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Fluorination of triptolide and its analogues and their cytotoxicity

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Abstract—The reaction of triptolide and its analogues with a fluorinating agent, that is, bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) or (diethylamino)sulfur trifluoride (DAST), was studied. One of the fluorinated products, 14β-dehydroxy-14β-fluoro triptolide, was found to be more cytotoxic than the parent natural triptolide.

Fluorination of biologically active natural products is known to sometimes enhance the activity. Therefore, in the medicinal chemistry, fluorination of such compounds is often designed and studied[1] by using dimethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor), well-known efficient nucleophilic fluorinating reagents for hydroxyl and carbonyl groups.[2] Of triptolide (**1a**) and its related compounds (**2**–**4**) isolated from *Tripterygium wilfordii* (Celastaceae) (Fig. 1), **1a**, **2**, and **3** have a unique triepoxide system on the B/C ring system, which is reported to be associated with the cytotoxic activity.[3,4] In our previous paper on the synthesis of triptolide analogues,[5] we reported that the stereochemistry at C-14 and the presence of 12α, 13α-oriented epoxide might be important and essential factors for the triptolide analogues to show cytotoxic activity. This present paper describes the reactions of natural triptolide and its analogues with these fluorinated agents and the cytotoxic activities of the products on human tumor cells.

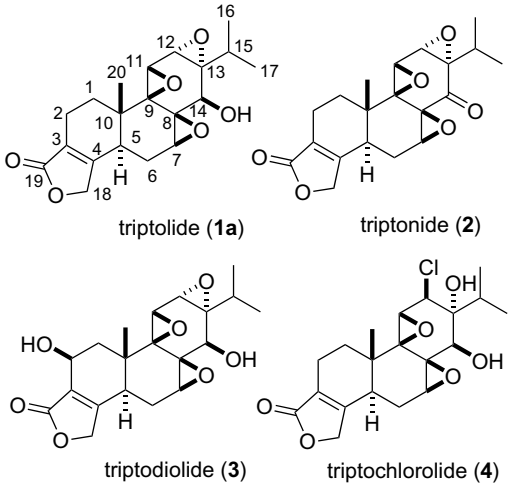

Figure 1. Triptolide (**1a**) and its related compounds (**2**–**4**) from *Tripterygium wilfordii*.

Starting material **1a** was isolated from *T. wilfordii*, and the other starting materials, 14-*epi*-triptolide (**1b**) and 12α-hydroxytriptolide (**8**), were prepared from **1a** according to the reported procedure.[4] Compound **2** was also prepared for comparison by the procedure described.[5] Fluorination of triptolide (**1a**) proceeded efficiently to give the corresponding 14α-fluorinated analogue (**5a**) in 77% yield, as reported in Ref. 6 (Scheme 1).

On the other hand, fluorination of 14-*epi*-triptolide (**1b**) gave the corresponding 14β-oriented fluorinated compound (**5b**) in very poor yields along with a series of by-products. The reactions of **1b** with DAST or Deoxo-Fluor under several different reaction conditions are summarized in Table 1. When the reaction was car-

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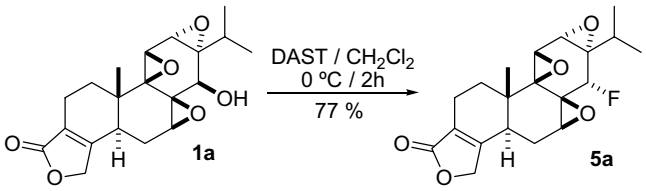


Scheme 1. Reaction of triptolide (**1a**) with DAST.

ried out with DAST at 0 °C for 3 h, for example, the corresponding 14β-fluorinated compound **5b** was obtained in a yield of 12%, along with **6**, **7**, **5a**, and the starting material **1b** in yields of 28%, 20%, 6%, and 2%, respectively (entry 2 in Table 1). The addition of bases[7] apparently had no effect (entries 6–8 in Table 1). The difference in the reactivity was not observed between the two fluorinating agents, DAST and Deoxo-Fluor (entries 3 and 9 in Table 1). The structures of the products were determined on the basis of ^{1}H and ^{13}C NMR, of which those of **5a**, **b**, and **6** were further confirmed by the X-ray crystallographic analysis. The ORTEP representation of **6** is shown in Figure 2.[8]

