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STRUCTURAL AND CONFORMATIONAL STUDIES ON CITREOVIRIDINOL AND ISOCITREOVIRIDINOL: SYNTHESES OF SOME 2,6-DIOXABICYCLO[3.2.1]OCTANES

Shigeru Nishiyama, Yoshikazu Shizuri, Daizo Imai, and Shosuke Yamamura*
Department of Chemistry, Faculty of Science and Technology, Keio University
Hiyoshi, Yokohama, Japan
Yukimasa Terada, Masatake Niwa, Kazuaki Kawai, and Hideyuki Furukawa
Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya, Japan

Summary: Isocitreoviridinol has been newly isolated from the mycelium of Penicillium citreo-viride B. (IFO 6050) together with citreoviridinol, and their stereostructures have also been elucidated by means of chemical method: the 2,6-dioxabicyclo[3.2.1]octanes have been made, one of which is regarded as a promising synthetic intermediate of citreoviridinol. In addition, isocitreoviridinol diacetate has been derived from citreoviridin in 3 steps.

In connection with citreoviridin and citreoviral,[1] we further examined toxic compounds produced by Penicillium citreo-viride B. (IFO 6050), and isolated isocitreoviridinol (1) in addition to citreoviridinol (2) whose stereostructure remained unsettled.[2]

According to the same procedure as described in the previous paper,[1] the AcOEt extract was chromatographed on silica gel (Wakogel C-100) using a gradient solvent of MeOH - $CHCl_3$ (1 - 20%). After elution with 4% MeOH - $CHCl_3$ giving rise to citreoviral,[1] further elution with the same solvent system afforded a yellow oil, which was also separated by repeating preparative TLC (Kieselgel PF_{254}) using AcOEt to give isocitreoviridinol (1) as a pale yellow oil, in ca. 1% yield[3]: $C_{23}H_{30}O_7$ [m/z 418.1977(M^+)]; IR (film) 3400, 1690br., 1620, 1570, and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.16(3H, d, J= 7Hz), 1.23(3H, s), 1.32(3H, s), 1.43(3H, s), 1.92 (3H, s), 3.66(1H, s), 3.80(3H, s), 3.96(1H, q, J= 7Hz), 4.07(1H, s), 5.46(1H, s), and 5.8 - 6.6(6H, complex). The IR and ^1H NMR spectra of isocitreoviridinol (1) are quite similar to those of citreoviridinol (2), suggesting that both of them are stereoisomers at the 2,6-dioxabicyclo[3.2.1]octane system. Thus, we could determine their stereostructures unambiguously on the basis of the following chemical evidence coupled with molecular mechanics calculations of some 2,6-dioxabicyclo[3.2.1]octanes. In addition, their absolute configuration was also elucidated in connection with citreoviridin (3) which had been already synthesized from D-glucose.[4]

The known synthetic intermediate (4)[4] of citreoviridin was treated with Ac_2O - pyridine (room temp., overnight) and then with m-chloroperbenzoic acid in CH_2Cl_2 (room temp., 17 h) to give two epoxides (5)[5] and (6)[6] in 72 and ca. 21% yields, respectively. On treatment of 5 with catalytic amount of p-TsOH in benzene (refluxing temp., 3 h), its stereospecific

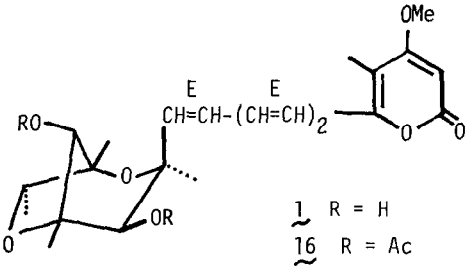
cyclization took place giving rise to a 2,6-dioxabicyclo[3.2.1]octane (7)[5] in 36% yield, in addition to an $\alpha\beta,\gamma\delta$-unsaturated ester (8)[5] in 31% yield. The epoxide (6) was rather unstable and directly subjected to stereospecific cyclization under the same conditions as shown above, affording another 2,6-dioxabicyclo[3.2.1]octane (9)[5] in 28% yield. In both cases, any other cyclization product has not been detected. The stereostructures and conformations of these two compounds (7 and 9) were elucidated on the basis of some chemical evidence together with molecular mechanics calculations (see Fig. 1).[7]

