Efficient Asymmetric Syntheses of β-Lactams Bearing a Cyclopropane or an Epoxide Moiety and Their Application to the Syntheses of Novel Isoserines and Taxoids

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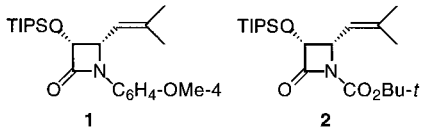
In the course of our study on the exploration of the β-lactam synthon method (β-LSM),[1−6] we became interested in the design and synthesis of novel isoserines bearing a cyclopropane or an epoxide moiety in the molecule. Because of their unique steric and electronic nature, these novel isoserines may serve as new and useful building blocks for peptides, peptidomimetics, protease inhibitors, and taxoid antitumor agents. We describe here highly efficient asymmetric syntheses of β-lactams bearing a cyclopropane or an epoxide moiety at the C-4 position and their application to the syntheses of novel methanoisoserine, oxaisoserines, and taxoids bearing these unique isoserines at the C-13 position.

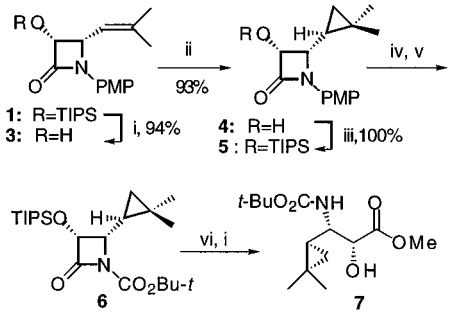
(3*R*,4*S*)-1-PMP-3-TIPSO-4-(2-methyl-1-propenyl) β-lactam **1** (PMP = *p*-methoxyphenyl, TIPSO = triisopropylsiloxy) and (3*R*,4*S*)-1-*t*-Boc-3-TIPSO-4-(2-methyl-1-propenyl) β-lactam **2** (*t*-Boc = *tert*-butoxycarbonyl) with high enantiomeric purity (>96% ee) were prepared in excellent yields through a highly efficient chiral ester enolate-imine cyclocondensation reaction previously reported from these laboratories.[7−10]



1 **2**

Attempted cyclopropanation of β-lactam **1** through a modified Simmons−Smith reaction using Et_2Zn and CH_2I_2[11] resulted in the recovery of the starting material. This may well be due to the bulkiness of the TIPS group at the C-3 position of β-lactam **1**. Accordingly, the TIPS group was removed using HF/pyridine to give 3-OH β-lactam **3** in high yield. Reaction of β-lactam **3** with Et_2Zn (5 equiv) and CH_2I_2 (10 equiv) in 1,2-dichloroethane[12] at room temperature afforded 4-((*S*)-2,2-dimethylcyclopropyl) β-lactam **4** as the sole product in 93% yield (Scheme 1). Protection of the C-3 hydroxyl group as the TIPS ether proceeded smoothly to give β-lactam **5** in quantitative yield by reacting **4** with TIPSCl (2 equiv) in the presence of Et_3N and (dimethylamino)pyridine (DMAP) at 35 °C. Treatment of β-lactam **5** with ceric ammonium nitrate (CAN), removing *N*-PMP, followed by protection with *N*-*t*-Boc gave *N*-*t*-Boc β-lactam **6** in 92% yield (Scheme 1). Ring opening of 4-cyclopropyl β-lactam **6** with methanol in the presence of NEt_3 (2 equiv) and DMAP (0.5 equiv) followed by deprotection of TIPS using HF/pyridine gave *N*-*t*-Boc-methanonorstatine methyl ester (**7**) in 92% yield for two steps (Scheme 1).

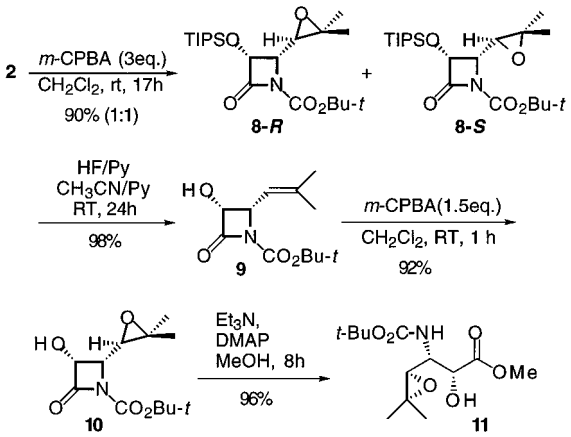
Scheme 1[a]



6 **7**

[a] Key: (i) HF/Py; (ii) Et_2Zn (5 equiv), CH_2I_2 (10 equiv), $ClCH_2CH_2Cl$, rt, 2 h; (iii) TIPSCl, NEt_3, DMAP; (iv) CAN; (v) $(t\text{-Boc})_2O$, NEt_3, DMAP; (vi) NEt_3, DMAP, MeOH.

