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SYNTHESIS OF (±)-1-(2,6,6-TRIMETHYL-4-HYDROXYCYCLOHEXENYL)-1,3-BUTANEDIONE (1), A MARINE NATURAL PRODUCT

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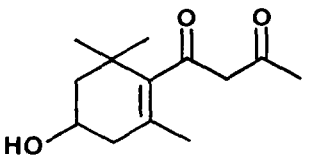
Summary: A short synthesis of racemic natural product (1) from the known compound (7) is described. A model study, using cyclohexanone as starting material, is also reported.

1-(2,6,6-Trimethyl-4-hydroxycyclohexenyl)-1,3-butanedione (1), which is structurally related to carotenoids and some of their degradation products, was recently isolated from cultures of the dinoflagellate *Prorocentrum minimum* and shown to have biological activity in laboratory tests[1].

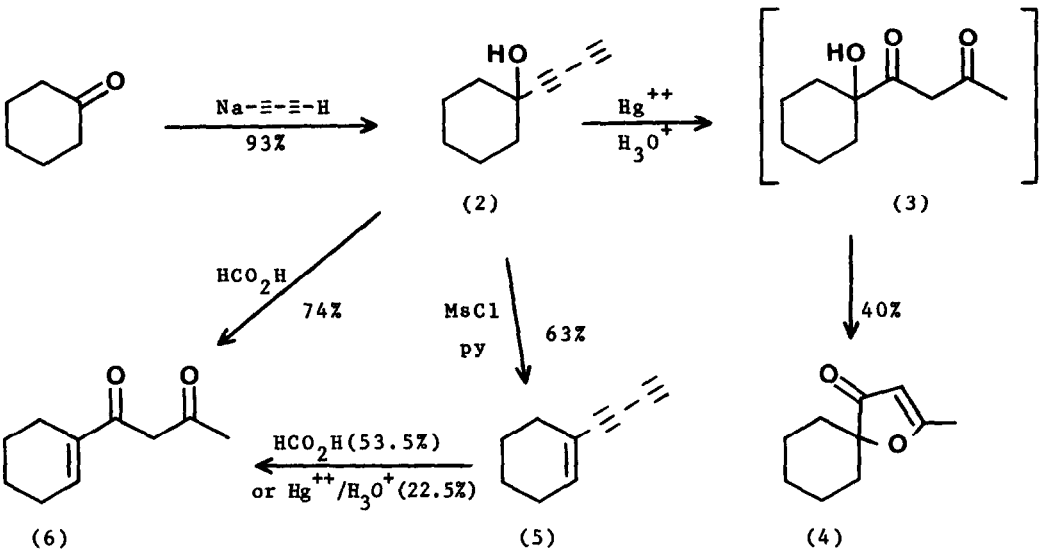


(1)

The key feature of the structure of (1) is the β-diketone system, for which an appropriate precursor would be a butadiynyl structure, it being known that conjugated diacetylenes usually give β-diketones on hydration[2]. The required diyne (8) should in turn be obtained upon addition of the mono-anion of butadiyne to the known compound (7)[3] (Scheme 2).

The feasibility of this route was established by a model study using cyclohexanone, as depicted in Scheme 1.

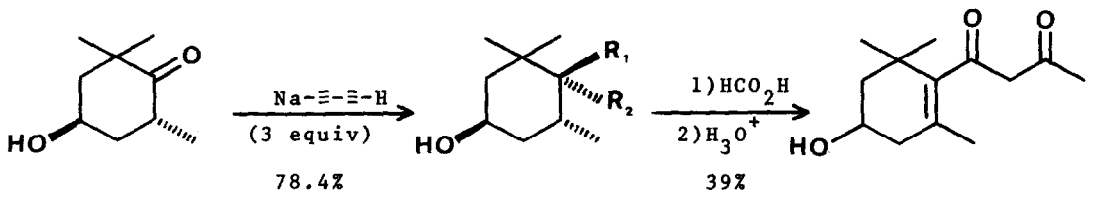
Scheme 1



Reaction of cyclohexanone with the mono-anion of butadiyne[4] gave the unstable compound (2) [^{1}H nmr ($CDCl_3$) δ 2.93(br.s, 1H), 2.23(s, 1H), 2.1-1.2(m, 10H); ir (liquid film) 3350(br.), 3295, 2210, 2045, 1055 cm^{-1}; ^{13}C nmr ($CDCl_3$) 80.3(s), 69.0(s), 68.6(s), 68.4(d, J_1~$5J_2$), 67.8(d, J_2), 39.6(t), 25.1(t), 23.1(t)][6] in good yield. However, upon treatment of (2) with a hydrating solution[7], only the spiro-furanone (4) [^{1}H nmr ($CDCl_3$) δ 5.40(s, 1H), 2.25(s, 3H), 2.0-1.1(m, 10H); ir (KBr) 3090, 1690, 1595, 1210, 1060, 840 cm^{-1}; ^{13}C nmr ($CDCl_3$) 207.2(s), 188.1(s), 102.5(d), 90.8(s), 31.7(t), 24.6(t), 21.8 (t), 17.0(q)] was obtained, presumably by cylization-elimination of the intermediate (3). This furanone formation from hydroxy-diacetylenes has been noted previously[8]. This undesired reaction could be circumvented by first dehydrating (2) to (5) [^{1}H nmr ($CDCl_3$) δ 6.4-6.1(m, 1H), 2.39(s, 1H), 2.4-1.9 (m, 4H), 1.8-1.4(m, 4H); ir (liquid film) 3300, 3020, 2210, 2200, 1620, 840cm^{-1}; ^{13}C nmr ($CDCl_3$) 139.8(d), 119.3(s), 77.5(s), 71.1(s), 70.3(d, J_1~$5J_2$), 68.5(d, J_2), 28.5(t), 25.9(t), 22.1(t), 21.3(t)] with methanesulfonyl chloride in pyridine. Upon hydration[10], (5) then gave the desired dione (6) [^{1}H nmr ($CDCl_3$) δ (enol form) 7.0-6.0(m, 1H), 5.83(s, 1H), 2.12(s, 3H); δ (keto form) 3.77(s, 2H), 2.23(s, 3H), δ (both forms) 2.5-2.1(m, 4H), 1.9-1.5(m, 4H); ir (liquid film) 1720, 1640, 1600(br.) cm^{-1}; ^{13}C nmr ($CDCl_3$) (enol form) 194.2(s), 182.6 (s), 136.3(d), 133.8(s), 95.7(d), 26.0(q+t), 23.6(t), 22.6(t), 21.7(t)]. The final product (6) could also be prepared directly, and in better yield, by treatment of (2) with refluxing 85% formic acid, possibly by a combination of Rupe rearrangement[11] and hydration.

