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TOTAL SYNTHESIS OF (±)-FUKINONE

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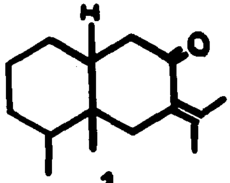
(+)-Fukinone is a bicyclic ketone isolated recently from flower stems of *Petasites japonicus* Maxim. A study of its chemical and spectral properties culminated in the structure and absolute stereochemistry depicted in 1.[1] The ketone is a member of the ever-increasing family of sesquiterpenes derived from eremophilane.[2]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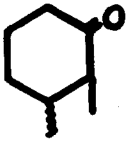
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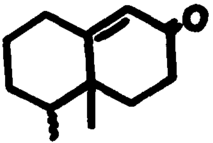
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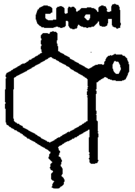
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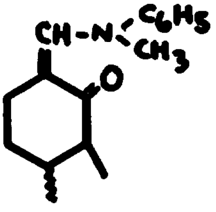
We describe here a stereospecific total synthesis of the racemic variety of fukinone (1). 2,3-Dimethylphenol was reduced catalytically[3] to a mixture of epimeric 2,3-dimethylcyclohexanols, which on chromic acid oxidation[3] afforded 2,3-dimethylcyclohexanone (2) (*cis* and *trans* isomers; approximately 6:1). Annelation of this mixture with methyl vinyl ketone[4] yielded octalone 3, in our hands in about 15% optimum yield, as a mixture of *cis* and *trans* forms (3:2).[4] Attempts to separate these by fractional distillation through a spinning band column were only partially successful;[5] a separation was ultimately achieved by fractional crystallization of the mixed semicarbazones. However, the low over-all yield of desired cis ketone corresponding to 3 necessitated a search for a better synthetic route.



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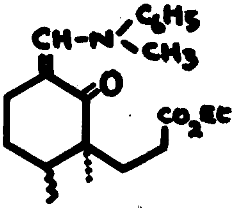

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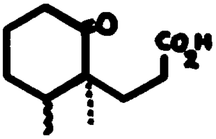

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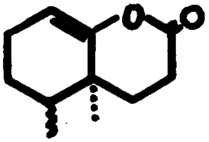

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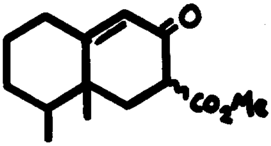
Whilst our investigations to this end were in progress Piers and his collaborators[6] described a synthesis of the cis form of 3. We used their procedure with slight modification. The mixture of isomers 2 was condensed with ethyl formate[6] to give the hydroxymethyleneketones 4, treatment of which with N-methylaniline[7] afforded the N-methylanilinomethyleneketones 5 (90% yield). Reaction of ethyl β-bromopropionate with 5 yielded the esters 6, direct hydrolysis of which yielded the acids 7 (67%). Lactonization of the latter[6] gave the epimeric lactones (89%), the cis isomer of which was obtained by fractional crystallization (76%). Exposure of this to methyllithium, followed by base treatment, yielded the pure cis ketone corresponding to 3 in 69% yield.[6,8]



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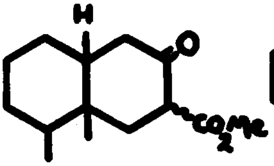

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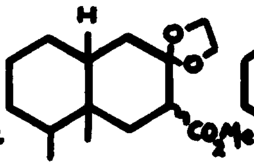

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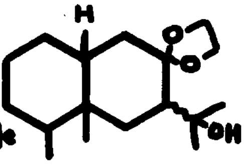

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Reaction of the foregoing cis octalone with dimethyl carbonate-sodium hydride furnished the β-ketoester 9 (81%), which, as anticipated, proved to have enolic properties. Rapid catalytic hydrogenation of 9, in acid medium,[9] generated the cis-2-decalone 10 (94%), with little evidence of formation of the trans isomer. This compound, which was also enolic in character, was converted into the ethylene ketal 11 in 85% yield in the usual manner. Reaction of the ketal with methyllithium gave the carbinol 12 (88%). Dehydration and hydrolysis of the latter to (±)-fukinone (1) was accomplished by boiling aqueous methanolic hydrochloric acid. The final product was purified by fractionation and column chromatography (57.5% yield; some retroaldol cleavage encountered), and finally through its crystalline semicarbazone,[10] m.p. 200-201°. It showed a single spot on thin layer chromatography, and its maximal u.v absorption, i.r. spectrum and n.m.r. spectrum were identical with the published data for the natural ketone.[1,11]

REFERENCES

[1] K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose and N. Shinoda, Tetrahedron, 24, 5871 (1968).

[2] For a review, see A. R. Pinder, Perf. Ess. Oil Record, 59, 280 (1968).

[3] H. E. Ulery and J. H. Richards, J. Amer. Chem. Soc., 86, 3113 (1964).

[4] C. Berger, M. Franck-Neumann and G. Ourisson, Tetrahedron Letters, 3451 (1968); see also R. B. Kelly and J. Zamecnik, Chem. Commun., 1102 (1970).

[5] We wish to thank Mr. B. J. Kane, Glidden Co., Organic Chemicals Division, Jacksonville, Florida, for valuable assistance with this fractionation.

[6] E. Piers, R. W. Britton and W. de Waal, Canad. J. Chem., 47, 4307 (1969).

[7] Cf. A. J. Birch and R. Robinson, J. Chem. Soc., 501 (1944).

[8] We wish to thank Dr. E. Piers, University of British Columbia, for establishing the identity of our cis ketone, after g.l.c. purification, with his product (ref. 6).

[9] Cf. R. L. Augustine, J. Org. Chem., 23, 1853 (1958); 28, 152 (1963); "Catalytic Hydrogenation", Dekker, New York, 1965, p. 45; R. L. Augustine and A. D. Broom, J. Org. Chem., 25, 802 (1960).

[10] Satisfactory analyses were obtained for all new compounds described herein.

[11] After the completion of our work alternative syntheses of racemic fukinone were described by J. A. Marshall and G. M. Cohen, Tetrahedron Letters, 3865 (1970), and by E. Piers and R. D. Smillie, J. Org. Chem., 35, 3997 (1970).