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A High Yield Preparation of 2-Fluoropodophyllotoxin[1]

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Abstract: The high yield synthesis of 2-fluoropodophyllotoxin is presented. This preparation represents the first example of a 100% diastereospecific electrophilic fluorination.

Podophyllum pelatum L. (commonly known as the American mandrake or May apple) (also *Podophyllum emodi L.*) is the source of the natural product podophyllotoxin (**1**), which is used clinically for the treatment of angogenital warts.[2] Two semisynthetic derivatives, etoposide (**2**) and teniposide (**3**), are clinically useful against various neoplasms, including germ-cell

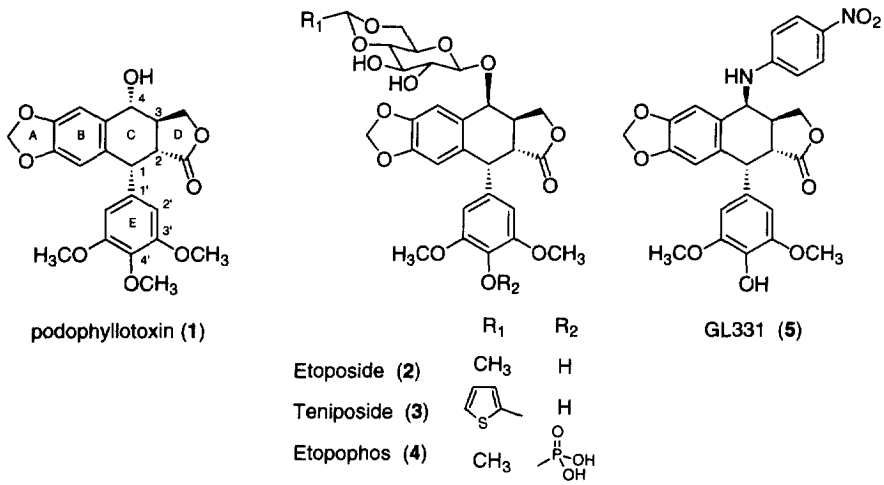

Figure 1. Structure of Podophyllotoxin and its Derivatives.

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malignancies, small-cell lung cancer, non-Hodgkin's lymphomas, leukemias, Kaposi's sarcoma, neuroblastoma, and soft-tissue sarcomas.[3] Recently, a water-soluble pro-drug of etoposide, Etopophos™ (**4**), was approved for clinical use.[4] Another semi-synthetic derivative, GL331 (**5**), prepared in our laboratory and licensed to Genelabs Technologies, Inc., is currently undergoing Phase II clinical trials against several forms of cancer, including gastric carcinoma, colon cancer, non-small cell carcinoma, and etoposide-resistant malignancies.[5]

Because of the rich biological activity associated with podophyllotoxin and its derivatives, its metabolism has also been extensively examined. Three non-conjugative hydrolytic metabolites, all involving the D ring lactone, have been observed in the metabolic inactivation

