Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2479-2482, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

N-ACYL-3-HYDROXY-β-LACTAMS AS KEY INTERMEDIATES FOR TAXOTERE AND ITS ANALOGS

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

(*Received* 1 *April* 1993)

Summary: (3*R*,4*S*)-3-(protected hydroxy)-4-substituted β-lactams bearing *N*-alkoxycarbonyl, *N*-aryloxycarbonyl, and *N*-carbamoyl groups are found to be useful for the syntheses of taxotère and its analogs through coupling with baccatin III.

The *"β-Lactam Synthon Method"* has proven to be useful for 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 analogues,[2] components of naturally occurring glycosphingolipids and antibiotics,[2] and a potent taxane anti-cancer agent, taxol,[3,4] . We have found that new β-lactams bearing carbamate and urea moieties involving the β-lactam nitrogen serve as key intermediates for the asymmetric syntheses 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. We describe here versatile and efficient routes to a variety of enantiomerically pure *N*-alkoxycarbonyl-, *N*-aryloxycarbonyl-, and *N*-carbamoyl-3-hydroxy-β-lactams which give taxotère and its analogs upon coupling with a protected baccatin III.

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, as well as the semisynthesis of taxol via enantiomerically pure (3*R*,4*S*)-3-hydroxy-4-phenylazedin-2-one (**1**) as the key intermediate in our laboratory.[3,4] We have found that the β-lactam **1** and its 4-substituted congeners serve not only as the key intermediate to taxol, but also as versatile common intermediates to a variety of taxol and taxotère analogs.

N-Alkoxycarbonyl- and *N*-aryloxycarbonyl-3-(*O*-protected hydroxy)-4-(substituted)azetidin-2-ones (**3**) were synthesized in high yields through protection of the 3-hydroxy moiety of β-lactam **1** with 1-ethoxyethyl (EE) or triethylsilyl (TES), forming 3-*O*-protected β-lactams (**2**) (>95% yield), followed by carbamate formation with chloroformates in the presence of dimethylaminopyridine (DMAP) and triethylamine (TEA) in dichloromethane at room temperature (Scheme 1). In a similar manner, *N*-(monosubstituted)carbamoyl-3-(EE-oxy)-4-phenylazetidin-2-ones (**4**) were obtained in good yields either by treating the 3-*O*-EE-β-lactam **2a** with n-butyllithium, followed by reaction with isocyanates in THF at -78 °C (Scheme 1). Alternatively, **4** was obtained by reacting the 3-*O*-EE-β-lactam **2a** with isocyanates in the presence of DMAP and triethylamine in dichloromethane at 0 °C – room temperature when phenyl- and ethyl isocyanates were employed. *N*-(*N*,*N*-(Disubstituted)carbamoyl)-3-(EE-oxy)-4-phenylazetidin-2-ones (**5**) were synthesized in good yields by reacting the 3-*O*-EE-β-lactam **2a** with carbamoyl

chlorides in the presence of DMAP and triethylamine in dichloromethane at 0 °C – room temperature (Scheme 1). For the β-lactams **2** in which the *O*-protecting group is *tert*-butyldimethylsilyl (TBS), the chiral ester enolate – imine cyclocondensation using a chiral TBS-oxyacetate directly gives 3-(TBS-oxy)-4-phenylazetidin-2-one (**2c**) in 76% yield with 94.5% ee, from which *N*-alkoxy- or *N*-aryloxycarbonylation and *N*-carbamoylation can readily be carried out. The results on the syntheses of β-lactams **3** - **5** are summarized in Table 1.[6]

