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Synthesis of Docetaxel and Butitaxel Analogues through Kinetic Resolution of Racemic β-Lactams with 7-*O*-Triethylsilylbaccatin III

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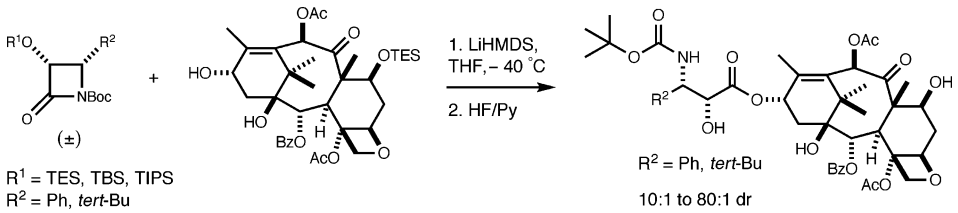

The kinetic resolution of racemic *cis*-4-phenyl- and *cis*-4-*tert*-butyl-3-hydroxy-β-lactam derivatives with 7-*O*-triethylsilylbaccatin III yielded paclitaxel and butitaxel analogues with high diastereoselectivity. The results demonstrated that the *tert*-butyldimethylsilyl protecting group at the C3-hydroxy group of the β-lactams provided optimum kinetic resolution in comparison with the sterically less demanding triethylsilyl group and the larger triisopropylsilyl group. In addition, it was found that the C4 β-lactam substituents also influenced diastereoselectivity. The C4 *tert*-butyl-β-lactams provided better diastereoselectivity than the corresponding C4 phenyl β-lactams.

Introduction

Paclitaxel (**1a**, Taxol, Figure 1), a cytotoxic agent from the bark of the Pacific yew (*Taxus brevifolia*),[1] exerts its activity by alteration of tubulin dynamics.[2] Paclitaxel and its semisynthetic analogue docetaxel (**1b**, Taxotere, Figure 1) are effective agents for the treatment of ovarian and breast cancer, Kaposi's sarcoma, and non-small-cell lung cancer.[3] The continued evaluation of new analogues is important because of paclitaxel drug-resistance, the inability of paclitaxel to cross the blood−brain barrier (BBB), and its lack of oral bioavailability.[4]

In the course of structure−activity relationship studies, series of highly potent second-generation analogues have been developed that overcome some of the deficiencies of paclitaxel.[5] For example, it has been reported that BMS-275183 (**2b**, Figure 1), a derivative of butitaxel (**2a,** Figure 1),[6,7] is orally bioavailable[8] and that TX-67 (**1c**, Figure 1) is able to cross the BBB in situ.[9]

Typically, paclitaxel analogues have been prepared by semisynthesis from baccatin III derivatives using nonracemic β-lactams, which serve as the precursors for the C13 *N*-acyl-3′-phenylisoserine side chain. The asymmetric ester enolate−imine cyclocondensation or enzyme-catalyzed resolutions are excellent methods to prepare enantiopure (3*R*,4*S*)-β-lactams.[10−14] However, several groups have reported the synthesis of paclitaxel

