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A one-pot, efficient and facile synthesis of 4β-arylaminopodophyllotoxins: synthesis of NPF and GL-331 as DNA topoisomerase II inhibitors

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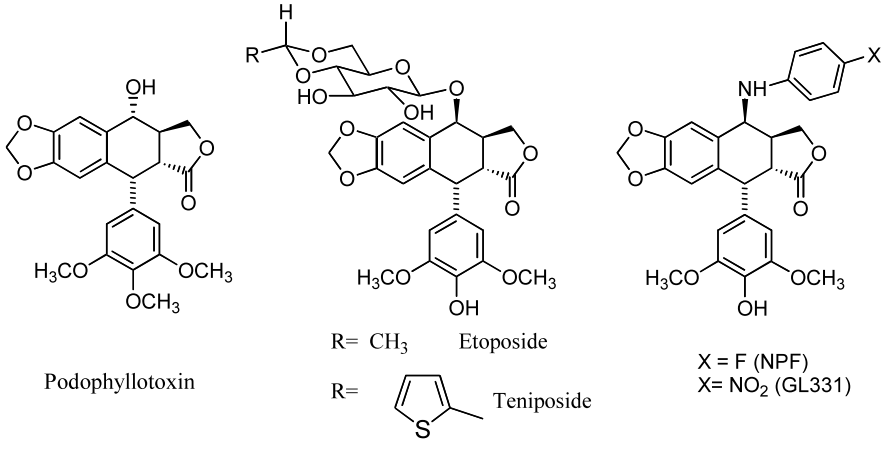
Abstract—A series of 4β-arylamino-4′-*O*-demethylepipodophyllotoxins and 4β-arylaminopodophyllotoxins have been synthesized with significant stereoselectivity and improved yields by employing the $BF_3{\cdot}OEt_2$/NaI reagent system. Compounds NPF, GL-331 and other DNA topoisomerase II inhibitors have been prepared in good to excellent yields by employing this methodology.

The biological activity of podophyllotoxin has led to extensive structure modifications resulting in several clinically useful compounds. Etoposide[1] and teniposide[2] developed in the late 1960s and early 1970s are two epipodophyllotoxins[3] in clinical use as anticancer agents. With a view to improving the clinical efficacy and to overcoming the problems of drug resistance and myelosuppression various 4β-substituted congeners of epipodophyllotoxin have been synthesized and evaluated for their biological properties.[4] Podophyllotoxin is known as an antimicrotubule agent while the epipodophyllotoxin and its 4β-congeners are potent DNA topoisomerase II inhibitors. A large number of 4β-amino substituted congeners have been prepared and some of these derivatives (e.g. NPF and GL-331)[5,6] have displayed a better pharmacological profile than those of etoposide. One of them, 4′-*O*-demethyl-4β-(4″-nitroanilino)-4-desoxypodophyllotoxin (GL-331) is currently in phase-II of the clinical trials against gastric carcinoma, colon cancer, non-small cell carcinoma and etoposide resistant malignancies.[7]

In the literature, 4β-amino substituted congeners such as 4′-*O*-demethyl-4β-(4″-fluoroanilino)-4-desoxypodophyllotoxin (NPF) have been synthesized by Lee's[8] approach, which involves the following reactions starting from podophyllotoxin: (i) one-pot C-4 epimerization and 4′-*O*-demethylation, (ii) C-4 bromination (100% crude yield) via a modified Khun's method and nucleophilic displacement with 4-fluoroaniline (45%



