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Diastereoselective 14β-Hydroxylation of Baccatin III Derivatives

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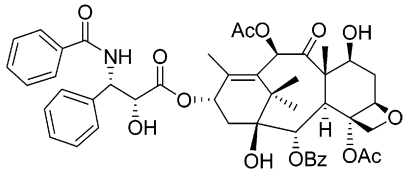
14β-Hydroxybaccatin III, a compound with limited availability by natural sources, is the starting material for the synthesis of the second-generation anticancer taxoid ortataxel. The 7-*tert*-butoxycarbonyl (**1a**) and 7-triethylsilyl (**1b**) derivatives of 14β-hydroxybaccatin III 1,14-carbonate were synthesized from 10-deacetylbaccatin III (**3**). The crucial steps were (a) the $C_{14}\beta$ hydroxylation of the corresponding 13-oxobaccatin III derivatives by oxaziridine-mediated electrophilic oxidation and (b) the reduction of the C_{13} carbonyl group with sodium or alkylammonium borohydrides. This protocol provides a practical way for the semisynthesis of ortataxel from 10-deacetylbaccatin III, a compound readily available from various yews.

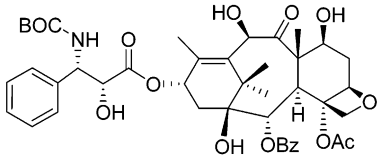
Introduction

The clinical efficacy[1] and the chemistry[2] of the natural diterpenoid Taxol[3] (paclitaxel) and its semisynthetic analogue Taxotere[4] (docetaxel) (Chart 1) have been extensively reported. While the taxoids have potent antitumor activity against solid tumors and unique mechanism of action, they also have numerous undesiderable side effects and poor activity against certain tumors. Since these drugs are sparingly soluble in water, they must be co-administered with a cosolvent (cremophor EL, Tween 80) which can induce adverse effects.[5] The development of resistance, due primarily to multiple drug resistance (MDR)[6,7] mechanisms, prompts initiatives to develop novel anticancer taxoids effective against paclitaxel-resistant cancer cell lines.

CHART 1. Taxol and Taxotere



Taxol



Taxotere

Recently, a new series of analogues derived from 14β-hydroxy-10-deacetylbaccatin III (14β-OH-DAB) were reported (Chart 2).[8,9] The new derivatives, which bear a

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CHART 2. 14β-OH DAB

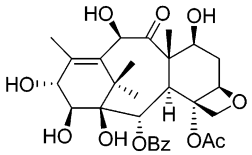


CHART 3. Ortataxel

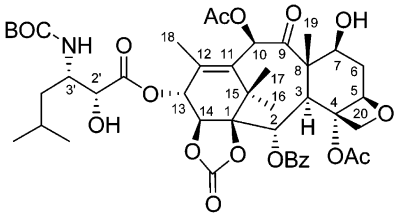
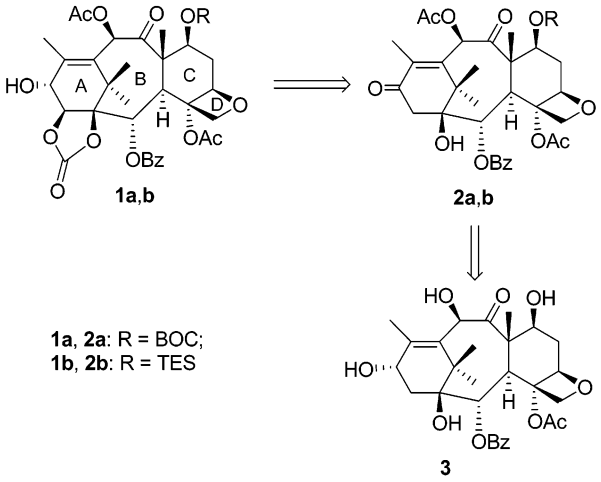


CHART 4. Retrosynthetic Analysis of 1a and 1b

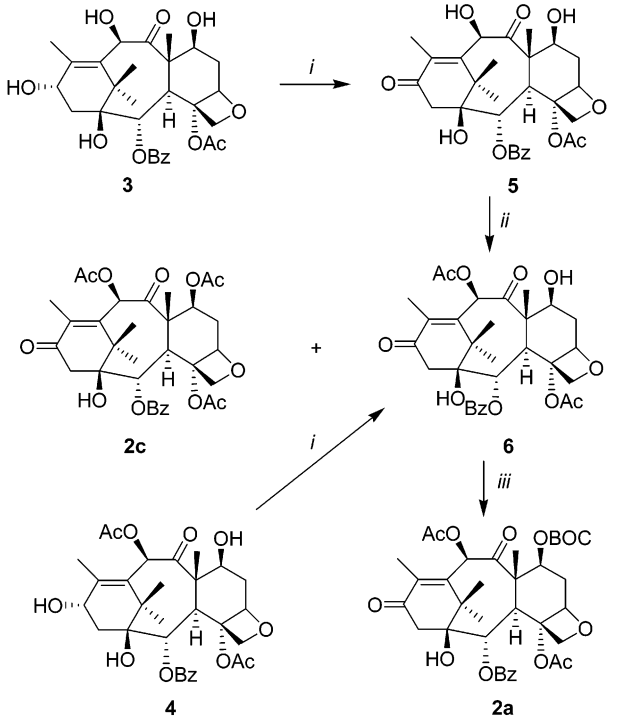


1,14-carbonate moiety, exhibit improved clinical properties such as oral bioavailability and a broader spectrum of antitumor activity.

