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Synthesis of Carbocyclic Lignan Variants Related to Podophyllotoxin

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Carbocyclic lignan variants related to podophyllotoxin were synthesized by a stereoselective BF_3-catalyzed coupling of podophyllotoxin derivative with chiral aminocyclitols.

The clinical efficacy of synthetic podophyllotoxin glycosides, VP-16 (etoposide, 1) and VM-26 (teniposide, 2),[1] have stimulated interest in the synthesis of new active analogues of podophyllotoxin glycoside. Our initial approach to modify 1 and 2 based on replacement of the glucose moiety with an amino sugar has led to highly active analogues, 3, 4, and 5,[2,3] suggesting ß-anomeric configuration was indispensable for the antitumor activity. 1-O-[2-(Methylamino)ethyl and 2-(dimethylamino)ethyl] ethers of 4'-O-demethyl-1-epipodophyllotoxin 6 and 7[4] have also demonstrated by the strong antitumor activity that considerable simplification in the sugar structure might be permitted so long as the free amino group was retained. These findings prompted us to change the 1-O-glycosyl group in 1 to a configurationally similar aminocyclitol, and to synthesize the carbocyclic variants of podophyllotoxin 24-27.

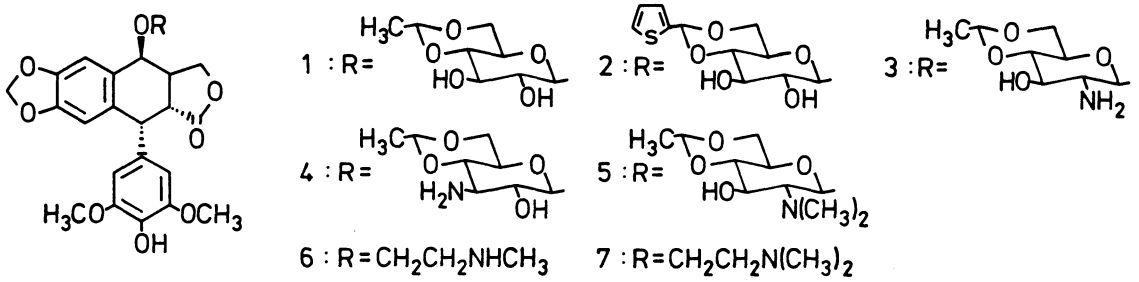


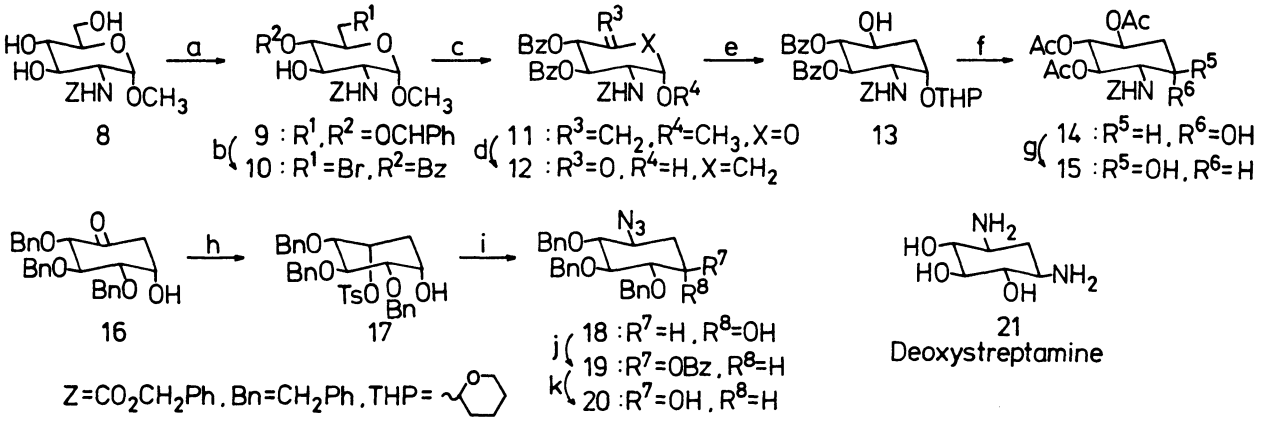
Fig. 1.