As expected from molecular mechanics calculation of [A], the compound (7) was successfully converted into a carbonate (10)[5] in 6 steps [1. $CH_2(OMe)_2/P_2O_5$ (room temp., 40 min); 2. K_2CO_3 in EtOH (room temp., overnight); 3. DMSO/DCC/pyridine/TFA in benzene (room temp., 3 h); 4. $NaBH_4$ in EtOH (0 °C, 20 min); 5. HCl in MeOH (40 °C, 3 h); 6. $(Imd)_2CO$ in DMF - benzene (60 °C, 6 h); ca. 30% overall yield]. Accordingly, the stereostructure of the remaining bicyclic compound must be depicted as 9, which adopts the most stable conformation of a boat form as judged from molecular mechanics calculation of [B]. Clearly, the secondary OH group in 9 is in an axial configuration, because 9 was completely recovered on oxidation (DMSO/DCC/pyridine/TFA in benzene) followed by $NaBH_4$ reduction in EtOH. Furthermore, the deacetyl compound (11)[5] of 9 was oxidized with DMSO - DCC in benzene containing trace amounts of pyridine and TFA (room temp., 2 h) to give a ketone (12),[5] in 60% yield, which was reduced with $NaBH_4$ in EtOH (0 °C, 30 min) to afford a tricyclic compound (13)[5] in high yield. Finally, citreoviridinol diacetate (14)[2] was subjected to ozonization [1. O_3 in MeOH (-67 °C, 13 min); 2. excess Me_2S (-67 °C - room temp., 3 h)] followed by Wittig reaction [Ph_3P=CHCOOEt in benzene (refluxing temp., overnight)] to give an $\alpha\beta$-unsaturated ester (15)[5] in 53% yield. The physical data of this ester including optical rotation ($[\alpha]_D^{23}$ +91.0°(c 0.45, $CHCl_3$)) was completely identical with those of the compound ($[\alpha]_D^{22}$ +93.7°(c 0.15, $CHCl_3$)) derived from 7 in 3 steps [1. PCC - Celite in CH_2Cl_2 (room temp., overnight); 2. excess $NaBH_4$ in EtOH (0 °C, 18 min); 3. Ac_2O in pyridine (room temp., overnight); 93% overall yield].

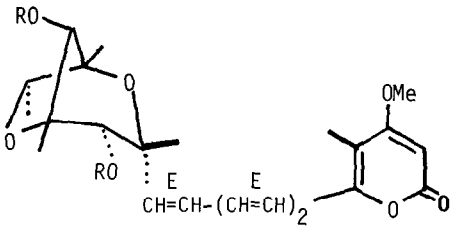
According to the same procedure as described above, isocitreoviridinol diacetate (16)[5] was also converted into another $\alpha\beta$-unsaturated ester (17),[5] in 56% yield, which was not identical with the diacetate (18)[5] of 9 although their spectral data were quite similar to each other. Thus, the ester (17) was treated with K_2CO_3 in EtOH (room temp., overnight) and then oxidized as usual to give the same ketone (12) as derived from 11, in 29% yield. Finally, citreoviridin monoacetate (19) was directly treated with m-chloroperbenzoic acid in CH_2Cl_2 (room temp., overnight) to give a complex mixture, from which isocitreoviridinol diacetate (16) was obtained in low yield after acetylation with Ac_2O - pyridine (room temp., overnight).

In the light of molecular mechanics calculations of [C] and [D], the stereostructures of isocitreoviridinol and citreoviridinol including the most favorable conformations are depicted as 1 and 2, respectively. From a biogenetic point of view, furthermore, it is quite interesting that both citreoviridinol and isocitreoviridinol are stereochemically different from aurovertin B[8] at the 2,6-dioxabicyclo[3.2.1]octane system.

