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ON THE REACTION OF TAXOL WITH DAST

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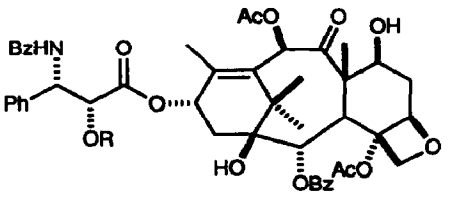
Abstract: Treatment of 2'Cbz taxol (2) with DAST yields several interesting new products, including 7-α-fluoro derivative 3a and a cyclopropane - containing product, 4a.

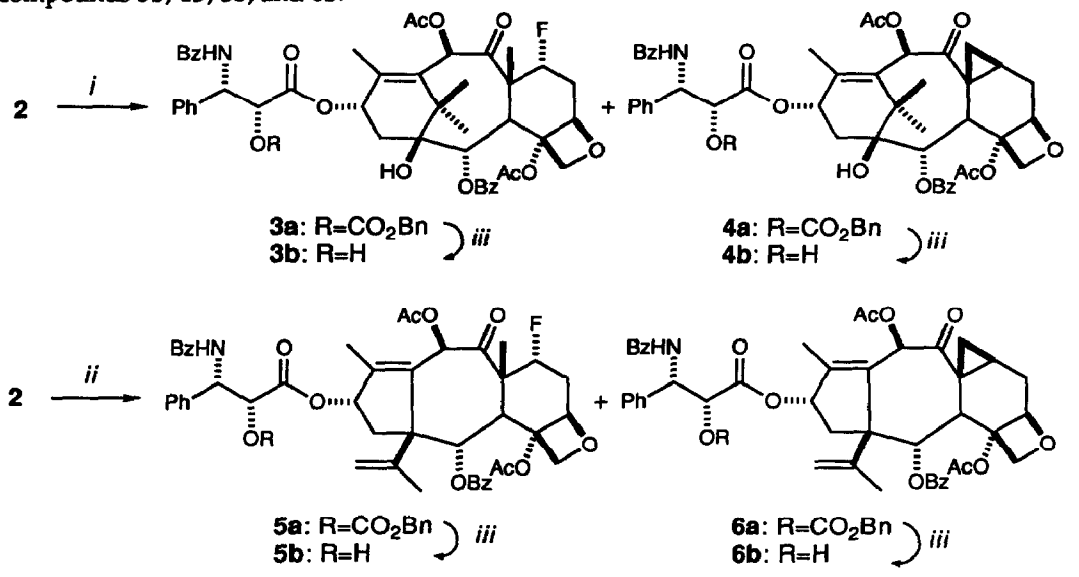
Taxol (1) is an exceptionally promising anti-tumor agent with an unusually broad spectrum of anti-tumor activity.[1,2] It has been shown that taxol prevents cell proliferation by stabilizing microtubules and therefore blocking mitosis.[3] The mode of interaction between taxol and microtubules at the molecular level is unknown, however, in order to begin to address this important issue, we have initiated a study aimed at the systematic modification of the many functional groups contained in the taxol tetracyclic core.



R=H; **1 *Taxol***
R=CO_2Bn; **2**

Replacement of hydroxyl groups with fluorine atoms in bioactive molecules has become an important area of medicinal research.[4] With this in mind, we have decided to prepare 7-fluorotaxol for biological evaluation. Protected taxol 2 was chosen as our starting material for this study since the direct fluorination of taxol with DAST caused an undesired reaction at the side chain.[5] When a dichloromethane solution of 2 was treated with DAST (2 eq), 7-(α)-fluoro derivative 3a [6] and 7,19-cyclopropane derivative 4a [7] were produced. More prolonged treatment with DAST led to A-ring contracted taxol derivatives 5a and 6a. Treatment of a dichloromethane solution of 2 with 4 eq of DAST yielded 57% of 5a together with 38% of 6a.

Control experiments established that **5a** or **6a** did not interconvert in the presence of DAST. Standard hydrogenation of these products with palladium on charcoal yielded compounds **3b**, **4b**, **5b**, and **6b**.

