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Lanthanide Trifluoromethanesulfonate Catalysed Selective Acylation of 10-Deacetylbaccatin III

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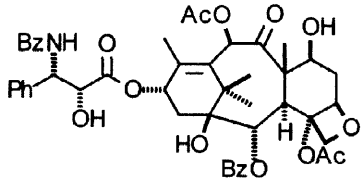
Abstract

The selective C-10 acylation of 10-deacetylbaccatin III to baccatin III and derivatives is very efficiently catalysed by lanthanide trifluoromethanesulfonates. Baccatin III, now readily available through this procedure, is an important precursor for an economically viable semisynthesis of paclitaxel and its derivatives.

Keywords: Lanthanide; Acylation; Taxoids

Isolated from the Pacific yew *Taxus brevifolia*, paclitaxel (**1**)[1] is a potent anticancer agent used clinically to treat advanced ovarian and breast cancers. Due to the limited natural supply,[2] as well as the growing demand for large quantities of paclitaxel, semisynthesis of paclitaxel is an attractive alternative. The most widely used and readily available precursor is 10-deacetylbaccatin III (**2**).



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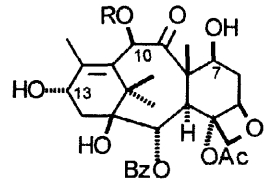

2 R = H **4** R = benzoyl
3 R = acetyl **5** R = 2-methyl-propionyl

The limited step in this semisynthesis is the preparation of a suitably protected baccatin III derivative which, until recently, only was achieved by protection of the C-7 hydroxyl, followed by acetylation of the C-10 hydroxyl in 73% overall yield.[3] A recent paper by Holton *et al.*[4] about the selective acylation of the C-10 hydroxyl of (**2**) has prompted us to present our results

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in this field.[5]

In our studies about selective acylation of (**2**) we focused on Lewis acid catalysed acylations and found that *lanthanide trifluoromethanesulfonates (triflates)* proved to be extremely effective in catalysing the selective acylation of (**2**). Only 1 to 3 mol% of catalyst and only a two fold excess of acetic anhydride is enough to complete the reaction within a few hours, making it more efficient than for example $CeCl_3$. The obtained yields were almost quantitative. The rare earth metal salts themselves are inexpensive, commercially available and relatively non-toxic materials. They can be recovered and reused after the reaction.[6]

Table 1: Acetylation of 10-deacetylbaccatin III with 2.0 eq. of acetic anhydride and various lanthanide catalysts

catalyst	mol%	solvent	reaction time (h)	yield %
$CeCl_3$	1	THF	24	>95[a]
$Yb(NO_3)_3$	1	THF	24	>95[a]
$Yb(OTf)_3$	1	CH_2Cl_2	24	>95[a]
$Yb(OTf)_3$	1	THF	3	98[b]
$Yb(OTf)_3$	1	EtOAc	3	>95[a]
$La(OTf)_3$	1	THF	2	97[b]
$Lu(OTf)_3$	1	THF	3	100[b,c]

[a] according to 300 MHz ^{1}H-NMR. [b] isolated yield. [c] at 80 % conversion

The new acylation method is also applicable with other symmetrical acid anhydrides although the reaction is somewhat slower and up to 20 equivalents of acid anhydride are required to complete the reaction. For example 10-benzoyl-10-deacetylbaccatin III (**4**) was obtained in 91 % yield and 10-(2-methyl-propionyl)-10-deacetylbaccatin III (**5**) in 96 %. After acylation of (**2**) protection or functionalisation of the C-7 hydroxyl becomes trivial and can be accomplished in very high yield with a variety of functional groups.

Baccatin III (**3**) and baccatin III derivatives modified at C-7 and C-10 are readily available using this new acylation method, serving as an intermediate for an efficient and more pliable route to semisynthetic paclitaxel and its derivatives.

Acknowledgement

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References and Notes

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