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(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327.
(2) For review: Zhou, J.; Giannakakou, P. *Curr. Med. Chem.: Anti-Cancer Agents* **2005**, *5*, 65−71.
(3) For review: Spencer, C. M.; Faulds, D. *Drugs* **1994**, *48*, 794−847.
(4) Ge, H.; Vasandani, V.; Huff, J. K.; Audus, K. L.; Himes, R. H.; Seelig, A.; Georg, G. I. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 433−436.
(5) For review: Kingston, D. G. I.; Jagtap, P. G.; Yuan, H.; Samala, L. *Prog. Chem. Org. Nat. Prod.* **2002**, *84*, 53−225.
(6) Ali, S. M.; Hoemann, M. Z.; Aubé, J.; Mitscher, L. A.; Georg, G. I.; McCall, R.; Jayasinghe, L. R. *J. Med. Chem.* **1995**, *38*, 3821−3828.
(7) Ali, S. M.; Hoemann, M. Z.; Aubé, J.; Georg, G. I.; Mitscher, L. A. *J. Med. Chem.* **1997**, *40*, 236−241.
(8) Mastalerz, H.; Cook, D.; Fairchild, C. R.; Hansel, S.; Johnson, W.; Kadow, J. F.; Long, B. H.; Rose, W. C.; Tarrant, J.; Wu, M.-J.; Xue, M.-Q.; Zhang, G.-F.; Zoeckler, M.; Vyas, D. M. *Bioorg. Med. Chem.* **2003**, *11*, 4315−4323.
(9) Rice, A.; Liu, Y.; Michaelis, M. L.; Himes, R. H.; Georg, G. I.; Audus, K. *J. Med. Chem.* **2005**, *48*, 832−838.
(10) For review: Boge, T. C.; Georg, G. I. The Medicinal Chemistry of β-Amino Acids: Paclitaxel as an Illustrative Example. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp 1−43.
(11) Kayser, M. M.; Mihovilovic, M. D.; Kearns, J.; Feicht, A.; Stewart, J. D. *J. Org. Chem.* **1999**, *64*, 6603−6608.
(12) Kayser, M. M.; Yang, Y.; Mihovilovic, M. D.; Feicht, A.; Rochon, F. D. *Can. J. Chem.* **2002**, *80*, 796−800. Yang, Y.; Wang, F.-Y.; Rochon, F. D.; Kayser, M. M. *Can. J. Chem.* **2005**, *83*, 28−36.

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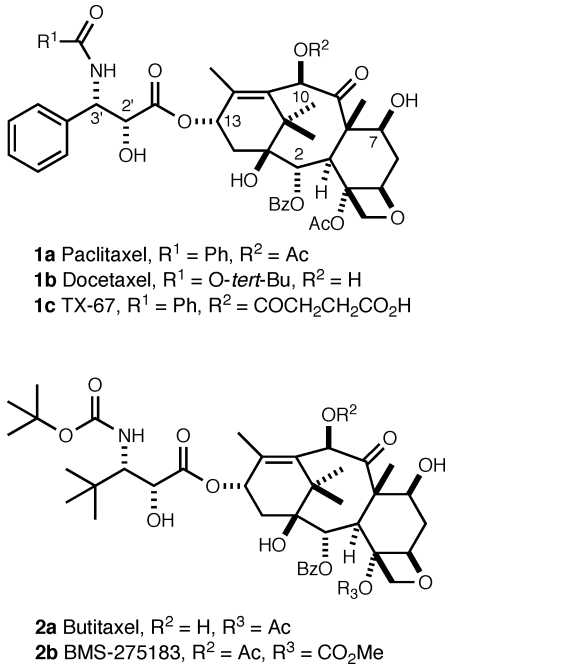
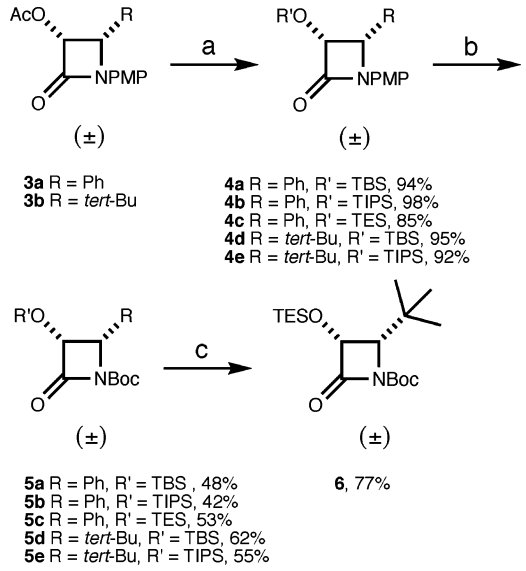


