

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

Ken Kanematsu,*^{1a} Michiko Tsuruoka,^{1a} Yumiko Takaoka,^{1a} and Takuma Sasaki^{1b}

Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University 62, Higashi-ku, Fukuoka 812, Japan^{1a} and Cancer Research Institute, Kanazawa University, Kanazawa 920, Japan^{1b}

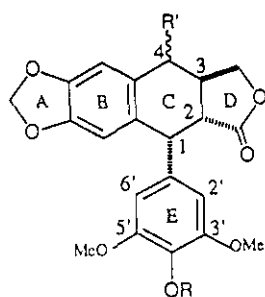
Abstract- The new route to dehydrodeoxypodophyllotoxin cyclic ether (10) has been realized via allene intramolecular Diels-Alder reaction of the propargyl ether (8).

Lignans have been recognized as synthetic challenging targets¹ 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 microtubule assembly³ and a key intermediate of clinical antitumor agents, etoposide (2) and teniposide (3).⁴

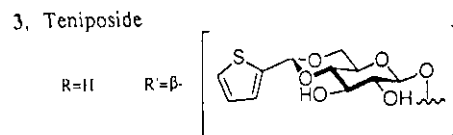
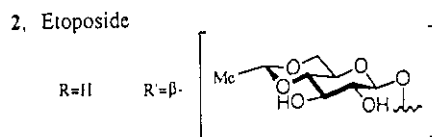
Recently, the syntheses of podophyllotoxin analogues have found renewed interest⁵ since Gensler's first synthesis in 1966.⁶

It is quite interesting to explore a new podophyllotoxin analogues.

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

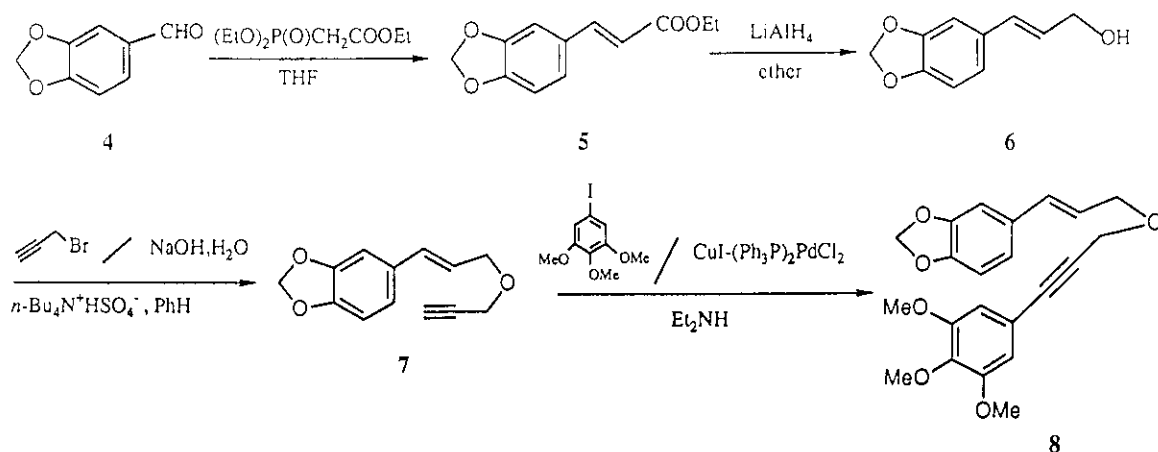


1, Podophyllotoxin
R=Me R'=α-OH



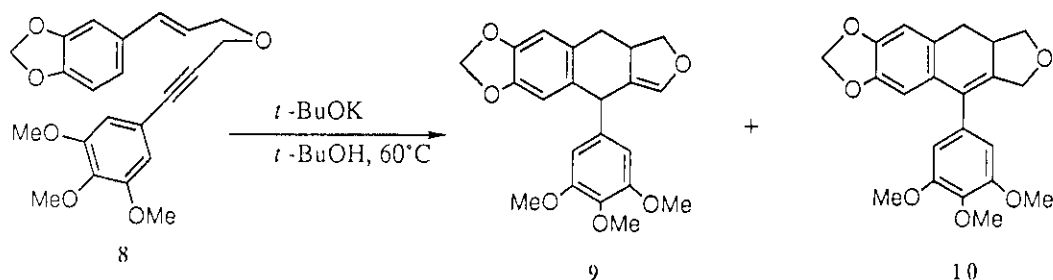
reported. In this paper, we described a new synthesis of the cyclic ether (10) *via* allene intramolecular Diels-Alder reaction of propargyl ether (8) and its cytotoxic activity.

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]. Propargylation⁷ 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. Arylation⁸ of 7 was carried out with bis(triphenyl phosphine) palladium dichloride complex to give the aryl propargyl ether (8) in 79% yield.

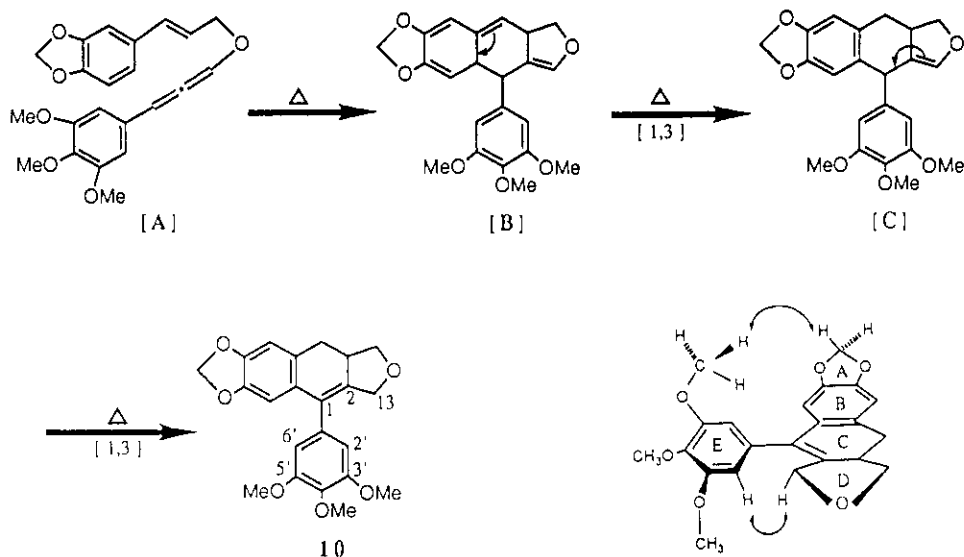


Scheme I

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% in 43% yield (Scheme III). Clearly, double [1,3] sigmatropic rearrangements ($[\text{B}] \rightarrow [\text{C}]$) 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



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 $\mu\text{g/ml}$) and KB Cel (IC_{50} 0.18 $\mu\text{g/ml}$).

Table I Cytotoxicity of Lignans (IC_{50} , $\mu\text{g/ml}$)

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

Conformational analysis of etoposide (2), podophyllotoxin (1) and dehydrodeoxypodophyllotoxin 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 dehydrodeoxypodophyllotoxin 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. al¹⁰ 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 dehydrodeoxypodophyllotoxin 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. Compound **10**: mp 189°C; ¹H-nmr δ (CDCl₃) 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 C₂₂H₂₂O₆: C 69.10, H 5.80. Found; C 68.92, H 5.78.
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