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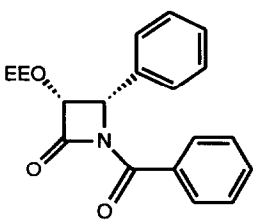
A HIGHLY EFFICIENT ROUTE TO TAXOTERE BY THE β-LACTAM SYNTHON METHOD

Iwao Ojima*, Chung Ming Sun, Martine Zucco, Young Hoon Park, Olivier Duclos, and Scott Kuduk
Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

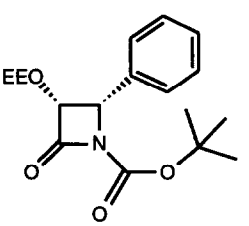
Summary: *Taxotère, a highly promising anticancer drug, is synthesized through an efficient coupling of 7,10-diTroc-10-deacetylbaccatin III with enantiomerically pure (3R,4S)-1-^{t}BOC-3-EEO-4-phenylazetidin-2-one which is obtained via chiral ester enolate – imine cyclocondensation.*

We have been applying our *"β-Lactam Synthon Method"* to the asymmetric synthesis of various non-protein amino acids and peptides containing non-protein amino acid residues,[1] which are potential enzyme inhibitors,[2] fragments of peptide hormone analogs[2] components of naturally occurring glycosphingolipids and antibiotics,[2] and a potent taxane anti-cancer agent, taxol,[3,4] . We have found that this method can effectively be applied to the synthesis of taxotère and its analogs. Taxotère is a taxane bearing a very strong anticancer activity reportedly even better than taxol in certain cell line assay as well as in preclinical experiments and also better pharmacological properties such as improved water solubility.[5] Taxotère is currently in phase II clinical trials in the U.S. and Europe. In the course of our study on efficient syntheses of taxol and related compounds,[3,4] we developed a highly efficient method for the coupling of a protected baccatin III and an enantiomerically pure β-lactam intermediate. We describe here a highly efficient route to taxotère and its analogs by means of the *β-Lactam Synthon Method.*

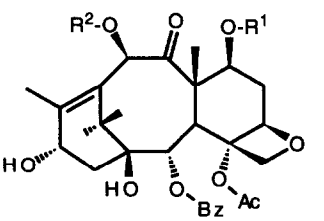
The lithium chiral ester enolate – imine cyclocondensation strategy has successfully been applied to the asymmetric synthesis of the C-13 side chain of taxol, i.e., (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine which is crucial for the strong anticancer activity, *via* enantiomerically pure (3*R*,4*S*)-3-hydroxy-4-phenylazetidin-2-one (**1**) as the key intermediate in our laboratory.[3,4] This C-13 side chain, 2-*O*-EE-(2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine (EE = ethoxyethyl) has been coupled to 7-TES-baccatin III (**3a**: R^1 = triethylsilyl (TES); R^2 = Ac) to give taxol after deprotection.[6] However, it was found that this reported coupling caused substantial racemization at the C-2 position of the side chain by our own examination. Holton has claimed in his patent application[7] that 1-benzoyl-(3*R*,4*S*)-3-EE-O-4-phenylazetidin-2-one (**2**) can be coupled with 7-TES-baccatin III (**3a**) in the presence of 4-dimethylaminopyridine (DMAP) and pyridine when the β-lactam is used in a large excess (5-6 equivalents).



2a



2b



3a,b

Although this procedure has been proved to work by us[4] and by others,[8] the use of a large excess β-lactam is obviously not efficient. Moreover, the Holton procedure did not work at all when 1-*tert*-butoxycarbonyl-(3*R*,4*S*)-3-EE-O-4-phenylazetidin-2-one (**2b**) was used for our attempted syntheses of taxotère and its 10-acetyl analog. This is due to the lack of reactivity of the 1-*tert*-butoxycarbonyl-β-lactam (**2b**) toward the C-13 hydroxyl group of a protected baccatin III (**3**) under the Holton conditions. The lack of reactivity is ascribed to the substantially weaker electron-withdrawing ability of *tert*-butoxycarbonyl group than that of benzoyl group.

