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# Synthesis of New Fluorinated Podophyllotoxin Derivatives

Xue Ying HE, Tian YI, Yan Guang WANG *

Department of Chemistry, Zhejiang University, Hangzhou 310027

**Abstract**: Five fluorinated podophyllotoxin derivatives were synthesized using dimethylaminosulfurtrifluoride (DAST).

**Keywords:** Podophyllotoxin derivatives, fluorination, dimethylaminosulfur trifluoride (DAST).

Semisynthetic analogues of the naturally occurring podophyllotoxin (**1**) have drawn much interest in the last two decades as a result of the development of etoposide (VP-16) and teniposide (VM-26) as anticancer drugs[1]. It is believed that such analogues of 4′-demethylepipodophyllotoxin exert their antitumor activity through stabilization of a cleavable complex between DNA and type II DNA topoisomerase. This leads ultimately inhibition of DNA catenation activity and produces single and double strand breaks[2].

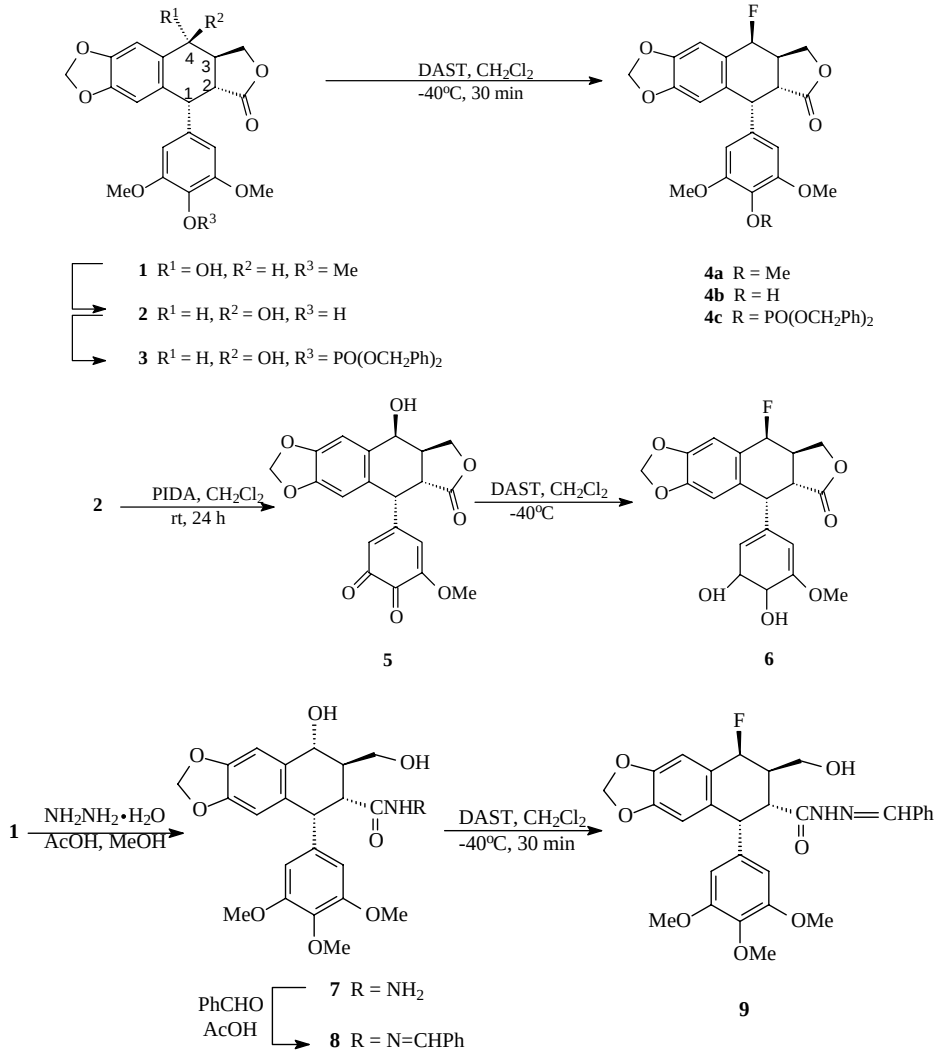
Previously, we have synthesized a series of 4-substituted podophyllotoxin derivatives and found that some of them exhibited superior pharmacological properties compared with podophyllotoxin as well as VP-16[3]. In the last two decades, it has been well established that the introduction of fluorine atom into some biomolecules could result important modifications of their biological properties[4]. More recently, Lee and co-workers[5] found that 2-fluoropodophyllotoxin exhibited potent activity against KB carcinoma. These results promoted us to synthesize and evaluate more fluorinated podophyllotoxins. In this letter, we would like to report the synthesis of five new 4-fluorinated podophyllotoxin derivatives **4a-c**, **6** and **9**.