Analogously, reaction of (7) with the mono-anion of butadiyne furnished (8) as a mixture of two stereoisomers[12] (78.4% yield). Since both isomers give the same desired final product, the mixture, purified from resinous by-products by column chromatography, was used in the subsequent step. Treatment of (8) with refluxing formic acid followed by acid-catalyzed hydrolysis and preparative TLC yielded the target compound (1) [60MHz ^{1}H nmr ($CDCl_3$) δ 5.53(s, 1H), 4.07(m, 1H), 2.15(s, 3H), 1.72(s, 3H), 1.22(s, 3H), 1.08(s, 3H); ir ($CHCl_3$) 3570, 3400(br.), 1600, 1360, 1060, 1020, 980,950 cm^{-1}; ^{13}C nmr ($CDCl_3$) 193.5(s), 189.3(s), 137.5(s), 130.1(s), 103.4(d), 64.1(d), 47.9(t), 41.1(t), 36.3(s), 29.6(q), 28.9(q), 25.7(q), 20.9(q)] as a pale-yellow oil (39% yield).

Scheme 2



(7) (8) (1)

a: R_1=OH, R_2=-C≡C-C≡C-H

b: R_1=-C≡C-C≡C-H, R_2=OH

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References and Notes

1 . R.J. Andersen, M.J. Le Blanc and F.W. Sum, J. Org. Chem. 45, 1169 (1980).

2 . T.F. Rutledge, "Acetylenes and Allenes", Reinhold, N. York, pg 128 (1969).

3 . H.G.W. Leuengerger, W. Boguth, E. Widmer and R. Zell, Helv. Chim. Acta, 59 1832 (1976).

4 . An ammonia solution of the mono-sodium salt of butadiyne was prepared according to Brandsma[5]; cyclohexanone (0.5 equivalent) was added to this solution, followed, after 15 minutes, by H_2O/THF and ethyl ether. Extraction and purification by column chromatography were performed in such a way as to maintain compound (2) in solution at all times.

5 . L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, pg 35 (1971).

6 . Except for the very unstable compounds (5) and (8), all compounds reported gave satisfactory elemental analyses.

7 . The hydrating solution was prepared from concentrated sulfuric acid (10.5 ml) water (39.5 ml) and red mercuric oxide (2.0 g).

8 . P.K. Gupta, J.G. Ll. Jones and E. Caspi, J. Org. Chem. 40, 1420 (1975); steroids containing spiro-furanone structures like that of compound (4) or the hydroxy-butadiynyl structure [as in (2)] are biologically active[9].

9 . G. Ortar and E. Morera, J. Org. Chem. 46, 452 (1981); J. N. Gardner, O. Gnoj, A. S. Watnick and J. Gibson, Steroids 4, 801 (1964).

10. Compound (5) was hydrated with Hg^{++}/H_3O^+ solution[7] (22.5% yield) or by refluxing with 85% formic acid (53.5% yield).

11. S. Swaminathan and K.V. Narayanan, Chem. Rev. 71, 429 (1971).

12. The two isomers (8) a,b , formed in a ratio of 85:15, exhibited the following spectral properties: (8)a: ^{1}H nmr ($CDCl_3$) δ 4.05(m, 1H, Σ_J14 Hz), 2.23(s, 1H), 2.4-1.5(m, 5H), 1.22(s, 3H), 1.13(s, 3H), 1.08(d, 3H, J=6 Hz); ir ($CHCl_3$) 3610, 3300, 2210, 2040, 1050, 1010, 995 cm^{-1}; ^{13}C nmr ($CDCl_3$) 79.2(s), 77.3(s), 71.2(s), 67.9(d, J_3~$5J_2$), 67.7(d, J_2), 66.6(d, J_1~$3.2J_2$), 44.2(t), 39.8(t), 39.2(s), 32.4(d), 27.4(q), 23.1(q), 16.0(q); (8)b: ^{1}H nmr ($CDCl_3$) δ 4.07(m, 1H, Σ_J=14 Hz), 2.20(s, 1H), 2.4-1.4(m, 5H), 1.33(s, 3H), 1.12(d, 3H, J=6 Hz), 1.10(s, 3H); ir ($CHCl_3$) 3610, 3300, 2210, 2045, 1020, 995, 965 cm^{-1}; ^{13}C nmr ($CDCl_3$) 78.6(s), 76.8(s), 69.8(s), 67.9(d, J_3~$5J_2$), 67.6(d, J_2), 66.9(d, J_1~$3.5J_2$), 40.2(t), 38.5(s), 35.6(t), 30.9(d), 26.9(q), 26.7(q), 16.7(q).

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