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SYNTHESES OF NEW FLUORINE-CONTAINING TAXOIDS BY MEANS OF β-LACTAM SYNTHON METHOD

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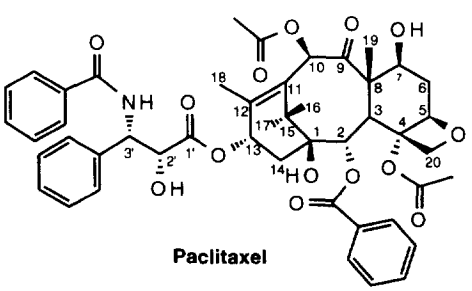
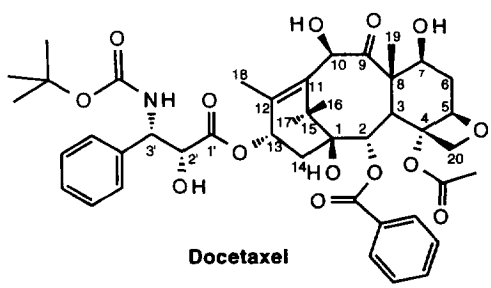
Summary: A series of new fluorine-containing analogs of paclitaxel and docetaxel are synthesized using the coupling of (3*R*,4*S*)-1-acyl-β-lactams with high enantiomeric purity with properly protected baccatin III, 10-deacetylbaccatin III, and 14β-hydroxy-10-deacetyl-baccatin III as the key step (β-*Lactam Synthon Method*). (3*R*,4*S*)-1-Acyl-β-lactams are prepared through efficient chiral ester enolate – imine cyclocondensation.

Taxol® (paclitaxel) is currently considered the most exciting lead in cancer chemotherapy.[1-3] Taxotere® (docetaxel), a semisynthetic analog, is also exceptionally promising.[1,4] Paclitaxel and docetaxel possess strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. Paclitaxel has been approved by FDA for the treatment of advanced ovarian cancer and breast cancer, and is currently in phase II and III clinical trials for other cancers.[1] Docetaxel is currently in phase II and III clinical trials for breast, lung and other cancers worldwide and expected to be on the market shortly.[1,5]



Paclitaxel



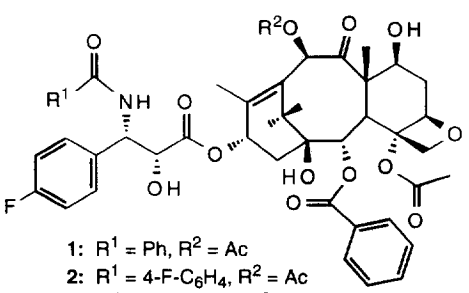
Docetaxel

Recent reports on clinical trials of paclitaxel and docetaxel, however, have disclosed that these highly effective drugs have a number of undesired side effects and are inactive against certain tumor types.[6]

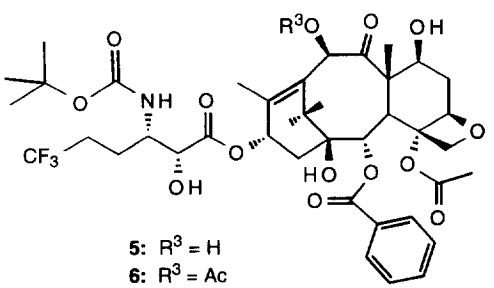
Therefore, it is very important to develop new generation taxoid anticancer drugs, which have less undesirable side effects and activity spectra against various tumor types different from those of these two drugs, on the basis of structure-activity relationship (SAR) study and rational design. In the course of our study on the rational design, synthesis and SAR of new antitumor taxoids,[7-12] we became interested in incorporating fluorine(s) into paclitaxel[13,14] and taxoids with regard to the effects of fluorine in cytotoxicity, blocking of known metabolic pathways, and use as a probe for investigating bioactive conformation of taxane antitumor agents.

Studies on the metabolism of paclitaxel have shown that the *para* position of the C-3' phenyl, *meta* position of the C-2 benzoate, C-6 methylene, and C-19 methyl groups are primary sites of hydroxylation by the cytochrome P450 family of enzymes.[15,16] Among these metabolic pathways, the predominant one is the hydroxylation of the C-3' phenyl at *para* position by cyctochrome 3A family.[15] It has been shown that the replacement of C-H bond with C-F bond can significantly slow down the enzymatic oxidation.[17] Accordingly, the introduction of a fluorine to the *para* position of the C-3' phenyl should be able to slow down the hydroxylation by cytochrome P-450 3A family. It has been strongly suggested that both paclitaxel and docetaxel take "hydrophobic cluster" conformation in aqueous media.[18,19] The introduction of a 4-fluorophenyl at the C-3' position instead of the phenyl may enhance the formation of the hydrophobic cluster with the phenyl of C-2 benzoate and the methyl of C-4 acetate. Fluoro-analogs of paclitaxel and docetaxel would serve as excellent probes for the conformational analyses on the basis of variable temperature ^{19}F NMR as well as ^{19}F–^{1}H hetero-NOSEY.

We describe here the syntheses of new fluorine-containing analogs of paclitaxel and docetaxel (**1-6**) by means of the *β-Lactam Synthon Method* developed in our laboratories,[20-22] which would have significance in medicinal chemistry and molecular pharmacology of paclitaxel and taxoid antitumor agents.



