SYNTHETIC STUDIES ON *PODOPHYLLUM* LIGNANS: TRIBUTYLTIN HYDRIDE-INDUCED RADICAL CYCLIZATION AND INTRAMOLECULAR HECK REACTION OF α-BENZYLIDENE-β-(*o*-BROMOBENZYL)-γ-LACTONES

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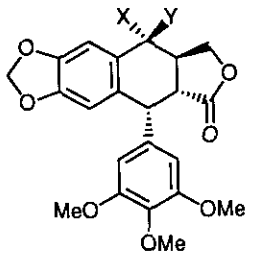
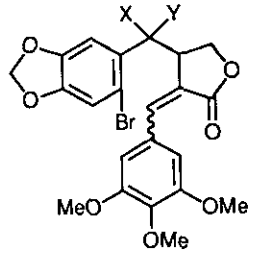
Abstract——Tributyltin hydride-induced radical cyclization of the (*Z*)-α-benzylidene-β-(*o*-bromobenzyl)-γ-lactone (**16**) gave the 6-*endo* cyclization product, (±)-deoxyisopicropodophyllin (**18**), and the 5-*exo* cyclization product (**19**). On the other hand, the intramolecular Heck reaction of **16** provided (±)-γ-apopicropodophyllin (**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.[1] 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.[2] 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



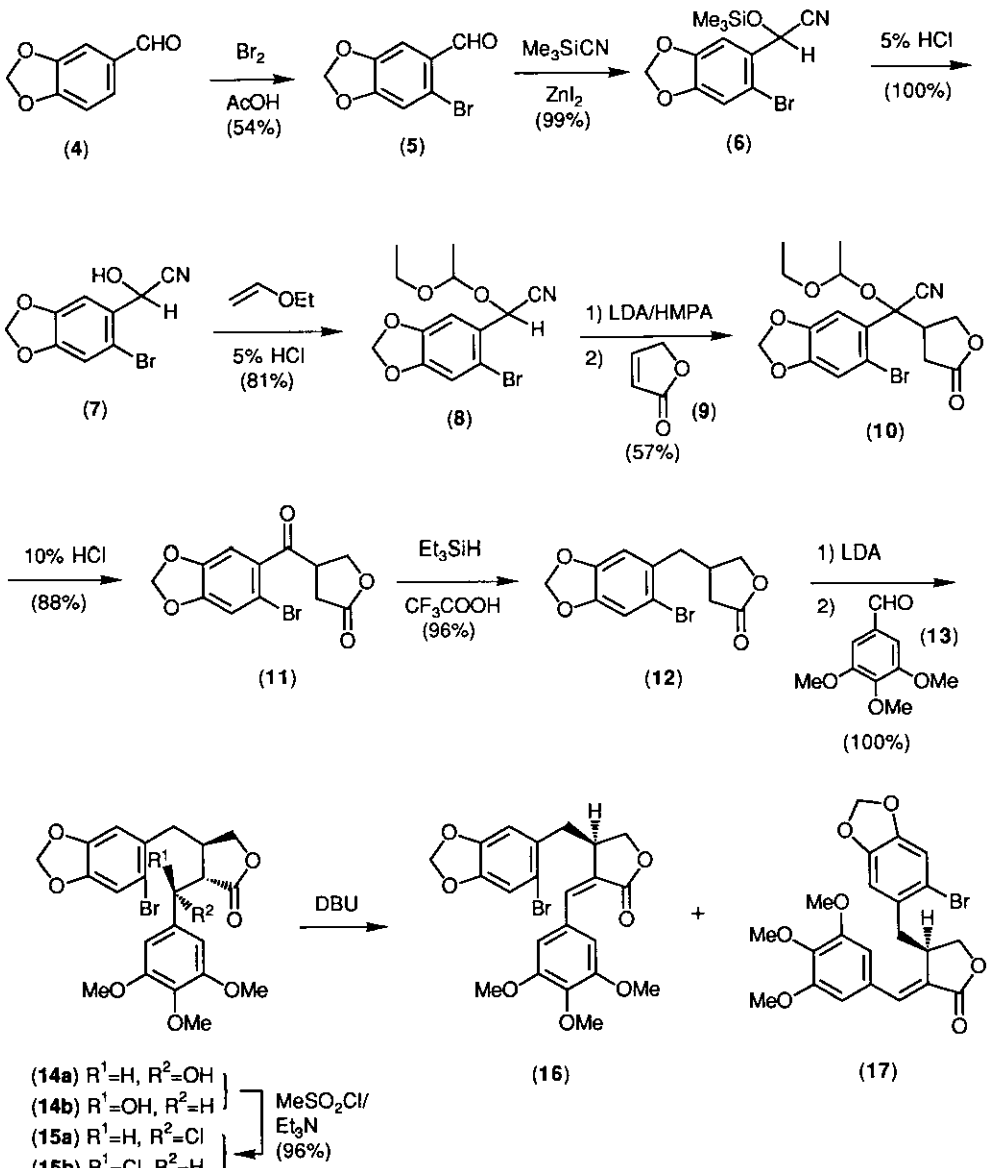
(**1**) : X = OH, Y = H
(**2**) : X = Y = H



(**3**)

of the α-benzylidene-β-(*o*-bromobenzyl)-γ-lactones (**3**) as a key step. Herein we report preliminary results obtained with the lactones (**16**) and (**17**).