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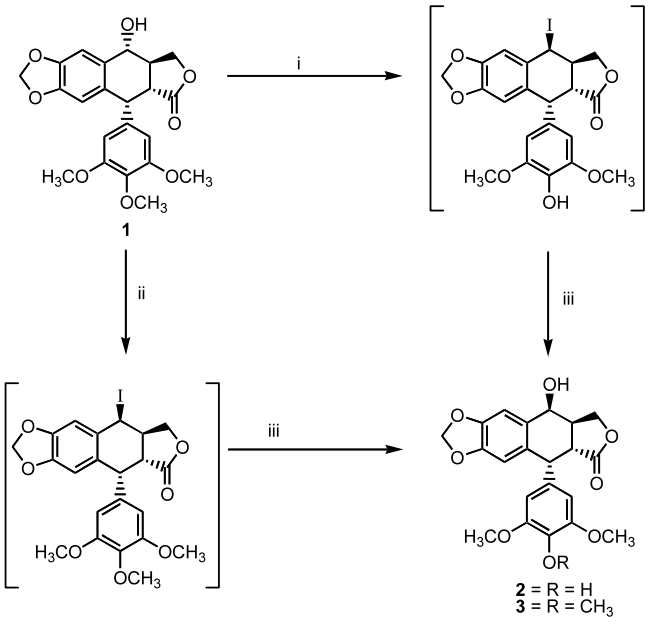
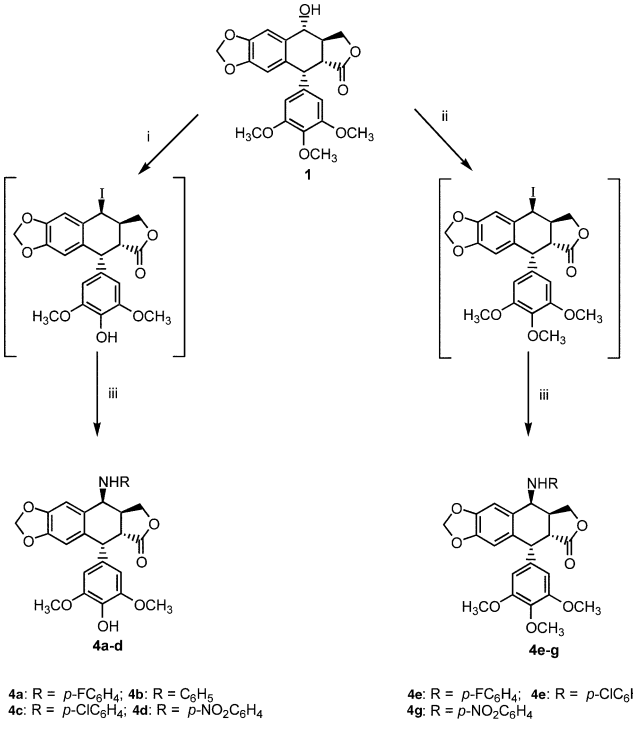


Scheme 1. *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$/NaI, CH_2Cl_2, 5 h, rt; (ii) $BF_3{\cdot}OEt_2$/NaI, MeCN, 15 min, rt; (iii) $BaCO_3$, CH_3COCH_3–H_2O, 2 h, rt.

yield) to afford NPF in 23% overall yield together with minor amounts of the 4α-substituted product. Later, Monneret[9] and co-workers reported a method employing TMSI to afford NPF in 52% yield. This method has recently been improved in our laboratory by the addition of tetrabutylammonium iodide[10] to afford the target compound in higher yields. We have also reported the synthesis of this compound by employing the methanesulfonic acid/NaI reagent system[11] and by reduction of the azido functionality by employing baker's yeast.[12] In continuation of these efforts, we herein report the synthesis of 4β-arylaminopodophyllotoxin derivatives including NPF and GL-331 by employing the $BF_3{\cdot}OEt_2$/NaI reagent system. This reagent system has recently been utilized for the iodination of alcohols but the present procedure describes the preparation of aminoaryl derivatives via the iodo intermediates. Moreover, iodination of allylic and benzylic alcohols by the use of the $BF_3{\cdot}OEt_2$/KI reagent system[13] is also known.

In view of our interest in the preparation of new podophyllotoxin congeners, we have investigated the use of the $BF_3{\cdot}OEt_2$/NaI reagent system in CH_2Cl_2 for iodination of the benzylic alcohol in the C-ring of the podophyllotoxin system followed by hydrolysis (water:acetone, $BaCO_3$) to afford 4′-*O*-demethyl epipodophyllotoxin. Interestingly, carrying out this iodination process in CH_3CN followed by hydrolysis provides the epipodophyllotoxin without 4′-*O*-demethylation. In this methodology 4′-*O*-demethylation could be maneuvered by using the required solvent (Scheme 1).

This procedure has been further extended towards the preparation of potential 4β-arylaminopodophyllotoxin congeners such as NPF and GL-331. The reaction of podophyllotoxin with the $BF_3{\cdot}OEt_2$/NaI reagent system followed by the addition of the corresponding arylamines in the presence of mild bases like $BaCO_3$ or K_2CO_3 or $CsCO_3$ affords the arylamino substituted podophyllotoxins. Similarly, in these reactions the process of 4′-*O*-demethylation has been controlled by employing the required solvents that is CH_2Cl_2 to give 4β-arylamino 4′-*O*-demethylpodophyllotoxins (**4a**–**d** in 40–55% yields)[14] and CH_3CN to give 4β-arylaminopodophyllotoxins (**4e**–**g** in 80–85% yield)[15] as shown in Scheme 2.



Scheme 2. *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$/NaI, CH_2Cl_2, 5 h, rt; (ii) $BF_3{\cdot}OEt_2$/NaI, MeCN, 15 min, rt; (iii) THF, RNH_2, $BaCO_3$, 8 h, rt.

In summary, we have demonstrated a convenient and practical one-pot process for the synthesis of 4β-arylaminopodophyllotoxin analogues. This procedure also exhibits selectivity in 4′-*O*-demethylation by using the appropriate solvent thus demonstrating the application of this methodology for the selective preparation of 4′-*O*-demethyl or epipodophyllotoxin congeners in high yields. Moreover, this procedure has been extended to the efficient synthesis of DNA topoisomerase II inhibitors such as NPF and GL-331 and hence it has potential for the preparation of other related amino substituted podophyllotoxin analogues.