One of these new taxanes, ortataxel (IDN5109, Bay 55-8862)[10] (Chart 3), was selected for preclinical development. The limited availability of 14β-OH-DAB[11] from Himalayan yew, *Taxus wallichiana Zucc*., prompted us to develop a research program aimed at the semisynthesis of orthogonally protected 14β-OH-baccatin III from 10-deacetylbaccatin III (10-DAB) (**3** of Chart 4), a readily available compound.

Such an intermediate would allow direct coupling with the appropriate C_{13} side chain. This would require protection of C_7-OH as either the 7-*tert*-butoxycarbonyl (7-BOC) or 7-triethylsilyl (7-TES) derivatives of 14β-OH-baccatin III 1,14-carbonate (**1a** and **1b**, respectively).

SCHEME 1. Synthesis of 2a from 3 or 4[a]



[a] Reagents and conditions: (i) O_3, CH_2Cl_2/MeOH, −78 °C; (ii) $Yb(OTf)_3$, Ac_2O, THF; (iii) 1-methylimidazole, $(BOC)_2O$, CCl_4.

Insertion of the C_{14}-OH moiety would require enolization of the C_{13} carbonyl moiety, eventually leading to 7-protected 13-oxo derivatives of baccatin III (**2**) as starting materials.

Results and Discussion

The formation of the 13-oxo-7-TES-baccatin III (**2b**) from 10-DAB **3** was previously reported, by sequential transformation of **3** via selective silylation and acetylation of the C_7 and C_{10} hydroxy groups[12] followed by MnO_2 oxidation to give **2b**.[13] However, a protocol for preparation of the 7-BOC analogue **2a** was not available; thus, we studied two different routes to obtain it (Scheme 1). In the initial approach, 10-DAB **3** was oxidized in very high yields (92%) to 13-oxo-DAB **5** with ozone on a multigram scale. The acylation of the C_{10} hydroxyl group of **5** with Ac_2O at 25 °C, to give 13-oxo-baccatin III (**6**), was facilitated by Lewis acid lanthanide triflate catalysts following a literature protocol.[14] A proper choice of the lanthanide was crucial to minimize competitive acylation of the C_7 hydroxyl group and/or formation of 7,10-bis-acetylated byproduct **2c**. Acylation of **5** in the presence of cerium or scandium triflates gave **6** in moderate amounts (62% and 33%, respectively). Notably, ytterbium triflate [$Yb(OTf)_3$] afforded **6** in 91% yields, with trace amounts of 7,10-bis-acetyl-13-oxo-DAB **2c** (5%). This material was identical to a sample of **6** made by ozonolysis of baccatin III **4** (62% yields).

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TABLE 1. Effect of the Type of Base,[a] Solvent,[b,c] and Oxidant on the Hydroxylation of Compounds 2a,b

entry	reagents	base	solvent	yield[d] (%)	entry	reagents	base	solvent	yield[d] (%)
1	**2a** + **7**	KHMDS	THF	30	8	**2b** + **7**	KHMDS	A	74
2	**2a** + **7**	KHMDS	CH_2Cl_2	45	9	**2b** + **8**	KHMDS	A	74
3	**2a** + **9**	NaHMDS	B	15	10	**2b** + **9**	KHMDS	A	71
4	**2a** + **9**	KHMDS	B	62	11	**2b** + **10**	KHMDS	A	70
5	**2a** + **9**	LDEA	B	74	12	**2b** + **11**	KHMDS	A	71
6	**2a** + **9**	^{t}BuOK	B	88	13	**2b** + **10**	^{t}BuOK	B	83
7	**2b** + **7**	^{t}BuOK	B	90[e]	14	**2b** + **11**	^{t}BuOK	B	85

[a] LDEA: lithium diethylamide. KHMDS: potassium hexamethyldisilazane. NaHMDS: sodium hexamethyldisilazane. ^{t}BuOK: potassium *tert*-butoxide. [b] HMPA: hexamethylphosporamide. DMPU: 2,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidone. THF: tetrahydrofuran. [c] A: THF/HMPA (83:17). B: THF/DMPU (83:17). [d] Isolated yield. [e] Yield based on HPLC analysis.

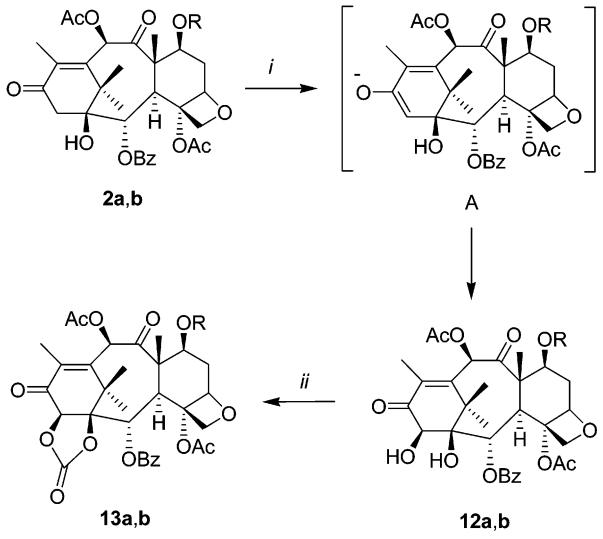
Treatment of **6** with BOC-pyrocarbonate (BOC_2O) in CH_2Cl_2 at 20 °C, in the presence of either acylation catalysts 4-(dimethylamino)pyridine (DMAP) or 1-methylimidazole (MEIM), afforded 7-BOC-13-oxobaccatin III (**2a**). When DMAP (10−20 mol %) was employed, yields of **2a** were moderate, with two byproducts whose structural assignments are still under investigation. However, with MEIM and excess BOC_2O (2.5 equiv), 7-BOC-13-oxobaccatin III (**2a**) was obtained in very high yields (95%) when the reaction was carried out in the apolar solvent CCl_4. Minor amounts of contaminants were formed when the polar solvent MeCN was used. Notably, we observed that MEIM also catalyzed the hydrolysis of excess BOC_2O, to *tert*-butyl alcohol, when water was added to the crude reaction mixture. This facilitates the in situ crystallization of **2a** which was used without additional purification.