FIGURE 1. Structures of paclitaxel (**1a**), docetaxel (**1b**), Tx-67 (**1c**), butitaxel (**2a**), and BMS-275183 (**2b**).

analogues through kinetic resolution using racemic *cis*-β-lactams with moderate to high diastereoselectivities.[8,15−17] Recently, dynamic kinetic resolution of racemic 3-oxo-4-phenyl-β-lactam was achieved by recombinant *Esherichia coli* (*E. coli*), overexpressing yeast reductase Ara1p.[18] Holton was the first to disclose the kinetic resolution of *N*-benzoyl- and *N*-Boc-4-phenyl-3-(triethylsilyloxy)-β-lactams with the lithium alkoxide of 7-*O*-(triethylsilyl)baccatin III and 10-deacetyl-7,10-bis(triethylsilyl)baccatin III and reported diastereoselectivities of 6:1 and 100%, respectively.[15] Excellent kinetic resolution was also observed by Ojima and co-workers when they employed *O*-ethoxyethyl-protected 3-hydroxy-4-(trifluoromethyl)-β-lactams in this reaction.[16] During these studies, it was found that variation of the baccatin III substituents typically had little effect on the stereoselectivity of the reaction. However, the kinetic resolution with *N*-Boc-3-(triethylsilyloxy)-4-*tert*-butyl-β-lactam was influenced by the structure of the baccatin III derivative.[8] Reaction between *N*-Boc-4-*tert*-butyl-3-(triethylsilyloxy)-β-lactam and 7-*O*-(diisopropylmethoxysilyl)baccatin III provided a 3:1 diastereomeric ratio, whereas the reaction with a 7-deoxy-9β-dihydro-9,10-acetalbaccatin III yielded only one diastereoisomer.[17]

We surmised from these studies that the structure of the β-lactam plays a major role in controlling the stereoselectivity of the kinetic resolution and that this effect would warrant some further study. We therefore decided to investigate in more detail the influence of the β-lactam substituents on the outcome of the kinetic resolutions with 7-*O*-(triethylsilyl)baccatin III.

SCHEME 1[a]



[a] (a) (i) LiOH in acetone or K_2CO_3 in MeOH; (ii) R′SiCl, imidazole/DMAP, CH_2Cl_2, rt. (b) (i) $Ce(NH_4)_2(NO_3)_6$, aq CH_3CN, −20 °C; (ii) $(Boc)_2O$, diisopropylethylamine, DMAP, CH_2Cl_2, rt. (c) (i) HF-Py in Py, 0 °C to rt; (ii) (TES)Cl, imidazole, CH_2Cl_2, rt.

Results and Discussion

The synthesis of the racemic β-lactams **5** and **6** is shown in Scheme 1. 4-Phenylazetidin-2-one (**3a**) and 4-*tert*-butylazetidin-2-one (**3b**) were prepared according to reported procedures.[8] The acetyl group on **3** was removed with lithium hydroxide in acetone (for **3a**) or potassium carbonate in methanol (for **3b**), followed by protection with a trialkylsilyl chloride to furnish 3-(trialkylsilyloxy)-β-lactams (**4a**−**e**) in high to excellent yields.[19,20] The 4-methoxyphenyl moiety (PMP) of **4** was removed oxidatively with ceric ammonium nitrate (CAN)[21] and then treated with *tert*-butyl dicarbonate to afford racemic 3-(trialkylsilyloxy)-4-phenylazetidin-2-ones (**5a**−**c**) and 3-(trialkylsilyloxy)-4-*tert*-butylazetidin-2-ones (**5d**,**e**). 3-(Triethylsilyloxy)-4-*tert*-butylazetidin-2-one (**6**) was prepared from **5d** by removal of the *tert*-butyldimethylsilyl protecting group with HF−pyridine, followed by triethylsilyl protection in 77% yield.