Scheme 2



Reaction of β-lactam **2** with *m*-chloroperoxybenzoic acid (*m*-CPBA) (3 equiv) in CH_2Cl_2 at room temperature resulted in the formation of a 1:1 mixture of β-lactams, **8-*R*** and **8-*S***, in 90% yield; i.e., no diastereoselection took place. In contrast, the reaction of 3-OH β-lactam **9** with *m*-CPBA (1.5 equiv) in CH_2Cl_2 at room temperature afforded 4-((*R*)-2-methyl-1,2-epoxypropyl) β-lactam **10** as the sole product in 92% yield (Scheme 2). *N*-*t*-Boc-oxanorstatine methyl ester (**11**) was obtained in 96% yield through ring opening of 4-epoxy β-lactam **10** with methanol in the presence of NEt_3 (2 equiv) and DMAP (0.5 equiv) (Scheme 2).

The single-crystal X-ray structures of β-lactam **4** (Scheme 1) and a derivative of β-lactam **10**, 3-[(4-nitrobenzoyl)oxy] β-lactam **12** are shown in Figure 1. The extremely high diastereoselectivity observed in these cyclopropanation and epoxidation reactions can be explained by taking into account the highly organized transition-state structures[13]

(1) Ojima, I. In *The Organic Chemistry of β−Lactam Antiobiotics*; Georg, G. I., Ed.; VCH Publishers: New York, 1992; pp 197−255.
(2) Ojima, I.; Park, Y. H.; Sun, C. M.; Zhao, M.; Brigaud, T. *Tetrahedron Lett.* **1992**, *33*, 5737−5740.
(3) Ojima, I.; Sun, C. M.; Park, Y. H. *J. Org. Chem.* **1994**, *59*, 1249−1250.
(4) Ojima, I. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, 1995; Vol. 1, pp 95−146.
(5) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389 and references therein.
(6) Ojima, I.; Ng, E. W.; Sun, C. M. *Tetrahedron Lett.* **1995**, *36*, 4547−4550.
(7) Ojima, I.; Duclos, O.; Kuduk, S. D.; Sun, C.-M.; Slater, J. C.; Lavelle, F.; Veith, J. M.; Bernacki, R. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2631−2634.
(8) Ojima, I.; Slater, J. C.; Michaud, E.; Kuduk, S. D.; Bounaud, P.-Y.; Vrignaud, P.; Bissery, M.-C.; Veith, J.; Pera, P.; Bernacki, R. J. *J. Med. Chem.* **1996**, *39*, 3889−3896.
(9) Ojima, I.; Slater, J. S.; Kuduk, S. D.; Takeuchi, C. S.; Gimi, R. H.; Sun, C.-M.; Park, Y. H.; Pera, P.; Veith, J. M.; Bernacki, R. J. *J. Med. Chem.* **1997**, *40*, 267−278 and references therein.
(10) Ojima, I.; Kuduk, S. D.; Pera, P.; Veith, J. M.; Bernacki, R. J. *J. Med. Chem.* **1997**, *40*, 279−285 and references therein.
(11) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53−58.
(12) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974−6981.
(13) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370 and references therein.

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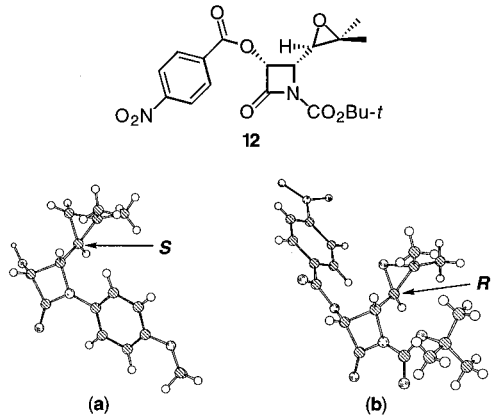


Figure 1. Chem 3D representation of the X-ray structues of β-lactams **4** (**a**) and **12** (**b**).

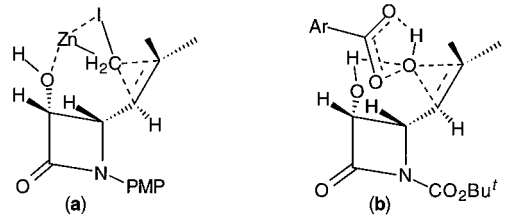


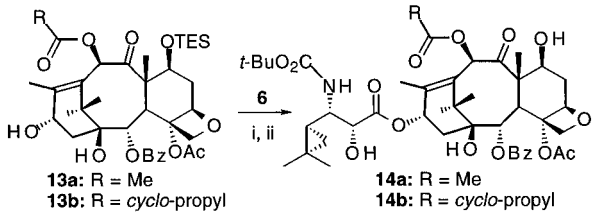
Figure 2. Proposed transition state structures for the formation of β-lactams **4** (**a**) and **10** (**b**).

illustrated in Figure 2. The constrained β-lactam skeleton maximizes the directing effect of C-3 hydroxyl group to achieve the exclusive formation of cyclopropane **4** or epoxide **10**.

