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FACILE AND IMPROVED SYNTHESIS OF 4β-AMINOPODOPHYLLOTOXIN CONGENERS

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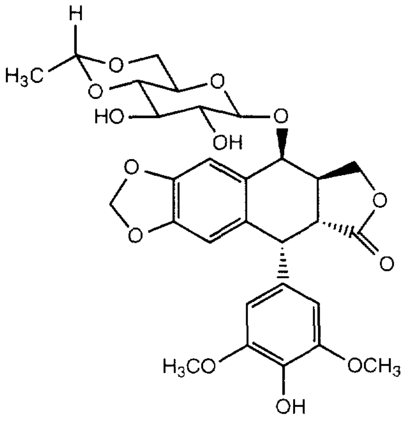
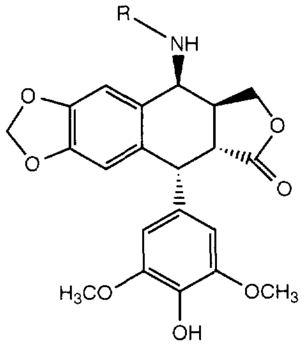
Abstract: An efficient synthesis of 4β-aminopodophyllotoxin from 4β-bromopodophyllotoxin using ammonia, and also a facile synthesis of 4β-amino-4'-*O*-demethylpodophyllotoxin from 4β-azidopodophyllotoxin by simultaneous azido reduction and selective demethylation at 4'-position employing chlorotrimethylsilane and sodium iodide, has been described. These are potential precursors for the various 4β-amino analogs of podophyllotoxin possessing DNA topoisomerase II inhibition activity.

Podophyllotoxin and desoxypodophyllotoxin are two well known naturally occuring aryltetralin lignans and the former is the major constituent of a number of plant species of podophyllum family.[1,2] Both these compounds are cytotoxic, and their derivatives are in use as antitumour agents (e.g., etoposide[3,4] and teniposide).[4b] These semisynthetic podophyllum lignans block the catalytic activity of DNA topoisomerase II and concurrent enzyme-mediated production of lethal DNA strand breaks leading to DNA damage and cytotoxicity.[5] This has stimulated a renewed interest in the chemical and biochemical studies of podophyllotoxin derived antitumour agents.[6,7] Some of the nonsugar substituted analogues, particularly the nitrogen containing congeners as 4β-N-arylamino/anilino derivatives of 4'-demethylepipodophyllotoxin, are active or more active than etoposide in their inhibition of the human DNA topoisomerase II.[8] In continuation of our interest in the 4β-amino congeners of podophyllotoxin, we have synthesized various 4β-amino analogues through 4β-aminopodophyllotoxin/4β-amino-4'-*O*-demethylpodophyllotoxins.[9,10]



etoposide



R = H
R = p-FC_6H_4 (NPF)
R = p-$NO_2C_6H_4$ (W-68)

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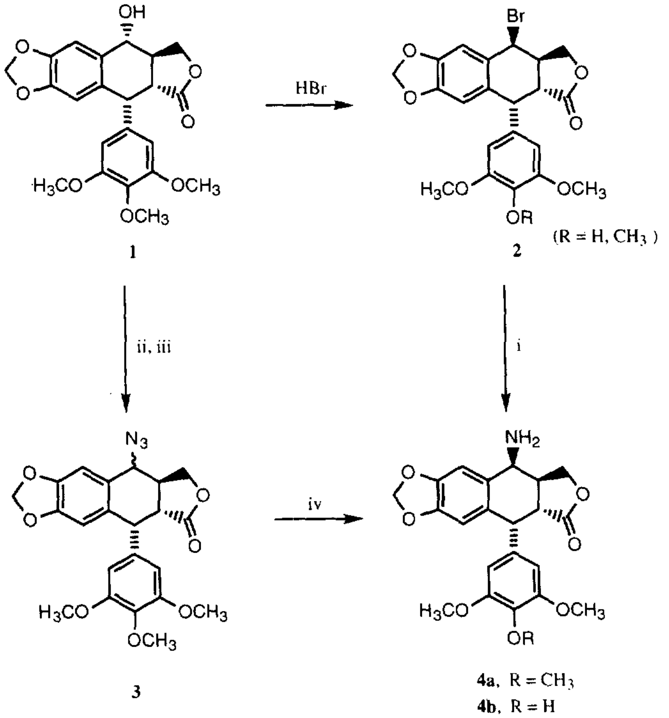
In this paper, we wish to report two new routes for the preparation of 4β-aminopodophyllotoxin and 4β-amino-4'-*O*-demethylpodophyllotoxin in high yields with stereoselectivity. These compounds have been employed by us as precursors in the synthesis of newer podophyllotoxin congeners.[10,11]