Scheme 1

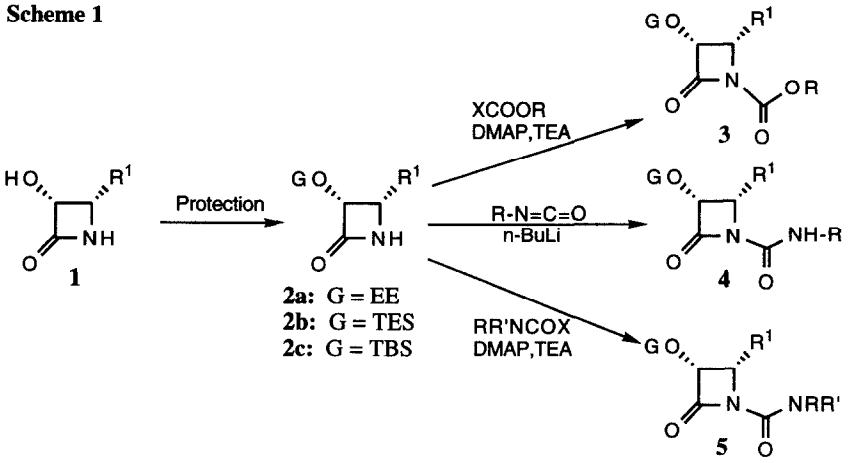


Table 1. Syntheses of β-lactams **3**, **4**, and **5** from β-lactam **2**

Entry	R^1	G	*N*-acylating agent	Base	Conditions	Isolated Yield (%)	
1	Ph	EE	ClCOOMe	DMAP, TEA	0 - r.t.	**3a**	72
2	Ph	EE	ClCOOEt	DMAP, TEA	0 - r.t.	**3b**	82
3	Ph	EE	$ClCOOBu^n$	DMAP, TEA	0 - r.t.	**3c**	83
4	Ph	EE	$ClCOOBu^t$	DMAP, TEA	0 - r.t.	**3d**	93
5	Ph	EE	$ClCOOCH_2Ph$	DMAP, TEA	0 - r.t.	**3e**	74
6	Ph	EE	ClCOOPh	DMAP, TEA	0 - r.t.	**3f**	80
7	*c*-Hexyl	EE	$ClCOOBu^t$	DMAP, TEA	0 - r.t.	**3g**	91
8	PhCH=CH-	EE	$ClCOOBu^t$	DMAP, TEA	0 - r.t.	**3h**	86
9	Me_2CHCH_2-	EE	$ClCOOBu^t$	DMAP, TEA	0 - r.t.	**3i**	80
10	*c*-Hexylmethyl	EE	$ClCOOBu^t$	DMAP, TEA	0 - r.t.	**3j**	93
11	Ph	TBS	$ClCOOBu^t$	DMAP, TEA	0 - r.t.	**3k**	94
12	Ph	EE	EtNCO	DMAP, TEA	0 - r.t.	**4a**	66
13	Ph	EE	PhNCO	DMAP, TEA	0 - r.t.	**4b**	63
14	Ph	EE	^{t}BuNCO	*n*-BuLi	-78°C	**4c**	74
15	Ph	EE	$PhCH_2NCO$	*n*-BuLi	-78°C	**4d**	60
16	Ph	EE	Me_2NCOCl	DMAP, TEA	0 - r.t.	**5a**	63
17	Ph	TES	$O(CH_2CH_2)_2NCOCl$	DMAP, TEA	0 - r.t.	**5b**	91

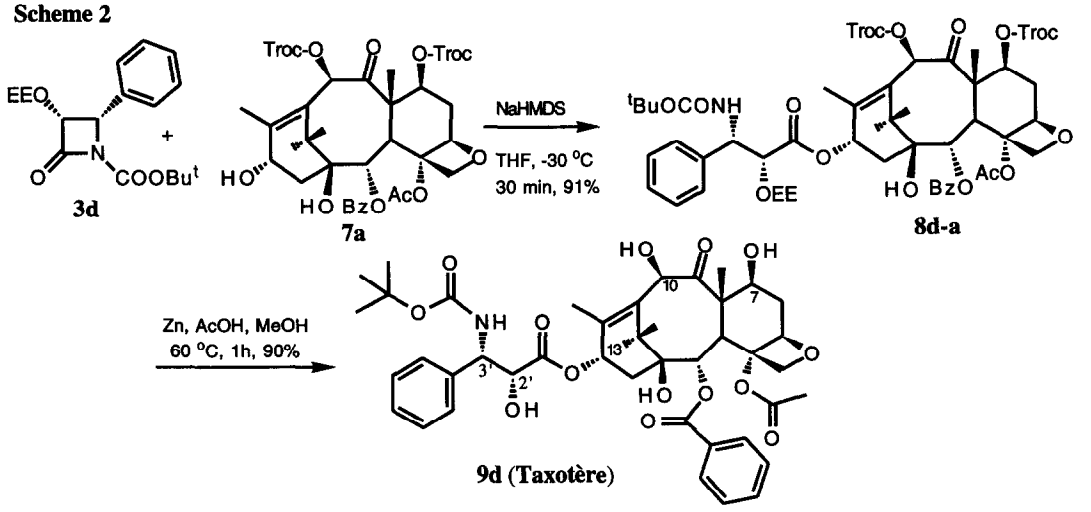
For the semisynthesis of taxol, Holton has claimed in his patent application that 1-benzoyl-(3*R*,4*S*)-3-(EE-oxy)-4-phenylazedin-2-one (**6**) can be coupled with 7-TES-baccatin III (**7b**) in the presence of DMAP and pyridine when the β-lactam is used in a large excess (5-6 equivalents).[7]

Although this procedure has been proven to work as shown 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*-butoxy-carbonyl(3*R*,4*S*)-3-(EE-oxy)-4-phenylazetidin-2-one (**3d**) 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 (**3d**) toward the C-13 hydroxyl group of the protected baccatin III (**7**) under the Holton conditions. The lack of reactivity is ascribed to the substantially weaker electron-withdrawing ability of *tert*-butoxycarbonyl group than that of the benzoyl group.[9]

