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A Facile and Efficient Synthesis of 4β-Aminopodophyllotoxins

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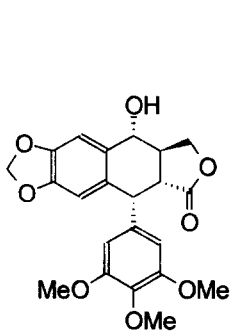
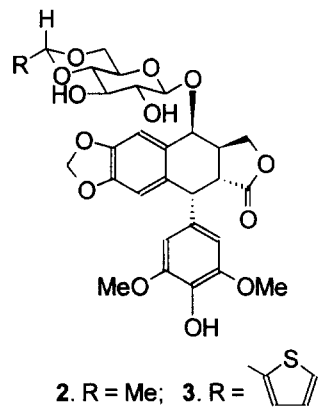
Abstract: 4β-amino-4-desoxypodophyllotoxin and 4β-amino-4'-desmethyl-4-desoxypodophyllotoxin have been synthesized by reduction of the corresponding 4β-azidopodophyllotoxin derivatives with samarium diiodide in excellent yields under convenient and mild conditions.

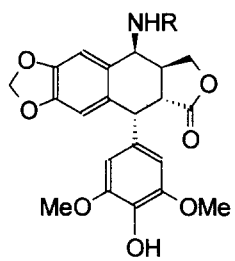
Semi-synthetic analogues of the naturally occurring podophyllotoxin (**1**) have drawn much renewed interest in recent years as a result of the development of etoposide (VP-16, **2**) and teniposide (VM-26, **3**) as anticancer drugs.[1] Several studies on podophyllotoxins have focused on replacement of the sugar residue of **2** and **3**.[2] 4β-Amino-podophyllotoxin (**4**) and a series of its *N*-substituted derivatives were found to exhibit superior pharmacological properties to VP-16, and some of them were brought into clinical evaluations.[3] In our previous studies,[4] we found that a number of 4β-amidopodophyllotoxins, such as compounds **5** and **6**, were as active as ,or more active than ,VP-16 and possessed lower toxicity, and therefore are promising new anticancer drugs.



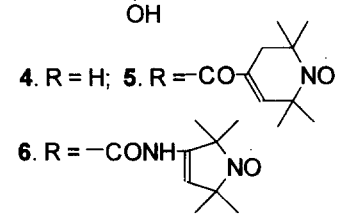
1



2. R = Me; **3**. R =



4. R = H; **5**. R =



6. R =

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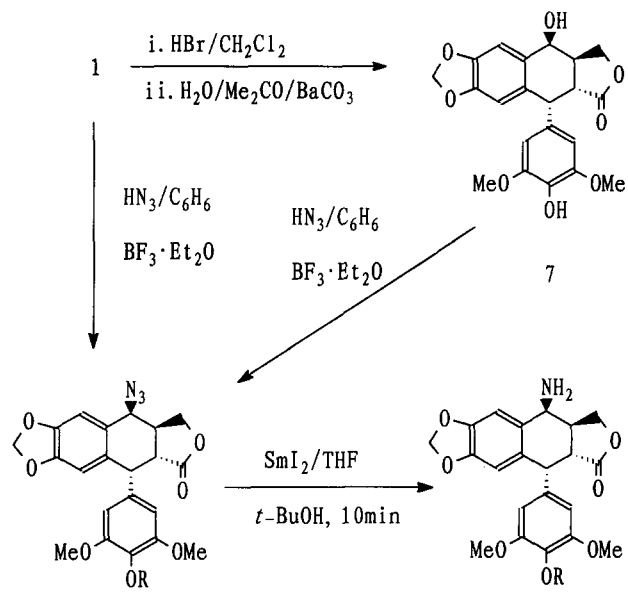
Compound **4**, a key precursor of **5** and **6**, was prepared by catalytic hydrogenation of 4β-azidopodophyllotoxin (**8a**) according to our previous method.[4a] The hydrogenation reaction was carried out under 40 psi of H_2 for 16 ~ 120 hours. As a part of an ongoing medicinal chemistry program[4,5] in the podophyllotoxin area, here we report a facile and efficient synthesis of **4** and its analogue **9** by reduction of the corresponding 4-azidopodophyllotoxins **8a** and **8b** with samarium diiodide. The overall sequence is shown in Scheme 1.



