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TOTAL SYNTHESIS OF (±)-ISOSESQUICARENE: A STRUCTURAL REVISION

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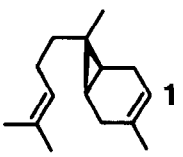
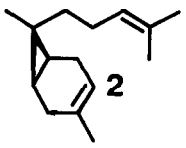
Abstract: We disclose the first total synthesis of (±)-isosesquicarene, the stereostructure of which has been revised consequently.

Unequivocal synthesis of the compound (**1**) having the structure reported for isosesquicarene[1] produced a hydrocarbon, the spectral properties of which were different from those of the natural product.[2] The ^{1}H-NMR spectral data of natural isosesquicarene were reinterpreted as those of the compound (**2**), the stereoisomer of (**1**), in comparison with the former to those of (**1**).[3] In this letter we revise the stereostructure of isosesquicarene to that of (**2**), on the basis of the total synthesis, outlined in Scheme 1.

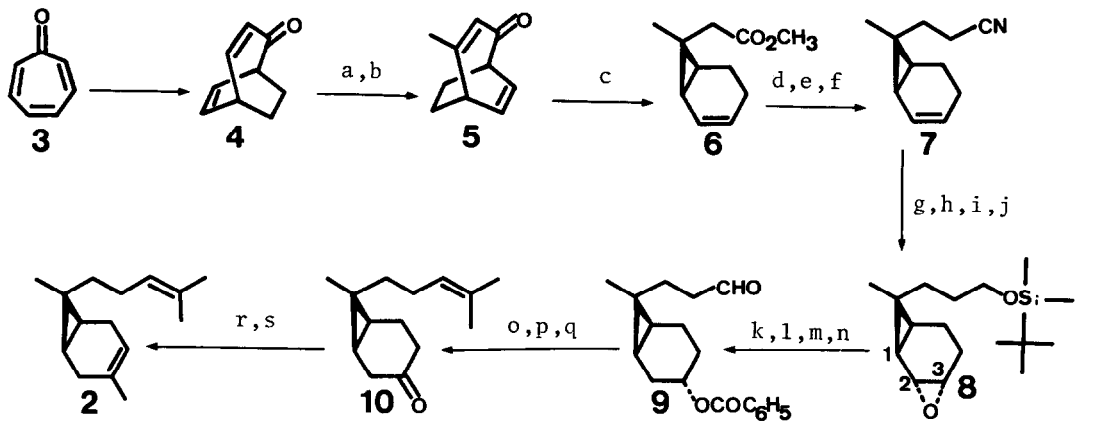




Bicyclo[3.2.2]nona-3,6-dien-2-one (**4**) was prepared from tropone (**3**) by heating with ethylene.[4] The Barbier reaction of (**4**) with methyl iodide and lithium was mediated by ultrasound irradiation,[5] and the resulting tertiary allylic alcohol was converted into the dienone (**5**)[6] by pyridinium chlorochromate oxidation.[7] The bicyclo[3.2.2]nonadienone (**5**) was photochemically transformed into the bicyclo[4.1.0]hept-2-ene (**6**) by irradiation of a methanolic solution using a 100W high-pressure mercury lamp through a Pyrex filter.[8] The ester (**6**) was reduced by lithium aluminium hydride, and the resulting alcohol was converted into the nitrile (**7**) *via* the *p*-toluenesulfonate. After stepwise reduction of the nitrile (**7**) to the alcohol followed by protection of the hydroxyl group as the silyl ether, *m*-chloroperbenzoic acid oxidation of which produced only the *anti*-epoxide (**8**).

When the epoxide (**8**) was treated with diisobutylaluminium hydride, the C_2-O bond was cleaved selectively. After the resulting secondary alcohol

Scheme 1



a: MeI, Li, ether, ultrasounds; b: PCC, CH_2Cl_2, 78%; c: $h\nu$, MeOH, 80%; d: $LiAlH_4$; e: TsCl, Py; f: NaCN, DMSO, 84%; g: DIBAL; h: $LiAlH_4$; i: TBDMS, DMAP, Et_3N, 70%; j: MCPBA, k: DIBAL; l: $(PhCO)_2O$, DMAP, Et_3N, 71%; m: AcOH, H_2O, THF, 90%; n: CrO_3-2Py; o: $Ph_3P{=}CMe_2$, 68%; p: $LiAlH_4$, q: CrO_3-2Py, 71%; r: MeLi, 74%; $POCl_3$, DMAP, Py, 45%.

was protected as the benzoate, removal of the silyl group gave the primary alcohol. Oxidation of the alcohol by Collins reagent afforded the aldehyde (**9**). In order to prepare the homoprenyl side chain, the aldehyde (**9**) was condensed with isopropylidenetriphenylphosphorane at -30°C. The resulting benzoate was cleaved by reduction with lithium aluminium hydride to the alcohol, oxidation of which gave the ketone (**10**).

Addition of methyl lithium at -95°C to the ketone (**10**) followed by dehydration gave a mixture of three hydrocarbons. The major product (**2**), isolated by preparative VPC, was identical spectroscopically with natural isosesquicarene.

References and Footnotes

1) F. Bohlmann, U. Fritz, H. Robinson, and R. M. King, Phytochem., 18, 1749 (1979).

2) T. Uyehara, J. Yamada, and T. Kato, Abstr. No. 1H25, 47th Annual Meeting of the Chemical Society of Japan, Kyoto, April 1983.

3) Isosesquicarene: δ1.02 (s, 3H), 5.12 (tm, 1H), and 5.25 (bs, 1H); the compound (**1**); δ0.75 (s, 3H), 5.12 (tm, 1H), and 5.27 (bs, 1H).

4) T. Uyehara and Y. Kitahara, Chem. and Ind. (London), 1971, 354.

5) J.-L. Luche and J.-C. Damiano, J. Amer. Chem. Soc., 102, 7926 (1980).

6) Satisfactory spectral data and appropriate elemental analyses have been obtained for all new compounds.

7) W. G. Dauben and D. M. Michno, J. Org. Chem., 42, 682 (1977).

8) T. Uyehara, K. Ogata, J. Yamada, and T. Kato, J. Chem. Soc. Chem. Commun., 1983, 17; and references cited therein.

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