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SYNTHETIC STUDY ON VERRUCOSIDIN AND ITS ABSOLUTE CONFIGURATION

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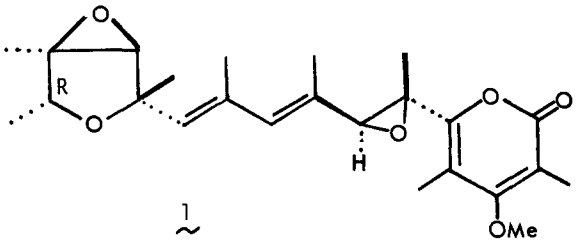
Summary: The optically active $\alpha\beta,\gamma\delta$-unsaturated aldehyde, a degradation product of verrucosidin, has been synthesized starting from D-glucose, in connection with which the absolute configuration of verrucosidin has been elucidated. This aldehyde is regarded as a promising synthetic intermediate of verrucosidin.

In connection with citreoviridin and citreoviridinol,[1] we are interested in verrucosidin (1),[2] a potent neurotoxin, which causes substained tremoring in experimental animals. In the present paper, we wish to describe the synthesis of the $\alpha\beta,\gamma\delta$-unsaturated aldehyde (2) derived from verrucosidin, which is regarded as a promising synthetic intermediate of 1, starting from D-glucose. In connection with D-glucose, furthermore, we could determine the absolute configuration of verrucosidin (1), which remained unsettled.



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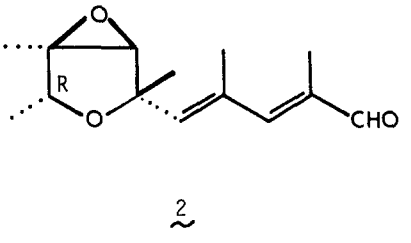

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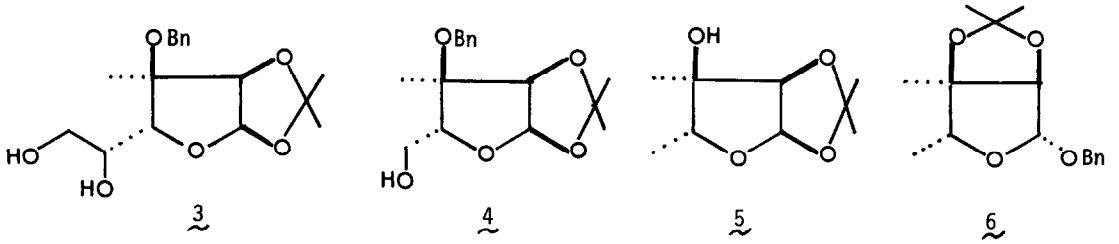
The known diol (3),[3] which was derived from D-glucose, was treated with $NaIO_4$ (1.1 equiv.) in MeOH - H_2O (1 : 1) (room temp., 1.2 h) and then directly reduced with $NaBH_4$ (1.2 equiv.) to afford a hydroxy compound (4)[4] in quantitative yield. This compound (4) was further converted into a ketal (5),[4] in 3 steps [1) CCl_4 (4.5 equiv.) - Ph_3P (3 equiv.)/pyridine under argon (70 °C, 1.2 h); 2) $Bu^n{}_3SnH$ (4 equiv.) - AIBN (cat.)/toluene under argon (80 °C, 7 h); 3) H_2 - Pd black/MeOH (room temp., 3 days) (97% overall yield)]. The ketal (5) so far obtained was subjected to transketalization [p-TsOH (0.1 equiv.)/acetone - benzyl alcohol (4 : 1) (refluxing temp., 2.5 days)] giving rise to a desired ketal (6),[4] in 95% yield, which was readily converted into the corresponding lactone (7)[4] in 2 steps [1) H_2 - Pd black/MeOH (room temp., 20 h); 2) PCC (3 equiv.) - Celite/CH_2Cl_2 (room temp., 1 day) (96% overall yield)]. Further-

more, the compound (7) was subjected to methylation [MeLi (2 equiv.)/THF under argon (-78 °C, 8 h)] followed by Wittig reaction [Ph_3P=CHCOOEt (2 equiv.)/CH_3CN in a sealed tube, under argon (160 °C, 2 days)][5] to afford a mixture of two products (8a and 8b), in 76% overall yield (relative ratio: 8a/8b = 9/5).[6]