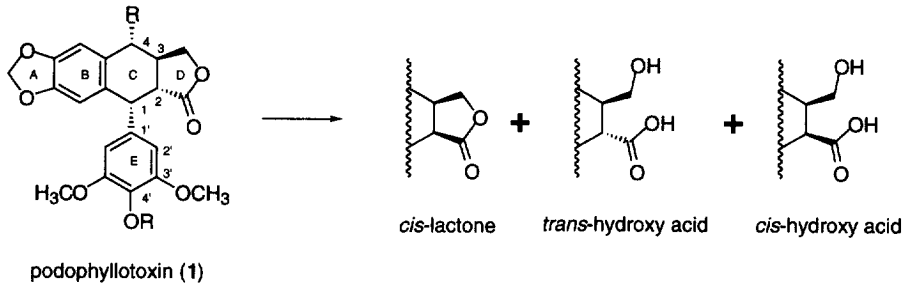
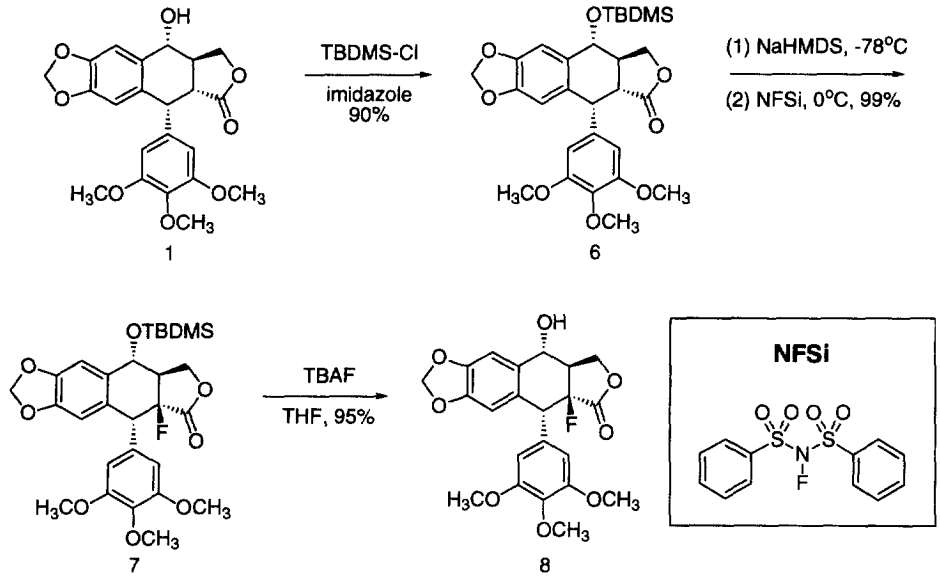


Figure 2. The Metabolism of Podophyllotoxin and its Derivatives.

and clearance of the drug: the *cis*-lactone, the *trans*-hydroxy acid, and the *cis*-hydroxy acid (Figure 2). All three metabolites are inactive as anti-neoplastic and anti-viral agents.[6]

Podophyllotoxin and etoposide also epimerize to the inactive *cis*-lactone when exposed to very mild base (piperidine in t-butyl alcohol).[7] The standard free-energy for this equilibrium was determined to be –2.18 kcal/mol at 31°C, translating to a 97.5:2.5 ratio favoring the inactive *cis*-lactone. These two problems have prompted extensive work into the preparation of nonenolizable podophyllotoxin derivatives. Many different approaches have been taken, including replacing the D-ring lactone with furan, thiolane, thiolanyl sulfone, and cyclopentane rings.[8] Derivatives substituted at the 2-position have also been prepared.[9] Glinski, *et al.*, were able to prepare the 2-methyl, 2-chloro, 2-bromo, and 2-hydroxy derivatives of **1**. In their attempt to prepare the 2-fluoro derivative using LDA/$FClO_3$ at –78°C, they reported 'a violent explosion, causing serious injury.'

Using a newly developed electrophilic fluorinating agent, we were able to successfully prepare 2-fluoropodophyllotoxin in excellent yield as shown in Scheme 1. Thus, using Corey's procedure, the secondary alcohol was protected as the TBDMS ether in 90% yield to give **6**,[10,11] which was fluorinated, using a combination of the procedures of Davis[12] and Differding,[13,14,15] to give **7**. This reaction was completely diastereospecific; only the correct isomer was evinced by NMR. The fluorine coupling constants, 36.1 Hz with H-3 and 10.9 Hz with H-1, confirmed the stereochemistry at the C/D ring junction as *trans*. Although others have obtained excellent diastereoselectivities in the fluorination of enolates,[16] to the best of our knowledge this reaction is the first example of a completely diastereospecific electrophilic fluorination. Deprotection of **7** with TBAF gave 2-fluoropodophyllotoxin (**8**) in 84.6% yield over three steps.[17]



Scheme 1. Synthesis of 2-Fluoropodophyllotoxin.

This family of compounds has exhibited excellent activity in both anti-viral and anti-neoplastic assays. The preparation and biological testing of related derivatives is underway and will be reported when it becomes available. The synthetic route outlined above provides an extremely efficient route for the preparation of 2-fluoropodophyllotoxin, and this methodology is being used to prepared 4β-anilino derivatives related to GL331.