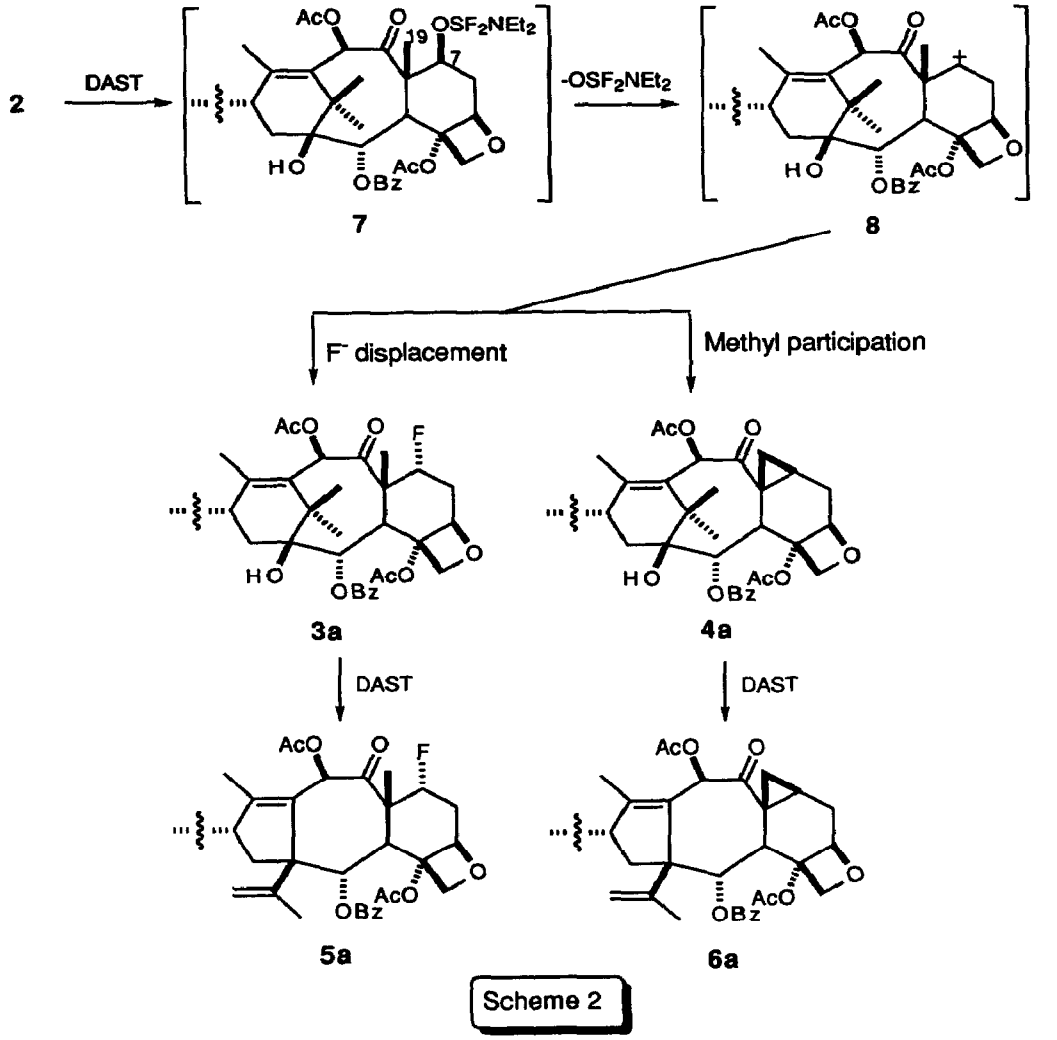


Scheme 1

Reagents and conditions: (i) DAST (2 eq.), CH_2Cl_2, rt: **3a**, 54.5%, **4a**, 32%; (ii) DAST (4 eq.), CH_2Cl_2, rt: **5a**, 57%; **6a**, 38%; (iii) H_2, Pd/C, EtOAc: **3b**, 88%; **4b**, 90%; **5b**, 82%; **6b**, 88%.

Mechanistically, the fluorination of **2** with DAST [8] (Scheme 2) is believed to proceed via intermediate **7**, which may suffer fluoride displacement in an S_N2 manner with inversion of configuration, or simply produce carbocation **8**. Fluoride ion is expected to preferentially attack **8** from the α face, due to the steric hindrance imposed by C-19 methyl group. The C-19 methyl group can also participate to form cyclopropane derivative **4a**, presumably via a protonated cyclopropane.[7] The A-ring contraction reaction has been described previously by Kingston.[2,9] It appears therefore that intermediate carbonium ion **8** is capable of explaining the formation of all products.

Some of the above taxol analogs modified at C-7 (i.e. **3b** and **4b**) showed excellent ability to polymerize tubulin *in vitro*, and displayed potent cytotoxicity in a typical sensitive line (HCT-116).[10] These data suggest that the functional group at C-7 in taxol does not significantly interact with the microtubule binding site.



Scheme 2

Acknowledgements: We thank Dr. S. Mamber for the tubulin polymerization data and Dr. C. Fairchild for the cytotoxicity results. We would also like to thank J.M. Wei for preliminary work. We are grateful to Dr. D.M. Vyas and Dr T.W. Doyle for suggestions and encouragement.

References and Notes:

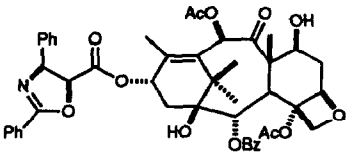
(1) Rowinsky, E.K.; Cazenave, L.A.; Donehower, R.C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247.

(2) For a recent review on taxol chemistry, see: Kingston, D.G.I. *Pharmac. Ther.* **1991**, *52*, 1.

(3) Manfredi, J.J.; Horwitz, S.B. *Pharmac. Ther.* **1984**, *25*, 83.

(4) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123.

(5) The following product was obtained when taxol was treated with DAST in CH_2Cl_2 at 0°C:



(6) The nOe experiment of **3a** showed a significant nOe between the H-6' proton and the H-19 proton, indicating a β-position for the H-6' proton. The ^1H NMR spectrum showed a large vicinal J(F, $H_{6\beta}$) coupling constant of 45.1 Hz. This suggests that H-7 has the β-configuration (δ: 4.55). Also, ^2J(F,H-7)=46.6Hz, ^3J(F,H-6β)=45.1Hz, ^3J(F,H-6α)=24.2Hz.

(7) The core structure of cyclopropane **4a** was secured by X-ray crystallography. The data will be published in forthcoming paper. Also see: Chen, S.H., Huang, S., Wei, J.M., Farina, V. *J. Org. Chem.* **1993**, *58*, 4520.

(8) Middleton, W.J. *J. Org. Chem.* **1975**, *40*, 574.

(9) Samaranayake, G., Magri, N.F., Jitrangsri, C., Kingston, D.G.I. *J. Org. Chem.* **1991**, *56*, 5114.

(10) The detailed biological evaluation of these compounds will be published in due time.

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