First Syntheses of Novel Paclitaxel(Taxol) Analogs Modified at the C4-Position

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Received July 29, 1994®

Summary: A highly regiospecific method for the modification of paclitaxel at the C-4 position has been invented, as exemplified by the synthesis of the C-4 cyclopropyl ester of paclitaxel (**4**) and the C-4 benzoate of paclitaxel (**5**).

Paclitaxel, **1**, an antimitotic agent isolated from the bark of *Taxus brevifolia*,[1] has recently attracted much attention due to its efficacy in the treatment of various types of cancer.[2,3] The exciting therapeutic profile of this compound, coupled with its limited availability[4] and unique mode of action,[5] have made it the subject of intensive synthetic[6] investigations and structure–activity relationship (SAR) studies (Figure 1).[7]

Potier's group has reported docetaxel (Taxotere, **2**), an analogue which contains a simple side chain modification and which has shown promising activity in early clinic trials.[8] Encouraged by this exciting result, we have launched a program aimed at modification of each position of the core. As a result of such efforts, we have found that removal of the functional groups at C-7[9] and C-10[10] does not alter drug potency dramatically. In contrast, modification of the C-2 benzoate at its para-position or removal of the C-2 benzoate moiety completely destroys the antitumor activity.[11,12] Very recently, Kingston,[13] Georg,[14] and Guéritte-Voegelein[15] reported the synthesis of C-4-deacetylpaclitaxel (**3**). Compound **3** was found to be less potent than paclitaxel **1** in several *in vitro* assays.[13,15] Nevertheless, no C-4 reacylated paclitaxel analogues have been reported. In view of these research efforts at the C-4 position, we are prompted to disclose our own methodology for the modification of the C-4 position. Herein, we report a highly regioselective method for the preparation of novel C-4 paclitaxel analogues, as exemplified by the synthesis of the C-4

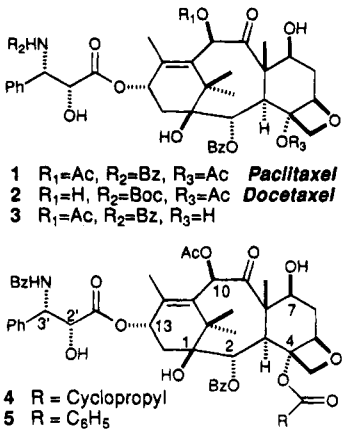

Figure 1.

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® Abstract published in *Advance ACS Abstracts,* October 1, 1994.

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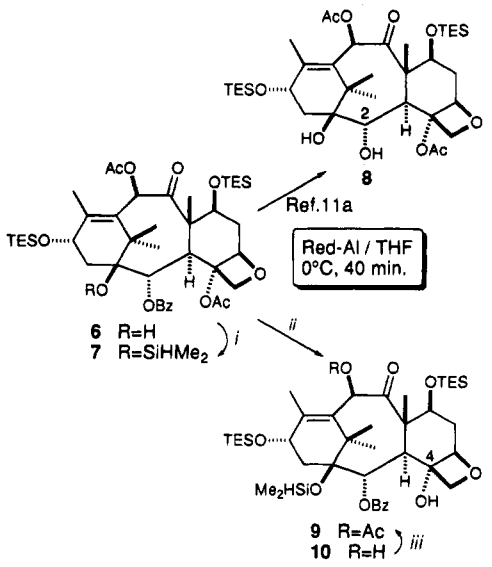
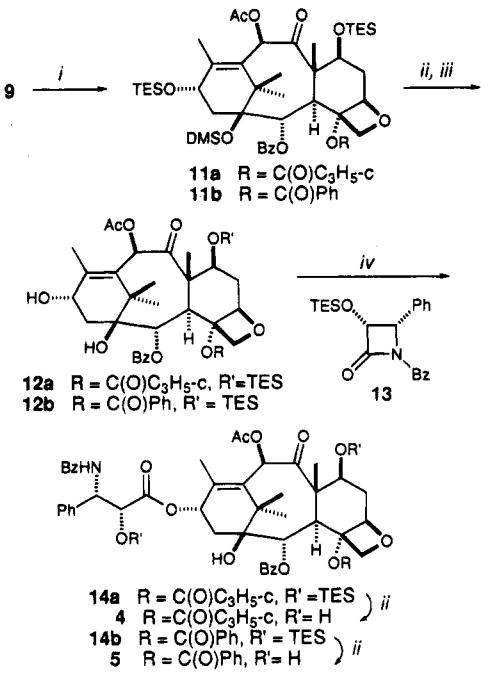
Scheme 1[a]



[a] Reagents and conditions: (i) Me_2HSiCl/imidazole/DMF/0 °C, 97%; (ii) Red-Al/THF/0 °C, 66% of **9**, plus 16% of **10**; (iii) AcCl/pyridine/5 °C, 84%.