First, we investigated the kinetic resolution between racemic **5a** and 7-*O*-(triethylsilyl)baccatin III (**7**)[22] under several different reaction conditions (Table 1). The resulting reaction products were subsequently treated with hydrogen fluoride in pyridine to furnish 10-acetyldocetaxel (**8**, Scheme 2). The isomeric ratios of **8** were determined by HPLC analysis (Table 1).

The results for the kinetic resolution are shown in Table 1. It was found that the diastereoselectivity of the reaction decreased slightly with an increase in reaction temperature (see entries 1−3). Although the stereoselectivity was not significantly influenced, the yield dramatically decreased when the amount

(13) Patel, R. N.; Howell, J.; Chidambaram, R.; Benoit, S.; Kant, J. *Tetrahedron: Asymmetry* **2003**, *14*, 3673−3677.
(14) Carr, J. C.; Al-Azemi, T. F.; Long, T. E.; Shim, J.-Y.; Coates, C. M.; Turos, E.; Bisht, K. S. *Tetrahedron* **2003**, *59*, 9147−9160.
(15) Holton, R. A.; Biedinger, R. J.; Boatman, P. D. Semisynthesis of Taxol and Taxotere. In *Taxol Science and Applications*; Suffness, M., Ed.; CRC: Boca Raton, FL, 1995; pp 97−121.
(16) Ojima, I.; Slater, J. C. *Chirality* **1997**, *9*, 487−494.
(17) Takeda, Y.; Uoto, K.; Iwahana, M.; Jimbo, T.; Nagata, M.; Atsumi, R.; Ono, C.; Tanaka, N.; Terasawa, H.; Soga, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3209−3215.
(18) Yang, Y.; Drolet, M.; Kayser, M. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2748−2753.
(19) Lin, S.-N.; Geng, X.-D.; Qu, C.-X.; Tynebor, R.; Gallagher, D. J.; Pollina, E.; Rutter, J.; Ojima, I. *Chirality* **2000**, *12*, 431−441.
(20) Spletstoser, J. T.; Flaherty, P. T.; Himes, R. H.; Georg, G. I. *J. Med. Chem.* **2004**, *47*, 6459−6465.
(21) Georg, G. I.; Kant, J.; Gill, H. J. *J. Am. Chem. Soc.* **1987**, *109*, 1129−1135.
(22) Denis, J.-N.; Greene, A. E.; Guénard, D.; Gu'eritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917−5919.

TABLE 1. Results from Reactions of β-Lactam 5a with 7 To Furnish 8 under Varied Reaction Conditions (Scheme 2)

entry	lactam equiv	base equiv	reaction temp (°C)	yield (%) 8[a]	isomeric ratio[b]
1	4	1.5 LiHMDS	−40	81	41:1
2	4	1.5 LiHMDS	−40 to 0	82	36:1
3	4	1.5 LiHMDS	0	84	34:1
4	2	1.5 LiHMDS	−40 to 0	46	32:1
5	4	1.5 NaHMDS	−40 to 0	62	7:1

[a] Yields for two steps. [b] The isomeric ratio (2′*R*,3′*S*):(2′*S*,3′*R*) was determined by HPLC.

SCHEME 2

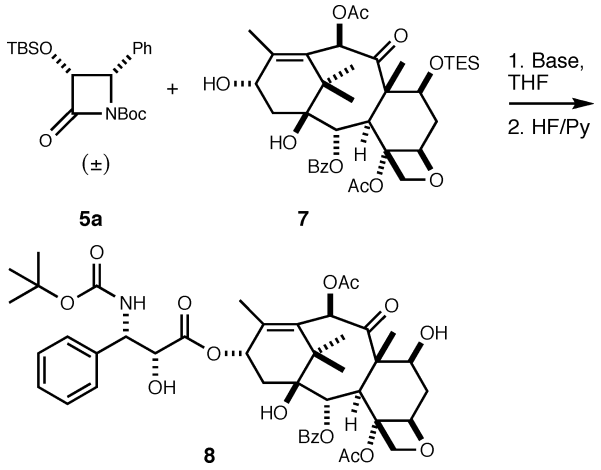


TABLE 2. Results of Reaction between β-Lactams 5a-e, 6, and 7-*O*-triethylsilylbaccatin III (7, Scheme 3) for the Formation of 8 (Entries 1−3) and 9 (Entries 4−6)

