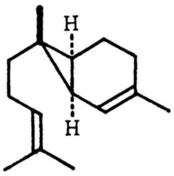
2 R = CH_2OH
5 R = CHO
6 R = $CH=NNH_2$
7 R = $CH=N_2$



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5) E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, J. Am. Chem. Soc., 91, 4318 (1969).

6) The starting material contained *ca.* 95-98% of all-*trans* geranylgeraniol. The authors thank Dr. Masao Nagahama and Dr. Masahisa Tanomura, Kuraray Co. Ltd., for a generous gift of geranylgeraniol.

7) IR (neat) 2050, 1675, and 1638 cm^{-1}.

8) The hydrocarbon fraction obtained from this product mixture contained two minor products besides main one (**1**). The structures of the minor products are under investigation.

9) MS; *m/e* 272.2480 (M^+, $C_{20}H_{32}$), 272 (52%), 136 (75%), 121 (100%), 107 (76%), 93 (87%). ^{1}H-NMR; δ ($CDCl_3$) 0.58 (1H, t, *J*=8.4 Hz), 0.93 (3H, s), 1.05 (3H, s), 1.22 (1H, t, *J*=8.4 Hz), 1.55 (3H, s), 1.58 (3H, s), 1.65 (3H, s), 4.88 (1H, d, *J*=8.4 Hz), 4.89 (1H, m), 4.97 (1H, m). ^{13}C-NMR; δ ($CDCl_3$) 135.96 (s), 135.26 (s), 133.18 (s), 125.59 (d), 123.53 (d), 121.23 (d), 40.39 (t), 39.52 (t), 39.34 (t), 30.72 (t), 28.91 (d), 25.84 (d), 25.06 (t), 24.08 (t), 24.08 (q), 19.75 (s), 16.47 (q), 16.31 (q), 15.74 (q) × 2.

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