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Synthesis of 4-Oxa-2-azapodophyllotoxin, a Novel Analog of the Antitumor Lignan Podophyllotoxin

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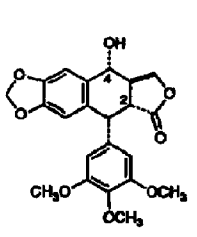
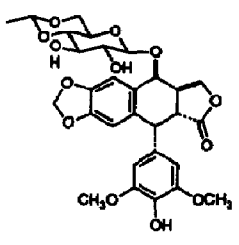
Abstract: 4-Oxa-2-azapodophyllotoxin (**5**) has been synthesized from sesamol (**6**). **5** showed significant activity against adriamycin-resistant P-388 leukemia cells.

Podophyllotoxin (**1**) is an antitumor lignan, and its derivatization led to a glycoside analog etoposide (**2**) which is now used clinically as an antitumor agent.[1] Recently 2-azapodophyllotoxin analogs (*e.g.*, **3** and **4**) have been synthesized by several groups[2] and attract much attention since they retain potent antitumor activity.[2b] To examine the efficacy of the modifications of **1** along these lines, we have designed and synthesized 4-oxa-2-azapodophyllotoxin (**5**). Substitution of the methylene group by an oxygen at position 4 in **3** would not significantly alter the whole stereo structure due to the similarity of the bond lengths (C-O *vs* C-CH_2) and the bond angles (C-O-C *vs* C-CH_2-C). However, the change in polarity would be expected to have some impact on the biological activity.

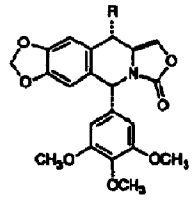
Sesamol (**6**) was benzylated and brominated in a usual manner to give the *O*-benzyl bromide **8**[3] (mp 65-66 °C) in 91% yield from **6**. **8** was lithiated through a metal-halogen exchange reaction with *n*-BuLi (1.1 eq) in THF at -45 °C, and successive treatment of it with 3,4,5-trimethoxybenzaldehyde (1.1 eq) afforded the benzhydrol **9** (mp 112-113 °C) in 88% yield. **9** was reacted with 2,4-oxazolidinedione[4] (1.2 eq) under Mitsunobu conditions[5] [diethyl azodicarboxylate (DEAD, 1.2 eq), triphenylphosphine (TPP, 1.2 eq), THF, r.t., 12 h] to give **10** (mp 158-159 °C) in 87% yield. Attempts to obtain aldehyde **12** or its cyclic hemiaminal through the partial reduction of **10** under various conditions were failed. Thus, **10** was reduced with sodium borohydride ($NaBH_4$) in THF-H_2O-EtOH (10:2.5:1), and the resultant alcohol **11** (98%, mp 175-178 °C) was reoxidized with Dess-Martin periodinane[6] in CH_2Cl_2. The aldehyde **12** (81%, mp 170-172 °C, δ_C 196.6) obtained does not cyclize to a hemiaminal possibly due to a sterically congested environment. However, careful debenzylation of **12** using H_2 and 10% Pd on carbon in EtOH gave the labile hemiaminal **13**, which



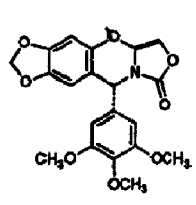
1



2



3 R=H
4 R=OH



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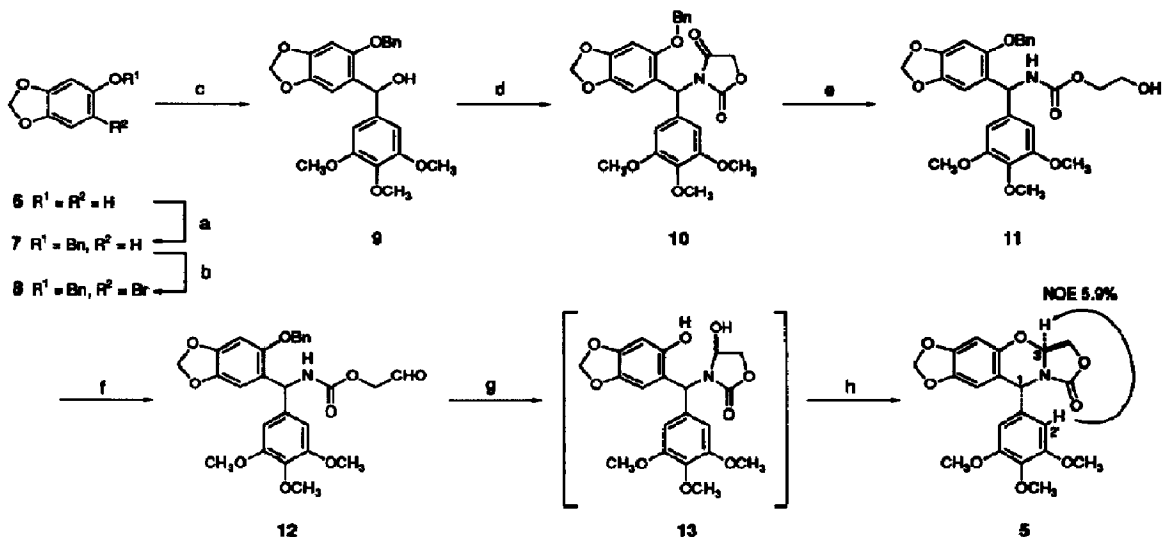

Reagents : a, BnCl, K_2CO_3, acetone; b, Br_2, AcONa, AcOH (91% from 6); c, n-BuLi, THF; 3,4,5-trimethoxybenzaldehyde (89%); d, TPP, DEAD, 2,4-oxazolidinedione, THF (87%); e, $NaBH_4$, THF-H_2O-EtOH (98%); f, Dess-Martin periodinane, CH_2Cl_2 (81%); g, H_2, Pd/C, EtOH; h, AcOH (95% from 12).

on treatment with acetic acid at 50 °C for 12 h gave **5**[7] (mp 168-169 °C) in 95% yield from **12** as a sole product. The relative stereochemistry was established by the observation of NOE (5.9%) between C_3-H (δ 5.43) and $C_{2'}$-H (δ 6.55) as shown in structure **5**. The exclusive formation of the *trans* analog **5** might be attributed to the thermodynamic stability.[8] **5** showed significant activity (IC_{50} = 0.031 μg/mL) against adriamycin-resistant P-388 leukemia cells.[9]

References and notes

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3. All compounds were fully characterized by elemental analyses, ^{1}H- and ^{13}C-NMR and mass spectral data.
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7. **5**: ^{1}H-NMR (400 MHz, $CDCl_3$, δ) 6.55 (2H, s), 6.47 (1H, s), 6.40 (1H, s), 5.94 (1H, d, J = 1.3 Hz), 5.92 (1H, d, J = 1.3 Hz), 5.75 (1H, s), 5.43 (1H, dd, J = 4.8, 1.6 Hz), 4.45 (1H, dd, J = 10.3, 1.6 Hz), 4.43 (1H, dd, J = 10.3, 4.8 Hz), 3.84 (3H, s), 3.81 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$, δ) 156.4, 153.6, 148.0, 147.3, 143.1, 138.4, 136.7, 112.0, 107.1, 105.8, 101.4, 99.2, 79.2, 68.2, 60.8, 56.3, 54.4.
8. A similar stereochemical tendency was observed for **3** and **4**; see, references 2b of this communication.
9. We are grateful to Dr. Keiji Yamagami and Mr. Akihiro Fujii of Yoshitomi Pharmaceutical Industries, Ltd. for the biological testing.

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