In order to overcome this difficulty, we have studied the metallation of 7,10-diTroc-10-deacetylbaccatin III (**3b**) (Troc = 2,2,2-trichloroethoxycarbonyl).[9] We examined NaH in THF and DME suspension,[9] *n*-BuLi, LDA, LiHMDS, NaHMDS, and KHMDS in THF solution, and found that NaHMDS is the best base for the coupling of the β-lactam **2b** with baccatin **3b** (Table 1). As Table 1 shows, the nature and amount of base and the reaction temperature exert remarkable influence on the coupling yield. When NaH was used as the base, the coupling took several hours to reach 90% conversion and the coupling yield was 90% (81% isolated yield). When the conversion exceeded 90%, we sometimes observed sudden decomposition. Thus, 90% conversion was the best value so far.

Table 1 Effects of base on the coupling of the β-lactam **2b** with the baccatin **3b**[a]

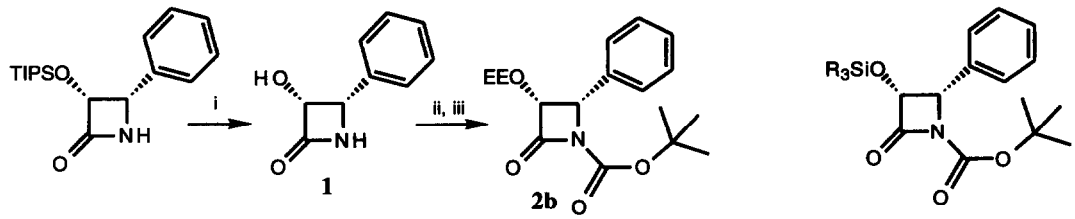
Entry	Base (equiv.)	Solvent	Temp. (°C)	Reaction Time	Conversion (%)	Isolated Yield (%)	Conversion Yield (%)
1	NaH (40)	THF	-10	1.0 hr	49	38	78
2	NaH (40)	DME	-10	6.5 hr	90	81	90
3	n-BuLi (1.2)[b]	THF	-78	30 min	<5	0	---
4	LDA (1.2)	THF	-78	30 min	<5	<5	---
5	LiHMDS (1.2)	THF	-78	30 min	22	12	55
6	KHMDS (1.2)	THF	-78	30 min	33	21	63
7	NaHMDS (1.2)	THF	-78	30 min	51	48	94
8	n-BuLi (2.5)	THF	-78	30 min	50	1.6[c]	3.2[c]
9	LDA (2.5)	THF	-78	30 min	19	11	58
10	LiHMDS (2.5)	THF	-78	30 min	50	48	96
11	NaHMDS (2.5)	THF	-78	30 min	96	92	96
12	KHMDS (2.5)	THF	-78	30 min	54	50	96
13	n-BuLi (1.2)[b]	THF	-30	30 min	91	70	77
14	LDA (1.2)	THF	-30	30 min	40	38	95
15	LiHMDS (1.2)	THF	-30	30 min	40	38	95
16	NaHMDS (1.2)	THF	-30	30 min	91	88	97
17	KHMDS (1.2)	THF	-30	30 min	78	75	96

[a] All reactions were run by adding a base to a cooled mixture of 0.06 mmol of **2b** and 0.05 mmol of **3b** in THF except for cases using NaH and *n*-BuLi. For the NaH reactions, a mixture of **2b** and **3b** in THF or DME was added to the NaH suspension. For *n*-BuLi reactions, **2b** was added after **3b** was treated with *n*-BuLi since the standard procedure caused serious decomposition. [b]Mixed with stereoisomers (24%). [c]Due to severe decomposition.

When homogeneous bases are used, the coupling proceeds much more rapidly. Since some decomposition of baccatin **3b** was observed with all homogeneous bases above -20°C, all couplings were carried out at or below -30°C.

