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First Synthesis of 2α-Thiol Ether Analog of Docetaxel

Wei Shuo FANG*, Ying LIU, Qi Cheng FANG

Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050

Abstract: A 2α-phenylthio ether analog **1c** of docetaxel was synthesized for the first time from 10-deacetylbaccatin III **3** via double inversion of C-2 configuration. This compound showed very weak cytotoxicity toward several tumor cell lines.

Keywords: Paclitaxel, docetaxel, thiol ether.

The chemistry of anticancer drug paclitaxel (=Taxol®, **1a**) has been extensively explored in recent years. A variety of its analogs with modified taxane frame work or substitutions to its core structure, as well as C-13 substituted isoserine side chains have been synthesized and biologically evaluated[1]. The marketing of docetaxel (=Taxotere®, **1b**) is one of the fruitful results from these research efforts. The beginning of clinical trial for analog **2** developed by Indena is the new example. Based on computational and spectroscopic studies of paclitaxel and its analogs, many postulations were made to explain and predict the conformations of paclitaxel analogs binding to tubulin dimers[2]. 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 are critical to its cytotoxicity.

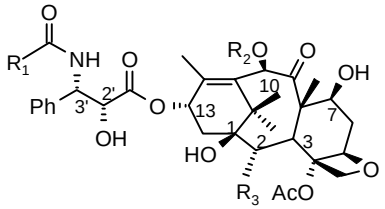
Studies on the SAR at the C-2 position showed that both the nature and stereochemistry of the 2-aroyl group were of great importance to activity[3, 4]. Many paclitaxel analogs with different aroyl ester groups at the C-2 position in place of benzoate were synthesized[5]. Recently the synthesis and biological evaluation of 2-amido analogs has been realised by our group[6a]. Those analogs, unlike C-13 amido analogs, retained cytotoxicity to a great extent. They exhibited similar SAR to that of paclitaxels with 2-benzoates[6].

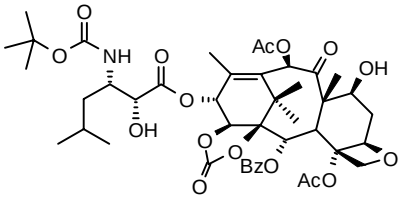
2-OH Baccatin **4**, prepared from 10-deacetylbaccatin III **3** in four steps, could be converted to a mixture of 2-mesylate and 2β-epoxide upon treatment of mesyl chloride and triethylamine. It has been found[6a] when this mixture was heated with sodium azide at 50-60°C, 2α-N_3 product **5** was obtained as a single product, in which the stereochemistry was assigned on the basis of NOE data. Treatement of the mixture with sodium thio-phenolate at room temperature yielded 2-debenzoyloxy-2α-phenylthio ether **6** (63% from **4**). The configuration of C-2 was assigned by analogy with **4**, and NOE

*E-mail: wfang@imm.ac.cn

data also supported the α orientation. Reduction of **5** with sodium borohydride did not give satisfactory result, whilst with DIBAL (-45°C) led to the formation of 13-hydroxyl compound **7** in 75% yield. The 13-OH in **6** was assigned as α orientation since the coupling constants of H-13 in **6** is analogous to those in **3** and 13α-OH derivative of **5**[6a], and it was distinguished from those in 13β-OH compound[7]. Coupling of **7** with enantiopure β-lactam **8** at low temperature (-45°C → -20°C), and subsequent desilylation with HF·Py at room temperature yielded thioether **1c** (40% for 2 steps).

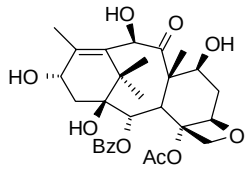
Figure 1 Structures of taxoids **1-5**





2

1a R_1=Ph, R_2=Ac, R_3=OBz
1b R_1=*t*-BuO, R_2=H, R_3=OBz
1c R_1=*t*-BuO, R_2=Ac, R_3=SPh



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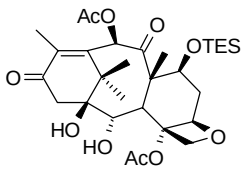

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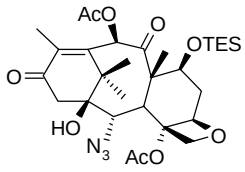
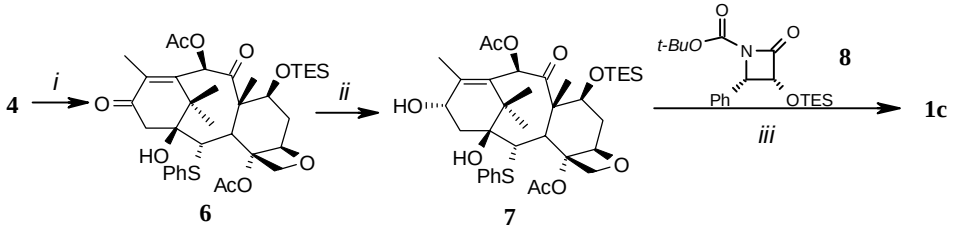


5

In MTT assay **1c** showed weak cytotoxicity toward several tumor cell lines (<10% inhibition to KB, A549 and MCF-7 at 0.1μM, while IC_{50} of paclitaxel toward KB, A549 and MCF-7 tumor cell lines were 0.0091, 0.012 and 0.0055 μM respectively). Further SAR studies on 2α-N, S and C substituted paclitaxel or docetaxel analogs are undergone in our lab, and results will be reported in due time.

Scheme 1



Reagents and conditions: (i)MsCl, Et_3N, CH_2Cl_2, -20°C; then PhSNa, DMF, rt, 63% for 2 steps; (ii)DIBAL, THF, -45°C, 75%; (iii)LHMDS, THF, -45°C→ -20°C; then 40% aq. HF in Py, rt, 40% for 2 steps.

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