In the next step, the compound (8a) was treated with PhMgBr (6 equiv.) in THF under argon (0 °C - room temp., 5 h) and then dehydrated with CsOH (0.8 equiv.) in benzene containing Drierite under argon (refluxing temp., 6 h) to afford an olefin (9),[4] in 95% overall yield, from which an α,β-unsaturated ester (10)[4,7] was stereoselectively produced in 3 steps [1) O_3/CH_2Cl_2 (-78 °C, 15 min) and 2) excess Me_2S/CH_2Cl_2 (room temp., 1 h); 3) Ph_3P=C(Me)COOMe (2 equiv.)/benzene under argon (refluxing temp., 15 h) (90% overall yield)]. This ester (10) was further stereoselectively converted into an α,β,γ,δ-unsaturated ester (11)[4] in 4 steps [1) DIBAL-H (2.4 equiv.)/THF under argon (-78 °C - room temp., 2.5 h); 2) PCC (2 equiv.) - Celite/CH_2Cl_2



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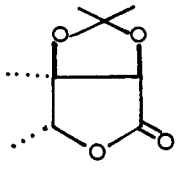

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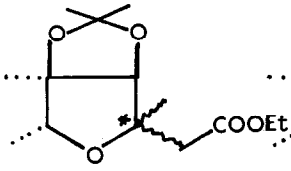
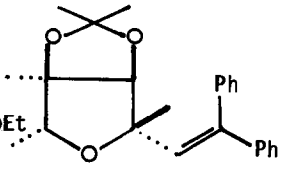


8a (β-Me)

8b (α-Me)



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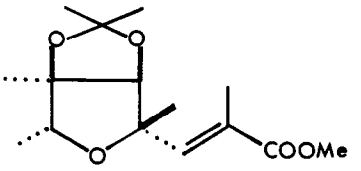

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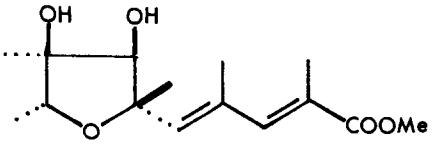

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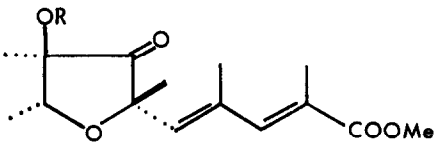
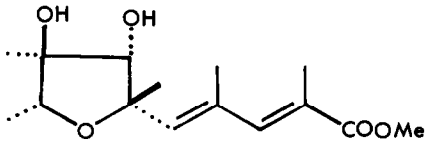


12 R = H

13 R = CH_2SMe



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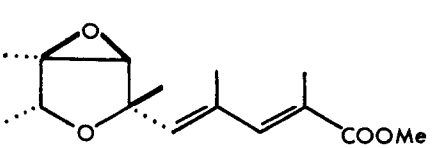

15

under argon (room temp., 1 h); 3) Ph_3P=C(Me)COOMe (2 equiv.)/benzene under argon (refluxing temp., 7 h); 4) 80% aqueous AcOH (refluxing temp., 1 h) (75% overall yield)].

