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Synthesis of the C-13 Side Chain Precursors of the 9-Dihydrotaxane Analogue ABT-271

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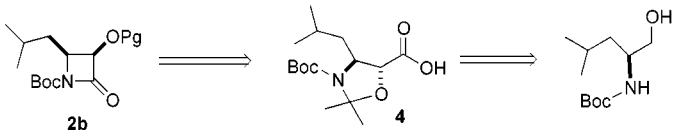
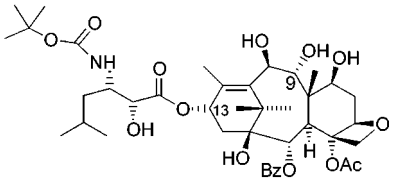
ABSTRACT



***N*-Boc-L-Leucinol was converted to two C-13 side chain precursors of the 9-dihydrotaxane analogue ABT-271. The *trans*-oxazolidine acid 4 and the *cis*-Boc-lactam 2b were prepared in 44% and 40% overall yield, respectively, and with excellent (>98%) stereochemical purity.**

The naturally occurring diterpene paclitaxel (Taxol) has shown remarkable antitumor activity and is currently approved for the treatment of metastatic ovarian, breast, and lung cancer.[1] However, paclitaxel exhibits poor water solubility and requires the use of a relatively toxic vehicle, containing Cremophor EL, for administration.[2] Identification of new analogues with increased water solubility that maintain potent antimicrotubular properties could potentially obviate this excipient, leading to a better safety profile.

The isolation and characterization of 13-acetyl-9(*R*)-dihydrobaccatin III (9-DHAB III) from a bush (*Taxus canadensis*) common to the northeastern United States and southern Quebec was reported in 1992 by several laboratories.[3] Extensive investigation of this 9-dihydrobaccatin core has led to the identification of new paclitaxel analogues with improved water solubility that maintain impressive antitumor activity.[4] From this study, ABT-271 was identified for further evaluation.



1 ABT-271

Central to the preparation of ABT-271 (**1**) was the design of a scalable stereoselective synthesis of the isoserine side chain coupling precursors **2b** and **4** and their efficient

(1) Taxol is the registered trademark of Bristol-Myers Squibb Company for paclitaxel. (a) For a review, see: Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 15−44; (b) *Future Oncol.* **1997**, *4*, 614−620.

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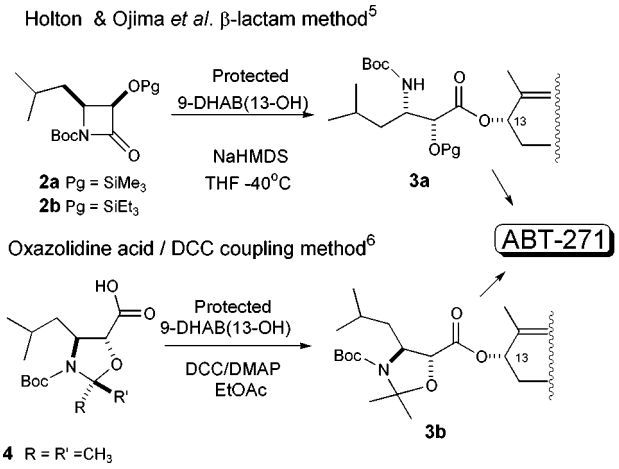
conversion to ABT-271 utilizing two standard coupling methods[5,6] (Scheme 1). Herein, we report a scalable stereoselective synthesis of the isoserine side chain precursors of ABT-271 on a kilogram scale.