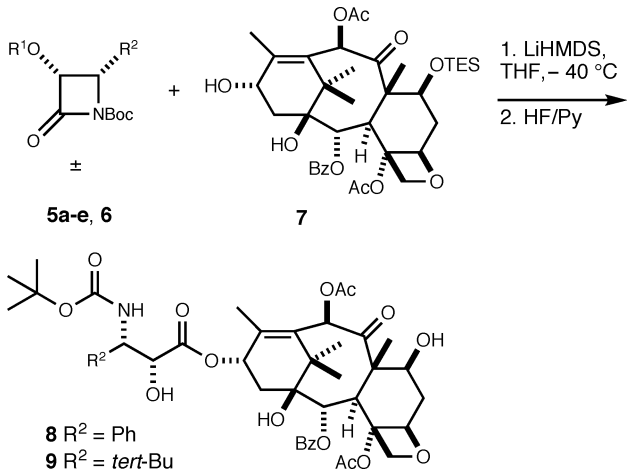
Entry	R^1	R^2	yield[a] (%)	isomeric ratio[b]
1	TIPS	Ph	80	32:1
2[c]	TBS	Ph	81	41:1
3	TES	Ph	84	10:1
4	TIPS	*tert*-butyl	76	57:1
5	TBS	*tert*-butyl	84	82:1
6	TES	*tert*-butyl	78	40:1

[a] Yields of **8** (entries 1−3) and of **9** (entries 4−6) for two steps. [b] The isomeric ratio (2′*R*,3′*S*):(2′*S*,3′*R*) was determined by HPLC. [c] Same as entry 1, Table 1.

of **5a** was reduced from 4 to 2 equiv (entries 2 and 4). It has been hypothesized that chelation between the C13 lithium alkoxide of the baccatin III derivative and the carbonyl group of the β-lactam is important for the high diastereoselectivity.[16] We therefore replaced LiHMDS with NaHMDS (entry 5) to study the effect of the presumably less chelating C13 sodium alkoxide on diastereoselectivity. Under these conditions, we noted a marked decrease in stereoselectivity and yield, confirming the hypothesis (see entries 2 and 5) that chelation is important for high diastereoselectivity.

We next investigated the effects of different substituents at the β-lactam skeleton on the kinetic resolution (Table 2). Since it had been previously reported that the 1-*tert*-butoxycarbonyl group was important to generate high diastereoselectivity in the kinetic resolution, we retained this group in our experiments.[15,16] We first probed the effects of different 3-hydroxylsilyl protecting groups. Reactions of β-lactams **5a**−**e** and **6** with **7** (Scheme 3) were carried out using the conditions of entry 1, in Table 1. The results are shown in Table 2. As expected, it was found that the large triisopropylsilyl protecting group (entry 1)

SCHEME 3



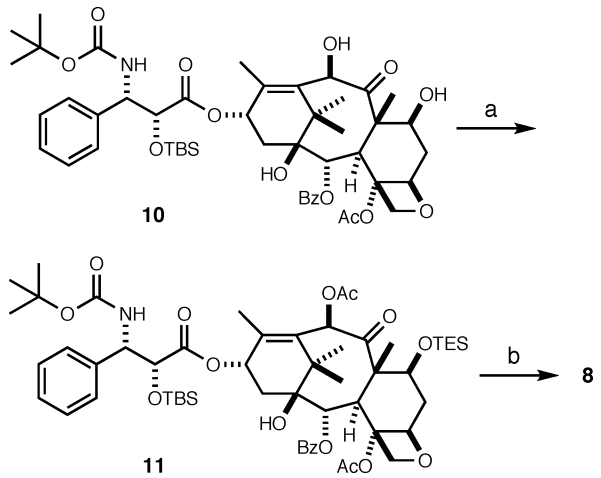
provided higher stereoselectivity than the smaller triethylsilyl group (entry 3). However, the *tert*-butyldimethylsilyl group proved to be optimal (entry 2), providing a 41:1 ratio of diastereoisomers. The results imply that the size of the C3-hydroxyl protecting group influences diastereoselectivity and that the *tert*-butyldimethylsilyl group, which is more sterically demanding than the triethylsilyl group, but smaller than the triisopropylsily protecting group, was optimal in this sequence of reactions.

