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Syntheses of All Four Possible Diastereomers of Etoposide and Its Aminoglycosidic Analogues via Optical Resolution of (±)-Podophyllotoxin by Glycosidation with D- and L-Sugars

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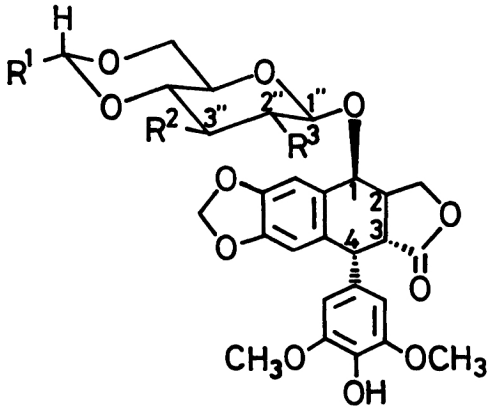
Syntheses of all four possible diastereomers of etoposide and its aminoglycosidic analogues have been achieved via optical resolution of (±)-podophyllotoxin by glycosidation with D- and L-sugars.

VP-16-213 (etoposide, 1) and VM-26 (teniposide, 2)[1] are useful in the treatment of lung cancer, etc.[2] Their clinical efficacy stimulates the synthesis of new active analogues of podophyllotoxin glycoside. In the previous papers,[3,4] we reported the syntheses of new active aminoglycosidic variants of podophyllotoxin. 2-Amino-, 3-amino- and 2-dimethylamino-ß-D-glucosidic variants (3, 4, 5) were found to have the superior activities to 1 in the mouse leukemia L-1210.



1: $R^1=CH_3$ $R^2=R^3=OH$ (VP-16-213)
2: $R^1=$ $R^2=R^3=OH$ (VM-26)
3: $R^1=CH_3$ $R^2=OH$ $R^3=NH_2$
4: $R^1=CH_3$ $R^2=NH_2$ $R^3=OH$
5: $R^1=CH_3$ $R^2=OH$ $R^3=N(CH_3)_2$

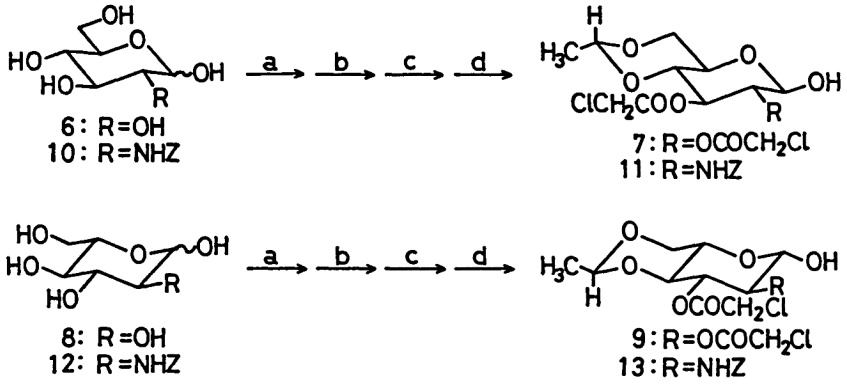
Here we wish to report the syntheses of four possible optical isomers (16 - 24) of etoposide (1) and its aminoglycosidic analogues (3, 5). The syntheses have been achieved via optical resolution of (±)-podophyllotoxin by glycosidation with D- and L-sugars.

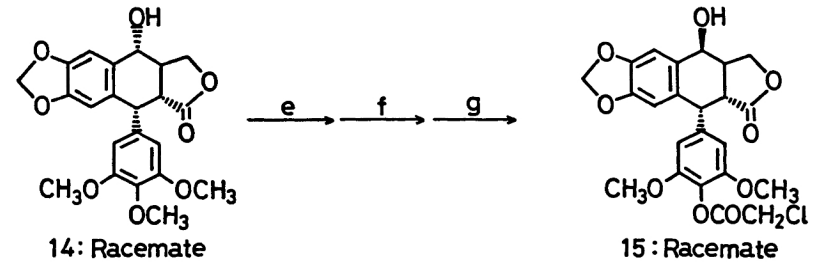
The suitably protected D- and L-sugars as the resolving reagents and the indispensable part for increasing antitumor activity were prepared from the corresponding D (or L)-glucopyranose and D(or L)-2-amino-2-deoxy-glucopyranose. 2,3-Di-O-chloroacetyl-4:6-O-ethylidene-ß-D-glucopyranose (7) and its enantiomer (9) were obtained from D-glucose and L-glucose, respectively, by the methods mentioned in Scheme 1.[5] 2-Benzyloxycarbonylamido-3-O-chloroacetyl-2-deoxy-4:6-O-ethylidene-