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10. Yield = 90%. Pure **6** had the following data: $[\alpha]^D$= -87.8 (c = 1.16, $CHCl_3$); m. p. = 174.5 – 176°C; R_f = 0.85 (7:3 $CHCl_3$:EtOAc; ^1H NMR ($CDCl_3$) (400 MHz): ∂ 0.08 (s, 3H, Si-CH_3), 0.25 (s, 3H, Si-CH_3), 0.91 (s, 9H, Si-C(CH_3)), 2.80 (m, 1H, H-2, $J^3_{1/2}$ = 4.0 Hz, $J^3_{2/3}$ = undet.), 2.81 (m, 1H, H-3, $J^3_{2/3}$ = undet., $J^3_{3/4}$ = 8.4 Hz, $J^3_{3/11\beta}$ = 9.4 Hz, $J^3_{3/11\alpha}$ = 8.2 Hz), 3.78 (s, 6H, 3'-OCH_3), 3.71 (s, 3H, 4'-OCH_3), 3.96 (dd, 1H, H-11β, $J^3_{3/11\beta}$ = 9.4 Hz, $J^3_{11\alpha/11\beta}$ = 8.4 Hz), 4.48 (dd, 1H, H-11α, $J^3_{3/11\beta}$ = 9.4 Hz, $J^3_{11\alpha/11\beta}$ = 8.4 Hz), 4.52 (d, 1H, H-1, $J^3_{1/2}$ = 4.0 Hz), 4.76 (d, 1H, H-4, $J^3_{3/4}$ = 8.4 Hz), 5.91 (s, 1H, H-14β), 5.94 (s, 1H, H-14α), 6.34 (s, 2H, H-2'), 6.45 (s, 1H, H-8), 6.91 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$) (100 MHz): ∂ -3.86 (Si – CH_3), -4.13 (Si – CH_3), 17.98 (Si – C(CH_3)), 25.73 (Si – C(CH_3)), 40.55 (C-3), 44.09 (C-1), 45.34 (C-2), 55.98 (3'-OCH_3), 60.71 (4'-OCH_3),71.70 (C-11), 73.04 (C-4), 101.27 (C-14), 106.95 (C-5), 108.06 (C-2'), 109.36 (C-8), 131.10 (C-9), 133.65 (C-10), 135.35 (C-1'), 136.90 (C-4'), 147.35 (C-6), 147.36 (C-7), 152.49 (C-3'), 174.32 (C-13).
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15. Using all dry reagents, **6** (8.5 mmol scale) was dissolved in THF (50 mL) and cooled to -78°C. The NaHMDS (1.05 equivalents, 0.92M in THF) was slowly added via syringe over 10 min. After stirring at -78°C for 30 minutes the reaction was warmed to 0°C for 5 min and recooled to -78°C. The NFSi (1.08 equiv.), in 10 mL of THF, was added dropwise over 10 minutes. The reaction was warmed to ambient temperature over two hours at which time a white precipitate filled the flask. The entire mixture was partitioned into 200 mL of 1:1 $CHCl_3$:water and stirred for 20 min. The layers were separated, and the water layer was extracted with 3 x 50 mL of $CHCl_3$. The combined organic layers were washed with 3 x 100 mL of $NaHCO_3$ (aq, sat'd), 3 x 100 mL of water, dried over $MgSO_4$, and evaporated under reduced pressure. The clear oil was chromatographed on the FlashElute™ System using a 40M silica cartridge eluting with 4:1 hexanes:EtOAc. Yield = 99%. Pure **7** had the following data: $[\alpha]^D$= -105.9 (c = 0.89, $CHCl_3$); m. p. = 72 - 74°C; R_f = 0.69 (7:3 hexanes:EtOAc; ^1H NMR ($CDCl_3$) (400 MHz): 0.10 (s, 3H, Si-CH_3), 0.29 (s, 3H, Si-CH_3), 0.92 (s, 