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Synthesis of 5(20)deoxydocetaxel, a new active docetaxel analogue

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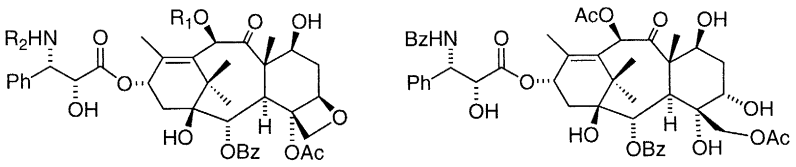
Abstract

5(20)Deoxydocetaxel was prepared from 13-oxo-10-deacetyl baccatin III. This compound is the first docetaxel analogue with a modified D-ring which is as active as paclitaxel on microtubules.

Keywords: taxoids; docetaxel; oxetane; 10-deacetyl baccatin III; microtubules.

Taxoids are a series of anticancer drugs[1] which inhibit cell growth by interacting with microtubules.[2] Paclitaxel (Taxol®) **1a**[3] and docetaxel, (Taxotere®) **1b**,[4] the leading compounds of this series, are effective clinical agents for the treatment of various cancers. Due to their original activity and their efficiency in cancer treatment, extensive studies have been made on structure–activity relationships in order to find out the minimal structural requirements to maintain microtubule binding.[5] These studies have established that the C-13 side chain, and the ester groups at C-2 and C-4 are essential for biological activity. Because of the inactivity of D-secopaclitaxel **2**,[6] the oxetan ring is also described to be essential for microtubule binding, but this compound lacks the C-4 ester group, known to be important for activity (Fig. 1).



Paclitaxel (Taxol®) **1a** R_1=Ac, R_2=Bz
Docetaxel(Taxotere®) **1b** R_1=H, R_2=Boc

2

Fig. 1.

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Only few taxoid analogues bearing modified D-ring have been synthesized: 5(20)aza derivative of a baccatin VI analogue,[7] 5(20)azadocetaxel and its N-derivatives **5**[8] and a close analogue of 5(20)thiopaclitaxel **6**[9] (Fig. 2). All demonstrated reduced interaction with microtubules, suggesting effectively an important role for the oxetan in microtubule binding. However, in the course of our structure–activity relationship studies on the oxetan ring, we have synthesized 5(20)deoxydocetaxel **7**, a new docetaxel analogue with a modified D-ring as active as paclitaxel on cold-induced microtubule disassembly. We wish to report in this letter its synthesis and its biological evaluation.

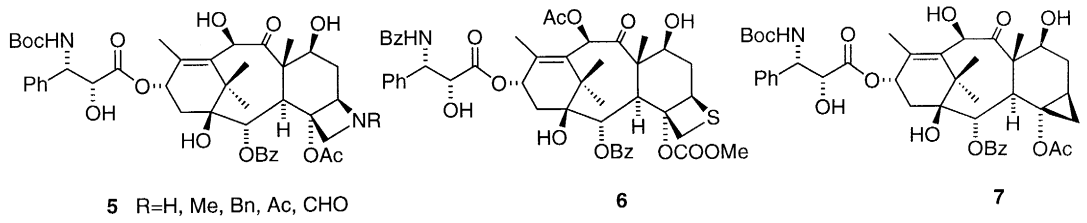
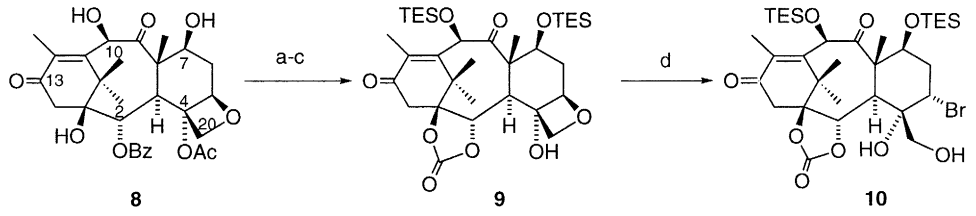


Fig. 2.

