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Synthesis of 14-Bromo and 14-Hydroxy Baccatin III Derviatives

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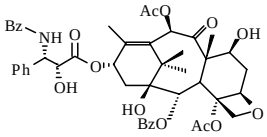
Abstract: Several 14α- and 14β-bromo baccatin III derivatives were synthesized by direct bromination and from silyl enol ether of 13-oxo-7-TES-baccatin III. 14β-Hyroxy baccatin III derivative was also obtained from the same silyl enol ether.

Keywords: 14-Bromo baccatin III, 14-hydroxy baccatin III, paclitaxel, silyl enol ether.

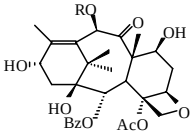
Numerous efforts towards synthesis of anticancer drug paclitaxel (Taxol®, **1a**) with improved activities led to the modification at 13-phenylisoserine side chain and different positions of its core structure—baccatin III **1c**[1]. At the same time, the activities of searching new taxoids for starting materials of new semi-synthetic paclitaxel analogs from *Taxus* spp. plant have not ever been stopped. Among these taxoids, 14β-hydroxy-10-deacetylbaccatin III **2**[2] and 13-acetyl-9-dihydrobaccatin III **3**[3] are the candidates of choice. Several groups described their research results on the semi-synthesis of new paclitaxel analogs from **2**[4] and **3**[5]. Recently, FDA approved Indena's IND request for the new analog **4** synthesized from **2,** allowing phase I clincal trial to begin[6]. The results from a group of our institute showed that attachment of phenylisoserine side chain at C-14 could not greatly improve the poor antitumor activity of 14β-taxoid without 4 (20), 5-oxetane ring (D ring) from *Taxus* cell cultures[7]. The activities of new paclitaxel analogs retaining C-13 isoserine side chain, together with 14-OH or other 14-substituted groups may be worthy of exploring.

The strategy for the synthesis of these 14-substituted compounds depends on the production of 14-substituted baccatin III derivatives, which can be converted from 10-deacetylbaccatin III **1c**, an abundant taxoid from regenerate parts of *Taxus* spp. plants. As a part of our continuing efforts on core structure modification of baccatin III[8], here we reported the synthesis of 14α-, 14β-bromo and 14β-hydroxy baccatin III derivatives.

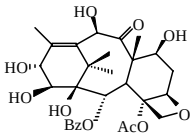
13-Oxo-7-TES-baccatin III **5** was easily obtained from **1b** by literature methods[9]. Direct bromiantion of **5** at C-14 position failed to give 14-bromo products. It was observed that 2-OBz may cause serious problems in the D-ring opening step during its modification process, and protection of 1,2-diol as cyclic carbonate may help to overcome these problems[9]. The 1,2-carbonte **6** was prepared from **5** by selective debenzoylation[10] with Triton B and then treatment of carbodiimidazole and imidazole[11] in 75% yield over 2 steps. Bromination of **6** with bromine was unsuccessful. Finally,



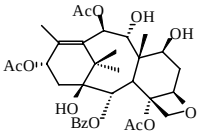
1a



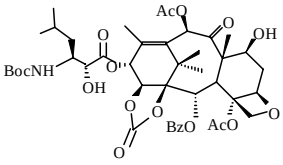
1b R=H
1c R=Ac



2



3



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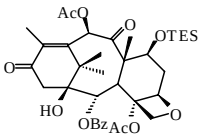
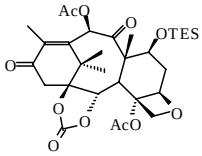


5



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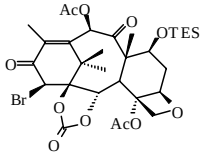

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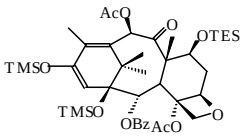
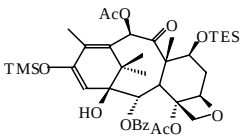
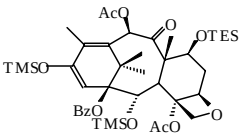


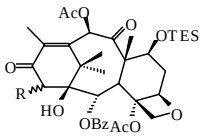
8a



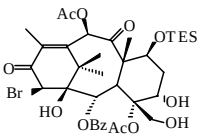
8b



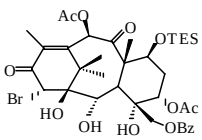
8c



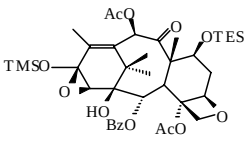
9a R=α-Br
9b R=β-Br



9c



9d



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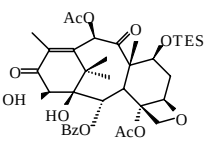

11

14β-bromo product **7** was obtained as single diastereomer in ~80% yield after treatment of **6** with pyridinum hydrobromide perbromide[12]. However, treatment of **6** with oxidizing agents such as dimethyldioxirane[13] is unable to lead the introduction of 14-hydroxyl. At this point, we tried another methodology—introduction of 14-substituted groups through silyl enol ether intermediate.

The silyl enol ether has been extensively applied to the synthesis of α-substituted ketone[14]. *In situ* TMSI preparation from TMSCl and NaI[15] was first applied to the formation of silyl enol ether of **5** but in vain. Treament of **5** with TMSCl and DBU, gently heated to 45°C[16], gave silyl enol ether products **8a** (75%), **8b** (3.5%) and **8c** (8%). The 1-O-TMS in **8a** are very sensitive to acidic impurities in the solvent. Thus the transformation of **8a** into **8b** could be realized by shaking **8a** with 1mol/L HCl at room temperature. The formation of **8c** was the results from intramolecular acyl migration of benzoyl from 2-OH to 1-OH and then silylation of 2-OH, a phenomenon frequently observed in taxane chemistry[17]. Bromination of **8b** with bromine at -78°C gave 14β products **9b** (2%) and **9c** (44%) as major proucts, together with 14α products **9d** (29%) as minor one. It seemed that 14β-bromo products may predominate in 14-bromination of baccatin III derivatives. But when **8a** applied to bromination under the same condition as that for **8b**, 14α product **9a** (43%) was obtained as the major product. A mixture of **9c** and **9d** identfied by TLC was also obtained, in which 14α product **9d** was the predominated one. It was reasoned that the bulky 1-O-TMS group in **8a** may favor the attack of brominating agent from less hindered α face, while such hindrance did not exist in **8b**.

Compound **8b** was successfully converted into the 14β-hydroxy product **11** in ~60% yield over 2 steps through the epoxide intermediate **10** by the standard transformation with mCPBA.

Having the desired 14-bromo and 14-hydroxy compounds in hand, we began to explore their transformations into the 13α-hydroxy compounds which will be further used for the synthesis of 14-substituted paclitaxel analogs. Unfortunately, reduction with several different borohydrides did not give the expected 13α-hydroxy products. Continous research efforts was undergoing in our lab and the results will be reported in due time.

Acknowledgment

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