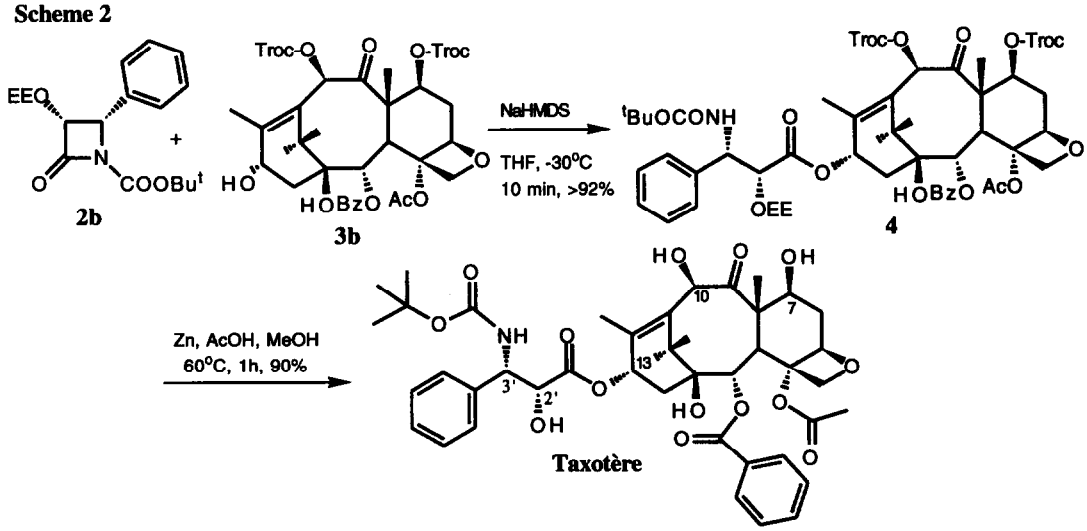
Under optimized conditions with the use of NaHMDS (1.2 equiv.) as the base, the coupling of **2b** (1.5 equiv.) and **3b** (1 equiv.) proceeded very smoothly in THF at -30 °C to give 2'-EE-7,10-diTroc-taxotère (**4**) in >92% isolated yield within 10 min. Taxotère was obtained in 90% yield after deprotection using the Commerçon conditions,[10] i.e., Zn/AcOH/MeOH at 60°C. Since the β-lactam **2b** with >99% e.e. is obtained in 78% overall yield (4 steps) from 2-phenylcyclohexyl TIPS-O-acetate and *N*-TMS-phenylaldimine (Scheme 1), this process provides the most efficient route to taxotère ever reported. The coupling reactions of 3-TES-O- and 3-TBDMS-O-β-lactams (**2c** and **2d**) proceeded in the same manner with the use of NaHMDS as the base to give the corresponding coupling products, 2'-TES-**4** and 2'-TBDMS-**4**, respectively, in 80% isolated yields.[11]

Scheme 1



i) NBu_4F, THF,100%; ii)EVE, H^+, 100%; iii) $(t\text{-BuOCO})_2O$, Et_3N, DMAP, CH_2Cl_2, 93%

Scheme 2



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9. Regarding the use of NaH as the base for the coupling of the β-lactam **2a** with the baccatin **3a**, see Ref. 4. After the metallation protocol using NaH as the base was worked out in this laboratory (Ojima, I.; Zucco, M. Invention Disclosure, Research Foundation of the State University of New York, 1992), Holton presented his new coupling protocol using *n*-BuLi and lithium amides (LiNRR') at the 203rd American Chemical Society National Meeting, April 5-10, 1992, San Francisco, CA: Abstracts ORGN 355 (This new protocol was not stated in the abstract).

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11. β-Lactam **2c** was prepared by reacting **1** with TES-Cl in pyridine. β-Lactam **2d** was prepared directly from (3*R*,4*S*)-3-TBDMS-O-4-phenyl-2-azetidinone which was obtained in 76% yield with 94.5% e.e. through the chiral ester enolate – imine cyclocondensation using (-)-10-dicyclohexylsulfamoyl-D-isobornyl TBDMS-O-acetate, *N*-TMS-phenylaldimine, and LDA in THF at -90°C. This reaction was reported in our preliminary communication (Ref. 3) with very low chemical yield. Recently, it was found that the low yield was due to the impure *N*-TMS-phenylaldimine at that time: Georg, G. I. Private communication. The authors thank Professor Gunda I. Georg for informing us of this finding prior to publication.

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