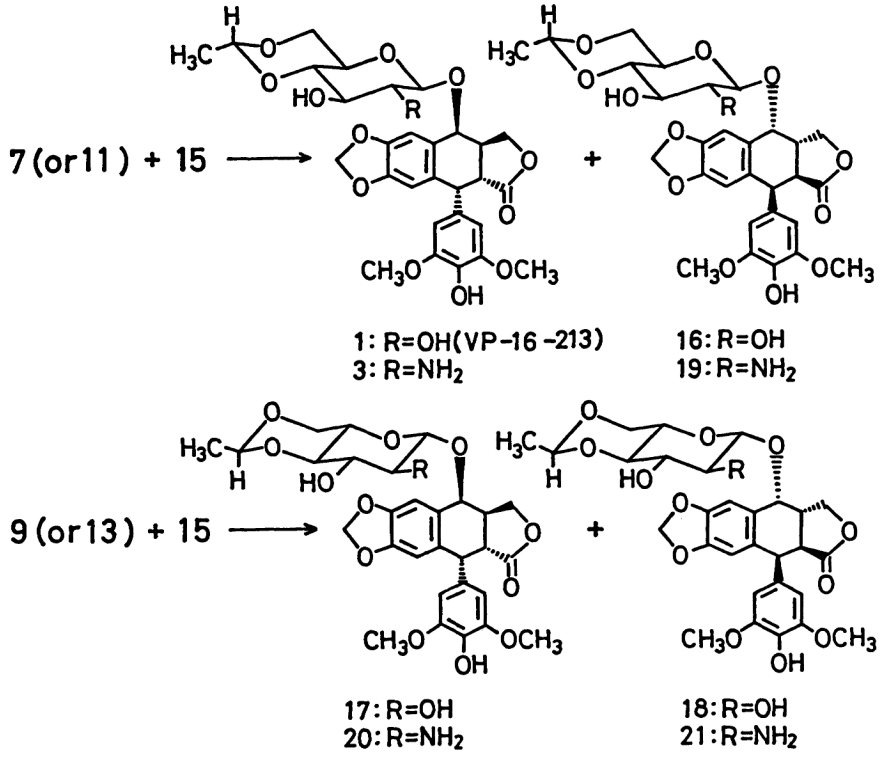
ß-D-glucopyranose (11) and its enantiomer (13) were also prepared from 2-benzyloxycarbonylamido-2-deoxy-D-glucopyranose (10) and its L-isomer (12), respectively (Scheme 1). On the other hand, (±)-4'-O-chloroacetyl-4'-O-demethyl-1-epipodophyllotoxin (15) was prepared from (±)-podophyllotoxin (14) synthesized by the method of Rajapaksa et al.[6] Treatment of 14 with saturated hydrogen bromide in a mixture of ether-ethylene dichloride (1:10) followed by alkaline hydrolysis with barium carbonate in aqueous acetone gave (±)-4'-O-demethyl-1-epipodophyllotoxin (70%), and subsequent chloroacetylation (chloroacetyl chloride, pyridine) afforded 15 in a yield of 90%.

Condensation of 7 with 15 in methylene chloride in the presence of boron trifluoride etherate[3,4,7] afforded the corresponding mixture of 1-O-(2,3-di-O-chloroacetyl-4:6-O-ethylidene-ß-D-glucopyranosyl)-[(-)-4'-O-chloroacetyl-1-epipodophyllotoxin] and its (+)-podophyllotoxin diastereomer. Condensation was carried out stereoselectively through a α,ß-unsaturated carbonium ion at C-1 of the aglycone moiety generated by BF_3.[7] The stereochemistry of the glycoside was also controled by the anomeric configuration of the original pyranose moiety. Removal of protecting groups of diastereomeric mixture by treatment with zinc acetate in refluxing methanol followed by column chromatography of silica gel gave VP-16-213 (etoposide, 1: $[\alpha]_D^{22}$ -107° ($CHCl_3$), mp 259-262 °C (dec.))[8] and its (+)-podophyllotoxin diastereomer (16: $[\alpha]_D^{26}$ +49° ($CHCl_3$), mp 253-256 °C (dec.))[8] in a yield of 32 and 32%, respectively. 1-O-(ß-L-Glucopyranosyl)-[(-)-1-epipodophyllotoxin] (17: $[\alpha]_D^{22}$ -49° ($CHCl_3$), mp 254-258 °C (dec.))[8] and its (+)-podophyllotoxin diastereomer (18, enantiomer of etoposide: $[\alpha]_D^{19}$ +107° ($CHCl_3$), mp 255-258 °C)[8] were also synthesized from 9 and 15 in a ratio of 1 to 1 (total yield of 64%) by the same scheme mentioned above. Condensation of 11 with 15 ($BF_3 \cdot Et_2O$, CH_2Cl_2) gave the corresponding diastereomeric mixture of 1-O-(2-Benzyloxycarbonylamido-3-O-chloroacetyl-2-deoxy-4:6-O-ethylidene-ß-D-glucopyranosyl)-[(-)-4'-O-chloroacetyl-1-epipodophyllotoxin] and its (+)-podophyllotoxin diastereomer. Removal of protecting groups of the diastereomeric mixture [i) $Zn(OAc)_2$, MeOH, reflux; ii) 10% Pd/C, EtOAc-EtOH] afforded 1-O-(2-amino-2-deoxy-ß-D-glucopyranosyl)-[(-)-1-epipodophyllotoxin] (3: $[\alpha]_D^{25}$ -105° ($CHCl_3$), mp 193-195 °C)[3,8] and its (+)-podophyllotoxin diastereomer (19: $[\alpha]_D^{20}$ +48° ($CHCl_3$), mp 183-185 °C)[8] in a yield of 32 and 33%, respectively. 1-O-(2-Amino-2-deoxy-ß-L-glucopyranosyl)-[(-)-1-epipodophyllotoxin] (20: $[\alpha]_D^{22}$ -49° ($CHCl_3$), mp 185-187 °C)[8] and its (+)-podophyllotoxin diastereomer (21, enantiomer of 3: $[\alpha]_D^{20}$ +106° ($CHCl_3$), mp 195-197 °C)[8] were prepared from 13 and 15 in a yield of 34 and 34%, respectively, by the same method mentioned above.