The α-hydroxylation of aliphatic ketones by either the oxidation of silyl enol ethers with peracids[15] or the direct oxidation of the enolates with oxaziridines[16] is a versatile procedure. A four-step synthesis of 7-TES-13-oxo-14β-OH-baccatin III (**12b**), via a silyl-enol ether route, starting from compound **2b** was recently reported.[17] The treatment of **2b** with trimethylsilyl chloride (TMSCl) and DBU gave a mixture of 7-TES-13-TMS-enol ether and 7-TES-1,13-bis-TMS-enol ether derivatives of **2b**. The latter compound was selectively desilylated with 1.0 M HCl to give the enol ether that was converted into **12b** by sequential oxidation with *m*-CPBA and desilylation. The laborious nature of this procedure prompted us to examine functionalization of an enolate to afford targets **12a**,**b** directly.

Significant efforts were expended to develop an efficient protocol to convert intermediates **2a**,**b** to 14-OH-13-oxobaccatin III derivatives **12a**,**b**. This was accomplished by treatment of the appropriate enolates with *N*-(sulfonyl)oxaziridines (**7**−**11**)[18] (Scheme 2). Various bases (LDEA, ^{t}BuOK, KHMDS, and NaHMDS), solvents (THF, THF/HMPA, 85:15, and THF/DMPU, 80:20) and oxaziridines [2-benzenesulfonyl-3-phenyloxaziridine (**7**), 2-benzenesulfonyl-3-(2-chloro-5-nitrophenyl)oxaziridine (**8**), 2-benzenesulfonyl-3-(3-nitrophenyl)oxaziridine (**9**), (1*R*)-(10-camphorsulfonyl)oxaziridine (**10**), and (1*S*)-enantiomer (**11**)] were studied (Table 1 and Chart 5). No appreciable differences were noticed with the type of substituent at the C_7 hydroxy group. Our first attempts to carry out the hydroxylation in THF or CH_2Cl_2, (entries 1 and 2) gave moderate amounts of the target product. However, yields increased significantly when the reactions were performed in THF, in the presence of 15−20% HMPA or DMPU.

A series of reactions performed on compound **2a,** in THF/DMPU (83:17), with 2-benzenesulfonyl-3-(3-nitrophenyl)-oxaziridine (**9**) clearly showed that the nature of the base was an important factor for yields (entries 3−6). The reactivity order was ^{t}BuOK > LDEA > KHMDS ≫NaHMDS. The greater efficiency of ^{t}BuOK with respect

SCHEME 2. Conversion of 2a,b to 12a,b[a]



[a] Reagents and conditions: (i) **2a**, **2b** (see Table 1); (ii) **13a**: carbonyldiimidazole, toluene; **13b**: $COCl_2$/pyridine, CH_2Cl_2, 0 °C.

CHART 5. Oxaziridines 7−11

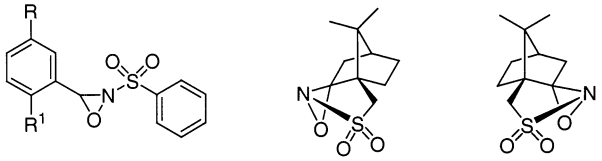


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TABLE 2. Synthesis of Compounds 1a and 1b (α-Epimers) and 14a and 14b (β-Epimers) by Reduction of Compounds 13a,b

entry	reagent	reductant	solvent	*T* (°C)	time (min)	OY[a] (%)	**1/14**[b]	**1** yield[c] (%)
1	**13b**	$Ca^+BH_4^-$	EtOH	−26	720	54	1.1	28
2	**13a**	$Ca^+BH_4^-$	EtOH	−26	400	22	1.0	15
3	**13b**	$Na^+BH_4^-$	EtOH	−15	180	82	1.8	52
4	**13a**	$Na^+BH_4^-$	EtOH	−10	300	46	1.2	25
5	**13b**	$Na^+BH_4^-$	EtOH	+20	20	80	1.0	40
6	13b	$Na^+BH_4^-$	DME[d]	−15	180	78	1.0	39
7	**13a**	$Na^+BH_4^-$	THF	+20	180	62	1.5	37
8	**13b**	$Na^+BH_4^-$	MeOH	−15	50	80	3.0	60
9	**13a**	$Na^+BH_4^-$	MeOH	−25	180	52	2.8	38
10	**13b**	nBu_4N^+ BH_4^-	MeOH	0	20	83	3.8	66
11	**13b**	$nBu_4N^+BH_4^-$	MeOH	−15	30	95	4.0	76
12	**13b**	$nBu_4N^+BH_4^-$	DME[d]	+20	30	80	1.0	40
13	**13a**	$nBu_4N^+BH_4^-$	MeOH	−25	80	81	3.2	62
14	**13a**	$Et_4N^+BH_4^-$	A[e]	−40	240	89	3.0	67
15	**13a**	$Et_4N^+BH_4^-$	A[e]	−55	360	87	3.6	68
16	**13a**	$Me_4N^+BH_4^-$	A[e]	−30	300	84	2.8	62
17	**13a**	Na^+BH_4[f]	THF	+20	30	69	0.13	8
18	**13a**	$nBu_4N^+BH_4$[f]	THF	+20	20	60	0.13	7

[a] Overall yields. [b] By ^{1}H NMR. [c] Isolated yields. [d] DME: dimethoxyethane. [e] A: MeOH/THF (2:1). [f] In the presence of Amberlyst 15.