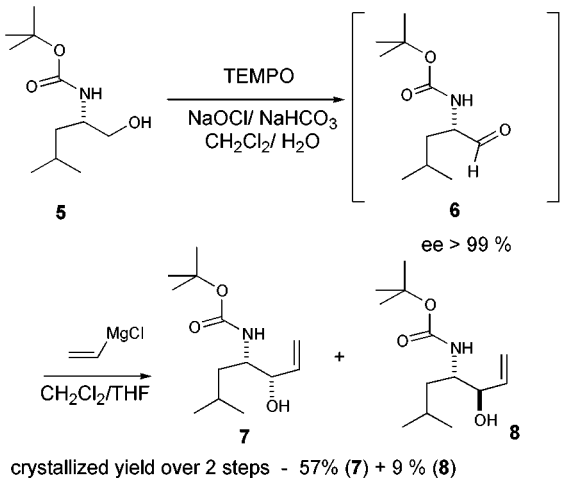
Scheme 1. C13 Baccatin Coupling Methods



As a result of the importance of paclitaxel, the most extensively studied isoserine is (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine; several stereoselective syntheses exist for this *β*-amino acid.[7] A number of these syntheses take advantage of the stereoelectronic effects of the aromatic ring to induce good regiocontrol of nucleophilic opening of the styrene oxide[8] or Sharpless amino-hydroxylation methodology.[9] However, these methods suffer from poor regiocontrol when applied to the requisite alkyl acrylate.[9b]

Utilization of the chiral pool was an attractive starting point, since leucine possesses a significant portion of the carbon framework. *N*-Boc-L-leucinol **5** was oxidized to *N*-Boc-L-leucinal **6** via a TEMPO-mediated oxidation (Scheme 2).[10] This method afforded the aldehyde in superior chemical purity in comparison to the Swern oxidation and without any detectable racemization.[11] After an aqueous workup, the dichloromethane solution of the aldehyde was added to 2.5 equiv of vinylmagnesium chloride (1.9 M THF solution) at room temperature to afford a 57% overall recystallized yield of the desired *syn*-amino alcohol (chelation controlled) contaminated with 9% of the epimeric *anti*-alcohol.[12] It was found that the crude epimeric mixture could be increased from 3:1 to 4.5:1 by carrying out the reaction in CH_2Cl_2/THF mixtures. Attempts to further increase selectivity by carrying out the reaction at −10 instead of 30 °C actually decreased the epimeric mixture from 4.5:1 to 2.8:1. Crystallization of the crude reaction mixture from cold heptane (−20 °C) afforded a 57% overall recrystallized yield of the desired *syn* diastereomer **7**.[13]

Scheme 2



Strategic protection of the alcohol as its *N*,*O*-acetonide serves a dual purpose of protection of the alcohol during oxidative cleavage of the olefin and removal of the unwanted epimer via a kinetically controlled ketalization.[14] The *syn* diastereomer readily cyclizes in CH_2Cl_2 at −20 °C (with 5 mol % PPTS) to form the desired *trans*-oxazolidine, whereas the *anti*-diastereomer proceeds to the sterically congested *cis*-oxazolidine very slowly as a result of torsional strain. The reaction was quenched after approximately 95% of the desired epimer had reacted by addition of Et_3N.

Efficient separation of the oxazolidine **9** away from the unreacted alcohols **7** and **8** was initially accomplished with chromatography. This was adequate for small scale but would hamper large scale synthesis. Instead we directed our efforts toward an in situ chemical modification of the unreacted alcohols (Scheme 3). Removal of the unreacted alcohols **7** and **8** (∼1:3 *syn/anti*) from the desired oxazolidine **9** was conveniently accomplished extractively by reacting the quenched reaction mixture with succinic anhydride (with 1.5 equiv DMAP).[15] After an aqueous workup, the desired

(8) Denis, J.-N.; Greene, A. E., Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1992**, *57*, 4320.

(9) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *108*, 2995−2999. (b) Extensive investigation into Sharpless amino-hydroxylation methodology on the requisite ethyl acrylate optimally afforded, after chromatagraphy, the desired *N*-acetyl-protected isoserine ester in 35% yield, regioselectivity 1.5:1, 90% ee. Conditions: $(DHQ)_2PHAL$/*t*-BuOH/H_2O, 4 °C.

(10) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029−5032.

(11) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000,** *41,* 1359−1362. The enantiomeric excess was determined by conversion back to *N*-Boc-leucinol (LAH/THF) and subsequently converted to its 3,5-dinitrobenzoate. Analysis by chiral HPLC (D-naphthylalanine, 9/1 hexane/IPA, 1.5 mL/min, 35 °C): retention times 12.5 (*R*-isomer) and 15.2 min (*S*-isomer).

