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# Selective C-2 and C-4 Deacylation and Acylation of Taxol: The First Synthesis of a C-4 Substituted Taxol Analogue

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***Abstract:*** Hydrolytic procedures for selective 2-debenzoylation and 2,4-dideacylation of 2'-*O*-*tert*-butyldimethylsilyl-7-*O*-(triethylsilyl)taxol are reported. The first synthesis and biological evaluation of a 4-substituted analogue, 4-deacetyl-4-isobutanoyltaxol, is presented. The chemistry described in this letter is suitable for the facile synthesis of taxol congeners modified at C-2 and/or C-4.

The clinical efficacy,[1] chemistry[2] and structure-activity relationships[3,4] of the anticancer drug taxol (**1**) isolated from the western yew, *Taxus brevifolia*,[5] have been studied extensively in recent years. Most structure-activity relationships studies have focused on the synthesis and biology of C-13 phenylisoserine side chain analogues.[3,4,6] However, more recently a number of reports have appeared, detailing the effects of structural alterations on the diterpene moiety of taxol on biological activity.[3,4,6] These studies revealed that modification at the southern part of the taxol molecule (C-1 to C-5) typically effect the biological activity more than alterations at the northern part (C-6 to C-12).[3,4,6]

In this letter we are reporting synthetic strategy for the preparation of 2-modified analogues which is superior to a recently reported method[7] for the selective 2-debenzoylation of silyl protected taxol.[8,9] In addition, we are detailing the synthesis and biological activity of the first 4-substituted taxol analogue, 4-deacetyl-4-isobutanoyltaxol (**11**).

In a continuation of our studies on the selective hydrolysis of baccatin III derivatives,[9] we have found that 2'-*O*-*tert*-butyldimethylsilyl-7-*O*-(triethylsilyl)taxol (**2a**) can be selectively hydrolysed with anhydrous KOH [10] to yield the corresponding 2-debenzoyl- and 2,4-dideacyltaxol derivatives **3a** and **6**, respectively (**Scheme**). When analogue **2a** was treated with 1.2 equiv of anhydrous KOH at -15 °C for 24 h, 2-debenzoyltaxol **3a** was obtained in 70-80% yield (**Scheme**). Utilization of 4 equivalents of anhydrous KOH at -20 °C for 72 h (**Scheme**) gave 75% of 4-deacetyl-2-debenzoyl-2'-*O*-*tert*-butyldimethylsilyl-7-*O*-(triethylsilyl)taxol (**6**).

The starting material (**2a**) for the synthesis of these derivatives is either generated by silyl protection of taxol (**Scheme**) or semisynthetically by reacting 7-*O*-(triethylsilyl)baccatin III with the appropriate optically active *N*-benzoyl β-lactam.[11] The silyl protecting group at the 7-hydroxyl group in **2a** is needed to avoid the well known base induced epimerization at C-7.[12] The rationale for our choice of protecting group at 2' is the generation of steric hindrance at the C-13 ester group, thereby avoiding its hydrolysis. Previous studies on taxol and baccatin III[13] had demonstrated that mild methanolysis results in the hydrolysis of the esters at C-10 and C-13.[5,14] The choice of placing a *tert*-butyldimethylsilyl protecting group at the 2' hydroxyl turned out to be of critical importance for the success of our reactions. For example, submitting 2',7-*O*-bis(triethylsilyl)taxol (**2e**) to the same reaction conditions led to a mixture of hydrolysis products, including C-13 side chain cleaved derivatives.[7] Our earlier studies[9] with baccatin III derivatives had demonstrated that the 2-benzoate group could be selectively hydrolysed with *tert*-BuOK while retaining the esters at C-10 and C-4. We believe that the selective 2-benzoate hydrolysis of taxol and baccatin III derivatives is facilitated by assistance of the neighboring C-1 hydroxyl. Debenzoylation of **2a** was also achieved with *tert*-BuOK at -15 °C for 72 h. The addition of $H_2O$ (formation of anhydrous KOH) enhanced the reaction rate (24 h instead of 72 h). Yields and product distribution were similar under both reaction conditions. In addition to 2-debenzoyl derivative **3a** (70-80% yield), we also isolated about 15% 2,4-dideacyl derivative **6**. The 4-acetate seems to be cleaved only in the absence of the 2-benzoate, suggesting assistance in its hydrolysis from the 2-hydroxyl. It is of interest to note that the analogous 2-debenzoylation of 10-acetyl-2'-*O*-(*tert*-butyldimethylsilyl)taxotere (**2b**) gave 85-89% yield of **3b**. No formation of 2,4-dideacylated product was observed. Standard acylation of **3a** with DCC/DMAP and 4-chlorobenzoic acid in toluene at 55 °C, followed by silyl deprotection gave 2-(4-chlorobenzoyl)-2-debenzoyltaxol (**5**) in 65% overall yield.