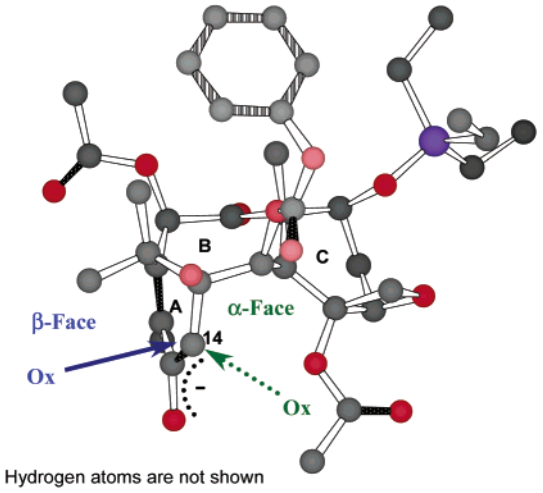


FIGURE 1. Chem 3D view of the enolate of **2b**.

to KHMDS was also confirmed for the analogue **2b** when oxaziridine **7** was the oxidant (entries 7 and 8). The stereo- and electronic effects of the enolate oxidation of **2b** were explored (entries 8−10). The reaction yields were only slightly affected by the electrophilicity of the oxidant with a range of 70−74% yields of compound **12b**. Notably, yields of products were not affected by the chirality of the oxidant when either enantiomer of camphorsulfonyl oxaziridine were used (entries 11−14). However, steric demand of these oxidants impeded conversion of the enolate, with recovery of variable amounts of starting materials (ca. 10%, see entries 13 and 14). The diastereoselectivity of the hydroxylation can be rationalized by a folded conformation of the terpenoid skeleton of the enolates, which precludes attack of the sterically demanding oxaziridines from the more hindered α-face of the A ring system, thus promoting formation of the 14β-OH epimers (Figure 1).

The formation of trace amounts of contaminants, whose structure and relative amounts depended on the type of reaction, was also observed. For instance, HPLC−MS showed at least five isomeric compounds of **12a**,**b**, ranging between 1 and 4%. A major problem related to the use of oxaziridines **7**−**9** was the purification of compounds **12a**,**b** which required multiple column chromatography and fractional crystallization due to the presence of unreacted oxaziridine, imine, and imine hydrolysis products. Thus, traces of unseparable byproducts were often detected after the purification process. When camphorsulfonyloxaziridines **10** and **11** were used, higher purities of **12a**,**b** were obtained.

To minimize losses of valuable taxoid intermediates **12a**,**b**, the crude products were converted to the carbonates **13a**,**b** by one of two protocols: (i) phosgene in pyridine[19] or (ii) carbonyldiimidazole (Scheme 2). Compound **13a** was obtained from crude **12a** with carbonyldiimidazole in 84% yield (entry 6), while compound **13b** was obtained from crude **12b** in 75−80% yields (entry 7 and 14).

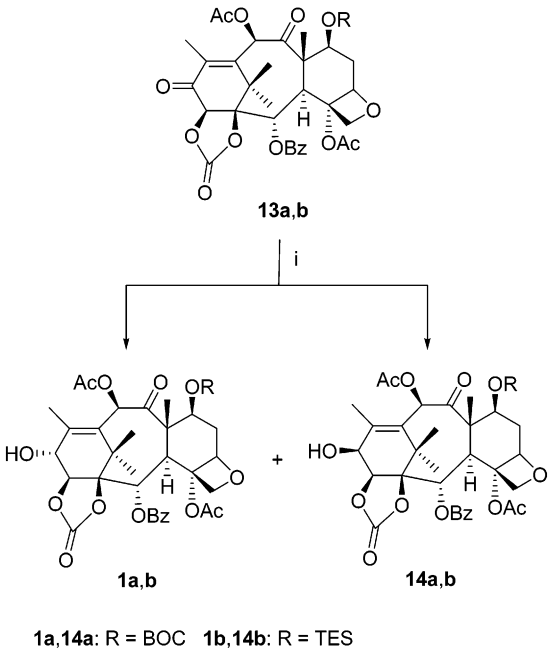
Reduction of the 13-keto group of **13a**,**b** consistently afforded the α-epimers **1a**,**b** (major products) with the β-epimers **14a**,**b** (Table 2, Scheme 3). Higher-order borohydrides, with substituents linked directly to the boron atom, such as (*R*)-Alpine hydride, (*S*)-Selectride, lithium triethylborohydride, and Ipc_2BCl, failed to reduce the 13-oxo group. The diastereoselectivity of the ketone reduction is dependent on a balance of steric demands of the ketone moiety and the reductant. The folded structure of the taxane skeleton, associated by the presence of the C_{14}-hydrogen atom in the α-face, favors hydride approach from the β-face, while the 1,14-carbonate moiety shields the β-face which inhibits reduction (Figure 2).[20] Thus, remarkable ratios of the α/β-epimers were obtained from the reduction.

Compounds (**1b**, **14b**) were usually obtained in higher yields vs **1a**, **14a** when metalated borohydrides were used (entries 1−4 and 8−9). $NaBH_4$ is more efficient than

(19) Attempted phosgenation with bis(trichloromethyl)carbonate (triphosgene) gave only moderate amounts (40−50%) of compounds **13a**.