We also examined the effects of different substituents at the C4 position toward resolution. As is illustrated in Table 2, we observed increased stereoselectivity for the reaction of **5d** (entry 5) with **7** compared to the reaction of **5a** with **7** (entry 2), which indicates that the size of the C4 substituent also influences diastereoselectivity. To evaluate whether the C3-hydroxy protecting groups have an effect for the 4-*tert*-butyl β-lactam derivatives, we replaced the *tert*-butyldimethylsilyl with the larger triisopropylsilyl group (entry 4) and the smaller triethylsilyl group (entry 6). Again, it was found that the triisopropylsilyl group provided higher diastereoselectivity than the triethylsilyl group, while the *tert*-butyldimethylsilyl group afforded the best resolution. These results suggest that at least one sterically demanding substituent is required at either C3 or C4 for satisfactory selectivity. This is supported by Ojima's observation that 3-(triisopropylsilyloxy)-4-(trifluoromethyl)-, 3-(triisopropylsilyloxy)-4-isobutyl-, and 3-(triisopropylsilyloxy)-4-isobutenyl-β-lactams gave high yields and stereoselectivities for the kinetic resolution with modified baccatins.[19]

To unambiguously prove the identity of the major product, we synthesized 10-acetyldocetaxel (**8**), as shown in Scheme 4. Starting from 2′-*O*-(*tert*-butyldimethylsilyl)docetaxel (**10**), prepared from commercially available docetaxel, triethylsilyl protection of the C7-hydroxy group followed by acylation of the C10-hydroxy group with acetic anhydride afforded intermediate **11**, which was converted to **8** by treatment with hydrogen fluoride in pyridine. Spectral data and HPLC retention times were identical for the products obtained by both methods, confirming that the major diastereomer obtained in the kinetic resolution had the same (2′*R*,3′*S*) configuration as docetaxel. 10-Acetylbutitaxel (**9**) has been synthesized previously and matched the reported spectroscopic data.[23]

In conclusion, a systematic study of the kinetic resolution of racemic 4-phenyl- and 4-*tert*-butyl-β-lactams with 7-*O*-(triethylsilyl)baccatin III was carried out. It was found that the size of the silyl protecting groups at the 3-hydroxy moiety of

SCHEME 4[a]



[a] (a) (i) (TES)Cl, imidazole, DMAP, CH_2Cl_2, rt; (ii) acetic anhydride, DMAP, pyridine, 0 °C to rt (96%). (b) HF-Py in pyridine, 0 °C to rt (90%).

β-lactams had an important influence on the diastereoselectivity of the resolution. The *tert*-butyldimethylsilyl protecting group was found to be superior to the smaller triethylsilyl group and the larger triisopropylsilyl group in the reactions investigated. The size of the 4-substituents at the β-lactams also influenced diastereoselectivity. The sterically more demanding 4-*tert*-butyl β-lactams gave rise to better kinetic resolution than the corresponding 4-phenyl β-lactams. Therefore, it can be concluded that high stereoselectivity can be obtained either by using sterically demanding C3-hydroxy protecting groups or C4 substituents.