Dimethylaminosulfur trifluoride (DAST) has been used in the preparation of monofluorinated and difluorinated derivatives from the corresponding alcohols and ketones[6]. We started our work by fluorination of podophyllotoxin **1** using DAST. As shown in **Scheme 1**, **1** was reacted with DAST in $CH_2Cl_2$ at –40℃ for 30 min to afford 4β-fluorinated 4-deoxypodophyllotoxin **4a** in 93% yield. The assignment of the configuration at C-4 position for compound **4a** was based on its $J_{3,4}$ coupling constants (2.2Hz). The 4β-substitued compounds have a $J_{3,4} \leq 4.5$Hz, due to the *cis* relationship between H-3 and H-4, while the 4α-substituted isomers have a $J_{3,4} \geq 10.0$Hz as H-3 is *trans* to H-4[7]. The $^1$H NMR signed with $J$=54 Hz showed the coupling constant between H and F at C-4 position.

Using similar procedure with the synthesis of compound **4a**, we obtained 4β-

* E-mail: orgwyg@css.zju.edu.cn

**Scheme 1**.




fluorided 4′-demethyl-4-deoxypodophyllotoxins **4b** and **4c** from 4′-demethylepi-podophyllotoxin **2**[8] and its phosphate **3**[9], respectively.

Compound **2** was oxidated with phenyliodonium diacetate (PIDA) in $CH_2Cl_2$ to give 3′,4′-orthoquinone of epipodophyllotoxin **5**[10] at room temperature. The fluorination of **5** with DAST resulted in 4β-fluorinated compound **6**. In this reaction, the orthoquinone of **5** was transformed into orthodiphenol simultaneously, which was confirmed by X-ray crystal structure data and by comparison of the chemical shift of 2′,6′-H of **6** (6.28 and 5.80 ppm) with that of **5** (6.53 and 5.20 ppm). We also synthesized a lactone-opening podophyllotoxin analogue **9** by regioselective fluorination of **8**[11], which could be prepared from **1** in two steps[12].

**Table 1** Physical properties and analytic data of compounds **4a-c, 6** and **9**

| Compound | Yield (%) | m.p. (°C) | IR (KBr) ($cm^{-1}$) | MS (ESI) *m/z* |
|---|---|---|---|---|
| **4a** | 93 | 177-179 | 1772 (lactone), 1586, 1506, and 1487 (aromatic C=C) | 439 ($[M+Na]^+$) |
| **4b** | 91 | 176-178 | 1765 (lactone), 1611, 1520 and 1483 (aromatic C=C) | 425 ($[M+Na]^+$) |
| **4c** | 90 | 68-70 | 1778 (lactone), 1599, 1508 and 1484 (aromatic C=C) | 663 ($[M+H]^+$) |
| **6** | 75 | 260-262 | 1773 (lactone), 1602, 1513 and 1486 (aromatic C=C) | 387 ($[M-H]^-$) |
| **9** | 78 | 180-182 | 1666, 1589 and 1493 (aromatic C=C) | 535 ($[M-H]^-$) |

