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Taxane Anticancer Agents

Basic Science and Current Status

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Chapter 19

Syntheses and Structure–Activity Relationships of New Taxoids

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A series of new taxoids are synthesized from 14β-hydroxy-10-deacetylbaccatin III (14-OH-DAB). These new taxanes possess strong cytotoxicities against human cancer cell lines, and at least one of them possesses excellent antitumor activity *in vivo*. *Pseudo*-taxoids bearing *N*-acylphenylisoserine side chain at C-14 are synthesized, which are less active, but retain a certain level of cytotoxicity. Novel nor-seco-paclitaxel and docetaxel analogs are synthesized, which retain a certain level of activity despite the destruction of the A ring. New analogs bearing cyclohexyl groups at the C-3' and/or C-2 positions are synthesized and their cytotoxicity examined. The results clearly indicate that phenyl group at C-3' or C-2 is not a requisite for biological activity. 3'-Isobutenyl and 3'-isobutyl analogs of docetaxel show excellent activity against a drug-resistant cancer cell lines.

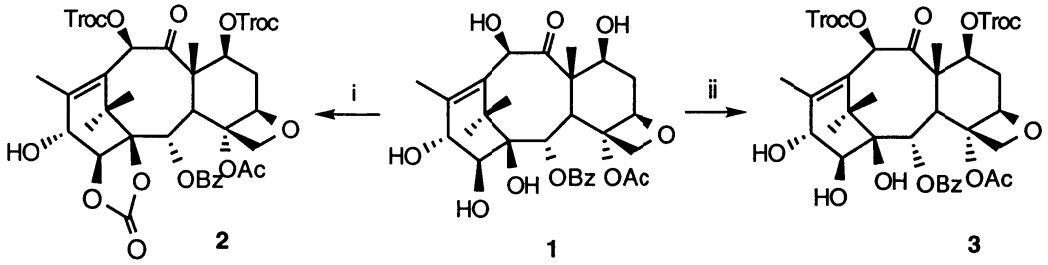
Taxol (paclitaxel), a complex diterpene isolated from the bark of the western yew (*Taxus brevifolia*) is currently considered the most exciting lead in cancer chemotherapy (*1-3*). Taxotere (docetaxel), a semisynthetic analog, also has shown great promise (*4*). Paclitaxel and docetaxel possess high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs

properties, and/or activity spectra against various tumor types different from those of these two drugs.

Recently, a novel taxane diterpenoid, 14β-hydroxy-10-deacetylbaccatin III (14β-OH-DAB), was isolated from the needles of *Taxus wallichiana Zucc.* and other plant parts (*8*). Because of an extra hydroxyl group at the C-14 position, 14β-OH-DAB has proven to possess much higher water solubility than the usual 10-deacetylbaccatin III (DAB) which is currently used for the practical production of paclitaxel and docetaxel as mentioned above. Therefore, the new antitumor taxanes derived from 14β-OH-DAB can be expected to have substantially improved water solubility, bioavailability, and hydrophobicity-related drug resistance (*7*). These improved pharmacological properties may well be related to the modification of undesirable toxicity and activity spectra against different cancer types. In fact, recent reports on the related "hydroxy-taxoids", 9-dihydrodocetaxel (*9*) and 19-hydroxydocetaxel (*10*), show quite promising results.

Syntheses of New Taxoids (*11*)**.** A series of new taxoids were synthesized from 14β-OH-DAB using a highly efficient and practical coupling protocol based on the *β-Lactam Synthon Method* developed in our laboratory (*13,14*). Thus, the C-13 side chain precursors, (3*R*,4*S*)-1-acyl-3-(EEO)-4-phenylazetidin-2-ones (**4-EE**) (EE = ethoxyethyl) with extremely high enantiomeric purity, were obtained through our efficient chiral ester enolate – imine cyclocondensation method (*12-14*) in four steps in 78-80% overall yields. The 7,10-ditroc-14β-OH-DAB (**3**, 75%) (troc = 2,2,2-trichloroethoxycarbonyl) and 7,10-ditroc-14β-OH-DAB-1,14-carbonate (**2**, 55%) were prepared by reacting 14β-OH-DAB with troc-Cl in pyridine (Scheme 1).

