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Synthesis of the 2α-benzoylamido analogue of docetaxel

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Abstract—The 2α-benzoylamido analogue of docetaxel **2** was synthesized with a double inversion of the C-2 configuration as the key step, and its cytotoxic activity towards three tumor cell lines was tested.

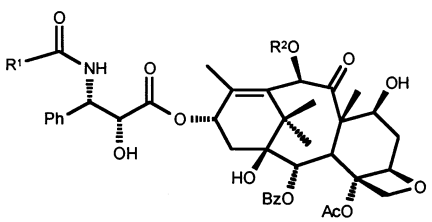
The chemistry of paclitaxel (=Taxol®, **1a**), a clinically important anticancer drug, has been extensively explored since the late 1980s. A variety of its analogues with modified core structures and C-13 substituted phenylisoserine side chains have been synthesized and biologically evaluated.[1,2] The marketing of docetaxel (=Taxotere®, **1b**), a paclitaxel derivative with better solubility in water and more potent cytotoxicities, is one of the fruitful results of these research efforts. It is now widely accepted that the southern hemisphere of the molecule, including the C-13 side chain, the C-2α aroyl and C-4 alkyl esters, is critical to the cytotoxicity of paclitaxel. 'Hydrophobic collapse' and other postulates were proposed to explain and predict the conformations of paclitaxel analogues binding to tubulin dimers.[3]

Studies on the SAR at the C-2 position showed that both the nature and stereochemistry of the 2-aroyl group are of great importance to activity. Loss of the 2-aroyl ester[4] or change of its orientation from α to β[5] were detrimental to its activity. Many paclitaxel analogues with different aroyl ester groups at the C-2 position in place of benzoate have been synthesized.[6] Replacement of the 2-ester with other heteroatom-containing linkages, such as amide or thioester, have not yet been realized. The synthesis and biological evaluation of 2-amido analogues will help to enrich our knowledge of the structural requirements of the 2-substituted groups. Herein we report a synthesis of the 2α-benzoylamido analogue of docetaxel **2** (Fig. 1).

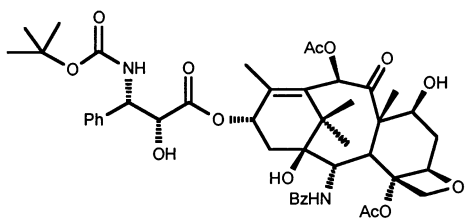
Our strategy for the introduction of the 2α nitrogen substituted group depended on the preparation of a key intermediate, the 2α-azido baccatin III derivative **6**, which was expected to be formed from a 2α-sulfonate by a double S_N2 substitution reaction.

10-Deacetylbaccatin III **3** was converted into 13-keto-7-TES-baccatin III **4** by the known procedure[7–9] with slight modification (Scheme 1).

Among the various methods for 2-debenzoylation,[10] Red-Al seemed to be the best choice for baccatin III



1a R^1=Ph R^2=Ac
1b R^1=*t*-BuO R^2=H



2

Figure 1.