8a. R=H
8b. R=Me

4. R=H
9. R=Me

Scheme 1

4'-Desmethylepipodophyllotoxin (**7**) was prepared from **1** by bromination and selective demethylation *via* a modified Kuhn's method.[6] Compound **7** was treated with HN_3 in the presence of $BF_3{\cdot}OEt_2$ to give 4β-azidopodo-phyllotoxin (**8a**) .[4a] Compound **8b** was synthesized from **1** *via* a similar procedure to **8a**.[7] Both **8a** and **8b** were reduced by 2 equivalents of samarium diiodode in the presence of *t*-BuOH to afford products **4** and **9**, respectively. In a typical experiment, a solution of **8a** (0.43g, 1.0mmol) and *t*-BuOH (2ml) in dry THF (5ml) was added to a stirring solution of SmI_2 in THF (0.1M, 20ml, 2.0mmol) at room temperature under nitrogen. After stirring for 10min, the deep blue colour of SmI_2 solution turned to yellow and TLC (CH_2Cl_2/EtOAc, 7/3) indicated that **8a** had disappeared. The solvent was evaporated *in vacuo*. Water (5ml) and EtOAc (30ml) were added to the residue. The resulting mixture was filtered and the precipitate was washed with EtOH (10ml). The combined organic extract was washed with aqueous sodium thiosulfate and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography eluting

with CH_2Cl_2/EtOAc (7/3) to give pure **4** in 85% yield. Similarly, **8b** was reduced to **9** in 86% yield. Compounds **4** and **9** gave satisfactory spectral data.[8]

In summary, we have developed and demonstrated a facile and efficient synthesis of 4β-aminopodophyllotoxins in improved yields and with chemoselectivity. This study will be of assistance to investigators involved in the preparation of biologically useful *N*-substituted derivatives of 4β-aminopodo-phyllotoxins.

Acknowledgements: This work was financially supported by the National Science & Technology Commission of China.

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7. The assignment of the configuration at C-4 was based on the of $J_{3,4}$ coupling constants.
   The C-4β-substituted compounds have a $J_{3,4}$≈4.0Hz due to a *cis* relationship between H-3 and H-4. The

C-4α-substituted compounds have a $J_{3,4}$≥10Hz as H-3 is *trans* to H-4.

Compound **8b**: 202-204 ℃. MS(FAB) m/e 414(M^++1), 413(M^+). IR(KBr) 2100(N_3),1770(lactone), 1590,1510 and 1490(aromatic C=C), 934(OCH_2O). ^{1}HNMR($CDCl_3$) δ6.74(s, 1H, H-5), 6.52(s, 1H, H-8), 6.20(s, 2H, H-2′,6′), 5.95(s, 2H, OCH_2O), 4.74(d, *J*=4.0Hz, 1H, H-4), 4.59(d, *J*=4.5Hz,1H, H-1), 4.26(m, 2H, H-11), 3.76(s, 3H, 4′-OCH_3), 3.72(s, 6H, H-3′,5′-OCH_3), 3.28-2.95(m, 2H, H-2,3).

8. Compound **4**: m.p. 227-229 ℃. MS(EI) m/e 399 (M^+). IR (KBr) 3360 (OH), 3290 (NH_2), 1745 (lactone), 1610,1500 and 1480(aromatic C=C), 931 (OCH_2O). ^{1}HNMR($CDCl_3$) δ 6.81 (s, 1H, H-5), 6.50 (s,1H, H-8), 6.30 (s, 2H, H-2′,6′), 5.98and 5.95 (2s, 2H, OCH_2O), 4.56 (d, *J*=5.2Hz, 1H, H-1), 4.30 (d, *J*=10Hz, 2H,H-11), 4.21(d, *J*= 4.0Hz, 1H, H-4), 3.78 (s, 6H, 3′,5′-OMe), 3.15(dd, *J*=5.2,14Hz, 1H, H-2), 2.80 (m, 1H, H-3).

Compound **9**: m.p. 110-112 ℃. MS(FAB) m/e 414 (M^++1), 413(M^+). IR(KBr) 3430,3380 (NH_2),1776(lactone), 1588, 1550 and 1484 (aromatic C=C), 935(OCH_2O). ^{1}HNMR($CDCl_3$) δ 6.84(s, 1H, H-5), 6.47(s, 1H, H-8),6.36(s, 2H, H-2′,6′),5.97(s, 2H, OCH_2O), 4.58(d,*J*=5.1Hz,1H, H-1), 4.32(m, 2H, H-11), 4.25(d, *J*=4.0Hz, 1H, H-4), 3.80(s, 3H, 4′-OCH_3), 3.75(s, 6H, 3′,5′-OCH_3), 3.32(q, 1H, H-2), 2.92-2.63(m, 1H, H-3), 1.86(d, 2H, 4-NH_2).