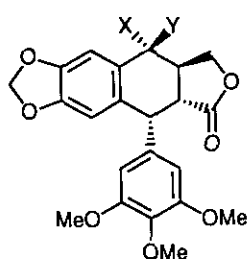


**SYNTHETIC STUDIES ON *PODOPHYLLUM* LIGNANS:  
 TRIBUTYLTIN HYDRIDE-INDUCED RADICAL CYCLIZATION  
 AND INTRAMOLECULAR HECK REACTION OF  $\alpha$ -  
 BENZYLIDENE- $\beta$ -(*o*-BROMOBENZYL)- $\gamma$ -LACTONES**

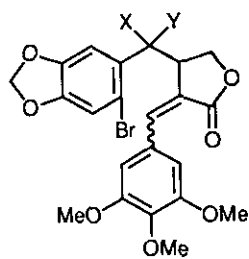
Hiroyuki Ishibashi,\* Katsuhiro Ito, Masayo Tabuchi, and Masazumi Ikeda\*  
*Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan*

*Abstract*—Tributyltin hydride-induced radical cyclization of the (*Z*)- $\alpha$ -benzylidene- $\beta$ -(*o*-bromobenzyl)- $\gamma$ -lactone (**16**) gave the 6-*endo* cyclization product, ( $\pm$ )-deoxyisopropopodophyllin (**18**), and the 5-*exo* cyclization product (**19**). On the other hand, the intramolecular Heck reaction of **16** provided ( $\pm$ )- $\gamma$ -apropropodophyllin (**20**) as a sole cyclization product.

Podophyllotoxin (**1**) and other related lactones from *Podophyllum* species are of considerable interest as synthetic targets since they can serve as precursors to the clinically used antitumor agents, etoposide and teniposide.<sup>1</sup> A number of methods have so far been reported for the construction of this tricyclic molecule and several efforts have culminated in the total synthesis of the podophyllotoxin derivatives.<sup>2</sup> Our interest in this area was stimulated by the prospect of designing a new entry to this class of compounds according to the strategy that involves a tributyltin hydride-induced radical cyclization or an intramolecular Heck reaction



