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SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 7727–7745

Selective synthesis of 14β-amino taxanes

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Received 16 March 2005; revised 11 May 2005; accepted 26 May 2005

Available online 16 June 2005

Dedicated to Professor J. Ojima on the occasion of his 60th birthday

Abstract—The base induced deprotonation of H-14 of 7-triethylsilyl- (7-TES-) and 7-*tert*-butoxycarbonyl- (7-BOC-) protected 13-oxo-baccatins gave the corresponding enolates, which were selectively aminated with electrophilic nitrogen donors, such as azodicarboxylates and tosyl azide. In particular, tosyl azide gave the corresponding 7-BOC- and 7-TES-13-oxo-14β-azido-baccatin III. Alternatively, the last compound was prepared via NaN_3 induced azidation of the 13-silyl enol ether of 7-TES-13-oxo-baccatin III under oxidative (cerium ammonium nitrate) conditions. The 13-silyl enol ether was obtained in a multistep process by DBU induced silylation of 7-TES-13-oxo-baccatin III. The 7-TES-13-oxo-14β-azido-baccatin III was used as a key intermediate for the synthesis of a new family of antitumour taxanes containing amino based functional groups at the C-14 position, such as: 14β-azido, 14β-amino, 14β-amino 1, 14-carbamate, 14β-amino 1, 14-thiocarbamate, and 14β-amino *N-tert*-butoxycarbonyl-1,14-carbamate.

1. Introduction

7-TES-13-oxo-baccatin III (**1**, Fig. 1)[1] is an intermediate of choice for studies on taxane chemistry, being used for the synthesis of 12, 13-dihydro-10-DAB III,[2] the 13-epi-7-TES-baccatin III,[3] the enol ester 12, 13-isobaccatin III,[4] and their 12, 13-isotaxanes analogues.[5] In addition, the 13-oxo group activates the functionalization of the C-14 atom via enolate chemistry. For example, the base induced hydroxylation with oxaziridines of the potassium enolate of **1** and its

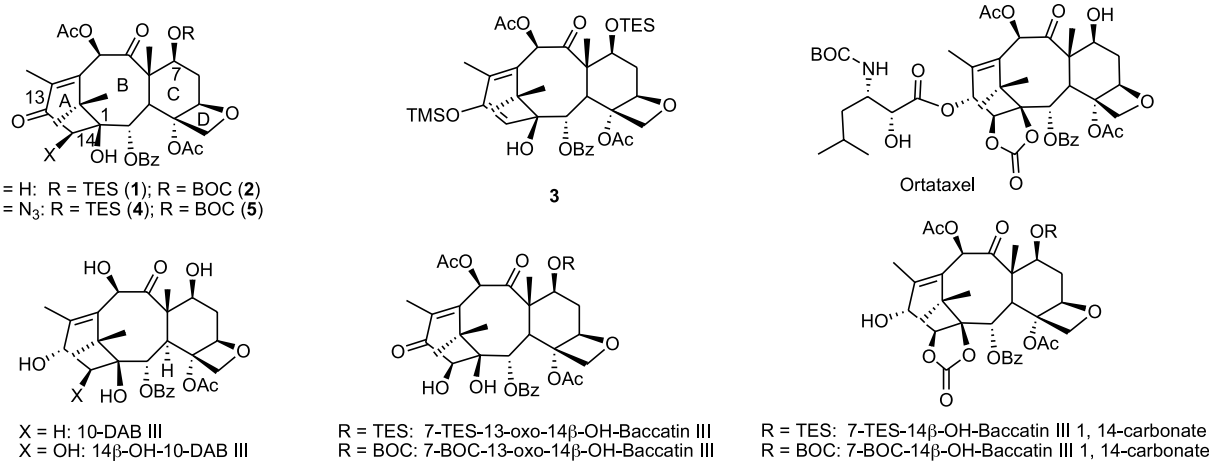

Figure 1. Baccatin III derivatives and Ortataxel.

Keywords: 14β-Amino taxanes; 10-DAB III; Silyl enol ethers; Electrophilic amination; 13-Oxo-baccatins.
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doi:10.1016/j.tet.2005.05.087

7-BOC analogue **2** gave 7-TES- and 7-BOC-13-oxo-14β-OH-baccatin III (Fig. 1).[6] The enolate of **1** was employed for the synthesis of the 13-OTMS enol ether **3**, which was converted into 7-TES-13-oxo-14β-OH-baccatin III by *m*CPBA oxidation.[7] A part from these results, the enolate chemistry was no longer explored since 13-oxobaccatins display a remarkable tendency to skeleton rearrangements when treated with bases such as NaH, pyridine, and DBU.[8a–d] Even so, the inherent potentiality of this chemistry opens new perspectives for innovative functionalizations of the C-14 position. For example, we performed the reduction of the 13-oxo group of 7-TES- and 7-BOC-13-oxo-14β-OH-baccatin III 1, 14-carbonate to afford the corresponding 14β-OH-baccatin III derivatives (Fig. 1), which are suitable intermediates of potent anticancer taxanes bearing 1,14 carbonate as masked 14β-OH group. These taxanes, which have been so far synthesized from the natural occurring 14β-OH-10-DAB III, a scarcely available chemical feedstock (Fig. 1),[9] display cytotoxic activity in cell lines, which express multi-drug resistance (MDR). The lead compound, Ortataxel, is now in phase II clinical trial.[10] We envisioned that the 'enolate chemistry' could be useful for the synthesis of new antitumor taxanes isosters of 14β-OH carbonates. The main support to this project was the observation that SAR studies have established that changes to the 'southern hemisphere', comprising C-14, exert a strong effect on taxol's activity.[11] Our efforts produced other potent antitumor taxanes, which bear an unsaturated and saturated baccatin[14, 1-*d*]-furan-2-one nucleus via aldol addition of ethyl glyoxylate to the enolate of **1**.[12]