Since 2,4-dideacyl derivative **6** was observed as a byproduct in the 2-debenzoylation reaction, we explored whether **6** could be obtained as the major product by a change of reaction conditions. We found that using 2-3 equivalents of anhydrous KOH at -20 °C for 72 h in the hydrolysis reaction gave 75% of 4-deacetyl-2-debenzoyl-2'-*O*-*tert*-butyldimethylsilyl-7-*O*-(triethylsilyl)taxol (**6**).

We then investigated the conversion of derivative **6** to 4-acetyl modified taxol analogue **11** (**Scheme**). As precedented in recent taxol total syntheses,[15,16] the introduction of the acetyl group at the sterically encumbered 4-hydroxy group of baccatin III derivatives is possible after formation of a 1,2 cyclic carbonate. Thus, reaction of **6** with 1,1'-carbonyldiimidazole provided cyclic carbonate **7**, which was acylated at the C-4 hydroxyl group using isobutyric anhydride and DMAP to form acylated derivative **8** in 67% yield. Regioselective opening of the carbonate in **8** with PhLi (formation of **9** and **10**) followed by silyl deprotection led to 4-deacetyl-4-isobutanoyltaxol (**11**) in 46% and 4,10-dideacetyl-4-isobutanoyltaxol (**12**) in 18% yield.[17] It is noteworthy that treatment of **8** with PhLi was relatively selective and did not lead to a significant amount of undesired hydrolysis products. Thus, we have demonstrated for the first time that the conversion of the 1,2-cyclic carbonate with PhLi to its 2-benzoate analogue can be achieved in the presence of the C-13 phenylisoserine side chain.

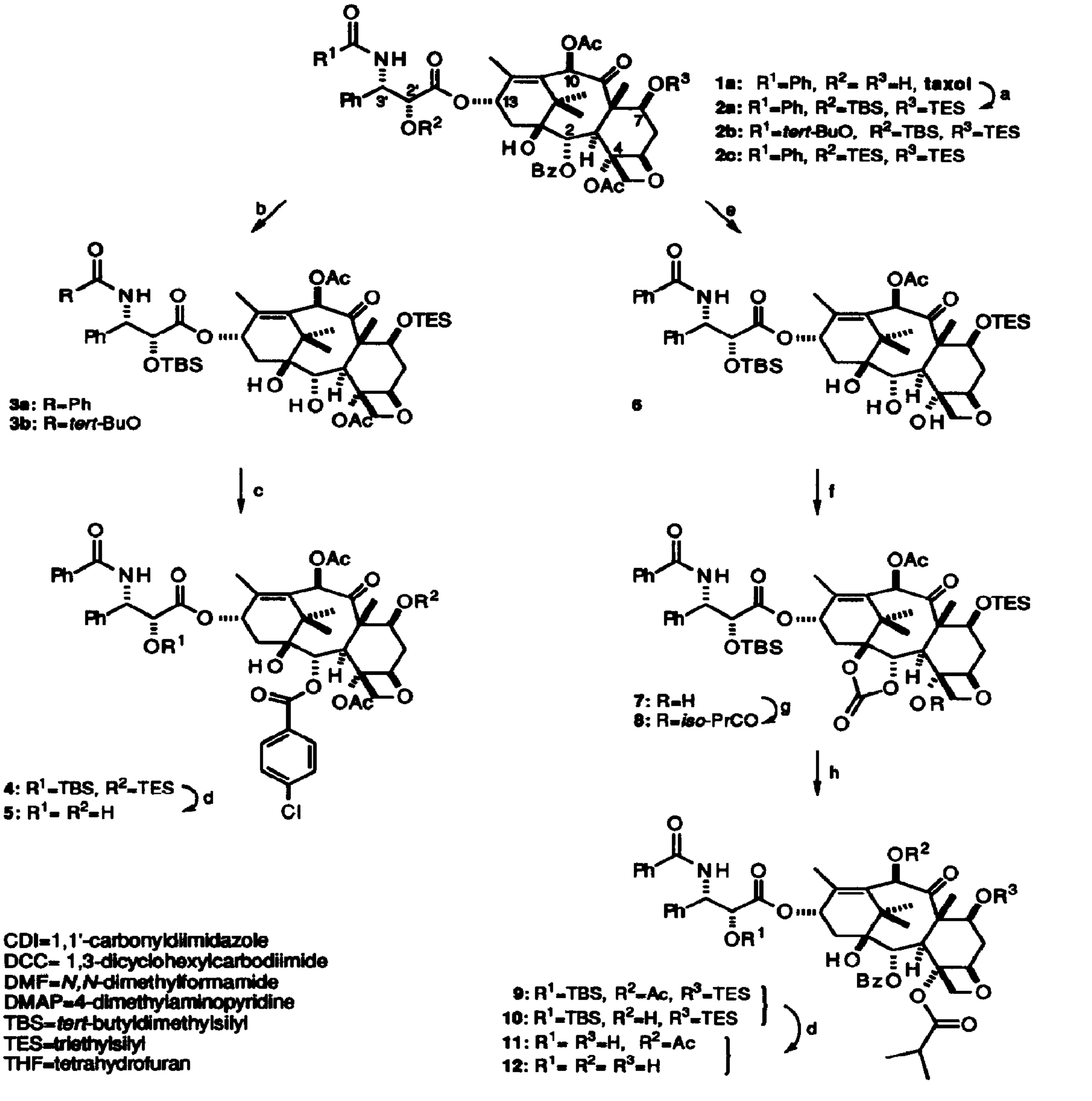
Derivatives **5** and **11** were investigated for their ability to stimulate the assembly of microtubules and for their cytotoxicity against B16 melanoma cells (**Table**). Derivative **5** was found to be slightly more active