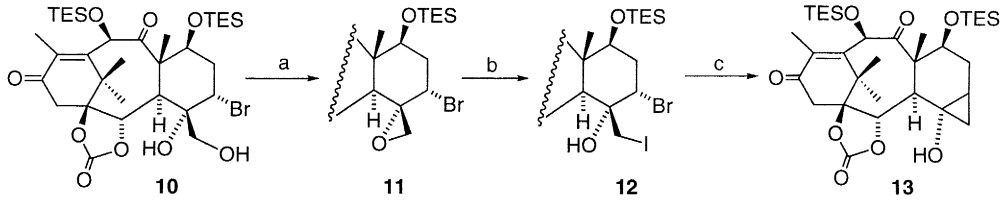
5(20)Deoxydocetaxel has been synthesized according to the same scheme as 5(20)azadocetaxel.[8] In order to further carry out selective deprotection of the C-13 alcohol, the C-7 and C-10 hydroxyl groups of 13-oxo,10-deacetylbaccatin III **8**,[10] were protected as triethylsilyl ethers (Scheme 1). Removal of the C-2 and C-4 ester groups and formation of the C-1,C-2 carbonate were realized as previously described. The oxetan ring of the completely protected compound **9** was opened according to our procedure[8] and led to compound **10** with a fairly good yield (63%).



Scheme 1. Reagents: (a) TESCl, imidazole, DMF, rt (69%); (b) Red-Al (4 equiv.), THF, 0°C (59%); (c) $(CCl_3O)_2CO$, CH_2Cl_2:pyridine (85:15), −15°C, (93%); (d) Et_4NBr, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt (63%)

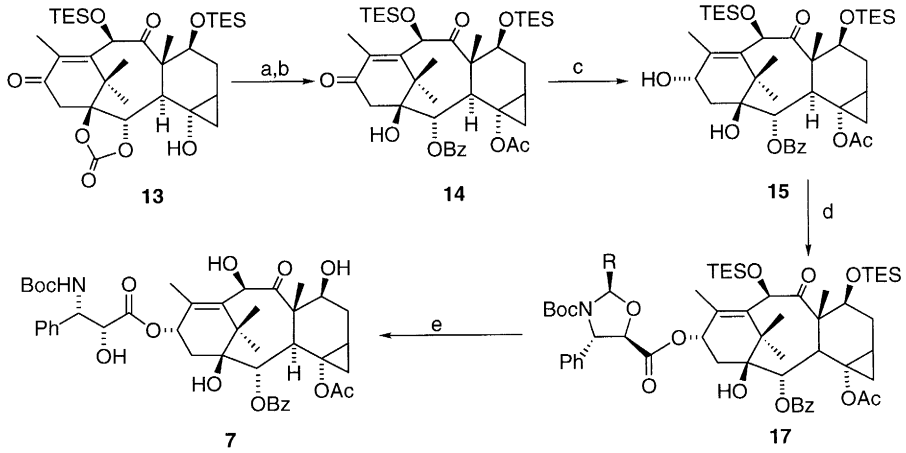
Our strategy for the construction of the cyclopropane ring was based on the Wurtz type reaction between two alkyl halides. Introduction of a halide at the C-20 position revealed to be troublesome. Classical methods for direct substitution were ineffective and substitution by means of a sulfonate only led to the C-4,C-20 epoxyde formation. Therefore, this compound was used for introduction of the halide. Direct formation of the epoxyde **11** was achieved with an acceptable yield with tributylphosphine and diethylazodicarboxylate.[11] The formation of the iodhydrin **12** was performed by treatment of the epoxide **11** with tetrabutylammonium iodide and $BF_3{\cdot}OEt_2$.[12] Cyclisation with Zn dust[13] afforded the cyclopropyl derivative **13** in good yield (Scheme 2).