Here, we wish to report our studies on the electrophilic amination of the enolates of 13-oxobaccatins **1** and **2**, and the 13-silyl enol ether **3**, to afford a new class of antitumor taxanes. It is worth noting that the insertion of the nitrogen functionality at the C-14 position can afford two epimers, since the new substituent may be located on the lower face of the baccatin skeleton (α-face), or the upper β-face. These α/β descriptors are defined observing the molecule with the methyl group at C-8 placed in the 'northern hemisphere' and pointing toward the observer.[13] To obtain isosteres of Ortataxel, only β-selective amination procedures, and a selective reduction of the C-13 oxo group to afford 13α-OH epimers, must be developed since the antitumor activity of the resulting taxane is related to the stereochemistry of the 13 and 14 positions of the precursor 14β-OH-10-DAB III.

2. Results and discussion

2.1. Amination studies of 13-oxobaccatins 1 and 2

Our synthesis of the target 14β-amino substituted taxanes starts from the natural synthon 10-DAB III. This economically available reagent can be transformed into suitable 7-protected 13-oxobaccatins III according to standard protocols.[14] Namely, the 7-TES derivative **1** was obtained by sequential silylation and acetylation of the C-7 and C-10 hydroxy groups followed by MnO_2 oxidation of the 13-OH, while the 7-BOC analogue **2** was prepared by ozonolysis of 10-DAB III followed by acetylation and carbonylation of the C-10 and C-7 hydroxy groups. The treatment of **1** and **2** with metallic bases at low temperatures (−78 °C) afforded relatively stable enolates. Alternatively, base induced silylation affords 13-silyl enol ethers via a multistep process. The selective amination of both the enolates of **1** and **2** (protocol A) and the 13-silyl enol ethers (protocol B) afforded the key intermediates 13-oxo-14β-azido-baccatins **4** and **5** (Fig. 1).

2.1.1. Protocol A. Amination of the enolates of 1 and 2. Among the variety of bases available for the synthesis of the enolates of **1** and **2**, potassium *tert*-butoxide (^{t}BuOK) in a 4:1 mixed solvent THF/DMPU at −72 °C turned out to be the best one. The enolate is stable for several hours in a range of temperatures (−70/−40 °C) even in the presence of the polar additive DMPU (10–25%). Dibenzyl- and di-*tert*-butyl-azodicarboxylate (**6** and **7**, respectively),[15] and tosyl azide (**8**)[16] were selected as amination reagents.

(i) *Reaction of* **1** *and* **2** *with azodicarboxylates*. The amination of enolates **1** and **2** with azodicarboxylates **6** and **7** provided 14-hydrazino baccatins, as possible precursors of the corresponding 14-amino taxanes. In particular, the addition of dibenzyl-azodicarboxylate **6** to the enolates of **1** and **2** afforded the 14-*N*,*N*′-di(benzyl-oxycarbonyl)-hydrazino derivatives **9** (76%) and **10** (65%), respectively, as single β-epimer (Scheme 1). Similarly, the stereoselective addition of di-*tert*-butyl-azodicarboxylate **7** to the enolate of **2** gave the β-isomer of the *N*,*N*′-di(*tert*-butyloxycarbonyl)hydrazino derivative **11** in 72% yield. The stereochemistry of the C-14 stereogenic center of compounds **9**–**11** was assessed by qualitative homonuclear NOE experiments. An enhancement of the H-14 proton (7–9%) upon irradiation of the H-3 proton clearly indicated a β-face selectivity of the reaction. As expected, no effect was observed upon irradiation of the vicinal H-2. Thus, the hydrazino group is placed on the β-face of the taxane skeleton. The chemoselective reduction of the 13-oxo group of compounds **9**–**11** with sodium or alkyl boron hydrides, according to the methodology developed for the reduction of 13-oxo-14β-OH-baccatins 1, 14-carbonates,[6] failed.

Next, the conversion of compounds **9**–**11** into the corresponding 13-oxo-14β-amino baccatins was in vain attempted. In fact, the deprotection of the BOC groups of **11** with formic acid, or TFA in MeOH, yielded several products derived from rearrangements of the taxane skeleton whose structures were no further investigated. Instead, the debenzylation of **9** with 10% Pd/C, followed by one-pot thermal decarbonylation, successfully gave the *N*,*N*′-unsubstituted hydrazino derivative **12**, which, however, was thermally unstable and rapidly decomposed in solution or in a neat state. In conclusion, all intermediates **9**–**12** were not workable to achieve our targets.

(ii) *Reaction of* **1** *and* **2** *with tosyl azide* **8**. It is well known that azides are useful reagents for synthesis of α-azido ketones.[17] Among the electrophilic azides usually employed for ketone enolates (phenylsulfonyl-, tosyl-, and the encumbered 2,4,6-triisopropylbenzenesulfonyl azide[18]) we selected the less sterically demanding tosyl azide **8**. Since this azide may serve both for diazo or azide transfer reactions,[19] the parameters of the quenching step must be carefully evaluated. The reaction of the enolate of **1** with **8**, performed at −78 °C in a THF/DMPU=4:1 mixed solvent,