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A NOVEL SYNTHESIS OF (±)-DESCARBOXYQUADRONE

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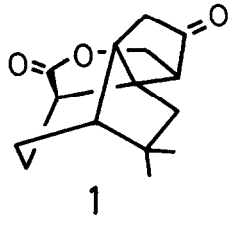
Summary: The novel synthesis of descarboxyquadrone (3) and its model compound 4 by using the acid-catalyzed rearrangement of [4.3.2]propellanones is described.

Since quadrone (1) was isolated from a fermentation broth of Aspergillus terreus and was found to display significant in vitro activity against KB human epidermoid carcinoma of the nasopharnx and in vivo activity against P-388 lymphocytic leukemia in mice in 1978,[1] much attention has been paid to the sesquiterpene as an attractive synthetic target because of its biological activities and the intriguing nature of its tetracyclic ring system.[2] Furthermore, terrecyclic acid A (2) having an α-methylene carbonyl group on tricyclo[4.3.2.0^{1,5}]undecane skeleton, nominally related to 1 in a retro-Michael sense, was also isolated from the same fungus and exhibited antitumor activity.[3] From the view point of their antitumor properties, the first biologically active analogue of 1, descarboxyquadrone (3), was synthesized.[4] However, these synthetic studies needed much elaboration on the step-wise ring construction with careful regio- and stereochemical controls. In this connection, we wish to report here the novel synthesis of descarboxyquadrone (3) along with its model compound 4 via one-step skeleton construction of them.



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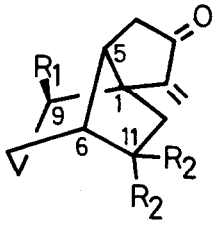
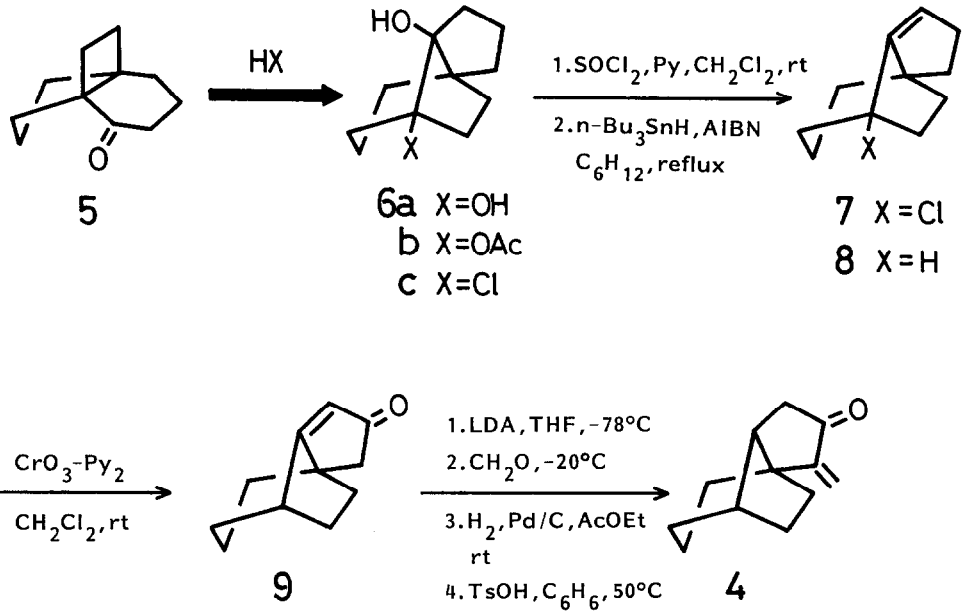


2 R_1=CO_2H, R_2=CH_3
3 R_1=H, R_2=CH_3
4 R_1=R_2=H

As part of study on the transformation of propellane system to other important ring system, we have already reported the novel acid-catalyzed rearrangement of [4.3.2]propellanone (5) to tricyclo[4.3.2.0^{1,5}]undecane