**Table 2** $^1$H NMR data of compounds **4a-c**, **6** and **9**

| Compound | δ (ppm), *J* (Hz) |
|---|---|
| **4a** | 6.94 (s, 1H), 6.59 (s, 1H), 6.27 (1s, 2H), 6.01 (d, 2H, *J*=14.7 Hz), 5.62, 5.51 (dd, 1H, *J*=2.2, 54.2 Hz), 4.68 (d, 1H, *J*=1.9 Hz), 4.41 (t, 1H, *J*=8.0 Hz), 4.33 (t, 1H, *J*=8.8 Hz), 3.80 (s, 3H), 3.74 (s, 6H), 3.27 (dd, 1H, *J*=5.0, 14.3 Hz), 3.02-2.83 (m, 1H). |
| **4b** | 8.29 (s, 1H), 7.12 (s, 1H), 6.61 (s, 1H), 6.18 (s, 2H), 6.05 (d, 2H, *J*=14.0 Hz), 5.78, 5.67 (dd, 1H, *J*=2.0, 54.1 Hz), 4.59 (s, 1H), 4.45(t, 1H, *J*=7.8 Hz), 4.13 (t, 1H, *J*=8.9 Hz), 3.62 (s, 6H), 3.25 (dd, 1H, *J*=5.1, 14.6 Hz), 3.02- 2.82 (m, 1H). |
| **4c** | 6.94 (s, 1H), 6.57 (s, 1H), 6.38 (s, 2H), 6.29 (s, 1H), 6.01 (d, 2H, *J*=14.0 Hz), 5.60, 5.49 (dd, 1H, *J*=1.9, 54.1Hz), 4.69 (d, 1H, *J*=2.2 Hz), 4.41 (t, 1H, *J*=8.1 Hz), 4.343 (t, 1H, *J*=10.5 Hz), 3.26 (dd, 1H, *J*=4.9, 14.3 Hz), 3.10- 2.79 (m, 1H). |
| **6** | 7.12 (s, 1H), 6.61 (s, 1H), 6.28 (s, 1H), 6.05 (d, 2H, *J*=10.0 Hz), 5.80 (s, 1H), 5.77, 5.66 (d, 1H, *J*=2, 54. 1 Hz), 4.52 (s, 1H), 4.46 (t, 1H, J=8.8 Hz), 4.12 (t, 1H, *J*=9.2 Hz), 3.63 (s, 3H), 3.21 (d, 1H, *J*=10.2 Hz), 2.87 (m,1H). |
| **9** | 8.39 (s, 1H), 7.75 (d, 2H, *J*=5.2 Hz), 7.41 (d, 2H, *J*=1.4 Hz), 7.40 (s, 1H), 6.97 (s,1H), 6.61 (s, 1H), 6.39 (s, 2H), 6.02 (d, 2H, *J*=14.5 Hz), 5.68, 5.57 (dd, 1H, *J*=2.7, 54.0Hz), 4.77 (s, 1H), 4.54 (t, 1H, *J*=8.0 Hz), 4.40 (t, 1H, *J*=8.7 Hz), 3.62 (dd, 1H, *J*=4.8, 13.9 Hz), 2.96- 2.88 (m, 1H). |

All fluorinated podophyllotoxins were characterized by IR, $^1$H NMR as well as MS spectra, and the results are summarized in **Table 1** and **Table 2**. The biological evaluation of synthesized compounds is in progress and the results will be reported elsewhere.

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10. Compound **5**: mp.211-213℃. $^1$H NMR (500MHz, $CDCl_3$) δ ppm 6.83 (s, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 6.01 (d, 2H, *J*=3.2 Hz), 5.20 (s, 1H), 4.83 (d, 1H, *J*=3.0 Hz), 4.51 (d, 2H, *J*=5.0 Hz), 4.28 (d, 1H, *J*=5.7 Hz), 3.85 (s, 3H), 3.48 (dd, 2H, *J*=5.7, 14.1 Hz), 2.81 (m, 1H).
11. Compound **8**: $^1$H NMR (500MHz, DMSO-$d_6$) δ ppm 11.56, 11.12, (d, 1H, *J*=220 Hz), 8.16, 7.92 (d, 1H, *J*=120 Hz), 7.75 (m, 1H), 7.63 (t, 1H, *J*=5.8 Hz), 7.40 (m, 3H), 6.84 (d, 1H, *J*=5.2 Hz ), 6.49 (d, 2H, *J*=16.9 Hz), 6.26 (d, 1H, *J*=7.6 Hz), 5.92 (s, 2H), 5.47, 5.41 (dd, 1H, *J*=4.5 Hz), 4.75 (d, 1H, *J*=3.3 Hz), 4.47 (m, 1H), 4.17 (t, 1H, *J*=10.1 Hz), 3.41 (d, 1H, *J*=7.6 Hz), 3.01-2.86 (m, 1H).
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