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AN ALTERNATIVE SYNTHESIS OF (±)-DESCARBOXYQUADRONE

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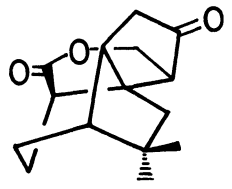
The alternative synthesis of descarboxyquadrone by using the acid-catalyzed rearrangement of [4.3.2]propellanone derivative and its antitumor activity are described.

Quadrone (1)[1] and its retrolactonization compound, terrecyclic acid A (2),[2] isolated from the same fungus, have been shown to display significant biological activities involving antitumor activity. From the view point of their biological activities, descarboxyquadrone (3), having an α-methylene cyclopentanone structure and geminal methyl groups at C-11 on tricyclo[4.3.2.$0^{1,5}$]undecane skeleton, has been synthesized and found to possess anti HeLa activity.[3] On the other hand, we have already reported the novel formal synthesis of 3 by using the acid-catalyzed rearrangement of [4.3.2]propellanone 5 to the quadrone skeleton.[4] Although this one-step skeleton construction was serviceable in securing the formal synthesis, we were dissatisfied with the preparation[5] of the propellanone 5, derived from the minor product of photocycloaddition of the enone 6 to allene. We describe herein an alternative and highly selective sequence for the total synthesis of 3 and the interesting antitumor activity of 3 along with that of the binor derivative, 2-methylenetricyclo[4.3.2.$0^{1,5}$]undecan-3-one (4).[4]



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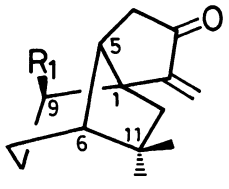
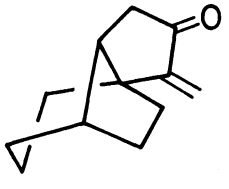


2 $R_1=CO_2H$
3 $R_1=H$



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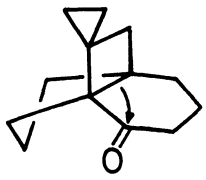

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On the basis of our studies on the acid-catalyzed rearrangements of [m.n.2]-propellanes,[6] we planed the skeletal transformation of [4.3.2]propellanone 7 to the quadrone skeleton as the initial step and then the introduction of geminal methyl groups to C-11 position as outlined in Scheme 1. To this purpose, photoreaction of 6 [CH_2=CHOAc, Et_2O, -78 °C, 3.5 h] was undertaken to give the propellanone 7[7] in 91% yield together with a small amount (<4%) of three other cyclo-

adducts. The regiochemistry[8] of 7 was assumed to be head to tail for the sake of previous works on photocycloaddition of α,β-enones to vinyl acetate,[9] and was finally ascertained by the synthesis of 3 from 7. The acid-catalyzed rearrangement of 7 [concd HCl, Et_2O, reflux, 36 h] afforded the diol 8[7] (mp, 127-130 °C) in 72% yield whose secondary hydroxyl group was oxidized quantitatively to the keto alcohol 9 with PCC[10] [$C_5H_5N \cdot CrO_3 \cdot HCl$, CH_2Cl_2, rt, 2.5 h]. Conversion of 9 into the keto olefin 11[7] was carried out by dehydration [$SOCl_2$, Py, CH_2Cl_2, rt, 4 h] followed by reduction of 10[7] with tributyltin hydride [2,2'-azobisisobutyronitrile, cyclohexane, reflux, 4 h] in 88% overall yield. The geminal methyl groups were introduced by treatment of 11 with sodium hydride and methyl iodide [5 equiv. NaH, THF, 50 °C, 2 h, then 6 equiv. CH_3I, reflux, 12 h] to yield the intermediate 12[7] in 78% yield.