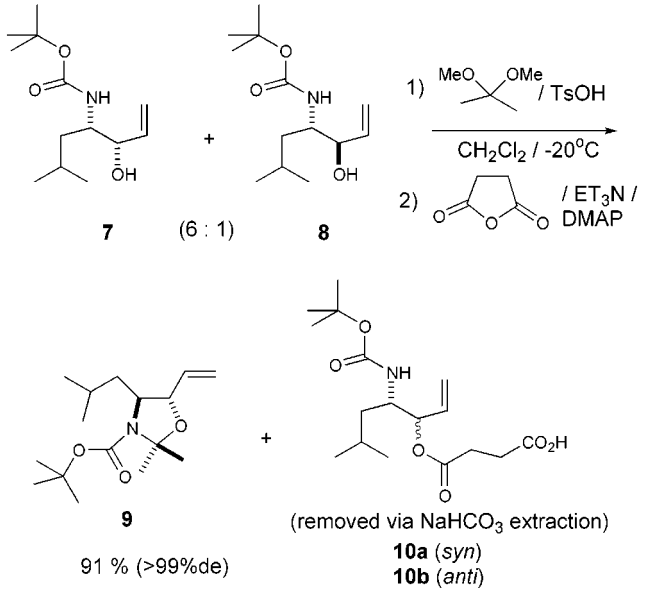
(12) The relative stereochemistry was confirmed by conversion of both epimers independently to lactam **2b** and **epi-2b,** where their coupling constants were 5.7 Hz for **2b** and 1.9 Hz for **epi-2b**, which is consistent with *cis* (*syn*) and *trans* (*anti*) relative stereochemistry for *β*-lactams, see: Alcaide, B.; Esteban, G.; Martin-Cantalejo, Y.; Plumet, J.; Rodriguez-Lopez, J. *J. Org. Chem.* **1994**, *59*, 7994−8002.

(13) Crystallization from 4 vol of heptane at −20 °C increased the epimeric ratio to ∼ 6:1 *syn*/*anti* alcohols.

(14) Weber, A. E.; Halgren, T. A.; Doyle, J. J.; Lynch, R. J.; Siegl, P. K. S.; Parsons, W. H.; Greenlee, W. J.; Patchett, A. A. *J. Med. Chem.* **1991**, *34*, 2692−2701.

(15) The use of succinic anhydride as an acyl donor in biocatalytic kinetic resolutions of alcohols has been established as a practical method for the extractive separation of product (succinate) away from the neutral unreacted starting material (alcohol): Terao, Y.; Tsuji, K.; Murata, M.; Achiwa, K.; Nishio, T.; Watanabe, N.; Seto, K. *Chem. Pharm. Bull.* **1989**, *37*, 1653.

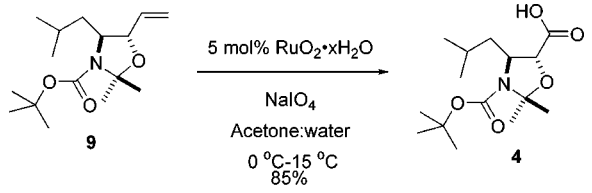
Scheme 3



oxazolidine **9** was isolated as a neat oil in 91% yield with >99.5% de and 99% HPLC purity versus a standard.

The vinyl oxazolidine **9** was then oxidized to the corresponding carboxylic acid with catalytic RuO_2 (5 mol %) and $NaIO_4$ (6.5 equiv) as the net oxidant in a 1:1 ratio of acetone/water (0.05 M) using modified Sharpless conditions (Scheme 4).[16] Initial reaction attempts were based on a literature