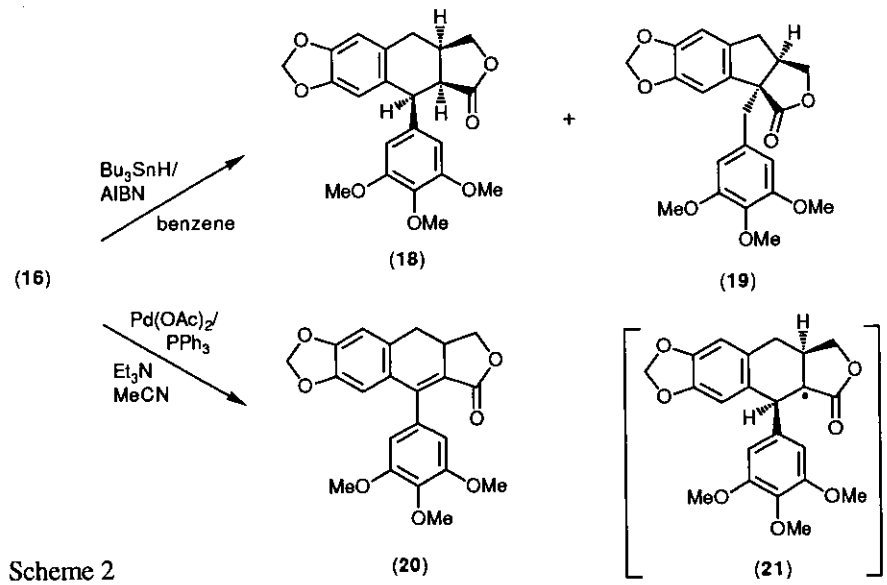
The key step for the synthesis of **16** and **17** involves the conjugate addition of the carbanion derived from the protected cyanohydrin (**8**) to γ-crotonolactone (**9**). The *O*-ethoxyethyl cyanohydrin (**8**), prepared from piperonal (**4**) via 4 steps (see Scheme 1), was treated with lithium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



Scheme 1

-60°C for 1 h to give the β-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 Et_3SiH (2 equiv.) in CF_3COOH (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 $MeSO_2Cl$ (2 equiv.) and Et_3N (2 equiv.) in CH_2Cl_2 gave a *ca.* 3:1 mixture of the chlorides (**15a**) and (**15b**)[3] in 96% yield. The mixture of **15a,b** was treated with DBU in MeCN to give the (*Z*)- and (*E*)- α-benzylidene lactones (**16**) and (**17**) in 64 and 22% yields, respectively. The stereochemistry of **16** and **17** was confirmed by the ^{1}H-nmr spectra: the olefinic proton of **16** appeared at δ 6.63 (d, J=1.7 Hz), whereas the corresponding proton of **17** shifted down-field to δ 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 Bu_3SnH (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 ^{1}H-nmr spectra of **18** were identical to those of (±)-deoxyisopicropodophyllin



Scheme 2

(lit.,[4] mp 208-210°C). The structure of **19** was deduced from the microanalysis and spectroscopic data.[5] The stereochemical outcome of the formation of **18** can be explained by an attack of the aryl radical formed from **16** to the β-face of the olefinic bond to give the new radical (**21**). This step is then followed by an attack of Bu_3SnH 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_3SnH 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 $Pd(OAc)_2$ (20 mol%), PPh_3 (40 mol%), and Et_3N (1 equiv.) in MeCN: this gave (±)-γ-apopicropodophyllin (**20**) (mp 252-253°C, lit., [4] 251-254°C) and the starting material (**16**) in 28 and 38% yields, respectively. Since the lactone (**20**) has already been converted into (±)-deoxypodophyllotoxin (**2**),[4] 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. δ (^{1}H-nmr) for R^1(=H) of **15a**: 5.30 (d, *J*=3.9 Hz) and for R^2(=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 (υ, cm^{-1}, $CHCl_3$) 1760; ^{1}H-nmr (δ, ppm, $CDCl_3$, 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).

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