Synthesis and Structure-Activity Relationships of Novel Nor-Seco Analogs of Taxol and Taxotere

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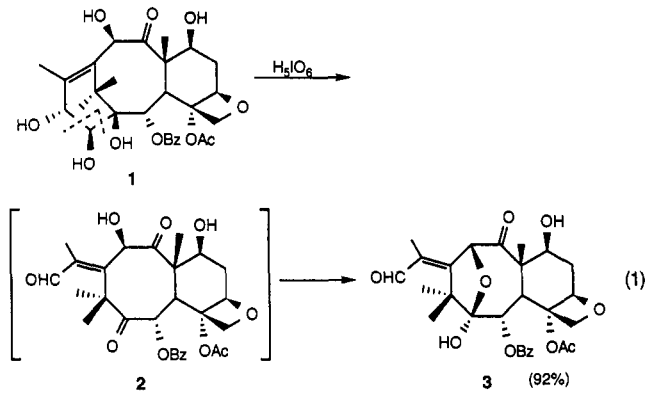
Summary: Novel nor-seco analogs of taxol and taxotere are synthesized from 14-hydroxy-10-deacetylbaccatin III through periodic acid oxidation and $NaBH_3CN$ reduction, followed by coupling with the C-13 side chain precursors using a highly efficient β-lactam synthon method. The new reduced structure analogs show muted cytotoxicity aganist human cancer cell lines compared with taxol but still retain a certain level of activity despite the destruction of the A ring.

Taxol isolated from the bark of *Taxus brevifolia* is currently considered one of the most exciting leads in cancer chemotherapy.[1-4] Taxotere, a semisynthetic analog, also has shown great promise.[5-9] Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs.[10,11] Taxol was approved by the FDA in late 1992 for the treatment of advanced ovarian cancer and is currently in phase II and III clinical trials for breast cancer and lung cancers.[12] Taxotere is currently in phase II and III clinical trials for different types of cancers in the United States, Europe, and Japan.[9,13]

Studies on the structure-activity relationships (SAR) of taxol and taxotere have disclosed the essential role of the *N*-acylphenylisoserine moiety at C-13 as well as the oxetane ring (D-ring) for their strong anticancer activity.[6,14-16] However, little is known of the SAR of the A and B rings of the baccatin framework. It is very important to clarify the minimum structural requirements for taxanes to exhibit anticancer activity by looking at simplified structure analogs of taxol. Along this line, we have investigated the role of the A ring by synthesizing novel nor-seco analogs of taxol and taxotere in which the A ring is cleaved but the B-D rings are retained.

The novel nor-seco baccatin 3 was synthesized in 92% yield through oxidative cleavage of the A ring of 14-β-hydroxy-10-deacetylbaccatin III (14-OH-DAB, 1) with periodic acid (eq 1). The new baccatin 1 was recently



isolated from the needles and other parts of *Taxus wallichiana Zucc.*[17,18] It should be noted that this oxidative cleavage is realized because of the presence of the hydroxyl group at C-14, i.e., this type cleavage is impossible for the usual 10-deacetylbaccatin III (DAB). The oxidative cleavage of 1 introduces a carbonyl to C-1 first, giving 2, which immediately reacts with the hydroxyl group at C-10 *in situ* to form the hemiacetal 3 (eq 1).

The hydroxyl group of 3 at C-7 was selectively protected as triethylsilyl (TES) ether to give 7-TES-nor-seco-baccatin (4) in 76% yield (eq 2). The aldehyde moiety of 4 was then reduced with sodium cyanoborohydride at pH 6[19] to afford 7-TES-nor-seco baccatin alcohol (5) in 80% yield (eq 2).

Finally, 7-TES-nor-seco baccatin alcohol (5) was coupled with *N*-acyl-3-EEO-β-lactams 6 (EE = ethoxyethyl; R = Ph or *tert*-butoxy)[20-23] using the new and highly efficient protocol developed in our laboratory[21] to give novel nor-seco-taxol (7) and nor-seco-taxotere (8) in fairly good to