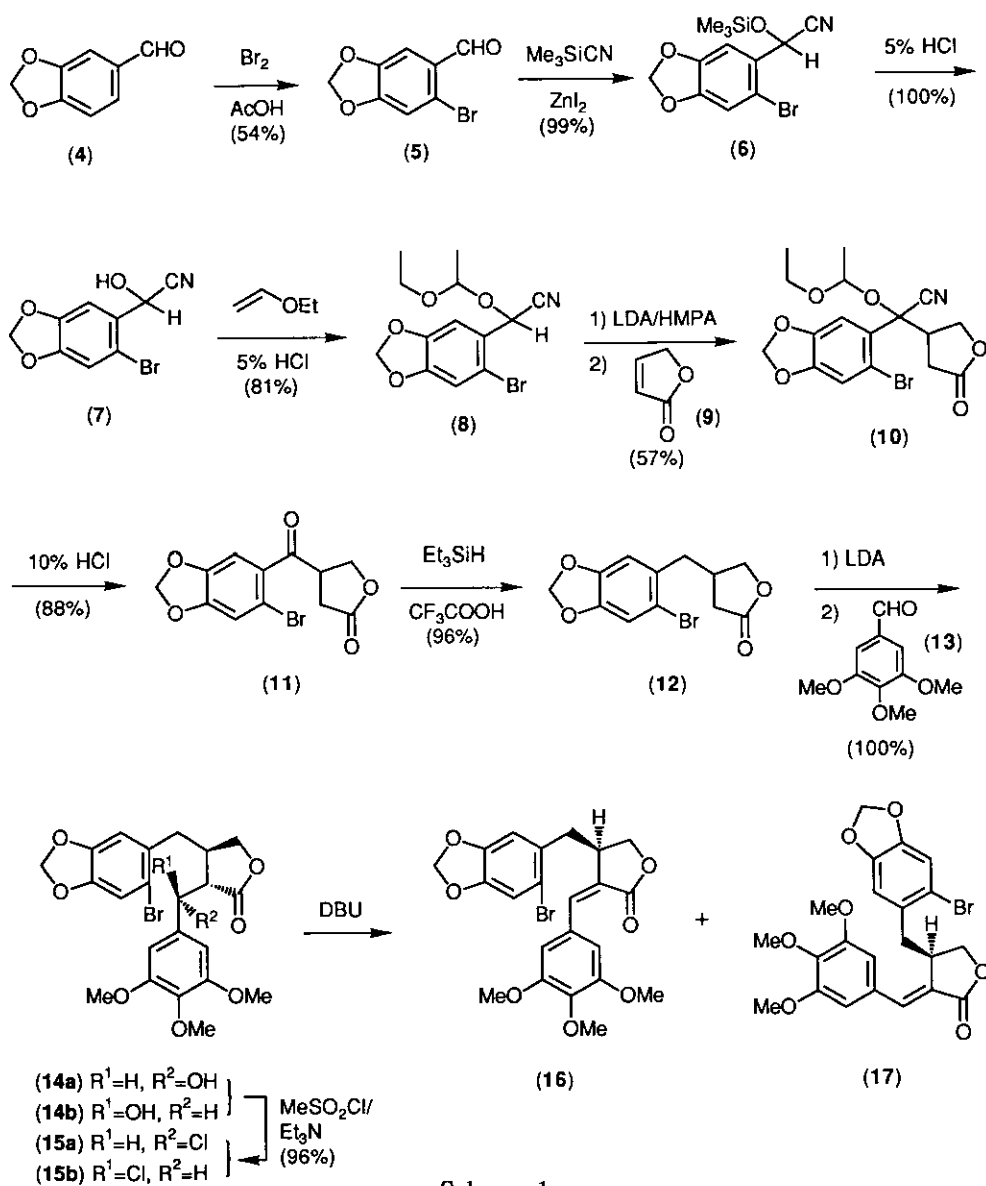
(1) : X = OH, Y = H  
 (2) : X = Y = H



(3)

of the  $\alpha$ -benzylidene- $\beta$ -(*o*-bromobenzyl)- $\gamma$ -lactones (**3**) as a key step. Herein we report preliminary results obtained with the lactones (**16**) and (**17**).

The key step for the synthesis of **16** and **17** involves the conjugate addition of the carbanion derived from the protected cyanohydrin (**8**) to  $\gamma$ -crotonolactone (**9**). The *O*-ethoxyethyl cyanohydrin (**8**), prepared from piperonal (**4**) via 4 steps (see Scheme 1), was treated with lithium diisopropylamide (LDA) in tetrahydrofuran in the presence of hexamethylphosphoric triamide at  $-78^\circ\text{C}$  and quenched with  $\gamma$ -crotonolactone at the same temperature for 2 h then at

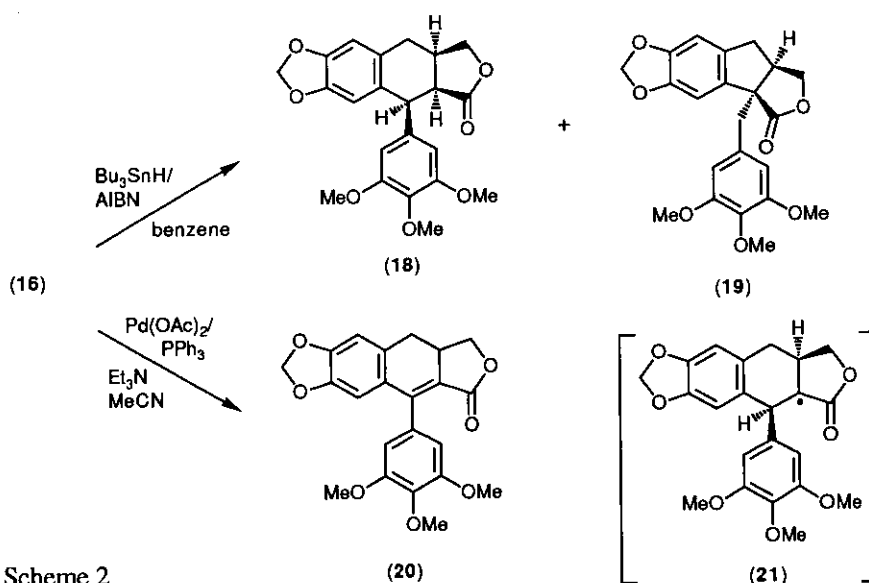


Scheme 1

-60°C for 1 h to give the  $\beta$ -substituted lactone (**10**) in 57% yield. A similar reaction in the absence of HMPA afforded only a 14% yield of **10**. The *O*-silyl cyanohydrin (**6**) or the *S*, *S'*-diphenyl thioacetal derived from **5** failed to give the desired conjugate addition product.

Deprotection of **10** with 10% HCl followed by reduction of the resultant ketone (**11**) with  $\text{Et}_3\text{SiH}$  (2 equiv.) in  $\text{CF}_3\text{COOH}$  (20 equiv.) afforded the lactone (**12**), which was then treated successively with LDA and 3,4,5-trimethoxybenzaldehyde (**13**) to give quantitatively a mixture of two diastereomeric alcohols (**14a**) and (**14b**) in a ratio of *ca.* 1:1. Treatment of the mixture of **14a,b** with  $\text{MeSO}_2\text{Cl}$  (2 equiv.) and  $\text{Et}_3\text{N}$  (2 equiv.) in  $\text{CH}_2\text{Cl}_2$  gave a *ca.* 3:1 mixture of the chlorides (**15a**) and (**15b**)<sup>3</sup> in 96% yield. The mixture of **15a,b** was treated with DBU in MeCN to give the (*Z*)- and (*E*)-  $\alpha$ -benzylidene lactones (**16**) and (**17**) in 64 and 22% yields, respectively. The stereochemistry of **16** and **17** was confirmed by the <sup>1</sup>H-nmr spectra: the olefinic proton of **16** appeared at  $\delta$  6.63 (d,  $J=1.7$  Hz), whereas the corresponding proton of **17** shifted down-field to  $\delta$  7.51 (d,  $J=1.6$  Hz) due to the deshielding effect of the neighboring carbonyl group.