Two key steps in the synthesis involved the preparation of a chiral aminocyclitol via carbocyclic ring closure of a hex-5-enopyranoside derivative and the stereoselective coupling of an aminocyclitol with podophyllotoxin. For our purpose, methyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (8)[5] was selected as the ideal carbohydrate precursor. Its 4,6-O-benzylidene derivative 9, $[\alpha]_D^{21}$ +53° (c 0.55, $CHCl_3$), mp 207-208 °C, was converted according to Hanessian's method[6] into the 6-bromide 10, $[\alpha]_D^{21}$ +23° (c 0.81, $CHCl_3$), mp 125-126 °C. Treatment of 10 with silver fluoride in pyridine[7] gave 6-deoxy-5-enohexopyranoside 11, $[\alpha]_D^{21}$ +21° (c 0.60, $CHCl_3$), in 50% yield. Transformation of 11 to a cyclo-

hexane derivative by Ferrier's reaction[8] was quite smoothly carried out. Thus, 11 was refluxed with mercuric chloride in aqueous acetone to afford 2L-(2,4,5/3)-2,3-di-O-benzoyl-4-benzyloxycarbonylamino-2,3,5-trihydroxycyclohexanone (12),[9] $[\alpha]_D^{21}$ -55° (c 1.1, $CHCl_3$), in 71% yield. In contrast to a recent report[10] on the Ferrier's reaction of the fully acetylated 2-benzoylamino-2-deoxy sugar, that of the corresponding 2-benzyloxycarbonylamino-2-deoxy sugar yielded the complex products. Protection of the hydroxyl group in 12 with tetrahydropyranyl group and the successive reduction with zinc borohydride in tetrahydrofuran gave almost exclusively 13, $[\alpha]_D^{21}$ -8° (c 0.86, $CHCl_3$), mp 112-113 °C, whose stereochemistry was determined at the next stage. For the later condensation with podophyllotoxin, 13 was converted to the triacetate 14,[9] $[\alpha]_D^{21}$ +33° (c 0.82, $CHCl_3$), mp 114-115 °C. Epimerization at C-1 in 14 was carried out by two step sequences, oxidation with ruthenium tetroxide and reduction with zinc borohydride, giving the 1D-(1,3,5/2,4)-isomer 15 in 60% yield, $[\alpha]_D^{21}$ +10° (c 0.68, $CHCl_3$), mp 151-152 °C, and the C-1 epimer 14 in 26% yield.