Experimental Section

HPLC Conditions Used in Tables 1 and 2. Jupiter 5 μ C4-reversed phase column (10 × 250 mm) from Phenomenex USA, employing a gradient of water−acetonitrile (0−70%, v/v) with 0.1% trifluoroacetic acid as the solvent system with a flow rate of 2.0 mL/min for 70 min. Average retention time for the major isomer (2′*R*,3′*S*)-**8** = 46.56 min; minor isomer (2′*S*,3′*R*)-**8** = 45.98 min. Average retention time for the major isomer (2′*R*,3′*S*)-**9** = 47.92 min; minor isomer (2′*S*,3′*R*)-**9** = 46.70 min.

***cis*-(±)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-4-phenylazetidin-2-one (5a).**[23] Yield = 48%, yellow solid; mp = 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.15 (s, 3H), 0.06 (s, 3H), 0.65 (s, 9H), 1.42 (s, 9H), 5.04−5.07 (m, 2H), 7.27−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.5, 18.2, 25.6 (3C), 28.2 (3C), 62.4, 77.7, 83.8, 128.2 (2C), 128.4 (2C), 128.6, 134.3, 148.3, 166.6; HRMS (ES+) *m*/*z* calcd for $C_{20}H_{31}NO_4SiNa$ [MNa^+] 400.1920, found 400.1910.

Synthesis of *cis*-1-(*tert*-Butoxycarbonyl)-3-(triethylsilyloxy)-4-*tert*-butylazetidin-2-one (6). To a solution of **5d** (115.0 mg, 0.3216 mmol) in pyridine (6.0 mL) were added 12 drops of a HF-pyridine solution dropwise at 0 °C under argon. The reaction mixture was stirred for 30 min, and then another 20 drops of HF-pyridine solution were added dropwise at the same temperature. The reaction mixture was warmed to room temperature overnight and then diluted with EtOAc, washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a white solid. To a solution of the solid thus obtained was added imidazole (43.8 mg, 0.643 mmol), (TES)Cl (108 μL, 96.9 mg, 0.643 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred under argon at room temperature for 24 h, diluted with CH_2Cl_2, and quenched with water (50 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography (silica gel) with EtOAc/hexanes afforded 96 mg (77%) of a colorless oil. The compound showed spectroscopic properties in agreement with the literature.[8]

Synthesis of 10-Acetyldocetaxel (8) and 10-Acetylbutitaxel (9). A solution of **5** or **6** (0.1696 mmol) and 7-*O*-(triethylsilyl)baccatin III (**7**, 30.0 mg, 0.042 mmol) in tetrahydrofuran (THF; 2.5 mL) under argon was cooled to −40 to 50 °C, and a solution of LiHMDS (64 μL, 0.064 mmol, 1.0 M in THF) was added. The reaction mixture was stirred for 50 min at the same temperature and then quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a white solid. To a solution of the solid thus obtained in pyridine (2.0 mL) under argon were added 8 drops of a HF−pyridine solution dropwise at 0 °C under argon. The reaction mixture was stirred for 30 min at the same temperature, and then another 10 drops of HF−pyridine solution were added dropwise. The reaction mixture was warmed to room temperature overnight, diluted with EtOAc (30 mL), washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography (silica gel) with EtOAc/hexanes afforded the product.

10-Acetyldocetaxel (8). Yield = 46−84%, off-white solid. The compound showed spectroscopic properties in agreement with the literature.[24]

10-Acetylbutitaxel (9). Yield = 78−84%, off-white solid. The compound showed spectroscopic properties in agreement with its structure.[25]

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Supporting Information Available: Full experimental procedures and characterization data for compounds **4a−e, 5a−e, 8**, and **11** and HPLC traces for the experiments in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Ojima, I.; Sun, C.-M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149−4152.

(24) Mangatal, L.; Adeline, M.-T.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177−4190.

(25) Compound **9** showed spectroscopic properties in agreement with the data reported: Holton, R. A.; Chai, K.-B.; Idmoumaz, H.; Nadizadeh, H.; Rengan, K.; Suzuki, Y.; Tao, C. U.S. Pat. 5739362, 1998.