Calculations were performed at Nagoya University Computation Center. This research has been supported in part by grants from the Ministry of Education, Science and Culture.



1 R = H
16 R = Ac



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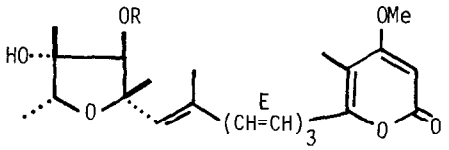
14 R = Ac



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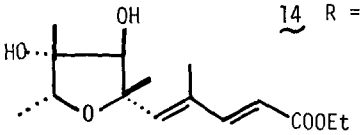
19 R = Ac



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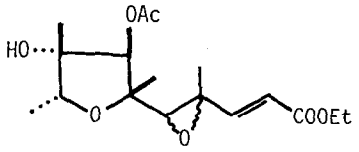
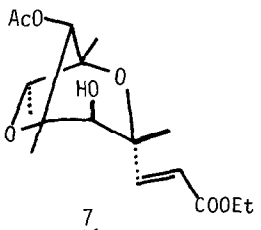


5 (β-epoxide)
6 (α-epoxide)



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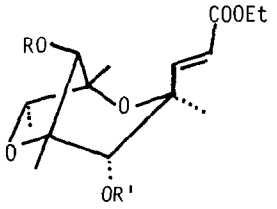
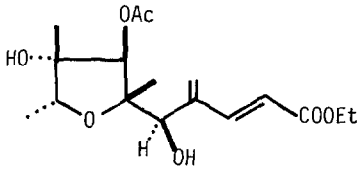


9 R = Ac, R'= H
11 R = R'= H
18 R = R'= Ac



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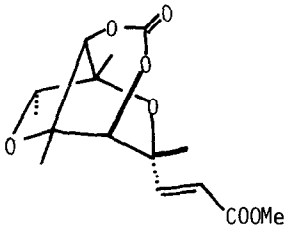

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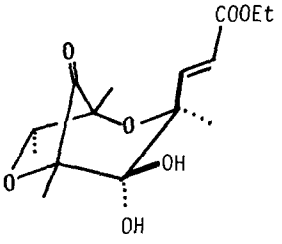

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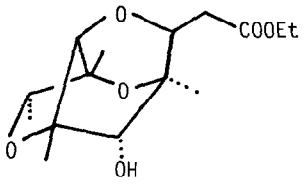

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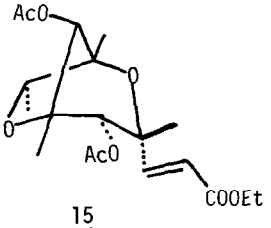

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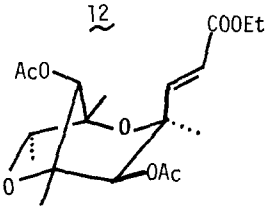

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REFERENCES AND NOTES

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3. Based on the weight of the AcOEt extract.
4. S. Nishiyama, Y. Shizuri, and S. Yamamura, Tetrahedron Lett., 26, 231 (1985).