Scheme 4



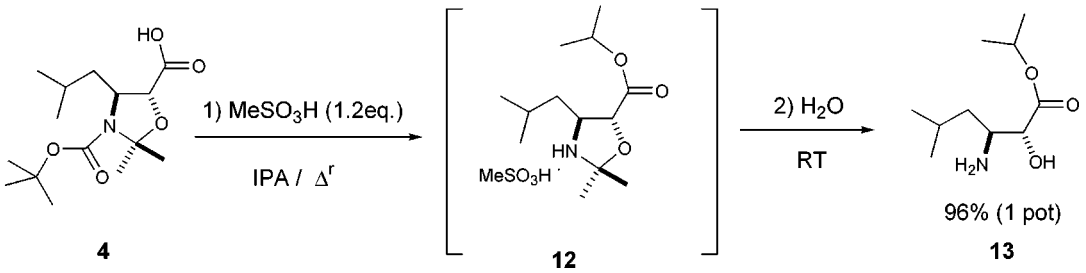
procedure in which RuO_2 was mixed with the substrate prior to slow addition of the $NaIO_4$.[14] Under these conditions, we observed exclusive formation of the aldehyde, which upon consumption of starting olefin **9** was rapidly and exothermically converted to the desired acid. This gave excellent yields but was considered unsafe. After several permutations, it was determined that pregeneration of the active catalyst RuO_4 (5 mol %) eliminated the observed exotherm. This was accomplished by mixing RuO_2 (5 mol %) with $NaIO_4$ (30 mol %) in water and aging 20 min before addition of the olefin/acetone mixture. More $NaIO_4$ was then added as an aqueous solution over 3 h at 15 °C. The reaction clearly proceeds in a different mode when run under this pregeneration protocol, as evidenced by the concomitant formation of diol, aldehyde, and acid. Additionally, no induction period was observed. This modification allowed for safe reaction conditions on a multi-kilogram scale. Following a 2-propanol quench and extractive base/acid purification, the desired acid **4** was isolated in 85% yield with 98% HPLC purity.[17]

Oxazolidine acid **4** was then successfully coupled to the baccatin core (9-DHAB III) using the DCC protocol (Scheme 1), in 94% yield, but ultimately suffered poor conversion to ABT-271 as a result of the relatively harsh reaction conditions required for *N*,*O*-acetonide cleavage.

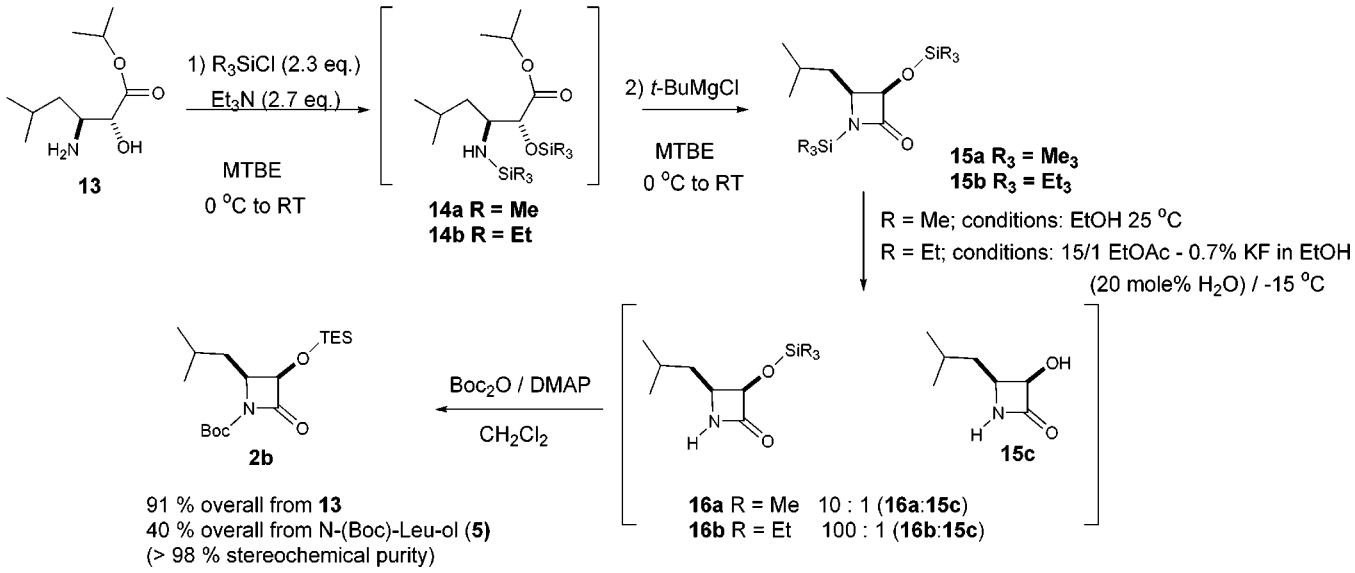
Attracted by the flexibility of the 2′-hydroxyl protecting groups utilized with the Ojima/Holton β-lactam coupling method,[5] the synthesis of the lactam **2b** was investigated. We and others have prepared β-lactams by intramolecular cyclocondensation of β-amino esters.[18] Preparation of the requisite norstatine ester **13** was accomplished by a one-pot solvolysis/esterification (Scheme 5). This was optimally accomplished by treatment of the *trans*-oxazolidine acid **4** with 1.2 equiv of $MeSO_3H$ in refluxing IPA. After the esterification was complete as judged by LC/MS, the reaction mixture was cooled to 25 °C, and water was added to facilitate removal of the acetonide. This gave norstatine isopropyl ester **13** in a one-pot yield of 96%. The isopropyl ester was chosen for its ease of extraction from water mixtures and its stability.[19]