The ester so far obtained was oxidized with Me_2SO (40 equiv.) and DCC (10 equiv.) in benzene containing a few drops of pyridine and CF_3COOH (room temp., 1 day) to afford a mixture of two ketones (12 and 13)[4] in 56 and 44% yields, respectively. However, the latter was readily converted into 12 in 92% yield on treatment with $HgCl_2$ (1.6 equiv.) in MeCN - H_2O (4 : 1) (70 °C, 5 h). Thus, the total yield of 12 from 11 was 96%. The ketone (12) was reduced with $NaBH_4$ (4 equiv.) in THF under argon (-78 - -20 °C, 20 h) to give a trans diol (14)[4] in 83% yield,[8] which was further converted into a desired epoxide (15)[4] in 2 steps [1) MsCl (6 equiv.) - pyridine (12 equiv.) - DMAP (cat.)/CH_2Cl_2 under argon (room temp., 2 days (85% yield); 2) NaOMe (1.5 equiv.)/MeOH under argon (room temp., 2 h) (95% yield)]. Finally, this compound (15) was successfully converted into the corresponding aldehyde (2) in 2 steps [1) DIBAL-H (2.4 equiv.)/THF under argon (-78 - -50 °C, 4 h) (86% yield); 2) PCC (2 equiv.) - Celite/CH_2Cl_2 under argon (room temp., 20 min) (64% yield)]. The synthetic sample as an oil [$C_{14}H_{20}O_3$ (m/z 236.1392(M^+))] was identical with the degradation product (2)[2] of verrucosidin in all respects (IR, ^1H NMR, and mass spectra). Particularly, the optical rotation of the synthetic sample ($[\alpha]_D^{28}$ -27.9° (c 0.46, MeOH)) is in a good agreement with that of the aldehyde (2) derived from verrucosidin ($[\alpha]_D^{27}$ -23.5° (c 0.4, MeOH)), indicating that the absolute configuration of verrucosidin (1) is quite similar to that of citreoviridin which has been already synthesized from D-glucose.[1]

Further synthetic study on verrucosidin (1) is in progress starting from the promising synthetic intermediate (2) which has been obtained in ca. 12% overall yield based on the known compound (3).

REFERENCES AND NOTES

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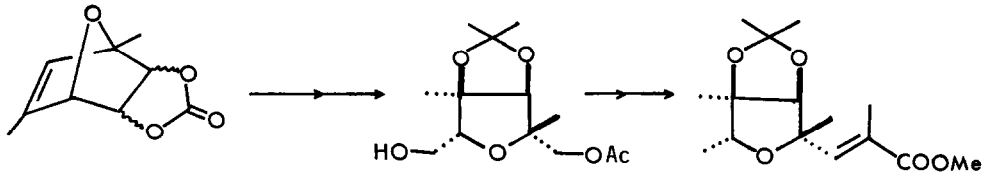
2. L. Burka, M. Ganguli, and B. J. Wilson, J. Chem. Soc., Chem. Commun., 1983, 544; M. Ganguli, L. T. Burka, and T. M. Harris, J. Org. Chem., 49, 3762 (1984).
3. J. S. Brimacombe, A. J. Rollins, and S. W. Thompson, Carbohyd. Res., 31, 108 (1973); M. Funabashi, S. Yamazaki, and J. Yoshimura, Tetrahedron Lett., 1974, 4331.
4. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: 4: mp 64 - 64.5 °C; $C_{15}H_{19}O_5$ [m/z 279.1230(M^+ - Me)]; δ ($CDCl_3$) 3.74(1H, d, J= 6Hz) and 3.74(1H, d, J= 5Hz). 5 as a crystalline solid: $C_8H_{13}O_4$ [m/z 173.0821(M^+ - Me)]; IR (film) 3500 cm^{-1}; δ($CDCl_3$) 1.17(3H, d, J= 7Hz). 6 as an oil: $C_{15}H_{19}O_4$ [m/z 263.1285(M^+ - Me)]; δ($CDCl_3$) 4.29(1H, s), 4.30(1H, q, J= 7Hz), 4.43 (1H, d, J= 12Hz), 4.73(1H, d, J= 12Hz), 5.03(1H, s), and 7.27(5H, br.s). 7 as a crystalline solid: $C_8H_{11}O_4$ [m/z 171.0668(M^+ - Me)]; IR (film) 1780 cm^{-1}; δ ($CDCl_3$) 1.30 (3H, d, J= 7Hz), 1.40(3H, s), 1.43(3H, s), 1.47(3H, s), 4.39(1H, s), and 4.64(1H, q, J= 7Hz). 9 as an oil: $C_{24}H_{28}O_3$ [m/z 364.2030(M^+)]; δ ($CDCl_3$) 6.23(1H, s). 10 as an oil:

$C_{14}H_{21}O_5$ [m/z 269.1374(M^+ - Me)]; IR (film) 1715 and 1650 cm^{-1}; $\delta(CDCl_3)$ 2.00(3H, br.s), 3.77(3H, s), and 6.94(1H, br.s). 11 as an oil: $C_{15}H_{25}O_5$ [m/z 285.1710(M^+ + 1)]; IR (film) 3450, 1700, and 1620 cm^{-1}; $\delta(CDCl_3)$ 1.94(3H, br.s), 1.98(3H, br.s), 3.73(3H, s), 5.76(1H, br.s), and 7.07(1H, br.s). 12 as an oil: $C_{15}H_{22}O_5$ [m/z 282.1425(M^+)]; IR (film) 3450, 1760, and 1715 cm^{-1}. 14 as an oil: $C_{15}H_{25}O_5$ [m/z 285.1706(M^+ + 1)]; $\delta(CDCl_3)$ 3.90 (1H, br.s). 15 as an oil: $C_{15}H_{22}O_4$ [m/z 266.1514(M^+)]; IR (film) 1710 and 1620 cm^{-1}; δ ($CDCl_3$) 1.17(3H, d, J= 7Hz), 1.40(3H, s), 1.46(3H, s), 2.00(3H, br.s), 2.02(3H, br.s), 3.40(1H, s), 3.74(3H, s), 4.12(1H, q, J= 7Hz), 5.64(1H, br.s), and 7.07(1H, br.s).

5. T. F. Tam and B. Fraser-Reid, J. Org. Chem., 45, 1344 (1980).
6. The mixture was treated with 80% aqueous AcOH (refluxing temp., 2.5 h). After separation of the resulting two alcohols, the main one was subjected to ketalization [2,2-dimethoxypropane (2 equiv.) - p-TsOH (0.2 equiv.) - Drierite/acetone (room temp., 6 h)] to yield a pure sample of 8a.
7. This compound (10) in racemic form was also synthesized from the known carbonate (I)*, as follows. The compound (I) was readily converted into a ketal (II) [$C_{13}H_{22}O_6$ (m/z 274.1405 (M^+)); IR (film) 3500 and 1740 cm^{-1}; $\delta(CDCl_3)$ 1.34(3H, s), 1.40(3H, s), 1.44(3H, s), 1.56 (3H, s), 2.13(3H, s), 3.55 - 3.65(2H complex), 3.9 - 4.2(2H, complex), and 4.05(2H, s)] in 9 steps: 1) OsO_4 (1.1 equiv.) - pyridine (2 equiv.)/dioxane (room temp., 1 h) and 2) aqueous $NaHSO_3$ (92% overall yield); 3) 2,2-dimethoxypropane (2 equiv.) - p-TsOH/acetone (room temp., 18 h) (100% yield); 4) 1M NaOH/MeOH - dioxane (1 : 1) (room temp., 1.5 h) (93% yield); 5) $NaIO_4$ (1.1 equiv.)/MeOH - H_2O (1 : 1) (room temp., 30 min) and 6) $NaBH_4$ (2.4 equiv.) (100% overall yield); 7) Bu^tPh_2SiCl (1.2 equiv.) - imidazole/benzene under argon (room temp., 6 h) (83% yield); 8) Ac_2O/pyridine (room temp., 7 h) (100%); 9) Bu^n_4NF (1.2 equiv.)/THF (room temp., 2 h) (94% yield). The compound (II) was further converted into (±)-10 in 6 steps: 1) MsCl (3 equiv.) - pyridine (3 equiv.) - DMAP (2 equiv.)/ CH_2Cl_2 under argon (room temp., 13 h) (100%); 2) NaI (10 equiv.)/DMF under argon (100 °C, 2 days) (92% yield); 3) H_2 - Raney Ni/EtOH (room temp., 10 h) (100% yield); 4) K_2CO_3/MeOH (room temp., 13 h) (90% yield); 5) DMSO (20 equiv.) - DCC (10 equiv.) - pyridine (cat.) - TFA (cat.) (room temp., 2 h) and 6) $Ph_3P{=}C(Me)COOMe$ (1.5 equiv.)/benzene under argon (refluxing temp., 14 h) (85% overall yield). Thus, the total yield of (±)-10 from I was 47%. * See Y. Shizuri, S. Nishiyama, H. Shigemori, and S. Yamamura, J. Chem. Soc., Chem. Commun., 1985, 292.



I II (±)-10

8. The cis diol (11) was also recovered in 16% yield, and so the desired trans isomer was obtained from 11 in almost quantitative yield.

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