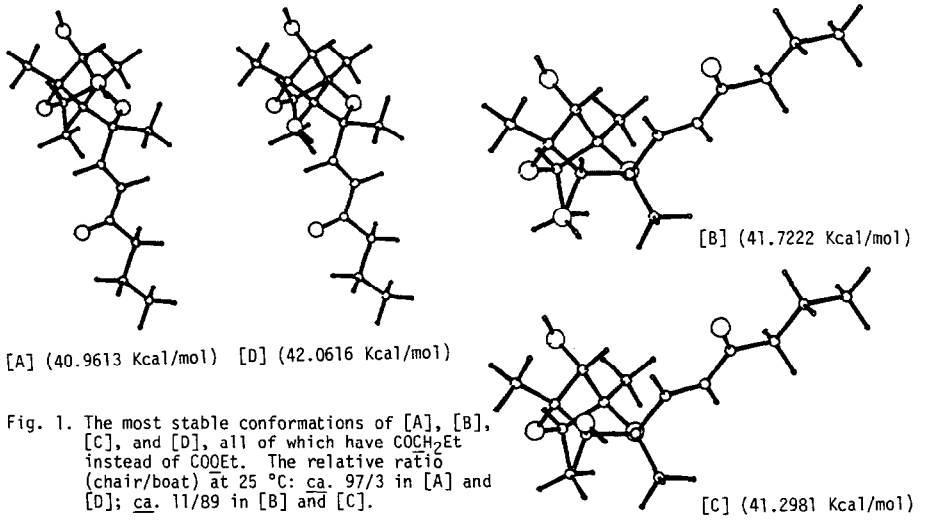

Fig. 1. The most stable conformations of [A], [B], [C], and [D], all of which have $COCH_2Et$ instead of COOEt. The relative ratio (chair/boat) at 25 °C: ca. 97/3 in [A] and [D]; ca. 11/89 in [B] and [C].