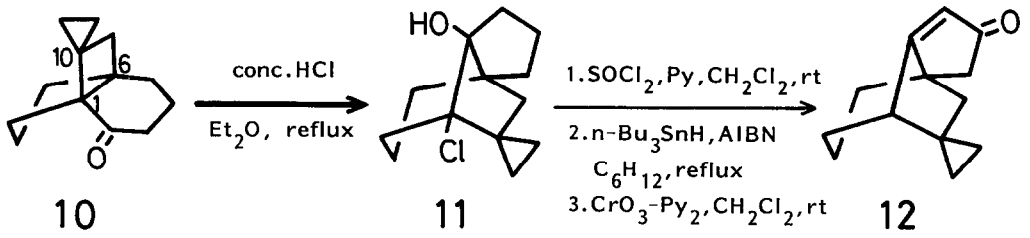
derivatives 6a-b through 1,2-alkyl shift of the central propellane bond.[5] Therefore, our synthetic strategy of the compounds related to quadrone consists mainly of utilizing this skeletal rearrangement to build up the basic skeleton of them.

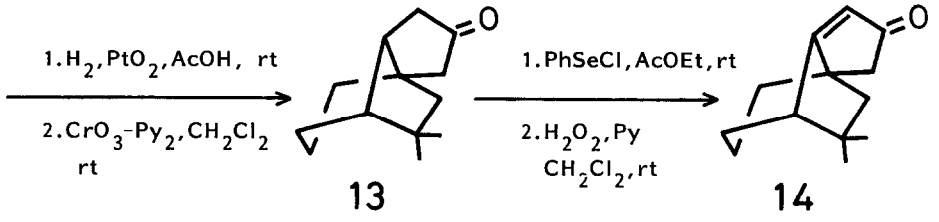
First of all, we tried the synthesis of the α-methylene ketone 4 as the model study. Our problem was to introduce the functional groups into the basic tricyclic skeleton. To this purpose, acid-catalyzed rearrangement of [4.3.2]-propellanone (5) in conc.HCl-Et_2O at reflux was undertaken to give crude 6-chlorotricyclo[4.3.2.$0^{1,5}$]undecan-5-ol (6c) which was followed by dehydration [$SOCl_2$-Py, CH_2Cl_2, rt] to afford the unsaturated chloride 7[6] in 80% overall yield. The reduction of 7 to the unsaturated hydrocarbon 8[6] was accomplished by tri-n-butyltin hydride [AIBN, C_6H_{12}, reflux] in 91% yield and then allylic oxidation of 8 with Collins reagent [CrO_3-Py_2, CH_2Cl_2, rt][7] gave the enone 9[6] in 70% yield. Final conversion of 9 to 4 was completed via the protocol employed by Smith et al. in their successful descarboxyquadrone synthesis.[4] Namely, condensation of the enolate of 9 [1.2 equiv. LDA, THF, -78°C] with gaseous formaldehyde followed by hydrogenation [Pd/C, AcOEt, rt] and acid-catalyzed dehydration [TsOH, C_6H_6, 50°C] afforded 4[6] in 47% overall yield from 9. Thus, the model compound 4, which is considered to be the basic biologically active compound closely related to quadrone, was prepared easily from the propellanone 5 in a 7 steps and 24% overall yield.



With the success of the model study, we attempted the synthesis of descarboxyquadrone (3). Toward this end, it was necessary to attach two

geminal methyl groups at C-11 position on the model compound. After several trials,[8] [4.3.2]propellanone 10[6] having a cyclopropane ring, equivalent to two geminal methyl groups,[10] was finally chosen as the starting material.[11] The key intermediate, enone 12,[6] was derived from 10 by the way similar to that for 9 as follows: acid-catalyzed rearrangement[12] and dehydration of the alcohol 11 (46%); reduction with tri-n-butyltin hydride (95%); allylic oxidation with Collins reagent (77%). Then, cyclopropane hydrogenolysis [PtO_2, AcOH, rt] followed by oxidation [CrO_3-Py_2, CH_2Cl_2, rt] gave the ketone 13[6] in 85% overall yield.[10] At the final stage, conversion of 13 to the enone 14[6] was accomplished by seleneylation [PhSeCl, AcOEt, rt] and the subsequent selenoxide elimination [H_2O_2, Py, CH_2Cl_2, rt] in 47% overall yield.[2a,13] The enone 14 proved to be identical with the authentic sample prepared by Takeda and Yoshii et al.[2e] by comparison of IR and 200 MHz ^1H NMR spectra. Since Smith had converted 14 to descarboxyquadrone (3) in three steps as described for 4,[4] the formal synthesis was then complete.