Scheme 2[a]



[a] Reagents and conditions: (i) LHMDS/THF/0 °C, then cyclopropanecarbonyl chloride, 75% for **11a**; 80% for **11b**; (ii) pyridine/48%HF/CH_3CN/5 °C; then (iii) TESCl/imidazole/DMF/0 °C, 68% for **12a**; 51% for **12b**; (iv) LHMDS/ THF/−40 °C, then **13**, 0 °C, 80% for **14a**; 70% for **14b**; (ii) 92% for **4**; 85% for **5**.

cyclopropyl ester analogue **4** and the C-4 benzoate analogue **5**.

We endeavored first to find a selective method for deacetylation at C-4 (from **7** to **9**), followed thereafter by C-4 reacylation of alcohol **9**, as shown in Scheme 1. Although methods for the regioselective deacylation at C-2,[11a] C-10,[7a,h] and C-13[4a] have been established, a method for *selective* C-4 deacetylation remained to be developed. Difficulties were indeed encountered in our initial attempts involving reduction of 7,13-bisTES baccatin III (**6**)[11a] with either $LiAlH_4$ or DIBAL, as complicated mixtures of products were generally obtained. After considerable experimentation, we finally decided to attempt the Red-Al-mediated reduction on the C-1 dimethylsilane (DMS)-protected baccatin III (**7**). This design was based on the assumption that the specific coordination of Red-Al with the oxetane ring oxygen would facilitate the selective reduction of the very hindered C-4 acetate in **7**. To prevent concomitant C-2 reduction, the coordination of Red-Al with the C-1 hydroxyl group had to be blocked. The coordination of Red-Al with the C-1 hydroxyl group leads to the chemoselective removal of C-2 benzoate (from **6** to **8**), as we recently reported (Scheme 1).[11a] It should be noted that this is the first example of the use of dimethylsilane (DMS) as a protecting group. Attempts to introduce the standard TMS group failed, presumably due to the hindered nature of the tertiary carbinol at C-1. The dimethylchlorosilane is a smaller, more reactive reagent than the corresponding trimethylsilyl chloride. Indeed, treatment of 7,13-bisTES-1-DMS baccatin III (**7**) with Red-Al afforded a good yield of the desired C-4 deacylated baccatin derivative **9** (66%), along with small amounts of the C-4,10 bisdeacylated baccatin derivative **10** (16%). Fortunately, diol **10** could be converted back to **9** in high yield *via* a C-10 reacetylation according to Greene's protocol[16] (see Scheme 1).

With the desired C4-deacetyl baccatin derivative **9** in hand, we had to develop a suitable C-4 reacylation method. Toward this end, the treatment of a tetrahydrofuran solution of **9** with lithium bis(trimethylsilyl)amide, followed by cyclopropanecarbonyl chloride or benzoyl chloride, afforded two C-4 acylated baccatin derivatives **11a** and **11b** in 75 and 80% yield (Scheme 2). *This constitutes a highly efficient sequence for the regioselective deacylation (**7** to **9**) and reacylation (**9** to **11**) of the C-4 position.* Intermediates **12a** and **12b** were obtained in 68% and 51% overall yield using a sequence of desilylation and selective C-7 resilylation. Final side chain attachment onto baccatin **12** (**a,b**), using β-lactam **13**[17] as the side chain precursor, was achieved readily *via* Holton's methodology,[18] and afforded **14a,b**. Standard desilylation provided the desired C-4 cyclopropyl paclitaxel **4** and C-4 benzoate paclitaxel **5** in excellent yield (Scheme 2).

Table 1. In Vitro Cytotoxicity Evaluation of Analogs 4 and 5

compd	IC_{50} (nM) HCT-116
1 (Paclitaxel)	2.4
4	1.0
5	411

Analogs **4** and **5** were evaluated in an *in vitro* cytotoxicity assay against a human lung carcinoma cell line (HCT-116) after 72 h drug exposure.[19] As can be seen in Table 1, C4-cyclopropyl paclitaxel analog **4** was more potent than paclitaxel. On the other hand, C4-benzoate analog **5** possessed only much reduced cytotoxicity. Additional *in vitro* and *in vivo* studies are in progress and the results of these investigations will be reported shortly.

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In summary, we believe that the methodology developed herein will be of great value for the preparation of novel C-4 substituted paclitaxel analogs.[20] The results from biological evaluation of these C-4 analogues will enable us to further our understanding of the interaction between the C-4 substituent and its receptor–tubulin, perhaps allowing us to design better paclitaxel analogs.

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Acknowledgment. We are grateful to Dr. D. M. Vyas and Dr. T. W. Doyle for their valuable suggestions and encouragement.

Supplementary Material Available: Full experimental details and ^{1}H-NMR data for all new compounds (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.