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# SYNTHESIS OF TRICYCLO[5.3.2.0$^{1,6}$]DODECENONES

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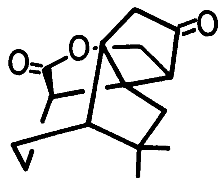
A new type of biologically active tricyclo[5.3.2.0$^{1,6}$]-dodecenones related to quadrone and terrecyclic acid A has been synthesized.

Quadrone (1)1) and terrecyclic acid A (2)2) isolated from the same fungus possess a new polycarbocyclic ring system, tricyclo[4.3.2.0$^{1,5}$]undecane, and are well-known to exhibit interesting antitumor and/or antimicrobial activities. As part of study on the unique transformation of [m.n.2]propellane system, we already synthesized biologically active descarboxyquadrone (3)3) by using the novel acid-catalyzed rearrangement of [4.3.2]propellanone to the quadrone framework.4) Furthermore, this rearrangement was found to be applicable to the higher homologue, [5.3.2]propellanone (4), to give tricyclo[5.3.2.0$^{1,6}$]dodecane derivatives 5a and 5b involving the "homoquadrone" ring system.5) From the view point of exploitation of a new type of biologically active substances related to 1 and 2, we wish to report here the synthesis of tricyclo[5.3.2.0$^{1,6}$]dodecanes 6-9 having a cyclohexenone moiety and their antitumor activities.



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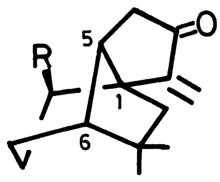
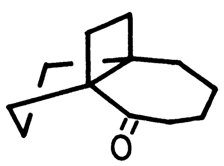


2 R=CO$_2$H
3 R=H



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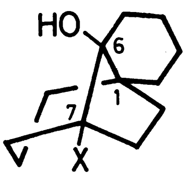
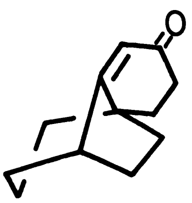


5a X=OH
5b X=Cl



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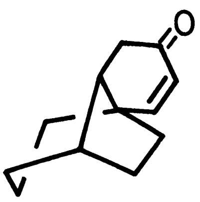

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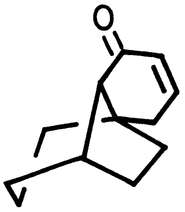

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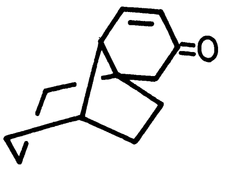

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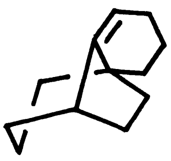
At first, we prepared the important key intermediate 10 from 5b by dehydration followed by reduction with tributyltin hydride as described in our previous paper.6) Allylic oxidation of 10 with Collins reagent [CrO$_3$-Py$_2$, AcOEt, rt, 48 h] gave the enone 6[7] in 92% yield. Hydrogenation of 6 [$H_2$, Pd/C, AcOEt, rt, 48 h] and the subsequent selenenylation of the ketone 11[8] [PhSeCl, AcOEt, rt, 3 h] followed by selenoxide elimination of the resulting selenide [$H_2O_2$, Py, $CH_2Cl_2$, rt, 1.5 h] gave the enone 7[7] in 34% overall yield along with 6 (12%) and the dienone 12[7] (10%). Next, to synthesize the enones 8 and 9, tricyclo[5.3.2.0$^{1,6}$]dodecan-5-one (13)[6] was used as the intermediate for them. Reaction of 13 with tosylhydrazide [MeOH, reflux, 5 h] followed by treatment with 1.2 M MeLi [$Et_2O$, 20-22 °C, 12 h] gave the olefin 14[7] in 81% overall yield. Allylic oxidation as described for 10 afforded the desired enone 9[7] and the rearranged enone 8[7] in 41% and 21% yields, respectively. The enone 8 was also obtained from 13 by selenenylation and the subsequent selenoxide elimination as described for 11 in 81% overall yield.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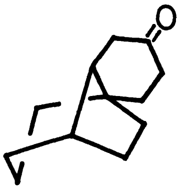
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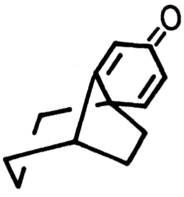
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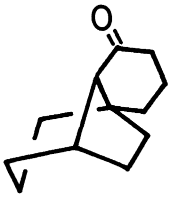
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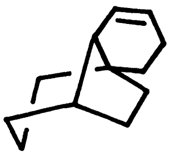
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In a preliminary bioassay, the cytotoxicity of 8 and 9 against tumor cells (P388, L1210, 3LL, B16, and LY) of mice in vitro has been observed and the details of the assay will be reported shortly.

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References

1) R. L. Ranieri and G. J. Calton, Tetrahedron Lett., 1978, 499.
2) M. Nakagawa, A. Hirota, H. Sakai, and A. Isogai, J. Antibiot., 35, 778 (1982).
3) A. B. Smith, III, B. A. Wexler, and J. Slade, Tetrahedron Lett., 23, 1631 (1982).
4) K. Kakiuchi, T. Nakao, M. Takeda, Y. Tobe, and Y. Odaira, Tetrahedron Lett., 25, 557 (1984).
5) K. Kakiuchi, K. Itoga, T. Tsugaru, Y. Hato, Y. Tobe, and Y. Odaira, J. Org. Chem., 49, 659 (1984).
6) K. Kakiuchi, T. Tsugaru, M. Takeda, I. Wakaki, Y. Tobe, and Y. Odaira, J. Org. Chem., in press.
7) All new compounds gave satisfactory spectral and analytical data. Selected data are as follows:
   6: $^1$H NMR ($CCl_4$) δ 1.2-2.5 (m, 14H), 2.72 (m, 1H), 5.60 (s, 1H); $^{13}$C NMR (CDCl3) δ 200.0 (s), 180.0 (s), 116.1 (d), 42.9 (s+d), 38.8 (t), 36.0 (2t), 34.7 (t), 34.5 (t), 26.4 (t), 18.6 (t).
   7: $^1$H NMR (CCl4) δ 1.2-2.2 (m, 14H), 5.66 (d, J=10 Hz, 1H), 6.52 (d, J=10 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 200.0 (s), 157.3 (d), 126.9 (d), 53.1 (d), 44.6 (s), 40.4 (d), 39.5 (t), 38.0 (t), 33.8 (t), 32.4 (t), 29.5 (t), 19.4 (t).
   8: $^1$H NMR ($CCl_4$) δ 1.2-1.8 (m, 10H), 1.87 (s, 1H), 2.26 (t, 2H), 2.83 (m, 1H), 5.85 (dt, J=10, 2 Hz, 1H), 6.60 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 200.0 (s), 149.8 (d), 128.8 (d), 59.8 (d), 43.7 (s), 40.5 (t), 37.4 (d), 34.9 (t), 32.5 (t), 32.2 (t), 27.5 (t), 19.2 (t).
   9: $^1$H NMR ($CCl_4$) δ 1.3-1.8 (m, 10H), 2.1-2.3 (m, 4H contains s at 2.26), 5.81 (dd, J=10, 3 Hz, 1H), 6.46 (dd, J=10, 2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 200.0 (s), 152.5 (d), 129.7 (d), 52.2 (d), 46.4 (t), 44.1 (s), 41.6 (d), 39.5 (t), 33.1 (t), 31.3 (t), 28.9 (t), 19.0 (t).
8) The product was contaminated with the C-6 diastereomer (≈10%, calculated by the $^{13}$C NMR spectrum).

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