Keywords: paclitaxel; docetaxel; 2-benzoylamido analogue of docetaxel; S_N2 double inversion.
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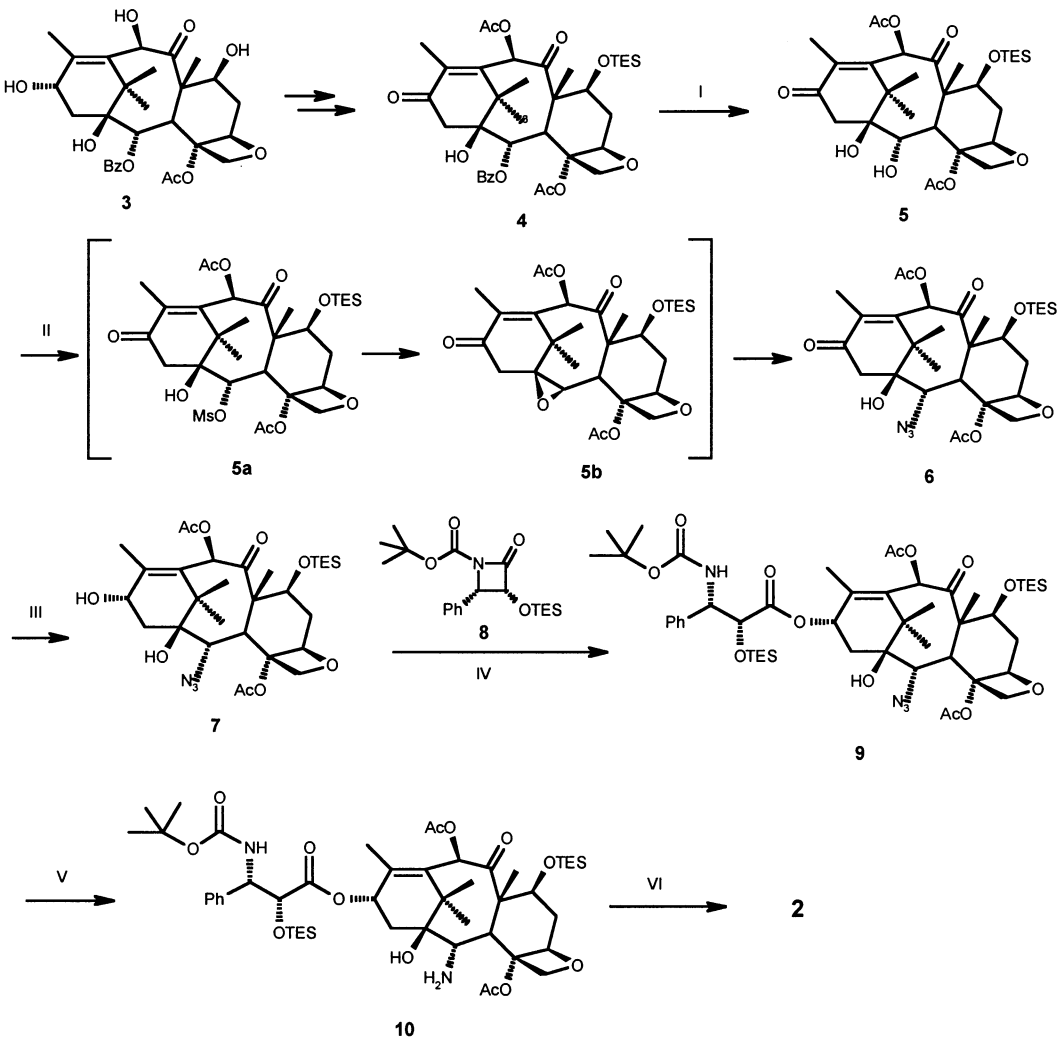
analogues. Unfortunately, treatment of **4** with Red-Al gave the desired product **5** in only 50% yield. After several experiments, **5** was finally obtained in 90% yield with Triton B (a modified Kingston's method).[5] Attempts to prepare the 2-*O*-triflate of **5** failed, whilst mesylation of **5** proceeded smoothly. Almost a single spot was detected as the product on TLC after mesylation. To our surprise, a mixture of two compounds in a 2:1 ratio was obtained after chromatography. It was shown by ^{1}H NMR that the major compound in this mixture is the 2-mesylate **5a**, and the minor one may be the 1,2-epoxide **5b** arising from intramolecular attack on the 2-mesylate by the 1-hydroxyl.[11]

It was reasoned that the 2-mesylate may not be stable to chromatography, hence we treated the mixture with sodium azide directly after aqueous workup. The desired 2α-azidobaccatin **6** was obtained in 72% yield over the two steps. The ^{1}H NMR of **6** showed the resonance of H-2 as a triplet (J=6.0 Hz), coupling to the 1-OH and H-3α.[12] The coupling constant between H-2 and H-3α revealed they are in a *trans* relationship. The β-orientation of H-2 was further confirmed by strong NOEs between H-2β, Me-16 and Me-19.

With the key intermediate **6** in hand, we embarked on further transformations to give the desired 2α-amido product. Stereoselective reduction of the 13-keto group in **6** to the 13α-hydroxyl compound **7** using $NaBH_4$ proceeded uneventfully. The attachment of the C-13 side chain was realized by coupling **7** with the β-lactam **8**.[13] The 2α-azido taxol analogue **9**, on catalytic hydrogenation, was transformed into the 2-amino compound **10** as the major product. Finally, **10** was subjected to benzoylation, and successive desilylation to obtain **2**.

Compound **2** showed antitumor activities towards three tumor cell lines, A-549, KB and A2780, although it was less potent than paclitaxel ($IC_{50}/IC_{50(paclitaxel)}$ 20.5, 16.8, 0.8). It is quite interesting to note that C-13 amido analogues of paclitaxel were inactive[14] whilst the C-2 amido analogue of docetaxel **2** retained activity to a great extent.



Scheme 1. (I) Triton B, CH_2Cl_2, −20°C, 88%; (II) (a) MsCl, Et_3N, CH_2Cl_2, −20°C; (b) NaN_3, DMF, 50°C, 72% for two steps; (III) $NaBH_4$, MeOH–THF, 0°C, 90%; (IV) LHMDS, THF, −15°C, 77% on 80% conversion; (V) H_2/Pd–C, EtOAc, rt, 60%; (VI) (a) BzCl, EtOAc–H_2O–$NaHCO_3$, rt; (b) HF–Py, rt, 46% for two steps.

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11. Mass spectrometry showed a weak peak at m/z 599 ($[M+Na]^+$) and a strong fragment at m/z 551 ($[M+H-O]^+$) suggesting the structure of the minor compound as the 1,2(β)-epoxide. It is not surprising that the 2α-N_3 compound **6** was obtained through this epoxide intermediate.
12. The coupling between H-2α and 1-OH is another puzzling observation. Although it was confirmed by ^1H–^1H COSY and deuterium exchange experiments, the unusual coupling across more than three bonds has not yet been explained reasonably.
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