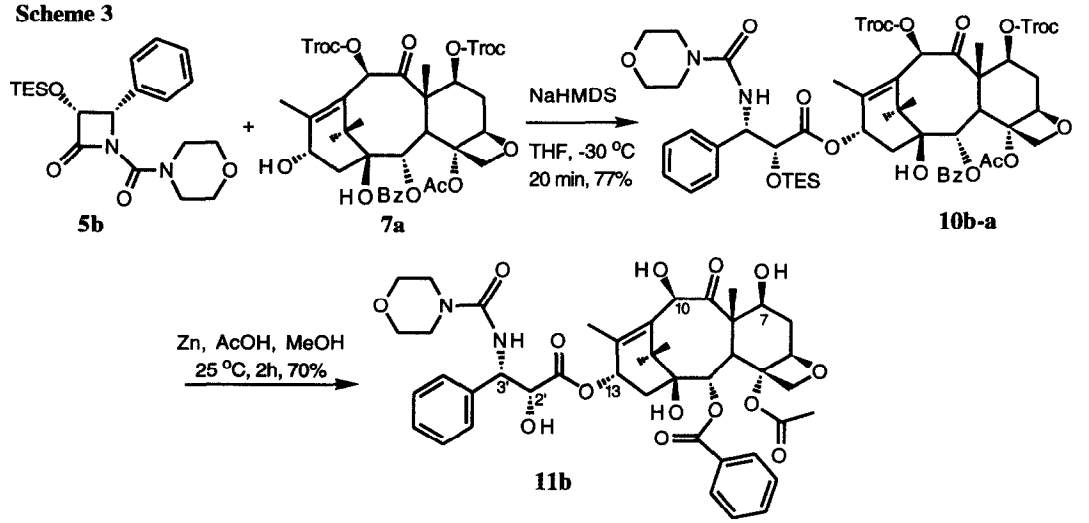
We have overcome this difficulty by metallating protected baccatin III (**7**) using NaHMDS as the base.[10] For example, under our standard conditions, the coupling of **3d** (1.5 eq.) with 7,10-diTroc-10-deacetyl baccatin III (**7a**) (Troc = 2,2,2-trichloroethoxycarbonyl) proceeded very smoothly in THF at -30 °C in the presence of NaHMDS (1.2 eq.) to give 2'-EE-7,10-diTroc-taxotère in 91% isolated yield (97% conversion yield) within 10 min; taxotère was obtained in 90% yield after deprotection using the Commerçon conditions,[11] i.e., Zn-AcOH-MeOH at 60 °C for 1 h (Scheme 2). Other *N*-alkoxycarbonyl- and *N*-aryloxycarbonyl-β-lactams **3** can readily be converted to the corresponding taxotère analogs.

N,N-(Disubstituted)carbamoyl-β-lactams **5** were successfully coupled with **7a** to give the corresponding new taxotère analogs in good yields: 54% yield (77% for the coupling; 70% for deprotection under modified Commerçon conditions) for *N*-morpholinocarbonyl analog (Scheme 3) and 50% yield for *N,N*-dimethylcarbamoyl analog.[6] For *N*-(monsubstituted)carbamoyl-β-lactams **4**, an extra protection was found to be necessary to promote the coupling with **7a**; we are currently working on the optimization of conditions. The results will be discussed in the future publications from this laboratory.

Scheme 2



Scheme 3



Further study on the design, syntheses and SAR of new analogs of taxol and taxotère is actively in progress. Antitumor activities of these new taxanes will be published elsewhere.

Acknowledgment: This research was supported by grants from Rhone-Poulenc Rorer and the National Institutes of Health (NIGMS).

References and notes

1. E.g., (a) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991,** *56*, 5263. (b) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990,** *31*, 977. (c) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990,** *112*, 770. (d) Ojima, I.; Chen, H.-J. C.; Nakahashi, K. *J. Am. Chem. Soc.*, **1988,** *110*, 278. (e) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988,** *44*, 5307, and references cited therein.
2. Jung, M. J. In *"Chemistry and Biochemistry of Amino Acids"* Barrett, G. C. Ed.; Chapman and Hall, New York, 1985, 227.
3. Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayashinge, L. R. *J. Org. Chem.* **1991,** *56*, 1681.
4. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992,** *48*, 6985.
5. E.g., (a) Burris, H.; Irwin, R.; Kuhn, J.; Kalter, L.; Smith, D.; Shafer, D.; Rodoriguez, G.; Gueiss, G.; Eckardt, J.; Vreeland, F.; Bayssas, Von Hoff, D. *Proc. Am. Soc. Clin. Oncol.* **1992,** *11*, 369. (b) Bissery, M. C.; Guéritte-Vogelein, F.; Guénard, D.; Lavelle, F. *Cancer Res.* **1991,** *51*, 4845.
6. All new compounds were unambiguously identified on the basis of ^{1}H and ^{13}C NMRs, IR, Mass and or elemental analyses.
7. Holton, R. A. *Eur. Pat. Appl.* EP 400,971, 1990: *Chem. Abstr.* **1991,** *114*, 164568q.
8. E.g., (a) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R.; Burke, C. T. *J. Med. Chem.* **1992,** *35*, 4230. (b) Kepler, J. A.; Taylor, G. F.; Thornton, S. S.; Wall, J. F.; *Second National Cancer Institute Workshop on taxol and Taxus, September 23-24, 1992, Alexandria, VA; Abstracts.*
9. Regarding the use of NaH as the base for the coupling of the β-lactam **6** with the baccatin **7a**, 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).
10. *N*-Methoxycarbonyl-β-lactam (**3a**) did not react with baccatin **7a** at all under the Holton conditions.
11. Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992,** *33*, 5185.