(20) The importance of the bulkiness of the 1,14-carbonate moiety on the selectivity is indirectly documented in the literature. In fact, the $Na^+BH_4^-$-induced reduction of a series of C_2 analogues of 7-TES-13-oxobaccatin III in MeOH stereoselectively led to the corresponding 13α-hydroxyl derivatives. See: Nicolau, K. C.; Coulaudouros, E. A.; Nantermet, P. G.; Renaud, J.; Guy, R. K.; Wradislo, W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1581−1582.

SCHEME 3. Reduction of Compounds 13a,b[a]



[a] Reagents and conditions: see Table 2.

$Ca(BH_4)_2$, while no reaction was observed with the more sterically demanding $Zn(BH_4)_2$. The reaction yields were significantly reduced due to partial hydrolysis of the C_4-acetoxy moiety which occurred to a greater extent with compounds **1a** and **14a** versus **1b** and **14b**. Best results were obtained with alkylammonium borohydrides which required shorter reaction times (entries 8, 11 and 9, 13), with minimal deacetylation.

The observed distereoselectivity is dependent on solvent, hydride, and temperature. Aprotic solvent dimethoxyethane (DME), which does not solvate the borohydride, was completely unselective (entries 6 and 12). Protic solvents such as MeOH and EtOH which solvate the borohydride ion[21] increased the bulkiness of the reductant, allowing partial diastereoselection. The best results were found when **13a**,**b** were reduced with a combination of $NaBH_4$ in MeOH (entries 8 and 9). This solvent appears more efficient than ethanol, confirming literature data.[20] Alkylammonium borohydrides increased the α-diastereoselectivity with respect to metalated borohyrides (entries 8, 11 and 9, 13). This can be rationalized by a steric approach control model.[22] Accordingly, in an early transition state for reduction of hindered ketones, the transition-state energy is controlled by such factors as ease of approach of the hydride. We postulate that better solvation of the hydride increases the bulkiness of the reductant. So steric considerations are relevant in protic solvents and for the more dissociated ammonium salts versus the metalated reducing agents. As a consequence, better diastereoselection has been observed with the $MeOH/R_4N^+ BH_4^-$ couple. On the basis of these results, the transition state corresponding to the attack of the

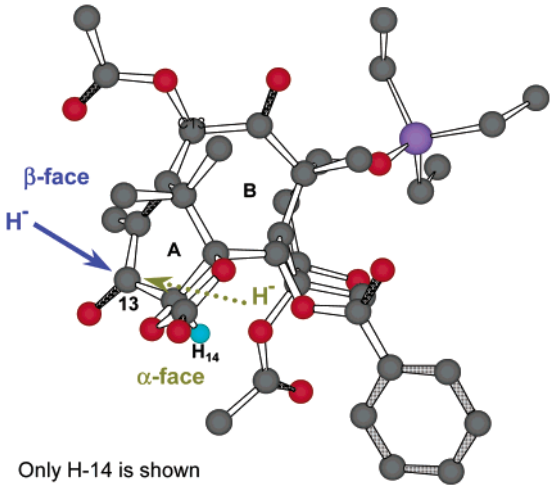


FIGURE 2. Chem 3D view of carbonate **13b**.

hydride to the β-face has lower energy than that the α-face. Confirmatory of this hypothesis, diastereoselection was improved at lower temperatures (entries 10, 11 and 14, 15).

Other reduction methods were attempted, such as acid-induced hydroboration and transfer hydrogenation. $NaBH_4$-induced reduction of **13a**,**b**, in the presence of the sterically demanding $CeCl_3$ Lewis acid catalyst, failed to improve diastereoselectivity. However, proton-induced catalysis, using Amberlyst 15, caused an inversion of the α/β ratio regardless of the size of the alkylammonium borohydride (entries 17 and 18). The adverse effect of the Lewis acid catalysts could be rationalized by the formation of a sterically congested five membered ring chelate between the catalyst, the C_{13}-carbonyl, and the C_{14}-oxygen atom.[23] Finally, transfer hydrogenation of **13a** with Pd/C in methanol, in the presence of ammonium formate, resulted in nucleophilic substitution of C_{14}-oxygen atom by the hydride ion with the formation of **2a**.

Spectral data of **1b** was compared with those reported in the literature. The α-stereochemistry of the C_{13}-OH group of **1a** and **14a** were confirmed by qualitative homonuclear NOE difference spectra. Irradiation of the C_2-H signal at 6.08 ppm of **1a** showed consistent enhancement (4%) of the C_{13}-H proton at 5.37 ppm, suggesting that both protons are located in the β-face of the taxane skeleton. Consistently, the irradiation of the C_2-H signal did not show any NOE-effect on the C_{14}-H proton at 4.81 ppm. The C_{13}-epimer **14a** showed an enhancement of the C_{13}-H proton at 5.31 ppm (6%) upon irradiation of the C_{14}-H signal at 4.18 ppm.

Conclusions

An efficient six-step protocol of preparation of **1a**,**b**, key intermediates for the synthesis of ortataxel and related taxoids, has been developed starting from the readily available 10-DAB III (**3**). Each step of the synthesis proceeds with high yields, which minimizes the require-

(21) (a) Haubenstock, H.; Eliel, E. L. *J. Am. Chem. Soc.* **1962**, *84*, 2368−2371. (b) Tsuda, Y.; Sakai, K.; Akiyama, K.; Isobe, K. *Chem. Pharm. Bull.* **1991**, *39*, 2120−2123.

(22) Wigfield, D. C.; Phelpss, D. J. *Can. J. Chem.* **1972**, *50*, 388−394.