With the desired compound 12 in hand, deoxygenation of carbonyl group at C-10 and then allylic oxidation at C-3 would lead the key intermediate 15 which had been synthesized by us.[4] However, attempted Wolff-Kishner reduction of 12 failed to produce the desired product 14, and, therefore, a more circuitous route for removal of the very hindered carbonyl group had to be employed. Reduction of 12 with $LiAlH_4$ [Et_2O, rt, 4 h] gave the alcohol 13[11] in 98% yield as a sole product. While radical deoxygenation[12] with $Li/EtNH_2$ via phosphoroamidate of 13 was inadequate to our aim, the Barton-McCombie reaction[13] of 13 [i) NaH, CS_2, imidazole, HMPA, THF, reflux, 22 h, then Me_2SO_4, reflux, 1 h; ii) n-Bu_3SnH, AIBN, toluene, reflux, 13 h] served admirably to give the olefin 14[7] in 33% overall yield. Allylic oxidation[14] of 14 [CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, -25 ~ -20 °C, 5 h] afforded the known enone 15[4] in 60% yield.

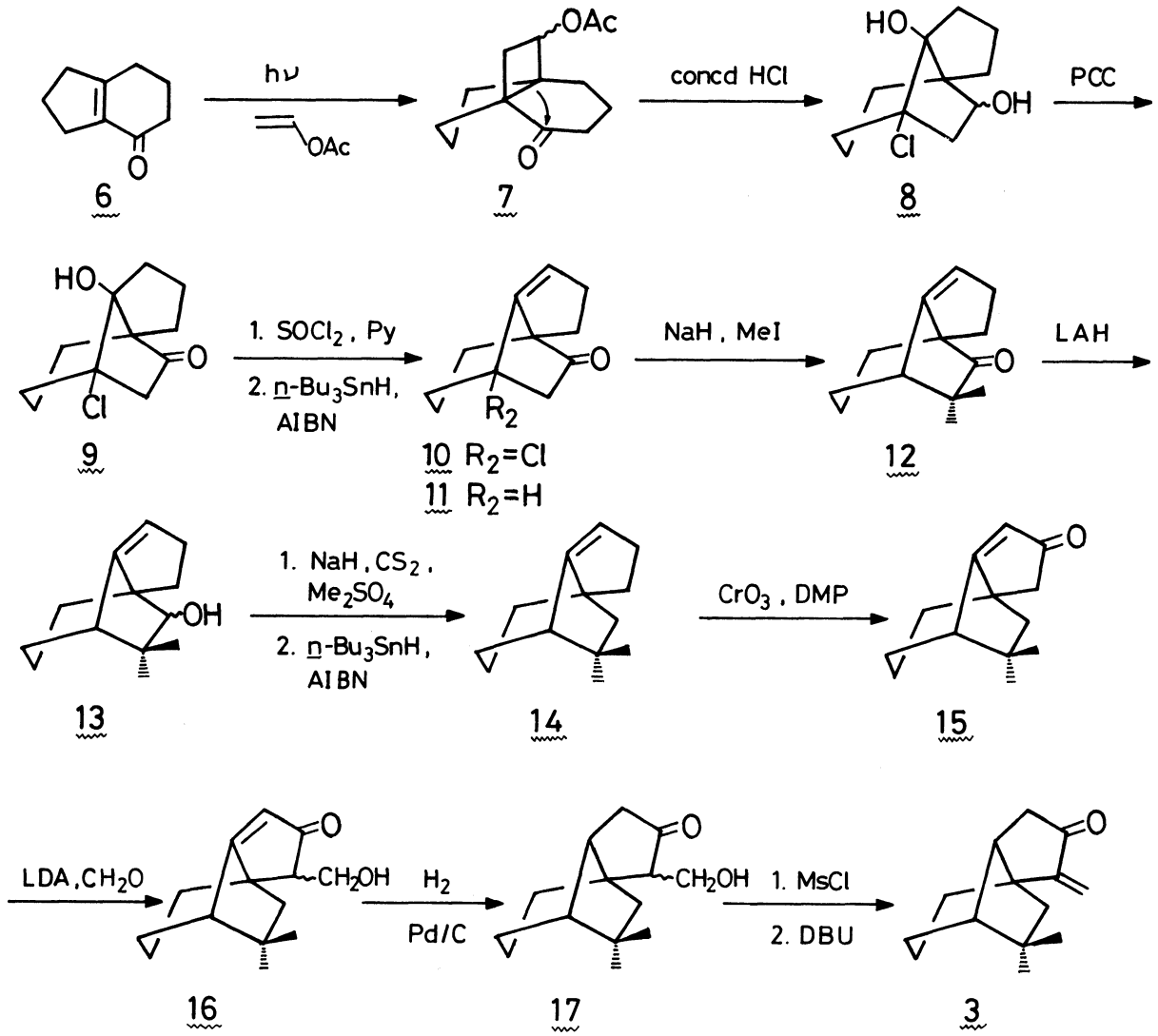
At the final stage, α-methylenation of 15 to descarboxyquadrone (3) was accomplished via almost the same procedure as that of Smith et al.[3] Namely, hydroxymethylation of 15 [1.1 equiv. LDA, THF, -78 °C, then CH_2O, -20 °C, 25 min] and subsequent hydrogenation of 16 [Pd/C, AcOEt, rt, 20 h] followed by dehydration of 17 [i)$MeSO_2Cl$, Py, rt, 7 h; ii) 1,8-diazabicyclo[5.4.0]undec-7-ene, C_6H_6, rt, 14 h] furnished 3[3,15] in 52% overall yield. Thus, the total synthesis of 3 has been achieved in 14 steps and 4.6% overall yield based on the bicyclic enone 6.