9H, Si-C(CH_3)), 2.96 (dq, 1H, H-3, $J^3_{2F/3}$ = 36.1 Hz, $J^3_{3/4}$ = 8.8 Hz, $J^3_{3/11\alpha}$ = 8.4 Hz, $J^3_{3/11\beta}$ = 10.2 Hz), 3.72 (s, 6H, 3'-OCH_3), 3.78 (s, 3H, 4'-OCH_3), 4.32 (dd, 1H, H-11β, $J^3_{3/11\beta}$ = 10.2 Hz, $J^3_{11\alpha/11\beta}$ = 8.0 Hz), 4.53 (dd, 1H, H-11α, $J^3_{3/11\alpha}$ = 8.4 Hz, $J^3_{11\alpha/11\beta}$ = 8.0 Hz), 4.63 (d, 1H, H-1, $J^3_{1/2F}$ = 10.9 Hz), 4.95 (d, 1H, H-4, J^3_{34} = 8.8 Hz), 5.93 (s, 1H, H-14α), 5.97 (s, 1H, H-14β), 6.39 (s, 2H, H-2'), 6.47 (s, 1H, H-8), 6.93 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$) (100 MHz): ∂ -4.00 (Si – CH_3), -4.17 (Si – CH_3), 17.89 (Si – C(CH_3)), 25.71 (Si – C(CH_3)), 43.59 (C-3, $J_{C/F}$ = 18.3 Hz), 49.14 (C-1, $J_{C/F}$ = 24.8 Hz), 56.01 (3'-OCH_3), 60.72 (4'-OCH_3), 69.17 (C-4, $J_{C/F}$ = 6.8 Hz), 70.47 (C-11), 96.61 (C-2, $J_{C/F}$ = 174.1 Hz), 101.38 (C-14), 106.79 (C-5), 108.29 (C-2'), 109.59 (C-8), 127.96 (C-9), 132.14 (C-10), 132.51 (C-1', $J_{C/F}$ = 10.8 Hz), 137.39 (C-4'), 147.54 (C-6), 147.87 (C-7), 152.85 (C-3'), 169.57 (C-13, $J_{C/F}$ = 23.9 Hz); ^{19}F NMR ($CDCl_3$) (376 MHz) (internal $CFCl_3$), ∂ -168,13 (dd, $J^3_{2F/3}$ = 36.1 Hz, $J^3_{1/2F}$ = 10.9 Hz).
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17. Yield = 95%. Pure **8** had the following data: $[\alpha]^D$= -121.1 (c = 0.30, acetone); m. p. = 166 - 167°C; R_f = 0.25 (1:1 hexanes: EtOAc; ^1H NMR ($CDCl_3$) (400 MHz): 2.46 (b, 1H, 4-OH), 2.90 (dq, 1H, H-3, $J^3_{2F/3}$ = 35.2 Hz, $J^3_{3/4}$ = 9.6 Hz, $J^3_{3/11\alpha}$ = 8.2 Hz, $J^3_{3/11\beta}$ = 9.4 Hz), 3.73 (s, 6H, 3'-OCH_3), 3.79 (s, 3H, 4'-OCH_3), 4.40 (dd, 1H, H-11β, $J^3_{3/11\beta}$ = 9.4 Hz, $J^3_{11\alpha/11\beta}$ = 8.4 Hz), 4.61 (dd, 1H, H-11α, $J^3_{3/11\alpha}$ = 8.2 Hz, $J^3_{11\alpha/11\beta}$ = 8.4 Hz), 4.67 (d, 1H, H-1, $J^3_{1/2F}$ = 12.1 Hz), 4.95 (d, 1H, H-4, J^3_{34} = 9.6 Hz), 5.95 (s, 1H, H-14α), 5.98 (s, 1H, H-14β), 6.40 (s, 2H, H-2'), 6.50 (s, 1H, H-8), 7.10 (s, 1H, H-5); ^{13}C NMR ($CDCl_3$) (100 MHz): ∂ 43.54 (C-3, $J_{C/F}$ = 18.3 Hz), 49.27 (C-1, $J_{C/F}$ = 25.1 Hz), 56.25 (3'-OCH_3), 60.73 (4'-OCH_3), 68.46 (C-4, $J_{C/F}$ = 8.2 Hz), 70.27 (C-11), 96.55 (C-2, $J_{C/F}$ = 174.4 Hz), 101.47 (C-14), 106.16 (C-5), 108.60 (C-2'), 109.86 (C-8), 127.94 (C-9), 132.07 (C-10), 132.55 (C-1', $J_{C/F}$ = 101.0 Hz), 137.50 (C-4'), 147.66 (C-6), 147.99 (C-7), 152.84 (C-3'), 168.72 (C-13, $J_{C/F}$ = 24.1 Hz); ^{19}F NMR ($CDCl_3$) (376 MHz) (internal $CFCl_3$) ∂ -168,82 (dd, $J^3_{2F/3}$ = 35.2 Hz, $J^3_{1/2F}$ = 12.1 Hz).