(23) These results could be in line with the observation that sodium and alkylboron hydrides failed to reduce compound **12a** (see ref 21). In this case, the reductant probably combines with the C_{13}-carbonyl and the C_{14}-OH of the substrate to form a sterically hindered five-membered-ring intermediate.

ment for chromatography purification in many steps. These results provide an efficient industrial synthesis of this class of taxoids.

Experimental Section

13-Oxo-10-deacetylbaccatin III (13-Oxo-DAB) (5). Ozone was passed through a solution of compound **3** (2.0 g, 3.67 mmol) in CH_2Cl_2/MeOH (200 mL, 5:1) at −78 °C for 35 min. The reaction mixture was left at −78 °C for 1 h. The excess of O_3 was destroyed by addition of an excess of Me_2S and pyridine. The temperature was raised to 20 °C and the solvent evaporated. The residue was treated twice with CCl_4 to yield 2.0 g of solid which was chromatographed (SiO_2, *n*-pentane/Et_2O/EtOAc, 2:1:1) to give 13-oxo-DAB **5** (1.83 g, 3.37 mmol, 92%).

13-Oxobaccatin III (6). $Yb(OTf)_3$ (0.21 g, 0.30 mmol) and Ac_2O (0.79 mL, 8.36 mmol) were added to a stirred solution of **5** (2.2 g, 4.06 mmol) in THF (20.0 mL) at 25 °C. EtOAc was added after 4 h, the solution washed with saturated NH_4Cl and dried, and the solvent was evaporated. Chromatography (SiO_2, *n*-hexane/EtOAc, 1.5:1) gave compound **6** (2.16 g, 3.69 mmol, 91%).

13-Oxo-7-BOC-baccatin III (2a). 13-Oxobaccatin III **6** (1.10 g, 1.9 mmol) in CH_2Cl_2 (0.5 mL) was added to CCl_4 (14.0 mL) at 20 °C. 1-Methylimidazole (23 μL, 0.28 mmol) and $(BOC)_2O$ (1.03 g, 4.7 mmol) were added under stirring. 1-Methylimidazole (16.0 μL, 0.20 mmol) was added after 8 h. The solution was left at 20 °C for 24 h. The solvent was evaporated, and the residue was dissolved in a mixture of acetone/H_2O (10.0 mL, 1:1) and left at 20 °C for 16 h. The precipitate was filtrated to yield **2a** (1.12 g, 1.63 mmol, 86%). The residue was chromatographed to yield an additional amount of **2a** (0.12 g, 9%): mp = 192−193 °C; $[\alpha]^{20}_D = -35.6$ ($c = 1.05$, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3483, 1731, 1676, 1371, 1274; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 2H), 7.61−7.64 (m 1H), 7.44−7.50 (m, 2H), 6.57 (s, 1H), 5.67 (d, 1H, $J = 6.8$ Hz), 5.39 (m, 1H, $J_1 = 10.4$ Hz, $J_2 = 7.2$ Hz), 4.94 (d, 1H, $J_1 = 9.5$ Hz, $J_2 = 2.0$ Hz), 4.32 (d, 1H, $J = 9.0$ Hz), 4.09 (d, 1H, $J = 9.0$ Hz), 4.02 (d, 1H, $J = 6.8$ Hz), 2.94 (d, 1H, $J = 19.6$ Hz), 2.66 (d, 1H, $J = 19.6$ Hz), 2.64 (m, 1H, $J_1 = 7.2$ Hz, $J_2 = 14.8$ Hz, $J_3 = 9.5$ Hz), 2.20 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.92 (b, 1H), 1.91 (m, 1H, $J_1 = 10.4$ Hz, $J_2 = 14.8$ Hz, $J_3 = 2.0$ Hz), 1.76 (s, 3H), 1.47 (s, 9H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 198.4, 170.3, 168.3, 167.0, 152.5, 152.4, 141.0, 134.3, 130.3, 129.0, 128.9, 84.0, 83.4, 80.5, 78.7, 77.4, 76.5, 76.3, 74.7, 72.8, 57.3, 46.7, 42.7, 33.6, 33.1, 27.9, 21.9, 21.0, 18.4, 14.0, 10.7; MS *m*/*z* 684.49 (M^+ calcd for $C_{36}H_{44}O_{13}$ 684.73). Anal. Calcd for $C_{36}H_{44}O_{13}$: C, 63.15; H, 6.48. Found: C, 63.39; H, 6.60.

13-Oxo-7-BOC-14β-hydroxybaccatin III (12a). 13-Oxo-7-BOC-baccatin III **2a** (0.65 g, 0.95 mmol), dissolved in THF/DMPU (11.0 mL, 8:3), was added under stirring to a THF (10 mL) solution of ^{t}BuOK (0.43 g, 3.79 mmol) at −65 °C. After 15 min, oxaziridine **9** (0.804 g, 2.63 mmol), dissolved in THF/DMPU (10.0 mL, 9:1), was added, and the temperature was raised to −55 °C h. An additional amount of ^{t}BuOK (0.10 g, 0.89 mmol) was added. After 30 min, acetic acid (0.2 mL) and aqueous NH_4Cl (10%, 25.0 mL) were sequentially added. The organic layer was extracted with water, dried, and evaporated. The residue was chromatographed, giving **12a** with minor impurities. The mixture was treated with Et_2O and filtered. After the solvent was evaporated, the residue was chromatographed to yield **12a** (0.60 g, 0.84 mmol, 88%).