Afterwards, we achieved the subsequent steps to complete the synthesis of the docetaxel analogue under the same conditions as for the 5(20)azadocetaxel derivatives. After acetylation of compound **13**, the C-1,C-2 carbonate was readily opened by phenyllithium in acceptable yield (**14**, 59%) without affecting the C-13 ketone. This function was then reduced with $NaBH_4$ to afford the C-13α isomer **15** in 49% yield. These two last steps occurred with lower yields than with the parent compounds bearing an oxetan or an azetidine ring. This may be due to the increased strain caused by the presence of the cyclopropane ring. Esterification was then realized with the 2-(4-OMe)phenyl 1,3-oxazolidine of *N*-Boc-phenylisoserine



Scheme 2. Reagents: (a) PBu_3, DEAD, DMF, rt (72%); (b) nBu_4NI, $BF_3 \cdot OEt_2$, CH_2Cl_2, rt (53%); (c) Zn, THF, Δ (70%)

16,[14] DCC and DMAP in toluene at room temperature in good yield (**17**, 92%). Deprotection of **17** with *p*-toluenesulfonic acid in methanol afforded the desired compound **7**[15] (74% yield) (Scheme 3).



Scheme 3. Reagents: (a) DMAP, Ac_2O, CH_2Cl_2, rt (83%); (b) PhLi, THF, −72°C (59%); (c) $NaBH_4$, EtOH:THF (75:25), rt (49%); (d) **16**, DCC, DMAP, toluene, rt (92%); (e) PTSA, MeOH, rt (74%)

We then measured for compound **7** the concentration required to inhibit 50% of the rate of cold-induced microtubule disassembly.[16] The ratio IC_{50}:IC_{50}(paclitaxel) gives the activity with respect to paclitaxel. The result is reported in Table 1 and compared with paclitaxel **1a**, docetaxel **1b** and 5(20)azadocetaxel **5**.

Table 1
Biological evaluation of 5(20)-deoxydocetaxel

compound	Microtubule disassembly inhibitory activity IC_{50}/IC_{50}(paclitaxel)
1a	1
1b	0.5
5 (R=H)	8
7	1.2

5(20)Deoxydocetaxel is thus the first compound without an oxetan ring that is as active as paclitaxel. Therefore, the oxetan ring is not essential for the interaction with microtubules. The cyclopropyl ring might act, as the oxetan, to rigidify the C-ring and point the C-4 acetoxy group in the appropriate direction for binding. The presence of the oxygen is not absolutely required but likely participates in the stabilization of the taxoid–tubulin complex as exemplified by the twofold decrease of activity compared to docetaxel **1b**. Other D-ring modified compounds are being synthesized in our laboratory to fully explore the actual contribution of this oxetan ring in microtubules binding.

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15. Spectroscopic data of compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (2H, d, J=8.5 Hz), 1.06 (1H, m), 1.10 (3H, s), 1.30 (3H, s), 1.32 (3H, s), 1.38 (9H, s), 1.39 (1H, m), 1.91 (3H, s), 2.20 (3H, s), 2.36 (2H, m), 2.57 (1H, m), 3.41 (1H, d, J=5.0 Hz), 4.07 (1H, dd, J=5.0 Hz, J′=11.0 Hz), 4.28 (1H, s), 4.41 (1H, d, J=6.5 Hz), 4.61 (1H, bs), 5.14 (1H, s), 5.27 (1H, bd, J=9.0 Hz), 5.48 (1H, d, J=9.0 Hz), 5.63 (1H, d, J=6.5 Hz), 6.33 (1H, t, J=9.0 Hz), 7.30 to 7.62 (8H, m), 8.18 (2H, d, J=7.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.4, 14.6, 17.3, 18.4, 21.8, 22.6, 26.6, 28.4, 28.8, 37.3, 42.8, 42.9, 56.4, 56.6, 59.2, 70.4, 72.9, 73.8, 75.0, 77.2, 77.9, 80.3, 126.8, 128.1, 128.7, 129.0, 129.9, 130.3, 133.5, 137.3, 139.2, 155.5, 166.7, 171.4, 172.6, 211.7; IR ($CHCl_3$) 3441, 1732, 1716, 1495, 1452 cm^{-1}; MS (ESI^+) *m/z* 792 (MH^+), 511 (MH^+ − side chain); HRMS (FAB^+) calcd for $C_{43}H_{53}NO_{13}Na$: (MNa^+) 814.3415, found: 814.3438.
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