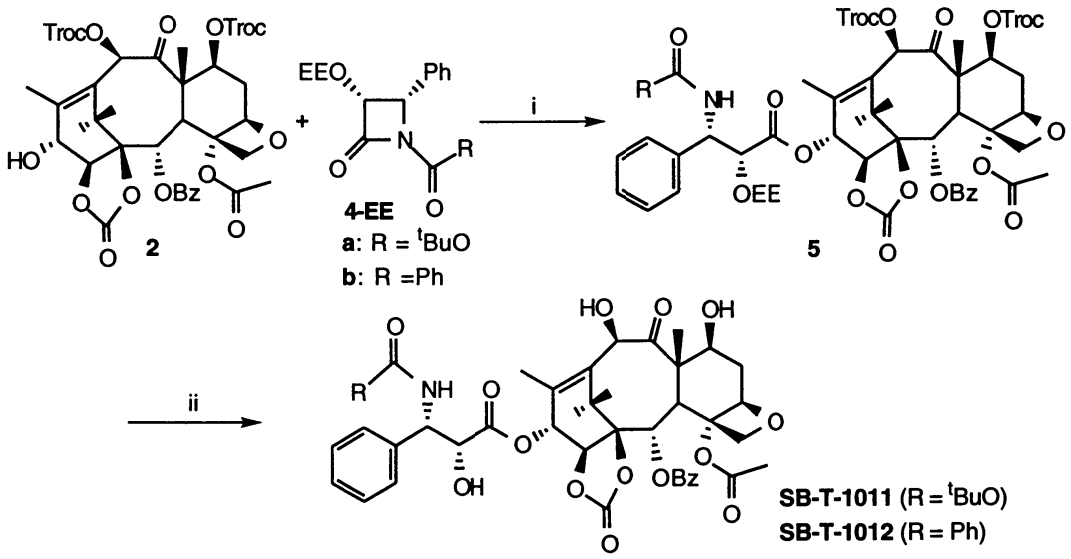
Scheme 1



(i) Cl_3CCH_2OCOCl (6 eq.), py, 80 °C, 5 min.; (ii) Cl_3CCH_2OCOCl (4 eq.), py, 80 °C, 5 min.

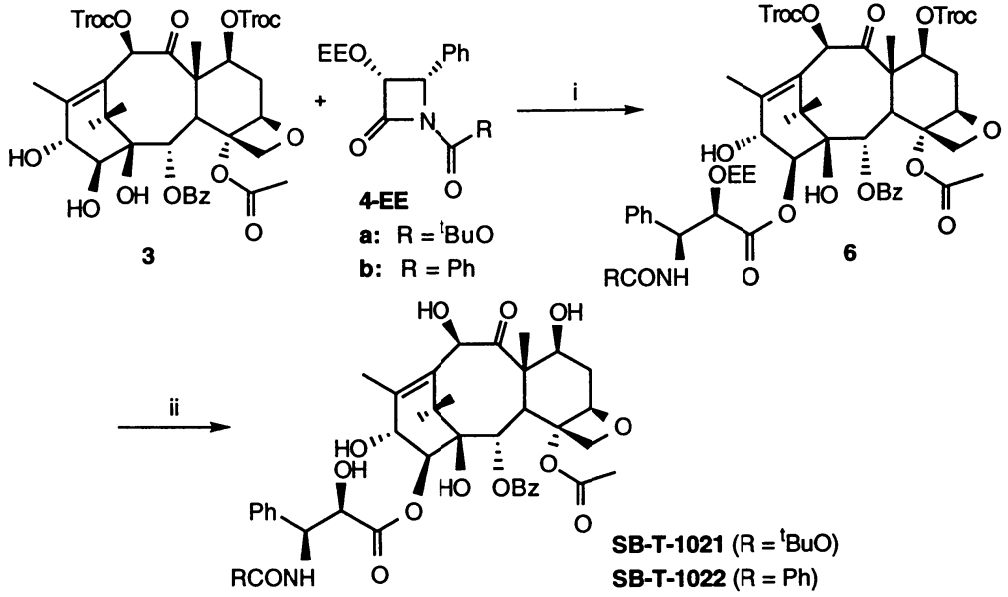
The reaction of **3** with β-lactam **4a-EE** (1.2 equiv.) was carried out in the presence of 1.2 equiv. of NaHMDS at -40 °C for 30 min to give 7,10-ditroc-2'-EE-14-hydroxy-docetaxel-1,14-carbonate (**5a**) in 86% yield (Scheme 2). The coupling product **5a** was deprotected under modified Commerçon conditions (*15*) by treating with activated Zn in acetic acid and methanol at 40 °C for 9 h to give 14-hydroxy-docetaxel-1,14-carbonate (**SB-T-1011**) in 70% yield (Scheme 2). 14β-Hydroxy-taxol-1,14-carbonate (**SB-T-1012**) was obtained in the same manner through the coupling of **2** with β-lactam **4b-EE** (1.2 equiv.) (89% yield) followed by deprotection (70% yield) (Scheme 2).