In conclusion, the novel synthesis of descarboxyquadrone (3) has been achieved in a 11 steps and 9.1% overall yield based on propellanone 10, which was comparable yield with those of the other groups.[2e,4] In particular, our strategy was characterized cleanly by one-step skeleton synthesis of the compounds related to quadrone, using the novel acid-catalyzed rearrangement of [4.3.2]propellanones.

Acknowlegement. We would like to thank Dr. K. Takeda and Prof. E. Yoshii of Toyama Medical and Pharmaceutical University for the measurement of 200 MHz ^1H NMR spectrum and for providing the IR and ^1H NMR spectra of the compound 14.

References and Notes

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6) All new compounds gave satisfactory spectral (IR, mass, and 100 MHz ^{1}H NMR) and analytical data except for 6c and 11, which could not be isolated because of instability of them under preparative GLC conditions. Selected data as follows:
   8: ^{1}H NMR (CCl_4) δ 1.0-2.1 (m, 12H), 2.4-2.7 (m, 3H), 4.87 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 158.4 (s), 109.4 (d), 56.2 (s), 39.3 (t), 35.9 (t), 35.8 (t), 35.5 (d), 34.8 (t), 34.0 (t), 31.1 (t), 19.9 (t).
   9: IR (neat) 1710, 1640 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.2-2.0 (m, 10H), 2.08 (s, 2H), 3.00 (m, 1H), 5.52 (s, 1H).
   4: ^{1}H NMR (CCl_4) δ 1.4-2.4 (m, 12H), 4.92 (s, 1H), 5.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 207.8 (s), 153.5 (s), 112.7 (t), 52.2 (t+d), 39.7 (t), 39.0 (d), 34.9 (s), 34.7 (t), 33.1 (t), 28.3 (t), 19.1 (t).
   10: ^{1}H NMR (CCl_4) δ 0.2-0.6 (m, 4H), 1.2-2.6 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 214.5 (s), 58.9 (s), 45.3 (s), 40.5 (t), 39.4 (t), 38.0 (t), 34.3 (t), 31.6 (t), 23.9 (t), 19.9 (t), 19.8 (s), 12.8 (t), 9.2 (t).
   12: IR (neat) 1710, 1640 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.3-0.9 (m, 4H), 1.2-2.4 (m, 11H), 5.56 (s, 1H).
   13: ^{1}H NMR (CCl_4) δ 1.16 (s, 3H), 1.20 (s, 3H), 1.3-1.9 (m, 10H), 2.05 (d, J=8 Hz, 2H), 2.29 (s, 1H), 2.40 (d, J=1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 219.9 (s), 55.2 (d), 51.3 (t), 50.0 (t+s), 49.3 (d), 42.8 (t), 41.3 (s), 39.4 (t), 34.8 (q), 30.8 (t), 27.0 (q), 19.8 (t).
   14: IR (neat) 1710, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (s, 3H), 1.23 (s, 3H), 1.31 (d, J=13 Hz, 1H), 1.42-1.74 (m, 4H), 1.80 (d, J=13 Hz, 1H), 1.92-2.01 (m, 2H), 2.21 (d, J=18 Hz, 1H), 2.30 (d, J=18 Hz, 1H), 2.42 (br t, J=ca. 3 Hz, 1H), 5.74 (s, 1H).
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8) The synthesis of [4.3.2]propellanone containing two geminal methyl groups at C-10 by photocycloaddition of isobutylene to the bicyclic enone seems to be disadvantageous since the photoreaction of cyclohexenone gave a large amount of byproducts.[9] Furthermore, the skeletal rearrangement of the propellanone prepared by hydrogenolysis of 10 did not occur even under forced conditions.
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11) The propellanone 10 was prepared excellently by photocycloaddition of allene to bicyclo[4.3.0]non-1(6)-en-2-one followed by cyclopropanation: Details will be reported elsewhere.
12) The rearrangement of 10 occurred smoothly although it gave 11 in somewhat lower yield than that of 6c.
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