SYNTHESIS OF DEHYDRODEOXYPODOPHYLLOTOXIN CYCLIC ETHER VIA ALLENE INTRAMOLECULAR CYCLOADDITION STRATEGY AND EVALUATION OF ITS CYTOTOXICITY

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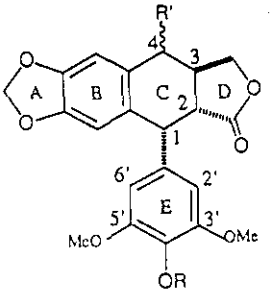
Abstract- The new route to dehydrodeoxypodophyllotoxin cyclic ether (**10**) has been realized via allene intramolecular Diels-Alder reaction of the propargyl ether (**8**).

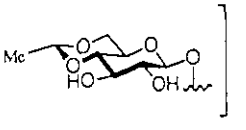
Lignans have been recognized as synthetic challenging targets[1] due to the variety of structural feature and the important biological properties exhibited by members of this class.[2] Podophyllotoxin (**1**), one of the naturally occurring lignan lactones, exerts a potent inhibition of microtuble assembly[3] and a key intermediate of clinical antitumor agents, etoposide (**2**) and teniposide (**3**).[4]

Recently, the syntheses of podophyllotoxin analogues have found renewed interest[5] since Gensler's first synthesis in 1966.[6] It is quite interesting to explore a new podophyllotoxin analogues.

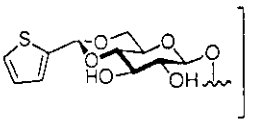


1, Podophyllotoxin
R=Me R'=α-OH

2, Etoposide
R=H R'=β-



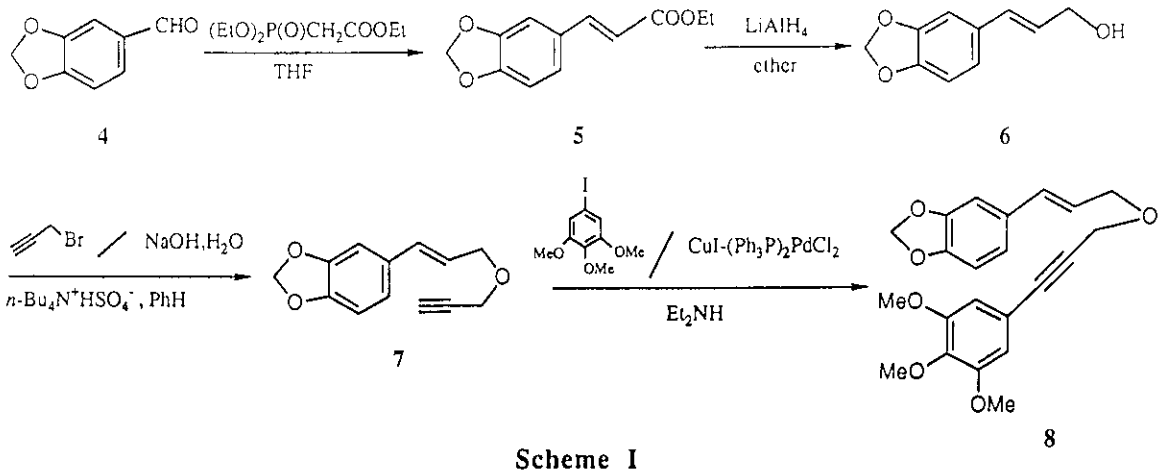
3, Teniposide
R=H R'=β-



Although the relationships between the biological activity and chemical structures have been reported,[4] the synthesis of dehydrodeoxypodophyllotoxin cyclic ether (**10**) has not yet been

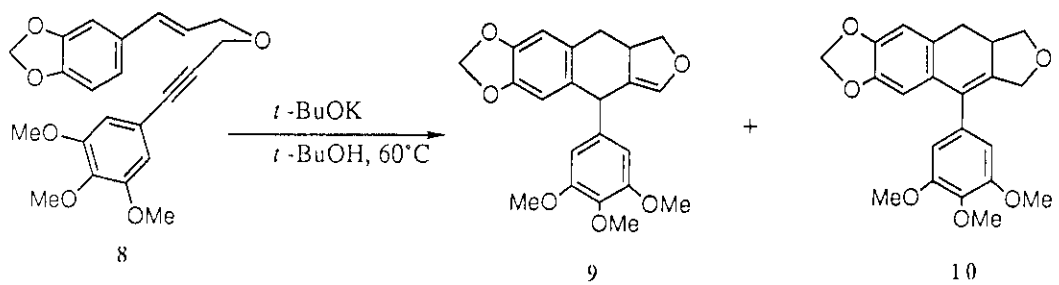
reported. In this paper, we described a new synthesis of the cyclic ether (**10**) *via* allene intramolecular Diels-Alder reaction of propargyl ether (**8**) and its cytotoxic activity.

The propargyl ether (**8**) was prepared from piperonal (**4**) as follows (Scheme I). The Wittig-Horner reaction of piperonal (**4**) [1.2 equiv. of sodium hydride, 1.2 equiv. of triethyl phosphonoacetate, room temperature, 1 h] gave **5**, which was converted into the alcohol (**6**) by reduction with LAH [1.2 equiv. of LAH, 0°C, 1 h]. Propargylation[7] of **6** [0.05 equiv. of tetrabutylammonium hydrogen sulfate, 1.2 equiv. of the propargyl bromide, room temperature] afforded the propargyl ether (**7**) in 72% yield. Arylation[8] of **7** was carried out with bis(triphenyl phosphine) palladium dichloride complex to give the aryl propargyl ether (**8**) in 79% yield.