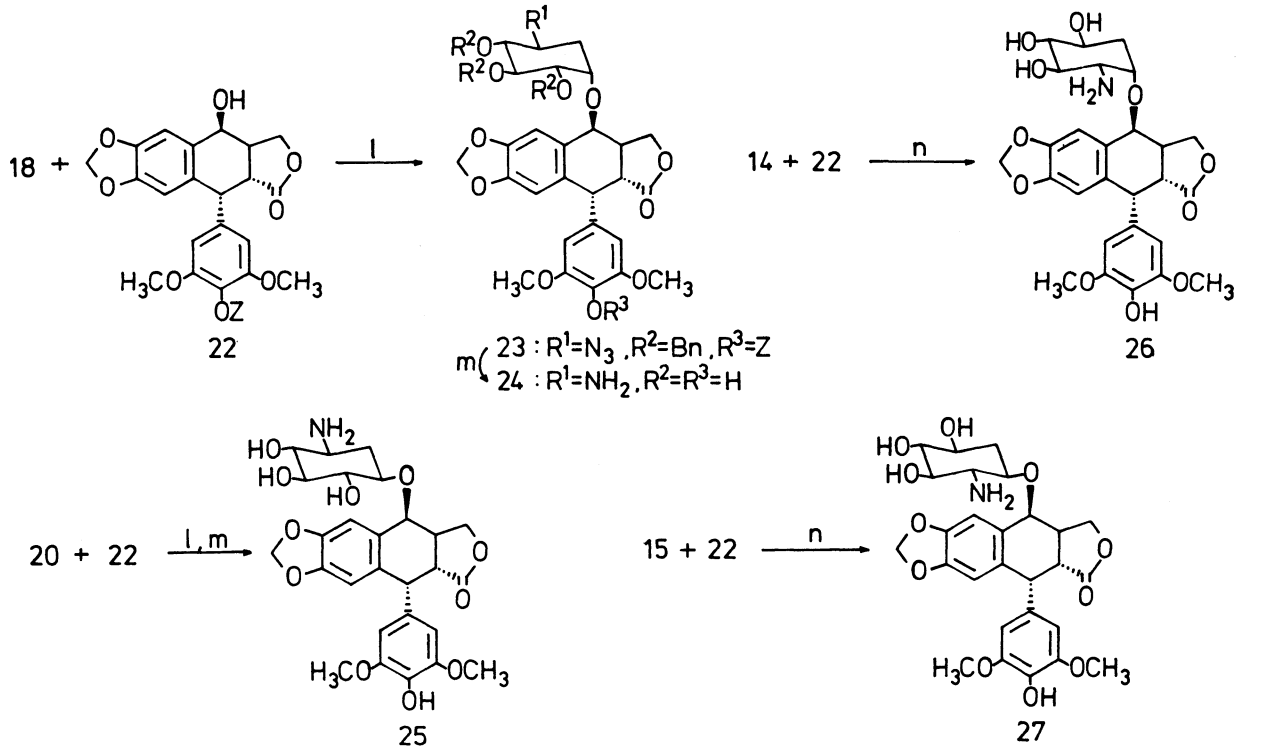
The second approach used 2L-(2,4,5/3)-2,3,4-tri-O-benzyl-2,3,4,5-tetrahydroxycyclohexanone (16) as the starting material prepared from methyl α-D-glucopyranoside using Ferrier's reaction according to Kuzuhara's procedure.[11] Tetrahydropyranylation of the hydroxyl group of 16 followed by reduction of the ketone with sodium borohydride afforded essentially the sole product with 1L-(1,2,4,5/3)-configuration, which, on a successive sequence of tosylation and acid hydrolysis, was transformed to 1L-(1,2,4,5/3)-2,3,4-tri-O-benzyl-1-O-p-toluenesulfony-1,2,3,4,5-cyclohexanepentol (17),[9] $[\alpha]_D^{21}$ -12° (c 0.82, $CHCl_3$), mp 135-136 °C. The stereoselectivity in reduction of 16 was found to be different from that of 12. The former might mainly be controlled by a steric hindrance of the 1,3-diaxial interaction between the tetrahydropyranyl ether and the hydride, while the latter mainly by a chelation of Zn with the neighbouring ether group at C-4 or C-1. Treatment of 17 with sodium azide gave 18, $[\alpha]_D^{21}$ -58° (c 1.0, $CHCl_3$), mp 59 °C, whose structure was also confirmed by transformation to the natural deoxystreptamine (21).[12] Mitsunobu reaction of 18 afforded 19,[9] $[\alpha]_D^{21}$ -65° (c 1.0, $CHCl_3$), with an inversion of configuration at C-1 in 54% yield. Alkaline hydrolysis of 19 gave 1L-(1,3/2,5,6)-6-azido-1,2,3-tri-O-benzyl-1,2,3,4-tetrahydroxycyclohexane (20), $[\alpha]_D^{21}$ -72° (c 0.6, $CHCl_3$), mp 93 °C. Thus, the four synthons, which were composed of two epimeric pairs related to 2- and 5-amino-6-deoxycyclohexanetetrol, have been prepared.

Acid-catalyzed coupling using boron trifluoride diethyl etherate[13] was successfully used in a condensation of the aminocyclitols with a partially protected podophyllotoxin. Condensation of 18 with 4'-O-benzyloxycarbonyl-4'-O-demethyl-1-epipodophyllotoxin (22)[2] in dichloromethane in the presence of $BF_3 \cdot OEt_2$ gave 1-ß-[1L-(1,3,4/2,6)-6-azido-1,2,3-tri-O-benzyl-1,2,3-trihydroxycyclohexyloxy]-4'-O-benzyloxycarbonyl-4'-O-demethyl-1-deoxypodophyllotoxin (23) in 66% yield, $[\alpha]_D^{21}$ -18° (c 0.99, $CHCl_3$), mp 148-149 °C, which was converted into the corresponding free base 24,[9] $[\alpha]_D^{21}$ -59° (c 0.33, $MeOH/H_2O$=1/1), mp >225 °C, by catalytic reduction over Pd/C in 63% yield. The condensation was stereoselectively carried out by the same fashion as had been reported in our previous articles.[2-4]



