SYNTHETIC STUDY ON VERRUCOSIDIN AND ITS ABSOLUTE CONFIGURATION

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Summary: The optically active $\mu\beta$, $\gamma\delta$ -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 vertucosidin (1),² a potent neurotoxin, which causes substained tremoring in experimental animals. In the present paper, we wish to describe the synthesis of the $_{\beta}$, γ_{δ} -unsaturated aldehyde (2) derived from vertucosidin, 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 vertucosidin (1), which remained unsettled.



The known diol (3),³ which was derived from D-glucose, was treated with NaIO₄ (1.1 equiv.) in MeOH - H₂O (1 : 1) (room temp., 1.2 h) and then directly reduced with NaBH₄ (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) CCl₄ (4.5 equiv.) - Ph₃P (3 equiv.)/pyridine under argon (70 °C, 1.2 h); 2) Buⁿ₃SnH (4 equiv.) - AIBN (cat.)/toluene under argon (80 °C, 7 h); 3) H₂ - 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) H₂ - Pd black/MeOH (room temp., 20 h); 2) PCC (3 equiv.) - Celite/CH₂Cl₂ (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 [Ph₃P=CHCOOEt (2 equiv.)/CH₃CN 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 **4.8**-unsaturated ester (10)^{4,7} was stereoselectively produced in 3 steps [1) 0₃/ CH₂Cl₂ (-78 °C, 15 min) and 2) excess Me₂S/CH₂Cl₂ (room temp., 1 h); 3) Ph₃P=C(Me)COOMe (2 equiv.)/benzene under argon (refluxing temp., 15 h) (90% overall yield)]. This ester (10) was further stereoselectively converted into an **48,76**-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/CH₂Cl₂



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 $\mathrm{Me_2SO}$ (40 equiv.) and DCC (10 equiv.) in benzene containing a few drops of pyridine and CF₃COOH (room temp., 1 day) to afford a mixture of two ketones $(12 \text{ and } 13)^4$ 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_20 (4 : 1) (70 °C, 5 h). Thus, the total yield of 12 from 11 was 96%. The ketone (12) was reduced with NaBH₄ (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.)/CH₂Cl₂ 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/CH₂Cl₂ under argon (room temp., 20 min) (64% yield)]. The synthetic sample as an oil $[C_{14}H_{20}O_3^2 (m/z \ 236.1392(M^+))]$ 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 $([\mathcal{A}]_D^{28} - 27.9^\circ (c \ 0.46, MeOH))$ is in a good agreement with that of the aldehyde (2) derived from verrucosidin ([\measuredangle]_D²⁷ -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.

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

REFERENCES AND NOTES

- S. Nishiyama, Y. Shizuri, and S. Yamamura, Tetrahedron Lett., <u>26</u>, 231 (1985); S. Nishiyama,
 Y. Shizuri, D. Imai, S. Yamamura, Y. Terada, M. Niwa, K. Kawai, and H. Furukawa, <u>ibid</u>.,
 26, 3243 (1985).
- L. Burka, M. Ganguli, and B. J. Wilson, J. Chem. Soc., Chem. Commun., <u>1983</u>, 544; M. Ganguli, L. T. Burka, and T. M. Harris, J. Org. Chem., <u>49</u>, 3762 (1984).
- J. S. Brimacombe, A. J. Rollins, and S. W. Thompson, Carbohyd. Res., <u>31</u>, 108 (1973); M. Funabashi, S. Yamazaki, and J. Yoshimura, Tetrahedron Lett., <u>1974</u>, 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)]; **s** (CDC1₃) 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; **s** (CDC1₃) 1.17(3H, d, J= 7Hz). 6 as an oil: $C_{15}H_{19}O_4$ [m/z 263.1285(M⁺ Me)]; **s** (CDC1₃) 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; **s** (CDC1₃) 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⁺)]; **s** (CDC1₃) 6.23(1H, s). 10 as an oil:

- 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-dimethoxy-propane (2 equiv.) p-TsOH (0.2 equiv.) Drierite/acetone (room temp., 6 h)] to yield a pure sample of <u>8a</u>.
- 7. This compound (10) in racemic form was also synthesized from the known carbonate $(1)^*$, as follows. The compound (I) was readily converted into a ketal (II) [C13H2206 (m/z 274.1405 (M^+) ; IR (film) 3500 and 1740 cm⁻¹; \S (CDCl₃) 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) OsO₄ (1.1 equiv.) - pyridine (2 equiv.)/dioxane (room temp., 1 h) and 2) aqueous NaHSO₃ (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) $(93\% \text{ yield}); 5) \text{ NaIO}_4$ (1.1 equiv.)/MeOH - H₂O (1 : 1) (room temp., 30 min) and 6) NaBH₄ (2.4 equiv.) (100% overall yield); 7) Bu^tPh₂SiCl (1.2 equiv.) - imidazole/benzene under argon (room temp., 6 h) (83% yield); 8) Ac20/pyridine (room temp., 7 h) (100%); 9) Buⁿ_dNF (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.)/ CH₂Cl₂ under argon (room temp., 13 h) (100%); 2) NaI (10 equiv.)/DMF under argon (100 °C, 2 days) (92% yield); 3) H₂ - 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) $Ph_{2}P=C(Me)COOMe$ (1.5 equiv.)/benzene under argon (refluxing temp., 14 h) (85% overall yield). Thus, the total yield of $(\frac{+}{2})$ -10 from I was 47%. * See Y. Shizuri, S. Nishiyama, H. Shigemori, and S. Yamamura, J. Chem. Soc., Chem. Commun., 1985, 292.



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

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