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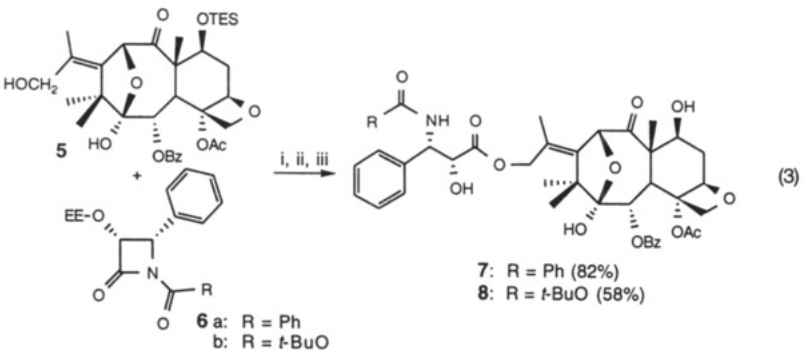
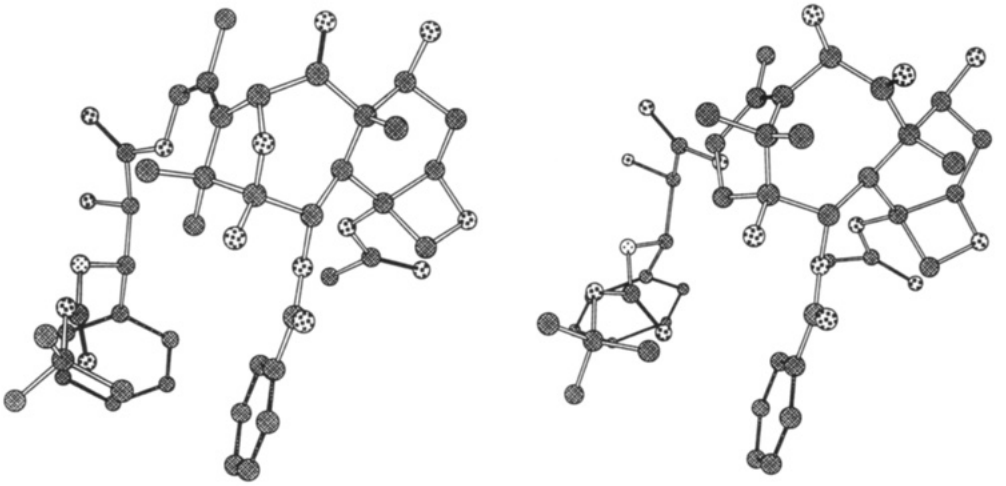
Scheme 1

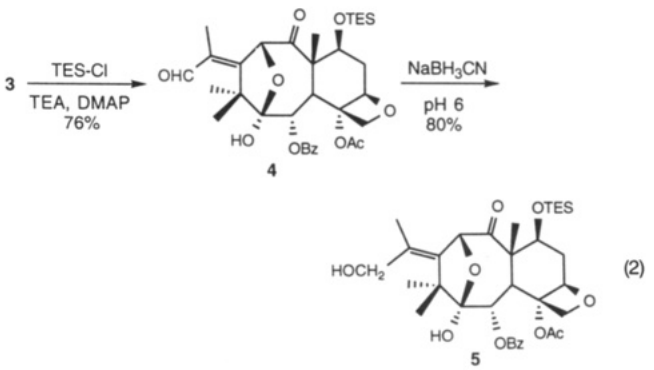


[a] Key: (i) NaHMDS, THF, −40 °C, 30 min; (ii) 0.5% HCl, 25 °C, 36 h; (iii) TBAF, THF, −10 °C, 5 min.



8 Taxotere®

Figure 1. Chem 3D representations of *nor-seco*-taxotere (8) and taxotere.



excellent yields (eq 3, Scheme 1). It is worthy of note that the removal of the 7-TES group was not possible under the standard acidic conditions (0.5% hydrochloric acid in methanol at room temperature for 36 h)[24] and was only accomplished with the use of tetra-*n*-butylammonium fluoride (TBAF) in THF at −10 °C for 5 min.

The antitumor activities of **7** and **8** were evaluated *in vitro* against human ovarian (A121), human non-small cell lung (A549), human colon (HT-29), and human breast (MCF7) cancer cell lines.[25] Both nor-seco analogs **7** and **8** showed 0.13–0.08 μM and 0.17–0.10 μM level IC_{50} values, respectively, which were 20–40 times weaker activities than taxol in the same cell line assay.[25] It is worthy of note that **7** and **8** exhibit IC_{50} values of 0.47 and 0.36 μM, respectively, against an adriamycin-resistant human breast cancer (MCF7-R) cell line,[25] i.e., **7** and **8** are only slightly weaker than the activities of taxol against this particular drug-resistant cancer cell.

The results obtained in this SAR study clearly indicate the importance of the A-ring for the strong cytotoxicity of taxol and taxotere. However, it is also very important to mention that these two reduced-structure analogs retain a certain level of cytotoxicity. As Figure 1 shows, the conformational analysis of **8** based on molecular modeling (SYBYL 6.0) indicates that this nor-seco analog can take

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(25) The tumor growth inhibitory activities of **7** and **8** were evaluated agaist human tumor cell lines A121 (ovarian carcinoma), A549 (non-small cell lung carcinoma), HT-29 (colon carcinoma), MCF7 (mammary carcinoma), or MCF7-R (mammary carcinoma cells 180 fold resistant to adriamycin) after 72 h drug exposure according to the assay method of Skehan et al.[26] IC_{50} values (nM) for **7** and **8** are as follows (the values in parentheses are for those of Taxol). A121: **7**, 117; **8**, 131 (6.1). A549: **7**, 133; **8**, 169 (3.6). HT-29: **7**, 134; **8**, 171 (3.2). MCF7: **7**, 79; **8**, 101 (1.7). MCF7-R: **7**, 471; **8**, 360 (299). The data represent the mean values of at least three separate experiments.

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a folded structure similar to that of taxotere or taxol. However, (i) **8** lacks hydroxyl groups at C-1 and C-10, (ii) the C-16 methyl is at the concave face (α-face) of the molecule, and (iii) the C-13 side chain conformation is rather flexible. These changes may account for the reduced cytotoxicity of the novel nor-seco analogs **7** and **8**. Further SAR study based on the modification of nor-seco-baccatins **35** is actively underway.

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Supplementary Material Available: General experimental procedures for the syntheses of **3–8** and characterization data for new compounds (4 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.