Acknowledgements

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14. **General procedure for 4a–d**: To a solution of podophyllotoxin (414 mg, 1 mmol) in dry CH_2Cl_2 (10 mL), NaI (447 mg, 3 mmol) was added and stirred for 5 min. To this suspension $BF_3{\cdot}OEt_2$ (425 mg, 3 mmol) was added dropwise by syringe at 0°C and stirring was continued for another 5 h at room temperature. This solution was then evaporated in vacuo and used for the next reaction without further purification. To the above crude product, anhydrous $BaCO_3$ (395 mg, 2 mmol) and then the appropriate arylamine (1.2 mmol) in 10 mL of dry THF under nitrogen were added and stirred for 8 h at room temperature. The reaction mixture was then filtered, diluted with ethyl acetate and washed with water, 10% $Na_2S_2O_3$ solution dried and purified via column chromatography (40 g of silica gel with ethyl acetate/hexane as eluent).
4′-Demethyl-4β-(4″-fluoroanilino)-4-desoxypodophyllotoxin (NPF) (4a): Yield 56%; mp 175–177°C; $[\alpha]_D^{30} = -102$ ($c = 1$, $CHCl_3$); IR (KBr) 3504 (OH), 3388 (NH), 1772 (lactone), 1619, 1513 and 1473 (aromatic C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (m, 2H, 3″, 5″-H), 6.75 (s, 1H, 5-H), 6.53 (s, 1H, 8-H), 6.49 (m, 2H, 2″, 6″-H), 6.29 (s, 2H, 2′, 6′-H), 6.00 and 5.98 (AB q, $J = 1.4$ Hz, 2H, OCH_2O), 5.36 (s, 1H, exchangeable, 4′-OH), 4.60 (d, $J = 4.2$ Hz, 2H, 4-H and 1-H), 4.36 (t, $J = 8.0$ Hz, 1H, 11-H), 3.99 (t, $J = 8.0$ Hz, 1H, 11-H), 3.80 (s, 6H, 3′, 5′-OCH_3), 3.68 (br, 1H, exchangeable NH), 3.15 (dd, $J = 4.8$, 13.7 Hz, 1H, 2-H), 3.05 (m, 1H, 3-H); MS (FAB) 493 $[M]^{+\bullet}$; HRMS (m/z): calcd for $C_{27}H_{24}O_7NF$ 493.5004; found: 493.1536.
15. **General procedure for 4e–g**: To a solution of podophyllotoxin (414 mg, 1 mmol) in dry CH_3CN (10 mL), NaI (298 mg, 2 mmol) was added and stirred for 5 min. To this suspension $BF_3{\cdot}OEt_2$ (425 mg, 3 mmol) was added dropwise by syringe at 0°C and stirring was continued for another 15 min at room temperature. This solution was then evaporated in vacuo and used for the next reaction without further purification. To the above crude product, anhydrous $BaCO_3$ (395 mg, 2 mmol) and then the appropriate arylamine (1.2 mmol) in 10 mL of dry THF under nitrogen were added and stirred for 8 h at room temperature. The reaction mixture was filtered, diluted with ethyl acetate and washed with water, 10% $Na_2S_2O_3$ solution dried and purified via column chromatography (40 g of silica gel with ethyl acetate/hexane as eluent).
4β-(4″-Fluoroanilino)-4-desoxypodophyllotoxin (4e): Yield 85%; mp 128–130°C; $[\alpha]_D^{30} = -78$ ($c = 1$, $CHCl_3$); IR (KBr) 3388 (NH), 1772 (lactone), 1619, 1513 and 1473 (aromatic C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (m, 2H, 3″, 5″-H), 6.75 (s, 1H, 5-H), 6.53 (s, 1H, 8-H), 6.49 (m, 2H, 2″, 6″-H), 6.29 (s, 2H, 2′, 6′-H), 5.97 and 5.99 (AB q, $J = 1.4$ Hz, 2H, OCH_2O), 4.60 (d, $J = 4.2$ Hz, 2H, 4-H and 1-H), 4.36 (t, $J = 8.0$ Hz, 1H, 11-H), 3.99 (t, $J = 8.0$ Hz, 1H, 11-H), 3.90 (s, 3H, 4′-OCH_3), 3.80 (s, 6H, 3′, 5′-OCH_3) 3.68 (br, 1H, exchangeable NH), 3.15 (dd, $J = 4.8$, 13.7 Hz, 1H, 2-H), 3.05 (m, 1H, 3-H); MS (FAB) 507 $[M]^{+\bullet}$; HRMS (FAB): calcd for $C_{28}H_{26}O_7NF$ 507.5114, found: 507.1693.