As a part of our continuing SAR study of paclitaxel and docetaxel analogues,[7−10] we synthesized novel taxoids bearing the methanonorstatine residue at the C-13 position using baccatins and the coupling protocol developed in these laboratories.[5,7−10,14−19] The coupling of 7-TES-baccatin (**13a**)[14,20] or 7-TES-10-(cyclopropanecarbonyl)-10-deacetylbaccatin (**13b**)[8] with β-lactam **6** was carried out under the standard conditions using LiHMDS in THF at −40 °C, followed by deprotection with HF/pyridine, to afford the corresponding new taxoid **14a** or **14b** in good to excellent yield (Scheme 3). In a similar manner, taxoids, **15-*R*** and **15-*S***, bearing the oxanorstatine residue at the C-13 position, were synthesized through coupling of β-lactams **8-*R*** and **8-*S*** with baccatin **13b** in good yields (Scheme 4).

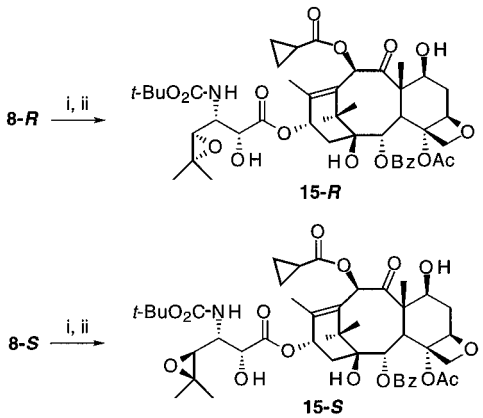
The anti-tumor activity of these novel taxoids was evaluated in vitro.[21] Taxoids **14a** and **14b** exhibited extremely high potency against a drug-resistant human breast cancer cell line LCC6-MDR (IC_{50} = 2.77 nM for **14a**, 2.95 nM for **14b**, while paclitaxel has a IC_{50} value of 346 nM), and the activity ratio for (drug resistant cells)/(drug sensitive cells) is 2.48 for **14b**, which is the best ratio ever reported. It is very intriguing that **15-*R*** is highly active (IC_{50} = 0.44−0.68 nM; 1 order of magnitude more potent than paclitaxel), while **15-*S*** is 1−2 orders of magnitude less active (IC_{50} = 6.50−21.7 nM) against human cancer cell lines A121 (ovarian), A549 (nonsmall lung), HT-29 (colon) and MCF-7 (breast).

Scheme 3[a]



[a] Key: (i) **13a** and **13b**, LiHMDS, THF, −40 °C, 30 min, 84−91%; (iii) HF/Py, 0 °C → rt, 24 h, 88−96%.

Scheme 4[a]



[a] Key: (i) **13b**, LiHMDS, THF, −40 °C, 30 min, 81−88%; (ii) HF/Py, 0 °C → rt, 24 h, 66−78%.

In summary, the asymmetric syntheses of β-lactams bearing a cyclopropane or an epoxide moiety has been achieved with complete stereochemical control. These β-lactams were further converted to the novel norstatine analogues and taxoids, which showed extremely potent cytotoxicity. The strong directing effect of the C-3 hydroxy group of β-lactams in both cyclopropanation and epoxidation is particularly noteworthy. Further studies on the scope and limitation of this methodology for preparation of a variety of β-lactams bearing a cyclopropane or an epoxide moiety as synthetic intermediates as well as the structure−activity relationships (SAR) of the new taxoids bearing these unique isoserine residues are actively underway.

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Supporting Information Available: Experimental procedures for the asymmetric syntheses of β-lactams **1-6**, **8-10**, and **12** as well as taxoids **14** and **15**; characterization data for new compounds **3-12**, **14**, and **15**; X-ray data for **4** and **12** (38 pages).

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(14) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C.-M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985−7012.
(15) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. D. *Tetrahedron Lett.* **1993**, *34*, 4149−4152.
(16) Ojima, I.; Zucco, M.; Duclos, O.; Kuduk, S. D.; Sun, C.-M.; Park, Y. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2479−2482.
(17) Ojima, I.; Kuduk, S. D.; Slater, J. C.; Gimi, R. H.; Sun, C. M. *Tetrahedron* **1996**, *52*, 209−224.
(18) Holton, R. A.; Biediger, R. J.; Boatman, P. D. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press: New York, 1995; pp 97−121.
(19) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Clowers, J. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. In *Taxol®: Science and Applications*; Suffness, M., Ed.; CRC Press: New York, 1995; pp 317−375.
(20) Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917−5919.
(21) The cytotoxicity assays of **14** and **15** were carried out by Dr. Ralph J. Bernacki and Paula Pera, Department of Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Cancer Institute. Detailed biological data will be published elsewhere.