13-Oxo-7-TES-14β-hydroxybaccatin III (12b). A solution of ^{t}BuOK (2.2 mL of 1.0 M in THF) was added, at −65 °C, to a solution of 13-oxo-7-TES-baccatin III **2b** (0.60 g, 0.86 mmol) in THF/DMPU (11.0 mL, 8:3). Then a solution of oxaziridine **11** (0.30 g, 1.29 mmol) in THF (2.0 mL) was added. The reaction mixture was quenched at −60 °C with acetic acid (0.2 mL, 40% in THF) and warmed to room temperature. After dilution with brine (10.0 mL), the mixture was extracted with EtOAc (2 × 10 mL). The organic layer was dried and evaporated. Workup of the residue as described above gave **12b** (0.52 g, 0.73 mmol, 85%): mp 189−190 °C (EtOAc/hexane); $[\alpha]^{20}_D = +20.0$ ($c = 1.0$, $CHCl_3$); IR (Nujol) ν_{max} 3395, 2921, 2853, 1749, 1726, 1690, 1463, 1375, 1273, 1242; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2H), 7.46−7.66 (m, 3H), 6.53 (s, 1H), 5.89 (d, 1H, $J = 7.0$ Hz), 4.93 (d, 1H, $J = 7.3$ Hz), 4.49 (dd, 1H, $J_1 = 10.7$, $J_2 = 6.6$ Hz), 4.31 (s, 2H), 4.14 (d, 1H, $J = 1.8$ Hz), 3.87 (d, 1H, $J = 6.9$ Hz), 3.73 (d, 1H, $J = 1.8$ Hz), 3.64 (s, 1H), 2.46−2.61 (m, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 1.83−2.05 (m, 1H), 1.75 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 0.91−0.99 (t, 9H, $J = 8.7$ Hz), 0.58−0.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 200.1, 170.4, 169.3, 166.0, 153.5, 137.4, 133.9, 130.3, 129.8, 129.0, 84.3, 81.4, 76.4, 75.4, 74.4, 73.1, 72.9, 72.5, 59.4, 45.4, 43.5, 37.4, 33.2, 22.9, 22.0, 21.1, 14.0, 10.2, 7.1, 5.6; MS *m*/*z* 714.59 (M^+ calcd for $C_{37}H_{50}O_{12}$-Si 714.87). Anal. Calcd for $C_{37}H_{50}O_{12}Si$: C, 62.16; H, 7.05. Found: C, 62.19; H, 6.98.

13-Oxo-7-BOC-14-β-hydroxybaccatin III 1,14-Carbonate (13a). Compound **12a** was prepared according to the synthetic procedure reported before from **2a** (2.0 g, 2.9 mmol) and **9** (1.65 g, 5.40 mmol). After removal of the solvent, the crude reaction mixture was dissolved in toluene (25.0 mL), and carbonyldiimidazole (2.0 g, 12.0 mmol) was added at 20 °C. The solution was stirred under argon for 50 min at 75 °C. After the solution was cooled at 20 °C, HCl (15.0 mL, 0.2 N) and AcOEt (15.0 mL) were added. The organic phase was separated, washed with water, and dried, and the solvent was evaporated. Chromatography of the residue (SiO_2, *n*-pentane/CH_2Cl_2/Et_2O, 14:3.5:2.5) gave 13-oxo-7-BOC-14-β-OH-1,14-carbonate baccatin III **13a** (1.77 g, 2.43 mmol, 84%).

13-Oxo-7-TES-14-β-hydroxybaccatin III 1,14-Carbonate (13b). (a) A solution of phosgene (20%) (4.3 mL, 8.6 mmol, 20% in toluene) and pyridine (1.4 mL, 17.2 mmol) was added to CH_2Cl_2 (15.0 mL) at 0 °C. A solution of **12b** (0.47 g, 0.76 mmol) in CH_2Cl_2 (5.0 mL) was added. The reaction was quenched after 20 min with methanol (1.0 mL) and diluted with CH_2Cl_2 (10.0 mL). The mixture was washed with aqueous $NaHCO_3$ (15.0 mL), dried, and evaporated. Chromatography (SiO_2, EtOAc/cyclohexane, 15:85) gave **13b** (0.48 g, 0.65 mmol, 85%). (b) Compound **12b** (crude reaction mixture prepared as reported above) was dissolved in CH_2Cl_2 (7.0 mL) and added dropwise to a stirred solution of phosgene (4.26 mL, 20% in toluene, 8.6 mmol) and pyridine (1.36 mL, 17.2 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After 20 min, the reaction was quenched, washed, evaporated, and purified as described in method a to give **13b** (using oxidant **11**: 75%; using oxidant **7**: 80%): mp 190−191 °C; $[\alpha]^{20}_D = +17.0$ ($c = 1.0$, $CHCl_3$); IR (Nujol) ν_{max} 2953, 1828, 1754, 1731, 1459, 1376, 1240, 1224; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, 2H, $J = 7.0$ Hz), 7.62−7.70 (m, 1H), 7.51 (t, 2H), 6.54 (s, 1H), 6.15 (d, 1H, $J = 7.0$ Hz), 4.93 (d, 1H, $J = 7.3$ Hz), 4.81 (s, 1H), 4.49 (dd, 1H, $J_1 = 11.0$, $J_2 = 7.0$ Hz), 4.30 (m, 2H), 3.83 (d, 1H, $J = 7.0$ Hz), 2.48−2.63 (m, 1H), 2.26 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H), 1.86−2.13 (m, 1H), 1.75 (s, 3H), 1.39 (s, 3H), 1.21 (s, 3H), 0.91−0.99 (t, 9H, $J = 8.7$ Hz), 0.58−0.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 190.9, 170.3, 168.7, 164.5, 151.3, 151.2, 139.4, 134.5, 129.9, 129.1, 127.7, 86.4, 83.9, 80.6, 75.9, 74.7, 72.0, 68.3, 59.3, 45.5, 41.7, 37.0, 32.7, 21.8, 20.7, 19.5, 14.0, 9.9, 6.7, 5.3; MS *m*/*z* 740.69 (M^+ calcd for $C_{38}H_{48}O_{13}Si$ 740.86). Anal. Calcd for $C_{38}H_{48}O_{13}Si$: C, 61.60; H, 6.53. Found: C, 61.81; H, 6.65.