The lactone (**16**) thus obtained was treated with  $\text{Bu}_3\text{SnH}$  (1.1 equiv.) and azobisisobutyronitrile (AIBN) (0.1 equiv.) in boiling benzene to give the 6-*endo* and 5-*exo* cyclization products (**18**) (mp 203-204°C) and (**19**) (mp 69-70°C) in 29 and 49% yields, respectively. The ir and <sup>1</sup>H-nmr spectra of **18** were identical to those of ( $\pm$ )-deoxyisopropodophyllin



Scheme 2

(lit.,<sup>4</sup> mp 208-210°C). The structure of **19** was deduced from the microanalysis and spectroscopic data.<sup>5</sup> The stereochemical outcome of the formation of **18** can be explained by an attack of the aryl radical formed from **16** to the  $\beta$ -face of the olefinic bond to give the new radical (**21**). This step is then followed by an attack of Bu<sub>3</sub>SnH from the convex face of **21** to lead to **18**.

The *E*-isomer (**17**), however, provided only the 5-*exo* cyclization product (**19**) in 64% yield when treated with Bu<sub>3</sub>SnH and AIBN.

Our attention was next turned to the intramolecular Heck reaction. Thus, the lactone (**16**) was heated at 120°C for 3 h in the presence of Pd(OAc)<sub>2</sub> (20 mol%), PPh<sub>3</sub> (40 mol%), and Et<sub>3</sub>N (1 equiv.) in MeCN: this gave ( $\pm$ )- $\gamma$ -apopicropodophyllin (**20**) (mp 252-253°C, lit.,<sup>4</sup> 251-254°C) and the starting material (**16**) in 28 and 38% yields, respectively. Since the lactone (**20**) has already been converted into ( $\pm$ )-deoxypodophyllotoxin (**2**),<sup>4</sup> the whole sequence of the reactions herein described constitutes in a formal sense a total synthesis of **2**. Improvement of the yield of the 6-*endo* cyclization products by the Heck reaction and its application to the synthesis of more functionalized molecules such as podophyllotoxin (**1**) are under intense investigation.

## REFERENCES AND NOTES

1. I. Jardine, "Anticancer Agents Based on Natural Product Models," ed. by J. M. Cassady and J. D. Douros, Academic Press, New York, 1980, pp. 319-351; B. F. Issell, *Cancer Chemother. Pharmacol.*, 1982, **7**, 73.
2. For reviews see: D. A. Whiting, *Nat. Prod. Rep.*, 1985, **2**, 192; *Idem, ibid.*, 1987, **4**, 499; *Idem, ibid.*, 1990, **7**, 349; R. S. Ward, *Tetrahedron*, 1990, **46**, 5029. See also T. Morimoto, M. Chiba, and K. Achiwa, *Tetrahedron Lett.*, 1990, **31**, 261; W. Choy, *Tetrahedron*, 1990, **46**, 2281; and Ref. 4.
3.  $\delta$  (<sup>1</sup>H-nmr) for R<sup>1</sup>(=H) of **15a**: 5.30 (d, *J*=3.9 Hz) and for R<sup>2</sup>(=H) of **15b**: 5.48 (d, *J*=2.6 Hz), respectively.
4. T. Kashima, M. Tanoguchi, M. Arimoto, and H. Yamaguchi, *Chem. Pharm. Bull.*, 1991, **39**, 192. The authors thank Professor H. Yamaguchi for providing spectra of compounds (**18**) and (**20**).
5. Ir ( $\nu$ , cm<sup>-1</sup>, CHCl<sub>3</sub>) 1760; <sup>1</sup>H-nmr ( $\delta$ , ppm, CDCl<sub>3</sub>, 300 MHz) 2.50 (1H, br d, *J*=16.2 Hz), 2.61 (1H, br dd, *J*=16.2, 6.8 Hz), 2.96 (1H, d, *J*=13.7 Hz), 3.09-3.18 (1H, m), 3.23 (1H, d, *J*=13.7 Hz), 3.68 (1H, dd, *J*=9.1, 8.1 Hz), 3.74 (6H, s), 3.81 (3H, s), 4.35 (1H, t, *J*=9.1 Hz), 5.97 (2H, s), 6.21 (2H, s), 6.61 (1H, s), 7.01 (1H, s).