5. The spectral data for the new compounds were in accord with the structures assigned. 5: $C_{17}H_{26}O_7$ [m/z 343.1748(M^+ + 1)]; IR (film) 3450, 1740sh., 1720, 1650 cm^{-1}; δ($CDCl_3$) 1.74 (3H, s), 2.15(3H, s), 3.00(1H, s), 5.13(1H, s). 7: mp 113 - 114 °C; $[\alpha]_D^{22}$ +50.3° (c 0.5, $CHCl_3$); $C_{17}H_{26}O_7$ [m/z 342.1680(M^+)]; IR (film) 3450, 1740, 1720, 1650 cm^{-1}; δ($CDCl_3$) 1.16 (3H, s), 1.18(3H, d, J= 6Hz), 1.30(3H, t, J= 6Hz), 1.32(3H, s), 1.42(3H, s), 2.15(3H, s), 2.40(1H, br.d, J= 6Hz), 3.90(1H, br.d, J= 6Hz), 3.97(1H, q, J= 6Hz), 4.18(2H, q, J= 6Hz), 5.43(1H, s), 5.85(1H, d, J= 15Hz), 7.19(1H, d, J= 15Hz). 8: $C_{17}H_{26}O_7$ [m/e 342.1682(M^+)]; IR (film) 3400, 1735, 1710, 1630 cm^{-1}; δ($CDCl_3$) 5.58(1H, br.s), 5.68(1H, br.s), 6.15(1H, d, J= 15Hz), 7.43(1H, d, J= 15Hz). 9: mp 119 - 120 °C; $[\alpha]_D^{22}$ -12.0° (c 0.23, $CHCl_3$); $C_{17}H_{26}O_7$ [m/z 342.1689(M^+)]; IR (film) 3500, 1750, 1720, 1650 cm^{-1}; δ($CDCl_3$) 1.18(3H, d, J= 6Hz), 1.25(3H, s), 1.27(3H, s), 1.32(3H, t, J= 6Hz), 1.33(3H, s), 2.12(3H, s), 3.17(1H, d, J= 8Hz), 3.67(1H, d, J= 8Hz), 4.03(1H, q, J= 6Hz), 4.20(2H, q, J= 6Hz), 5.35(1H, s), 6.05(1H, d, J= 15Hz), 7.05(1H, d, J= 15Hz). 10: $C_{15}H_{20}O_7$ [m/z 312.1215(M^+)]; IR (film) 1750, 1720, 1640 cm^{-1}; δ($CDCl_3$) 1.25(3H, d, J= 6Hz), 1.27(3H, s), 1.45(3H, s), 1.62(3H, s), 3.77(3H, s), 3.90(1H, q, J= 6Hz), 4.23(2H, s), 5.75(1H, d, J= 15Hz), 7.23(1H, d, J= 15Hz). 11: mp 149 - 150 °C; $C_{15}H_{24}O_6$ [m/z 300.1564(M^+)]; IR (film) 3450, 1710, 1635 cm^{-1}; δ($CDCl_3$) 3.15(1H, br.d, J= 10.5Hz), 3.61(1H, br.d, J= 10.5Hz), 4.03(1H, br.s). 12: $C_{15}H_{22}O_7$ [m/z 314.1354(M^+); IR (film) 3400, 1780sh., 1720, 1695, 1650 cm^{-1}; δ($CDCl_3$) 1.2 - 1.4(12H, complex), 1.65(3H, s), 3.10(1H, br.s), 3.32(1H, br.s), 4.17(2H, q, J= 6Hz), 4.32(1H, q, J= 6Hz), 6.05(1H, d, J= 15Hz), 7.13(1H, d, J= 15Hz). 13: $C_{15}H_{24}O_6$ [m/z 300. 1579(M^+)]; δ($CDCl_3$) 1.2 - 1.4(15H, complex), 2.54(1H, dd, J= 3, 17Hz), 2.95(1H, dd, J= 10, 17Hz), 3.57(1H, br.s), 3.82(1H, q, J= 7Hz), 4.16(2H, q, J= 7Hz), 4.53(1H, br.dd, J= 3, 10Hz). 15: $[\alpha]_D^{23}$ +91.0° (c 0.45, $CHCl_3$); $C_{19}H_{28}O_8$ [m/z 384.1781(M^+)]; IR (film) 1750, 1720, 1650 cm^{-1}; δ($CDCl_3$) 1.15(3H, s), 1.17(3H, s), 1.27(3H, d, J= 6Hz), 1.27(3H, t, J= 6Hz), 1.57 (3H, s), 2.08(3H, s), 2.17(3H, s), 4.10(1H, q, J= 6Hz), 4.18(2H, q, J= 6Hz), 4.98(1H, s), 5.07(1H, s), 5.90(1H, d, J= 15Hz), 7.35(1H, d, J= 15Hz). 16: $C_{27}H_{34}O_9$ [m/z 502.2197(M^+)]; IR (film) 1740, 1710, 1620, 1600sh., 1580, 1540 cm^{-1}; δ($CDCl_3$) 2.06(3H, s), 2.14(3H, s), 4.98(1H, s), 5.38(1H, s). 17: $[\alpha]_D^{22}$ -37.4° (c 0.67, $CHCl_3$); $C_{19}H_{28}O_8$ [m/z 384.1765(M^+)]; IR (film) 1750, 1720, 1655 cm^{-1}; δ($CDCl_3$) 1.12(3H, s), 1.23(3H, s), 1.27(3H, d, J= 6Hz), 1.32(3H, t, J= 6Hz), 1.53(3H, s), 2.07(3H, s), 2.13(3H, s), 4.02(1H, q, J= 6Hz), 4.18(2H, q, J= 6Hz), 5.05(1H, s), 5.30(1H, s), 6.07(1H, d, J= 15Hz), 6.81(1H, d, J= 15Hz). 18: $[\alpha]_D^{22}$ -29.9° (c 0.4, $CHCl_3$); $C_{19}H_{28}O_8$ [m/z 384.1784(M^+)]; IR (film) 1750, 1720, 1655 cm^{-1}; δ($CDCl_3$) 1.17(3H, s), 1.27(3H, s), 1.28(3H, d, J= 6Hz), 1.32(3H, t, J= 6Hz), 1.33(3H, s), 2.13(3H, s), 2.20(3H, s), 4.07(1H, q, J= 6Hz), 4.20(2H, q, J= 6Hz), 5.05(2H, s), 6.10(1H, d, J= 15Hz), 7.08(1H, d, J= 15Hz).
6. This epoxide was not obtained in completely pure state and directly used for the next experiment.
7. Program MM2: N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977); QCPE #395.
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