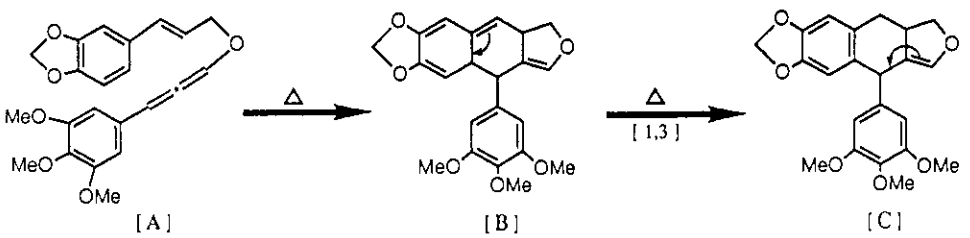


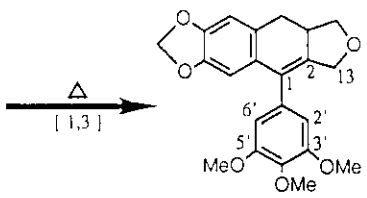
Scheme I

The propargyl ether (**8**) was reacted with 3.5 equiv. of *t* - BuOK in *t* - BuOH to give a mixture of cycloadducts (**9**) and (**10**) in 46% yield (Scheme II). The cycloadduct (**9**) was gradually transferred to isomer (**10**) at room temperature. While the intramolecular Diels-Alder reaction of the propargyl ether (**8**) by the use of 10 equiv. of *t* - BuOK gave only **10**[9] in 43 % yield (Scheme III). Clearly, double [1,3] sigmatoropic rearrangements ([**B**] → [**C**]) of the initially formed intermediary [**B**] *via* the intramolecular Diels-Alder reaction of allenyl ether [**A**] proceeded to give the thermodynamically stable isomer (**10**).



Scheme II





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Scheme III

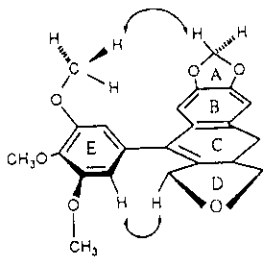

Figure 1

It is to be noted that dehydrodeoxypodophyllotoxin cyclic ether (**10**) appeared to be much the same to naturally occurring podophyllotoxin for the cytotoxic activity. As shown in Table I, compound **10** exhibited promising growth inhibition of L1210 (IC_{50} 0.086 μg/ml) and KB Cel (IC_{50} 0.18 μg/ml).

Table I Cytotoxicity of Lignans (IC_{50}, μg/ml)

sample	L1210	KB cell
dehydrodeoxypodophyllotoixn cyclic ether	0.086	0.18
podophyllotoxin	<0.01	0.2

Conformational analysis of etoposide (**2**), podophyllotoxin (**1**) and dehydrodeoxy-podophyllotoxin cyclic ether (**10**) was carried out in order to explore the structure-activity relationship for these compounds. The results of nuclear Overhauser enhancement (NOE) measurement suggest that the conformations of podophyllotoxin (**1**) and etoposide (**2**) were found to be similar. Irradiation at the H-2' or H-6' resonance position in these compounds produced enhanced signal intensity in the H-1 and H-3 resonances, which is consistent with the bent conformation of E ring. While similar observation with dehydrodeoxy-podophyllotoxin cyclic ether (**10**) demonstrated enhancement effect at the H-13 proton. In addition, irradiation at the methylenedioxy group in **10** demonstrated similarly enhancement effect on the methoxyl protons at the 3' and 5' positions. As depicted in Figure 1, a hint of importance of bond bending with E ring to the ABCD ring system is contained in this

NOE analysis of **10**. In this connection, Ritner et. al[10] have reported that the 2-1-1'-2' dihedral angles in **1** and **2** were below 90° and the *trans* D-ring controls the E-ring rotation. Therefore, the 1,2-unsaturated bond in dehydrodeoxypodophyllotoxin cyclic ether (**10**) can be regarded to play an important role with the D ring of podophyllotoxin (**1**) and etoposide (**2**). From the results, their inhibitory activities were shown to be sensitive to their conformations.

In conclusion, we have demonstrated a new synthesis and a short route of dehydrodeoxy-podophyllotoxin cyclic ether (10) via allene intramolecular Diels-Alder reaction and that its cytotoxicity *in vitro* appears to be potential. Further conformational studies including structure and activity relationship for podophyllotoxin congeners will be currently reported in our laboratory.

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9. Compoud **10** : mp 189°C ; ^{1}H-nmr δ ($CDCl_3$) 2.66 (t, *J*= 13.5 Hz, 1H), 2.83 (dd, *J*= 6.3, 13.5 Hz, 1H), 3.09-3.17 (m, 1H), 3.57 (dd, *J*= 9.2, 8.6 Hz, 1H), 3.83 (s, 6H), 3.90 (s, 3H), 4.26 (dd, *J*= 13.5, 2.3 Hz, 1H), 4.38 (t, *J*= 8.1 Hz), 4.72 (dd, *J*= 13.5, 1.89 Hz, 1H), 5.90 (s, 2H), 6.41 (s, 2H), 6.45 (s, 1H), 6.72 (s, 1H) ; ms m/z 382 (M^+). *Anal. Calcd* for $C_{22}H_{22}O_6$: C 69.10, H 5.80. Found ; C 68.92, H 5.78.
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