The plausible reaction mechanism involved in the reactions producing **5a**, **b**, **6**, and **7** from **1b** is shown in Scheme 2. Thus, by the reaction with DAST, **1b** gave a carbocation **B** via the corresponding intermediate **A**. Some of the carbocation **B** gave, by further skeletal rearrangement, an intermediate **C**. By a nucleophilic attack

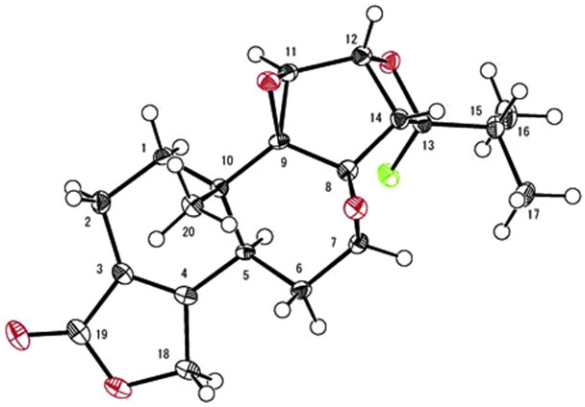
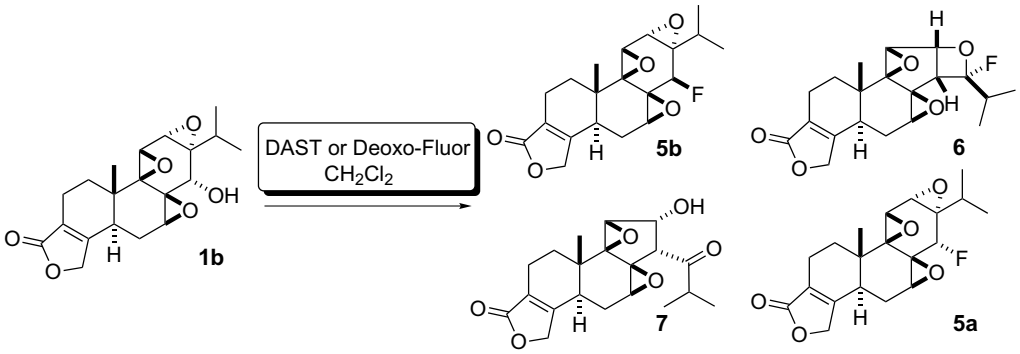


Figure 2. ORTEP representation of compound **6**.

by a fluoride anion, **B** gave 14α- and β-fluoro triptolide analogues **5a** and **b**, whereas **C** gave **6**. When the reaction mixture was treated with water after the reaction, **7** was considered to have been produced from the remaining **C** via hemi-acetal **D** (Scheme 2). Rearrangement of bicyclic α-oxiranyl cyclohexanol to the oxabicyclo[3.2.0] system is to be reported for the first time in this paper, though a skeletal rearrangement of bicyclic α-oxiranyl cyclooctanol to oxabicyclo[5.2.0] system with DAST is known.[9]

Fluorination of **8** gave, as shown in Scheme 3, α- and β-fluorinated triptolide analogues (**9a** and **9b**) in 11% and

Table 1. Reactions of 14-*epi*-triptolide (**1b**) with fluorinating agents under several reaction conditions



Entries	Reaction conditions[a]				Yields[b] (%)				
	Fluorinating agents (equiv)	Additives (equiv)	Reaction temp. (°C)	Reaction time (h)	**5b**	**6**	**7**	**5a**	**1b**
1	DAST (5)	None	−78	3	—	—	—	—	89
2	DAST (5)	None	0	3	12	28	20	6	2
3	DAST (5)	None	0	4	12	32	32	7	—
4	DAST (5)	None	rt	4	13	35	35	6	3
5	DAST (10)	None	0	4	10	23	28	6	2
6	DAST (5)	Pyridine (10)	0	4	—	—	—	—	62
7	DAST (5)	Et_3N (10)	0	4	—	—	—	—	88
8	DAST (5)	Et_3N (5)	60	4	—	—	—	—	85
9	Deoxo-Fluor (5)	None	0	4	11	32	32	10	2
10	Deoxo-Fluor (5)	None	rt	4	10	23	27	6	4

[a] The reaction was performed by adding a fluorinating reagent to a CH_2Cl_2 solution of **1b**. After the reaction, the reaction mixture was treated with AcOEt, washed with water, and evaporated to give a crude reaction product, which was separated by HPLC (column RP-18; eluting solvent MeCN:H_2O (45:55); detection by UV 215 nm).

[b] Yield after HPLC separation.