The bioassay of 3 and its binor derivative 4[4] without geminal methyl groups at C-11 in 3 was undertaken against tumor cells of mice in vitro and the results are summarized in Table 1 together with those of natural quadrone (1). Interestingly, 3 and 4 exhibited higher cytotoxicity than the antibiotic 1. Therefore, it is reasonable to conclude that the α-methylene cyclopentanone

Table 1. Antitumor Activity of Quadrone (1), Descarboxyquadrone (3), and the Related Compound 4

	IC_{50}, ng/ml		
Test cell	1	3	4
P388	190	136	94
L1210	650	64	185

structure on the tricyclic skeleton plays more important role in the appearance of antitumor activity of quadrone and the related compounds than the carboxyl and geminal methyl groups.



Scheme 1.

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7) All new compounds isolated gave satisfactory spectral and analytical data. Selected data are as follows:
7: IR (neat) 1730, 1690, 1230, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 1.1-2.6 (m, 17H containing s at 2.00), 4.64 (t, J = 7 Hz, 1H).
8: IR (KBr) 3400, 1040, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2-2.6 (m, 16H), 3.72-3.94 (m, 1H).
12: IR (neat) 3050, 1740, 1680, 1380 cm^{-1}; ^1H NMR (CCl_4) δ 0.96 (s, 3H), 1.11 (s, 3H), 1.4-1.8 (m, 8H), 2.4-2.7 (m, 3H), 5.20 (t, J = 2 Hz, 1H).
14: IR (neat) 3050, 1680, 1380 cm^{-1}; ^1H NMR (CCl_4) δ 0.94 (s, 3H), 1.12 (s, 3H), 1.2-1.8 (m, 10H), 1.93 (m, 1H), 2.36-2.62 (m, 2H), 4.96 (t, J = 2 Hz, 1H).

8) The configuration of the acetoxyl group of 7 was not determined.

9) For example, see: E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, J. Am. Chem. Soc., 86, 5570 (1964).

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11) The stereochemistry of the hydroxyl group of 13 was not assigned.

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15) ^{13}C NMR data not reported in ref. 3 are as follows: ($CDCl_3$) δ 208.2 (s), 154.1 (s), 114.2 (t), 54.0 (d), 53.6 (s), 51.4 (t), 49.3 (d), 41.8 (t), 41.6 (s), 36.8 (t), 35.1 (q), 31.0 (t), 27.1 (q), 19.5 (t).

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