**Table.** *In vitro* biological evaluation of taxol analogues **5** and **11**.[a]

| compound | microtubule assembly[b] $ED_{50}/ED_{50(taxol)}$ | B16 melanoma cytotoxicity[b] $ED_{50}/ED_{50(taxol)}$ |
|---|---|---|
| **1** | 1.0 | 1.0 |
| **5** | 0.79 | 3.1 |
| **11** | 2.6 | 4.5 |

[a]For experimental procedures see ref. 18. [b]Data reported relative to taxol = 1.0.

**Scheme**




(a) i. Imidazole (15 equiv), TBSCl (15 equiv), DMF, rt, 12 h, quant. ii. TESCl (10 equiv), pyridine, rt, 12 h: **2a**, 90%. (b) *tert*-BuOK (1.4 equiv), $H_2O$ (1.2 equiv), THF, -40 to -15 °C, 24 h: **3a**, 70-80%; **3b**, 85-89%. (c) DMAP (12 equiv), DCC (12 equiv), 4-chlorobenzoic acid (12 equiv), toluene, 55 °C, 6 h. (d) Pyridinium hydrofluoride, pyridine, 0 °C to rt, 4-6 h: **5**, 65% (from **3a**); **11**, 48% (from **8**); **12**, 18% (from **8**). (e) *tert*-BuOK (2.4 equiv), $H_2O$ (2.2 equiv), THF, -40 to -20 °C, 48 h, then *tert*-BuOK (1.2 equiv), $H_2O$ (1.1 equiv), THF, -40 to -20 °C, 24 h: **6a**, 75%. (f) CDI (20 equiv), THF, 55 °C, 6 h: **7**, 87%. (g) Isobutyric anhydride (20 equiv), DMAP (20 equiv), $CH_2Cl_2$, rt, 48 h: **8**, 67%. (h) PhLi (10 equiv), THF, -78 °C, 10 min.

than taxol in the microtubule assembly assay. However, compound **5** was about three times less cytotoxic against B16 melanoma cells, suggesting that the reduced activity is due to a difference in uptake and/or metabolism.[19] The 4-isobutyric derivative **11** was less active than taxol in both assays (**Table**).

In conclusion, we have developed efficient methodology for the hydrolysis of taxol derivative **2a** to its 2-debenzoyl and 2,4-dideacyl analogues **3a** and **6**, respectively.[20] The availability of these products will allow the investigation of structure-activity relationships of C-2 and C-4 modified taxol analogues. An efficient synthetic pathway was devised, suitable for the convergent synthesis of C-4 analogues of taxol.

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(19) Compound **5** also displayed reduced cytotoxicity in comparison to taxol against P388 murine leukemia cells and HL60 human leukemia cells. See reference 7.

(20) All newly prepared compounds displayed spectroscopic properties in agreement with their structures. Yields are unoptimized.


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