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Synthesis of Taxol from Baccatin III via an Oxazoline Intermediate

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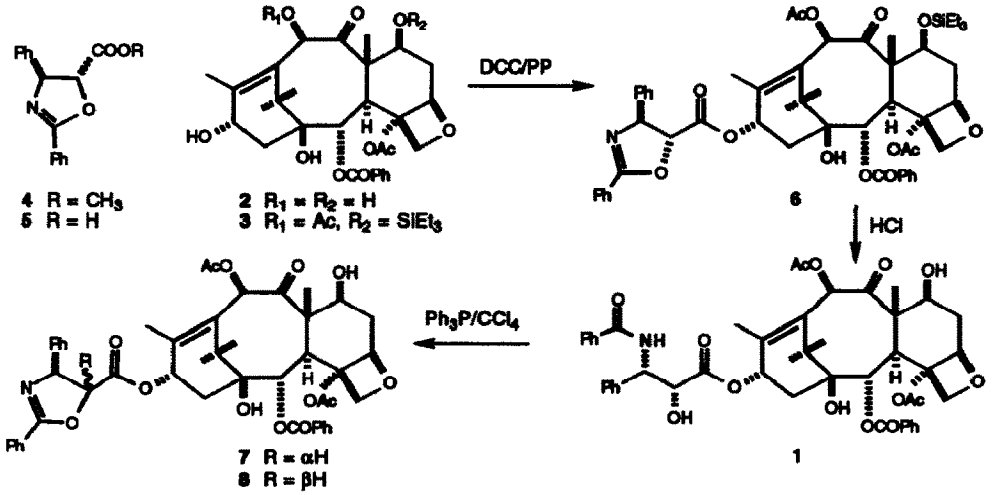
Abstract: **Taxol (1) can be prepared in good yield by coupling the oxazoline carboxylic acid 5 with 7-(triethylsilyl)baccatin III, followed by hydrolysis. The oxazolines 7 and 8 can also be prepared directly from taxol.**

The important anticancer drug taxol (1) was originally isolated from the bark of the western yew, *Taxus brevifolia*.[2] This source, however, is far from ideal, since it involves the large-scale harvesting of a slow-growing tree, and an active search for an alternate supply has been carried out over the past few years.[3] The most promising approach, at least in the short term, has involved the partial synthesis of taxol from 7-(triethylsilyl)baccatin III (3), prepared from 10-deacetylbaccatin III (2), which is available in yields of at least 0.1% from the English or European yew, *T. baccata*.[4]

Although the attachment of a β-phenylisoserine side chain to the C-13 position of 7-(triethylsilyl)baccatin III appears to be a trivial task, it is complicated by significant steric hindrance around this position and by hydrogen bonding between the 13-hydroxyl group and the 4-acetoxyl group.[5] The first successful partial synthesis of taxol thus used the unhindered cinnamic acid,[6] and a protected β-phenylisoserine was only attached in modest yield under forcing conditions.[4] Other synthetic routes have included an efficient pathway from a β-lactam intermediate,[7] and a pathway that involves coupling of an oxazolidine derivative followed by hydrolysis and benzoylation.[8] Very recently it has been shown that this method allows the use of precursors with both the natural 2*R*,3*S* and the unnatural 2*S*,3*S* stereochemistry.[9]

We now report that taxol can be prepared in good yield from 7-(triethylsilyl)baccatin III by the simple procedure of esterification with (4S,5R)-2,4-diphenyloxazoline-5-carboxylic acid (5) followed by hydrolysis of the resulting oxazoline ester 6 with dilute hydrochloric acid.



Hydrolysis of (4*S*,5*R*)-(+)-2,4-diphenyl-5-(methoxycarbonyl)-2-oxazoline (**4**)[10] with 0.1N NaOH yielded the oxazoline carboxylic acid **5** in 96% yield. Reaction of **5** with 7-(triethylsilyl)baccatin III (**3**)[4] in the presence of DCC and PP gave the coupled product **6** in 95% yield based on **3**.[11] Hydrolysis of **6** with 0.1N HCl at 95^0 for 2 hr yielded taxol (**1**), identical with the natural product in all respects, in 75% yield.

Compounds analogous to the intermediate **6** can also be prepared directly from taxol. Thus treatment of taxol with Ph_3P in the presence of CCl_4 at 80^0 gave the *cis* oxazoline **7** as the major product, together with minor amounts of the *trans* oxazoline **8**.

This chemistry allows the facile synthesis of taxol in good yield from available starting materials,[4,10] and provides an alternate route to the literature routes described above for the preparation of this important compound.[12]

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11. To a solution of the oxazoline carboxylic acid **5** (30 mg, 0.11 mmol) in dry toluene was added 7-(triethylsilyl)baccatin III (**3**, 8.2 mg, 0.011 mmol) and DCC (23.2 mg, 0.11 mmol). A catalytic amount of 4-pyrrolidinopyridine was added and the reaction mixture was stirred at room temperature for 30 min. Purification of the crude product by PTLC (hexanes: ethyl acetate, 2:1) gave the coupled product **6** (10.6 mg, 95%).

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