Preparation of the bis-silyl lactam **15a,b** was accomplished by in situ formation of the bis-silylated intermediate **14a,b** followed by addition of *t*-BuMgCl (4 equiv) (Scheme 6). Selective monohydrolysis of the *N*,*O*-bis-TMS lactam **15a** to the desired *O*-TMS lactam **16a** was modestly selective (10:1); however, the corresponding TES derivative was better controlled. Extensive investigation led to the identification of conditions that selectively *N*-desilylate the *N*,*O*-bis-TES

Scheme 5



Scheme 6



lactam **15b** (>100:1 [OTES/OH]) using 15:1 EtOAc/0.7% KF (0.06 equiv) solution in EtOH (with 20 mol % H_2O) at − 15 °C. After an aqueous workup and solvent switch, the lactam **16b** was reacted with 1.5 equiv Boc_2O (0.5 equiv DMAP) in 5 vol of CH_2Cl_2, to afford the Boc-lactam silyl ether **2b** in 91% overall yield from **13**.[20]

In summary, both side chain precursors **4** and **2b** can be synthesized in excellent stereochemical purity (>98%)[21] from commercially available *N*-Boc-Leu-ol without chromotography in 44% and 40% (**4** and **2b**, respectively) overall yield. This process should be amenable to other alkyl isoserines derived from the chiral pool, where other general methods are not satisfactory. This process has been carried out on multi-kilogram scale and has been utilized in the synthesis of ABT-271. Synthesis of ABT-271 and full experimental details will be reported elsewhere.

Supporting Information Available: Experimental procedures and characterization data for **2b**, **4**, **6**−**9**, **13**, **15b**, and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006508O

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(17) Preparing its DCHA salt in acetonitrile could further purify the acid. For a nonstereoselective route to this oxazolidine acid, see: Veeresha, G.; Datta, A. *Tetrahededron Lett*. **1997**, *38*, 5223−5224.

(18) (a) Lynch, J. K.; Holladay, M. W.; Ryther, K. B.; Bai, H.; Hsiao, C.-N.; Morton, H. E.; Dickman, D. A.; Arnold, W.; King, S. A. *Tetrahedron Asymm*. **1998**, *9*, 2791−2794. (b) Alcaide, B.; Biurrun, C.; Plumet, J.; Borredon, E.; *Tetrahedron Lett.* **1992**, *33*, 7413−7416.

(19) Preparation of straight-chain alkyl esters invariably afforded mixtures of dimeric byproducts, especially upon scale-up. Although the isopropyl ester greatly enhances stability, this lactamization method has only been previously demonstrated on unbranched isoserine esters.

(20) The lactam was isolated in approximately 70−75% potency, contaminated with 20 wt % of ethoxytriethylsilane, which could be removed by concentrating under very good vacuum (94% potency).

(21) The C3-**epi**-**2b** was not detected by ^1H NMR; furthermore **2b** was reacted with both (*R*)- and (*S*)-α-methylbenzylamine to provide diastereoisomers set. By HPLC, <1% of a diastereomeric impurity was observed from this diastereomeric set.