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STEREOSELECTIVE SYNTHESIS OF 9-HYDROXYELLIPTICINE GLYCOSIDES,
NOVEL AND HIGHLY ACTIVE ANTITUMOR AGENTS

Tadashi Honda,* Minako Inoue, Mika Kato,
Keiyuu Shima, and Tetsuo Shimamoto
Suntory Institute for Biomedical Research,
Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618, Japan

A series of novel and highly active antitumor agents, 9-hydroxy-ellipticine glycosides were stereoselectively synthesized in good yields by an improved condensation reaction between 9-acetoxy-ellipticine and peracylated glycosyl halides using cadmium carbonate, followed by the removal of acyl groups with methanolic ammonia.

KEYWORDS—9-hydroxyellipticine glycoside; antitumor activity; stereoselective synthesis; condensation reaction; N-glycosidation; cadmium carbonate

Ellipticine (1) and 9-methoxyellipticine (2) are alkaloids originally isolated from *Ochrosia elliptica*¹⁾ with antitumor activity against several animal and human tumors.²⁾ However, their poor solubility in water has led to considerable difficulty in developing formulations for clinical use. Various efforts have been made toward development of active and hydrophilic derivatives, but none were significantly better than their parent compounds.³⁾ Recently, 9-hydroxy-2-methylellipticinium acetate (3), a water-soluble derivative, was prepared and was found to be effective in the treatment of human breast cancer.⁴⁾

We intended to synthesize water-soluble ellipticine derivatives with a more selective toxicity towards tumor cells by N-glycosidation of the 2-position. Consequently, 9-hydroxyellipticine glycosides (III) were found to be water-soluble with much higher activity than the parent compounds in various murine tumor systems. Herein, an efficient and stereoselective synthesis of 9-hydroxyellipticine glycosides (III) is described.

9-Acetoxyellipticine glycosides (II) can be synthesized according to the method used for the condensation of peracylated glycosyl halides (I) with nicotinamide.⁵⁾ However, this method is not satisfactory, due to low yield

and poor stereoselectivity. As a model system for improved synthesis, the condensation reaction of 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide (**4**) and nicotinamide was investigated.

When the mixture of nicotinamide (1 mmol) and glucosyl bromide (**4**) (1 mmol) were heated under reflux in dry nitromethane (10 ml) for 10 min, nicotinamide glucoside (**5**, α -isomer: β -isomer=12:88) was obtained in low yield (35%). The low yield of the desired glucoside (**5**) seemed to be due to the side reactions which formed products such as nicotinamide hydrobromide (**6**) (acid scavenging reaction), 2,3,4,6-tetra-O-acetyl- α -D-glucose (**7**) (hydrolysis),⁶⁾ and 2,3,4,6-tetra-O-acetyl-2-hydroxy-D-glucal (**8**) (elimination) (Chart 1).

We therefore postulated that the use of an acid scavenger with excess (1.5–2.0 eq) glucosyl bromide (**4**) should increase the yield of glucoside (**5**). Screening of various acid scavengers revealed that the use of CdCO_3 (1.5 eq) provide predominantly the desired β -glucoside (α -isomer: β -isomer=3:97) in excellent yield (99%).

Stereoselective condensation of 9-acetoxyllipticine (**9**)^{3a)} (1 mmol) with 2,3,4-tri-O-acetyl- β -L-arabinopyranosyl bromide (**13**)⁷⁾ (2 mmol) using CdCO_3 (1.5 mmol) in refluxing (10 min) dry nitromethane (30 ml) afforded 9-acetoxy-2-(2,3,4-tri-O-acetyl-L-arabinopyranosyl)ellipticinium bromide (**19**, 1',2'-trans-isomer:1',2'-cis-isomer=97:3) in 97% yield. Other peracetylated glycosyl halides also gave good results. Deprotection was achieved with methanolic ammonia to give the desired 9-hydroxyellipticine glycosides (**III**)⁸⁾ (Chart 2 and Table).

Most of the glycosides (**III**) showed remarkably higher antitumor activity in

Table. Synthesis and Antitumor Activity of 9-Hydroxyellipticine Glycosides

I a)	II	Yield ^{b, c)} (%)	III	Yield ^{b)} (%)	1',2'- <i>trans</i> : ^{d)} 1',2'- <i>cis</i>	Effect on L1210 ^{e)}	
						Optimal dose(mg/kg)	80 days' survival
	16	96	23	77	95 : 5	30	1 / 6 ^{f)}
	17	77	24	80	100 : 0	10	0 / 6
	18	74	25	94	100 : 0	30	4 / 6
	19	97	26	87	97 : 3	30	5 / 6
	20	95	27	84	97 : 3	30	3 / 6
	21	58	28	75	96 : 4	10	0 / 6
	22	91	29	79	98 : 2	20	4 / 6

a) For preparation, see footnote 7.

b) Isolated yield.

c) Isomer ratios of II were almost equal to those of III.

d) Determined by HPLC analysis.

e) Antitumor activity was assayed according to the established protocols of the National Cancer Institute.

f) Survival mice/test mice.

Cf. Activity of 3: 80 days' survival mice were not observed (0/6) at optimal dose (5 mg/kg).

various murine tumor systems (L1210, P388, B16, Colon 38 etc.). Their effects on L1210 are summarized in the Table. L-Arabinopyranoside (26) is the most promising of these antitumor agents.⁹⁾

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- 6) Due to the trace amount of H₂O (0.01-0.02% by Karl Fischer's titration) in nitromethane.
- 7) Glycosyl halides (I) can be prepared from the corresponding parent sugars by acylation, followed by treatment with HBr or HCl, e.g. 15: R. G. Hansen, W. J. Rutter, and P. Krichevsky, *Biochem. Prepar.*, **4**, 1 (1955).
- 8) All the glycosides were well characterized by their physicochemical data: e.g. 2- α -L-arabinopyranosyl-9-hydroxy-5,11-dimethyl-6H-pyrido[4,3-b]carbazolium bromide (1',2'-trans-isomer of 26): mp 240-245°C (dec.); $[\alpha]_D^{18}$ -213° (c 0.15, H₂O); IR (KBr) 3250, 1640, 1600, 1480, 1420, 1220, 1200, 1150, 1090, and 1060 cm⁻¹; UV (EtOH) 227 nm (ϵ 14000), 268 nm (ϵ 24000), 281 nm (ϵ 21000), and 325 nm (ϵ 47000); MS (SIMS) m/z 395 [C₂₂H₂₃N₂O₅]⁺; ¹H-NMR (360 MHz, DMSO-d₆) δ : 2.85 (3H, s, 5-CH₃), 5.74 (1H, d, J=8.5 Hz, 1'-H), 7.18 (1H, dd, J=2 Hz and 9 Hz, 8-H), 7.55 (1H, d, J=9 Hz, 7-H), 7.86 (1H, d, J=2 Hz, 10-H), 8.51 (2H, brs, 3-H and 4-H), 9.45 (1H, brs, 9-OH), 10.03 (1H, s, 10-H), and 12.08 (1H, brs, 6-H); Anal. Calcd for C₂₂H₂₃N₂O₅Br·2H₂O: C, 51.67; H, 5.32; N, 5.48. Found: C, 51.71; H, 5.06; N, 5.37.
- 9) Details of antitumor activity will be reported elsewhere.

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