The syntheses of four possible optical isomers of 1-O-(2-deoxy-2-dimethylamino-ß-D(and L)-glucopyranosyl)-[(-) or (+)-1-epipodophyllotoxin] derivatives (5: $[\alpha]_D^{21}$ -107° ($CHCl_3$), mp 196-198 °C;[4] 22: $[\alpha]_D^{26}$ +47° ($CHCl_3$), mp 267-269 °C; 23: $[\alpha]_D^{26}$ -46° ($CHCl_3$), mp 267-269 °C; 24: $[\alpha]_D^{26}$ +107° ($CHCl_3$), mp 195-196 °C) have been achieved by methylation of the corresponding 2-amino-2-deoxy-ß-D(and L)-glucopyranoside and analogues (3, 19, 20, 21) with sodium cyanoborohydride and formaldehyde in methanol, respectively.


6: R=OH
10: R=NHZ
7: R=OCOCH2Cl
11: R=NHZ
8: R=OH
12: R=NHZ
9: R=OCOCH2Cl
13: R=NHZ
a:(CH3CHO)n,cat.conc.H2SO4 b:ZCl,2M aq.NaOH,dioxane
c:ClCH2COCl,pyridine,CH2Cl2 d:H2,10%Pd/C,acetone-EtOH


14: Racemate
15: Racemate
e:satd.HBr/CH2ClCH2Cl-Et2O
f:BaCO3,acetone-H2O
g:ClCH2COCl, pyridine,CH2ClCH2Cl


7(or11) + 15
1: R=OH(VP-16-213)
3: R=NH2
16: R=OH
19: R=NH2
9(or13) + 15
17: R=OH
20: R=NH2
18: R=OH
21: R=NH2

Scheme 1.

Among all four possible optical isomers synthesized, only isomers prepared by the combination of D-sugar and (-)-1-epipodophyllotoxin (1, 3,and 5) showed the strong antitumor activities against mouse leukemia L-1210. The antitumor effects of synthesized compounds will be reported elsewhere.

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6) a) D. Rajapaksa and R. Rodrigo, J. Am. Chem. Soc., 103, 6208 (1981). b) R. Rodrigo, J. Org. Chem., 45, 4538 (1980).
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8) Partial ^{1}H-NMR data ($CDCl_3$, 400 MHz); 1 and 18: 6.82 (1H s, H-8), 6.55 (1H s, H-5), 4.91 (1H d, J=3.8 Hz, H-1), 4.66 (1H d, J=8.0 Hz, H-1"), 4.61 (1H d, J=5.6 Hz, H-4), 4.42 (1H dd, J=9.0 and 10.5 Hz, H-11) and 4.22 (1H t, J=9.0 Hz, H-11); 16 and 17: 6.97 (1H s, H-8), 6.56 (1H s, H-5), 4.93 (1H d, J=3.6 Hz, H-1), 4.43 (1H d, J=8.0 Hz, H-1"), 4.60 (1H d, J=5.0 Hz, H-4), 4.63 (1H dd, J=9.0 and 11.0 Hz, H-11) and 4.33 (1H t, J=9.0 Hz, H-11); 3 and 21: 6.86 (1H s, H-8), 6.54 (1H s, H-5), 4.91 (1H d, J=3.8 Hz, H-1), 4.64 (1H d, J=8.0 Hz, H-1"), 4.60 (1H d, J=5.5 Hz, H-4), 4.42 (1H dd, J=9.0 and 11.0 Hz, H-11) and 4.21 (1H t, J=9.0 Hz, H-11); 19 and 20: 6.97 (1H s, H-8), 6.50 (1H s, H-5), 4.98 (1H d, J=3.2 Hz, H-1), 4.35 overlapped with H-11 (1H d, J=8.0 Hz, H-1") and 4.61 overlapped with H-11 (1H d, J=5.0 Hz, H-4).

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