In the first method, 4β-aminopodophyllotoxin (**4a**) has been prepared through the 4β-bromopodophyllotoxin (**2**) by passing ammonia gas in good yield. This has some advantages over earlier reports,[7] it gives β-isomer as the major product, further in this method, the methyl group or any other protecting group remains intact at 4'-position. The starting material 4β-bromopodophyllotoxin (**2**) has been prepared by the modified Kuhn's method[12] as illustrated in Scheme 1. In a typical procedure; to a solution of 4β-bromopodophyllotoxin (3 g, 6.2 mmol) in dry dichloromethane (30 mL) was added $BaCO_3$ (0.6g, 3 mmol) at 0 °C and NH_3 was passed to this solution near to saturation for 20 min and continued stirring at 0 °C till the completion of reaction, $BaCO_3$ was removed by filteration and the filterate was extracted with dichloromethane and washed with water. The organic layer was separated, dried over Na_2SO_4 and evaporated under vacuum, to give the crude compound, this was purified by column chromatography ($CHCl_3$:MeOH; 9.8:0.2) to give the pure product **4a** in 70% yield.



Scheme 1. *Reagents and conditions* (i) NH_3 (g), $BaCO_3$, CH_2Cl_2, 20 min; (ii) $MeSO_2Cl$, Et_3N, THF; (iii) NaN_3,THF, 3 h; (iv)TMSCl-NaI, CH_3CN, 90 min

Recently, we have also investigated the reduction of azides to amines by *in situ* generation of iodotrimethylsilane using chlorotrimethylsilane and sodium iodide.[13] Further, this reagent is also known for the cleavage of hindered methoxy groups under mild conditions.[14] Therefore, we envisioned an efficient one-pot synthesis of 4'-demethyl-4β-amino-4-desoxypodophyllotoxin from 4β-azidopodophyllotoxin by the simultaneous reduction of azido group and 4'-demethylation employing the above reagent. It was interesting to observe that this one-pot synthesis gave excellent yields. Further, this method is devoid of CBZ-protection and deprotection at 4'-OH as described in the literature procedure.[7a] Another noteworthy aspect observed in this reaction is that the γ-lactone ring is intact at room temperature conditions though this reagent is known for lactone ring opening in the literature.[15] The starting material 4β-azidopodophyllotoxin (**3**) has been prepared from podophyllotoxin **1** by employing the literature method.[7a] Hence, **1** on mesylation followed by substitution of an azido group gave the precursor **3**. This has been reacted with chlorotrimethylsilane and sodium iodide at room temperature in MeCN to afford 4'-*O*-demethyl-4β-aminopodophyllotoxin (**4b**) as illustrated in Scheme 1. During the course of this work, 4'-demethylepipodophyllotoxin and 4β-arylamino derivative of podophyllotoxin (NPF) have been synthesized in literature employing trimethylsilyl iodide.[16]

In a typical procedure, to a solution of 4-azidopodophyllotoxin (0.44 g, 1.0 mmol) in MeCN (4 mL) was added to a stirred suspension of sodium iodide (0.36 g, 2.4 mmol) and chlorotrimethylsilane (0.5 mL, 2.4 mmol) in MeCN (15 mL) and continued stirring, after the completion of reaction as indicated by TLC ($CHCl_3$:MeOH, 9.7: 0.3). The reaction mixture was quenched with saturated sodium thiosulphate solution (15 mL). This reaction mixture was extracted with ethylacetate (30 mL) and washed with brine solution (15 mL). The organic layer was separated, dried over anhydrous Na_2S0_4, and evaporated under vacuum to give the crude product. This was purified by column chromatography ($CHCl_3$:MeOH, 9.5:0.5) to give the pure product [17] **4b** in 60% yield.

In conclusion, this investigation has led to an efficient and facile synthesis of 4β-aminopodophyllotoxin and 4β-amino-4'-*O*-demethylpodophyllotoxin of biological significance, employing ammonia, and chlorotrimethylsilane and sodium iodide (*in situ* generation of trimethylsilyliodide), respectively. These compounds are useful precursors in the synthesis of 4β-amino analogues of podophyllotoxin of biological significance.

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17. Compound **4b** ^{1}H NMR (200 MHz, $CDCl_3$) 6.81 (s, 1H,) 6.55 (s, 1H, H-8), 6.25(s, 2H,) 5.96 (J = 1 Hz, 2H, 4.7 (d, J = 5.2 Hz, 1H) 4.3 (d, J = 9.5 Hz, 2H) 3.96 (d, J = 4.1 Hz, 1H) 3.77 (s, 6H) 3.28 (dd, J = 5.2, 14 Hz, 1H) 2.85 (m, 1H); IR(KBr) 3360 (OH), 3290 (primary amine), 2900, 1745 (lactone), 1590 (aromatic C-H) cm^{-1}; m/z 413 [$M^{+\cdot}$].

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