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FACILE SYNTHESIS OF 4β-AMINOPODOPHYLLOTOXINS*

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Abstract: 4β-amino-4-desoxypodophyllotoxin and 4β-amino-4′-demethyl-4desoxypodophyllo-toxin were synthesized by reduction of the corresponding 4β-azidopodophyllotoxin derivatives with HCO_2NH_4/Pd-C in excellent yields under convenient and mild reactive condition.

Key words: podophyllotoxin, ammonium formate, synthesis.
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INTRODUCTION

Semisynthetic 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 (Estape et al., 1982). Most of the studies on podophyllotoxins focused on the simplification in the sugar structure of 2 and 3 (Lee et al., 1995). 4β-aminopodophyllotoxin (4) and a series of its N-substituted derivatives were found to exhibit pharmacological properties superior to those of VP-16, and some of them were brought into clinical evaluation (Lee et al., 1995). Our previous studies showed a number of 4β-amidopodophyllotoxins, such as compounds 5 and 6, were as active or more active than VP-16 and possessed lower toxicity, and therefore are promising new anticancer drugs (Tian et al., 1997).

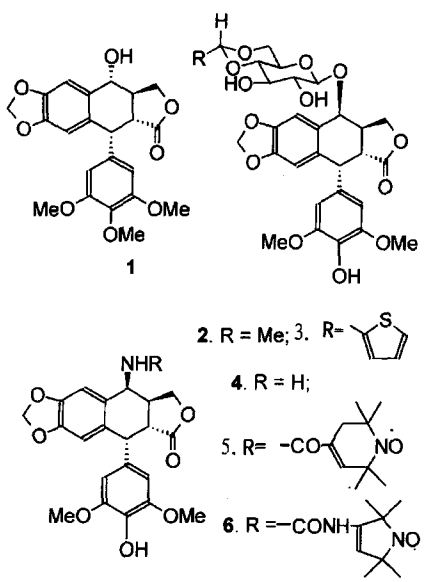

Fig.1 Podophyllotoxin derivatives

The use of ammonium formate as a reductant for functional groups in moderate reaction condition is interesting and promising (Siya et al., 1988). As part of an ongoing medicinal chemistry program in the podophyllotoxin area (Pan et al., 1997), we now report the synthesis of 4-aminopodophyllotoxin derivatives 4 and 9 by reduction of the 4-azidopodophyllotoxins 8a and 8b employing HCO_2NH_4/Pd-C. The overall sequence was as follows: 4′-demethylepipodophyllotoxin (7) was prepared from 1 by bromination and selective demethylation via a modified Kuhn's method (Kuhu et al., 1969). The 4β-azidopodophyllotoxins 8a and 8b were prepared as described in our previous work. Reduction of 8a and 8b respectively using ammonium formate as the hydrogen source in the presence of palladium/carbon yielded products 4 and 9.

It was noted that the reduction of the azides was chemoselective. The γ-lactone was not opened. Furthermore, the products 4 and 9 retained C-4β isomers. The assignment of the configuration at C-4 was based on the difference of

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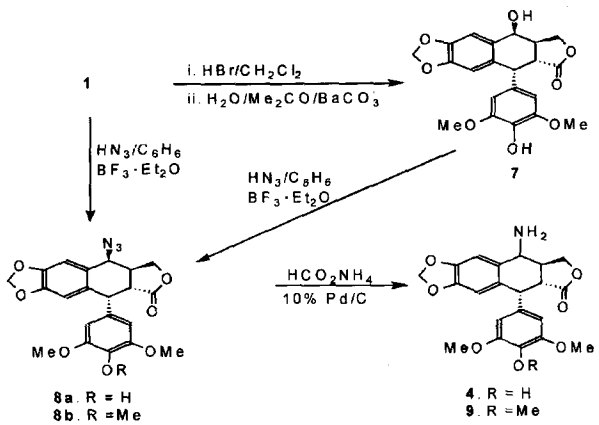

Fig.2 Synthesis of 4β-aminopodophyllotoxins

$J_{3,4}$ coupling constant. The C-4β-substituted derivative of podophyllotoxin had a $J_{3,4} \cong 4.0$ Hz due to a cis relationship between H-3 and H-4. The C-4α substituted derivative of podophyllotoxin, however, had a $J_{3,4} \geq 10$ Hz as H-3 trans to H-4.

Our use of ammonium formate as the hydrogen source, did not require manipulating under pressure, and was a convenient and mild reactive condition for the preparation of 4β-aminopodophllotoxin derivatives.

EXPERIMENT

Melting points were obtained on a YANACO apparatus and uncorrected. IR spectra were recorded on a NICOLET-5DX spectrometer, MS were recorded on a VGZAB-HS spectrometer, ^{1}H-NMR were recorded on a JEOL-FX-90Q spectrometer, using TMS as internal standard.

General procedures

A mixture of 4β-azdopodophylloyoxin 8a(0.43 g, 1mmol), HCO_2NH_4 (0.25 g, 4.0 mmol) and 10%Pd/C(0.04 g) in EtOAc (20 ml) was placed in a dry round bottom flask containing a magnetic stirrer bar. The reaction solution was stirred at 50 ℃ for 5 hr. The mixture was filtered and the filtrate was washed with water and brine. The organic phase was dried over anhydrous $MgSO_4$. Removal of solvent yielded the crude product for purification by chromatography (eluent with 3 : 7 EtOAc/CH_2Cl_2) to yield 0.26 g(65%) of pure products 4 or 9

Compound 4: Yield 65%. m.p. 227 – 228 ℃ (Lit – 230 ℃). MS m/z[m +]399. IR(KBr) 3360(OH) 3290(NH_2) 1745(lactone), 1610, 1590(– Ar)cm^{-1}, ^{1}HNMR($COCl_3$)δ 6.69(s, 1H, H-5), 6.49(s, 1H, H-8), 6.30(s, 2H, H-2',6'), 5.96(d, 2H, OCH_2O), 5.08(s, 1H, 4'-OH), 4.55(d, J = 5.2 Hz, 1H, H-1), 4.28(d, J = 9.5 Hz, 2H, H-11), 4.20(d, J = 4.0 Hz, 1H, H-4), 3.77(s, 6H, 3', 5'-OCH_3), 3.28(dd, J = 5.2, 14 Hz, 1H, H-2), 2.85(m, 1H, H-3).

Compound 9: Yield(62%). m.p. 112 – 113 ℃. MS m/z[m +]411, IR 3295(NH_2), 1745 (lactone), 1610, 1590(– Ar)cm^{-1}, ^{1}HNMR δ6.70(s, 1H, H-5), 6.50(s, 1H, H-8), 6.30(s, 2H, H-2',6'), 5.96(d, 2H, OCH_2O), 4.58(d, J = 5.3 Hz, 1H, H-1), 4.28(d, J = 9.5 Hz, 2H, H-11), 4.20(d, J = 4.1 Hz, 1H, H-4), 3.78 (s, 6H, 3', 4', 5'OCH_3), 3.28(dd, J = 5.2, 14 Hz, 1H, H-2), 2.86(m, 1H, H-3).

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