a: $PhCH(OMe)_2$, TsOH, DMF b: NBS, $BaCO_3$, $ClCH_2CH_2Cl$ c: BzCl, DMAP, CH_2Cl_2; AgF, Py
d: $HgCl_2$, acetone-H_2O e: dihydropyrane, H^+, CH_2Cl_2; $Zn(BH_4)_2$, THF
f: K_2CO_3, MeOH; Ac_2O, Py; HCl, AcOH-H_2O g: RuO_4, CH_2Cl_2-CCl_4; $Zn(BH_4)_2$, CH_2Cl_2
h: dihydropyrane, H^+, CH_2Cl_2; $NaBH_4$, EtOH; TsCl, Py; H^+, MeOH i: NaN_3, DMF
j: BzOH, Ph_3P, $(NCO_2Et)_2$, THF k: K_2CO_3, MeOH

Scheme 1.



l: $BF_3 \cdot OEt_2$, CH_2Cl_2 m: $PdCl_2$, H_2, MeOH-AcOH
n: $BF_3 \cdot OEt_2$, CH_2Cl_2; $Zn(OAc)_2$, MeOH; Pd/C, H_2, EtOH-EtOAc

Scheme 2.

A BF_3-catalyzed coupling of 14 with 22 followed by a removal of the masking groups by a sequence of methanolysis with $Zn(OAc)_2$ and hydrogenolysis with Pd/C afforded 1-ß-[1L-(1,3/2,4,6)-6-amino-1,2,3-trihydroxycyclohexyloxy]-4'-O-demethyl-1-deoxypodophyllotoxin (26),[9] $[\alpha]_D^{21}$ -19° (c 0.43, MeOH/H_2O=1/1), mp >220 °C (decomp), in 39% yield. The C-1" epimers 25 and 27 of 24 and 26, respectively, were also prepared by the same procedures using 20 or 15; 25, $[\alpha]_D^{21}$ -45° (c 0.63, MeOH/H_2O=1/1), mp >220 °C (decomp); 27, $[\alpha]_D^{21}$ -88° (c 0.43, MeOH/H_2O=1/1), mp 216-217 °C.

All four compounds synthesized showed the inferior activity to 1 in mice bearing leukemia L-1210 cells. The antitumor effects of the compounds will be reported elsewhere.

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9) Partial ^{1}H-NMR data; 12 ($CDCl_3$, 270 MHz) δ=2.82 (1H dd, J=3.5 and 15 Hz, H-6) and 2.93 (1H dd, J=12 and 15 Hz, H-6'); 14 ($CDCl_3$, 400 MHz) δ=1.67 (1H brt, J=13 Hz, H-6ax) and 2.31 (1H dt, J=13 and 3.9 Hz, H-6eq); 17 ($CDCl_3$, 400 MHz) δ=1.71 (1H dt, J=14 and 4 Hz, H-6ax) and 2.35 (1H dt, J=14 and 7 Hz, H-6eq); 19 ($CDCl_3$, 400 MHz) δ=1.52 (1H q, J=12 Hz, H-6ax) and 2.41 (1H dt, J=12 and 4 Hz, H-6eq); 24 (pyridine-d_5, 270 MHz) δ=2.43 (1H t, J=13 Hz, H-6"ax), 3.18 (2H m, H-2 and H-6"eq), 4.77 (1H d, J=5.6 Hz, H-4) and 5.02 (1H d, J=3 Hz, H-1); 26 (pyridine-d_5, 270 MHz) δ=1.71 (1H q, J=12 Hz, H-6"ax), 2.49 (1H dt, J=13 and 3.5 Hz, H-6"eq), 4.80 (1H d, J=5.3 Hz, H-4) and 5.57 (1H d, J=3.4 Hz, H-1).
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