7-BOC-14-β-hydroxybaccatin III 1,14-Carbonates (1a) and (14a). (a) Compound **13a** (0.71 g, 0.98 mmol) in THF (3.0 mL) was added at −55 °C to a MeOH solution (11.0 mL) of ^{n}Bu$_4$N$^+$BH$_4^-$ (1.29 g, 9.0 mmol). The reaction was quenched after 6 h with solid citric acid (0.6 g) and then with saturated aqueous citric acid (10.0 mL). The reaction was extracted with AcOEt and dried, and the solvent was evaporated. The crude material was chromatographed (SiO_2, *n*-hexane/ethyl acetate, 1.4:1.0) to yield **1a** (0.49 g, 0.67 mmol, 68.0%) and **14a** (0.13 g, 0.18 mmol, 19.0%).

7-TES-14-β-hydroxybaccatin III 1,14-Carbonates (1b) and (14b). To a solution of **13b** (0.14 g, 0.2 mmol) in MeOH (8.0 mL) was added $^{n}Bu_4N^+BH_4^-$ (0.12 g, 0.49 mmol) at −15 °C. Citric acid (0.1 g) and water (10.0 mL) were sequentially added after 40 min, and the reaction mixture was extracted with EtOAc, dried, and evaporated. The crude material was chromatographed (SiO_2, cyclohexane/EtOAc, 80:20−70:30) to yield **1b** (0.11 g, 0.15 mmol, 76%) and **14b** (0.027 g, 0.037 mmol, 19%). **1b**: mp 216−218°C; $[\alpha]^{20}_D = -54.0$ (c = 1.0, $CHCl_3$); IR (Nujol) ν_{max} 3448, 2929, 2852, 1815, 1731, 1454, 1376, 1238; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 2H, J = 7.0 Hz), 7.60−7.68 (m, 1H), 7.50 (t, 2H), 6.45 (s, 1H), 6.11 (d, 1H, J = 7.4 Hz), 5.00−5.03 (m, 1H), 4.99 (d, 1H, J = 7.3 Hz), 4.82 (d, 1H), 4.49 (dd, 1H, J_1 = 10.3 Hz, J_2 = 6.6 Hz), 4.12−4.35 (m, 2H), 3.74 (d, 1H, J = 7.4 Hz), 2.47−2.65 (m, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 2.06 (s, 3H), 1.85−2.14 (m, 1H, 6-H), 1.74 (s, 3H), 1.28 (s, 3H), 1.16 (s, 3H), 0.91−0.99 (t, 9H, J = 8.7 Hz), 0.58−0.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 170.5, 169.2, 164.9, 153.0, 142.2, 134.2, 132.9, 129.9, 128.9, 128.2, 88.5, 84.2, 84.0, 80.4, 76.0, 75.1, 71.9, 71.8, 69.5, 58.8, 46.7, 41.5, 37.0, 25.9, 22.3, 21.7, 20.8, 14.8, 10.1, 6.8, 5.3; MS m/z 742.96 (M^+ calcd for $C_{38}H_{50}O_{13}Si$ 742.88). Anal. Calcd for $C_{38}H_{50}O_{13}Si$: C, 61.44; H, 6.78. Found: C, 61.68; H, 6.87. **14b**: mp 234−236°C; $[\alpha]^{20}_D = -10.0$ (c = 0.7, $CHCl_3$); IR (Nujol) ν_{max} 3457, 2955, 2920, 2852, 1814, 1736, 1731, 1455, 1375, 1240; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 2H, J = 7.0 Hz), 7.61−7.68 (m, 1H), 7.49 (t, 2H), 6.45 (s, 1H), 6.14 (d, 1H, J = 7.3 Hz), 4.92 (d, 1H, J = 7.7 Hz), 4.83 (d, 1H, J = 8.0 Hz), 4.41 (m, 2H, 13-H), 4.28 (m, 2H), 3.70 (d, 1H, J = 7.0 Hz), 2.46−2.65 (m, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 1.85−2.10 (m, 1H), 1.73 (s, 3H), 1.44 (s, 3H), 1.18 (s, 3H), 0.91−0.98 (t, 9H, J = 8.7 Hz), 0.58−0.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 170.1, 169.2, 164.7, 152.6, 139.8, 139.0, 134.2, 129.8, 128.9, 128.2, 92.3, 84.0, 81.0, 76.0, 75.0, 74.8, 71.9, 69.5, 68.7, 59.2, 46.2, 40.8, 37.1, 30.5, 22.1, 21.4, 20.8, 20.0, 10.0, 6.8, 5.3; MS m/z 742.64 (M^+ calcd for $C_{38}H_{50}O_{13}Si$ 742.88). Anal. Calcd for $C_{38}H_{50}O_{13}Si$: C, 61.44; H, 6.78. Found: C, 61.33; H, 6.71.

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Supporting Information Available: General techniques and spectroscopic and analytical data for compounds **1a**, **5**, **6**, **12a**, **13a**, and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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