Scheme 2



(i). NaHMDS, THF, -40 °C, 30 min.; (ii) Zn (activated), AcOH, MeOH, reflux, 2 h.

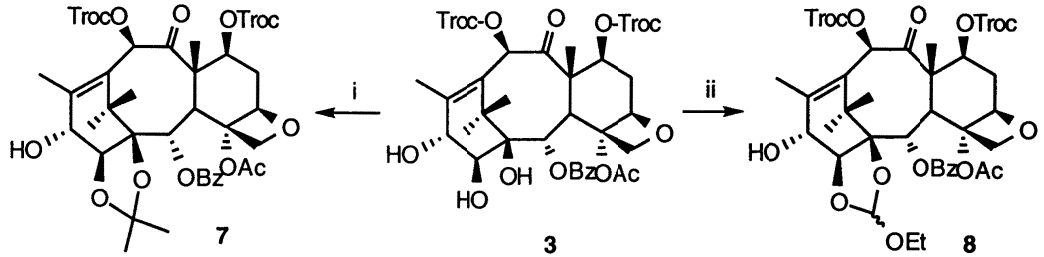
Scheme 3



(i). NaHMDS, THF, -40 °C, 30 min.; (ii) Zn (activated), AcOH, MeOH, 40 °C, 9 h.

(**8**) in 93% yield (Scheme 4) (*16*). This protecting group was found to be quite appropriate for the coupling with the C-13 side chain precursor (*vide supra*) and subsequent deprotections to give the desired 14β-hydroxydocetaxel (**SB-T-1001**).

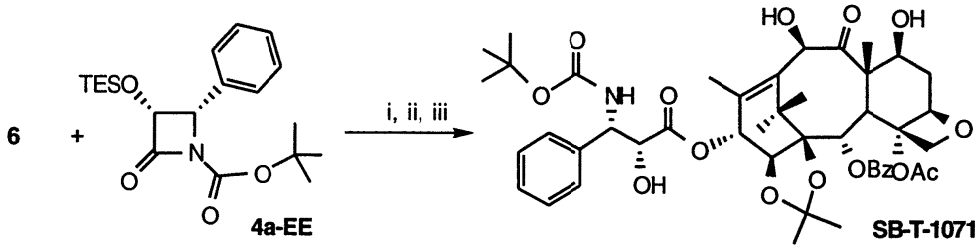
Scheme 4



(i) $Me_2C(OMe)_2$, TsOH, RT, 30 h; (ii) $HC(OEt)_3$, Ts_2O, CH_2Cl_2, RT, 30 min.

The protected 14-OH-DAB **7** was coupled with enantiopure (3*R*,4*S*)-1-t-BOC-3-TESO-4-phenylazetidin-2-one (**4a-TES**) using our protocol (*14*), i.e., NaHMDS in THF at -40 °C for 45 min, to give the corresponding coupling product in 82% yield. Since the 1,14-acetonide moiety of this compound cannot be removed without affecting the D-ring, the TES group at the 2'-position and the troc groups at the 7 and 10 positions were removed sequentially by treating with 0.5*N* HCl – THF (1:4) and then with zinc in 0.5*N* HCl – THF (1:4), respectively to give 14β-hydroxydocetaxel-1,14-acetonide (**SB-T-1071**) in 72% overall yield (Scheme 5) (*16*).

Scheme 5



(i) NaHMDS, THF, -40 °C, 30 min; (ii) 0.5*N* HCl in EtOH, RT, 2 h; (iii) Zn, 0.5*N* HCl/THF, 0 °C, 20 min.

In the same manner, the protected 14-OH-DAB **8** was coupled with **4a-TES**, giving **9** in 78% yield. Subsequently, **9** was first treated with 0.5*N* HCl in EtOH to remove the TES group at the 2'-position (96%), followed by reacting with formic acid in dioxane at room temperature for 24 h, yielding 14-formyl-7,10-ditroc-14-hydroxydocetaxel, which was treated *in situ* with 1% aqueous $NaHCO_3$ in THF–MeOH (1:7:3) at room temperature for 5 h to give 7,10-ditroc-14-hydroxydocetaxel (73% for two steps). The troc groups of this compound at the 7 and 10 positions were deprotected

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