1: R^1 = Ph, R^2 = Ac
2: R^1 = 4-F-C_6H_4, R^2 = Ac
3: R^1 = *t*-BuOCO, R^2 = H
4: R^1 = *t*-BuOCO, R^2 = Ac



5: R^3 = H
6: R^3 = Ac

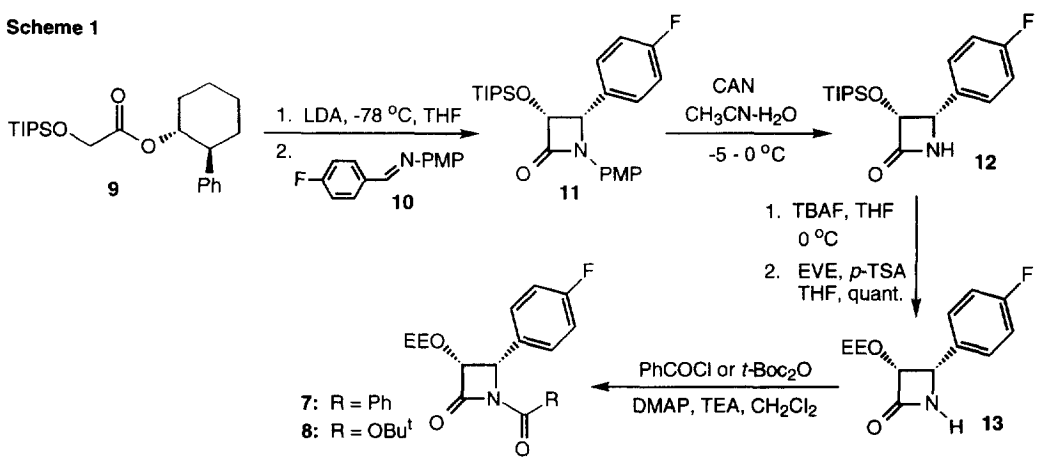
RESULTS AND DISCUSSION

Syntheses of (3R,4S)-1-acyl-β-lactams

According to our protocol for the semisyntheses of paclitaxel and taxoids, (3*R*,4*S*)-1-acyl-3-silyloxy-4-phenyl(or alkyl or alkenyl)-β-lactams are the key intermediates, which are coupled with properly protected baccatins.[23-25] Thus, we synthesized fluorine-containing (3*R*,4*S*)-1-acyl-β-lactams through chiral ester enolate

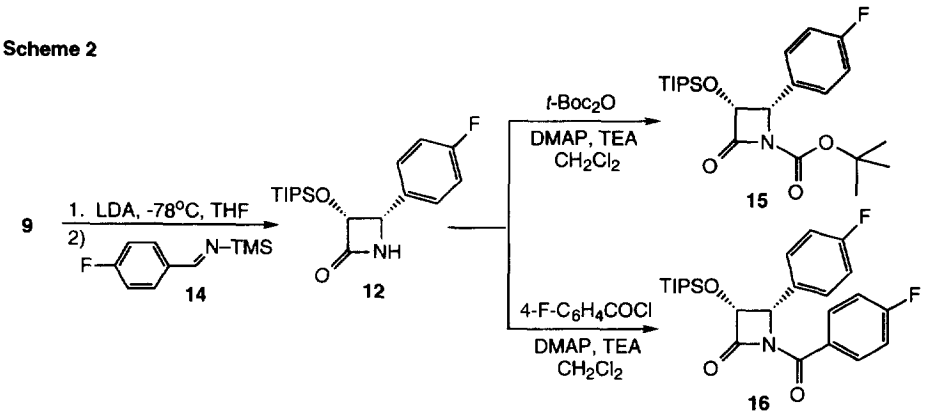
– imine cyclocondensation.[23,26] For the syntheses of 3'-(4-fluorophenyl)paclitaxel (**1**) and 3'-(4-fluorophenyl)-paclitaxel (**3**), we first prepared (3*R*,4*S*)-1-benzoyl-3-EEO-4-(4-fluorophenyl)azetidin-2-one (**7**) and (3*R*,4*S*)-1-*t*-Boc-3-EEO-4-(4-fluorophenyl)azetidin-2-one (**8**) as shown in Scheme 1 (EE = ethoxyethyl; *t*-Boc = *tert*-butoxycarbonyl). To a chiral ester enolate generated from (1*R*,2*S*)-*trans*-2-phenylcyclohexyl triisopropylsilyloxyacetate (**9**) and LDA in THF at -78°C was added *N*-(4-methoxyphenyl)-4-fluorobenzaldimine (**10**) and the mixture was stirred at -78 °C for 4 h, slowly warmed to room temperature, and further stirred overnight. The reaction was quenched by ammonium chloride to give 1-PMP-β-lactam **11** (PMP = *p*-methoxyphenyl) with 99% ee (chiral HPLC) in 81% yield. The PMP protecting group of **11** was removed by cerium ammonium nitrate (CAN) at -5 ~ 0 °C to give 3-TIPSO-β-lactam **12** (TIPS = triisopropylsilyl) in 78% yield. The TIPS group was deprotected using tetra-*n*-butyl ammonium fluoride, followed by protection of the hydroxyl group by reacting with ethyl vinyl ether in the presence of catalytic amount of *p*-toluenesulfonic acid (TSA) to afford 3-EEO-4-(4-fluorophenyl)-β-lactam **13** in quantitative yield. The (3*R*,4*S*)-1-acyl-β-lactams, **7** and **8**, were obtained in 92-95% yields by reacting **13** with benzoyl chloride and di-*tert*-butyl dicarbonate, respectively, in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and triethylamine (TEA) in dichloromethane at room temperature.

Scheme 1



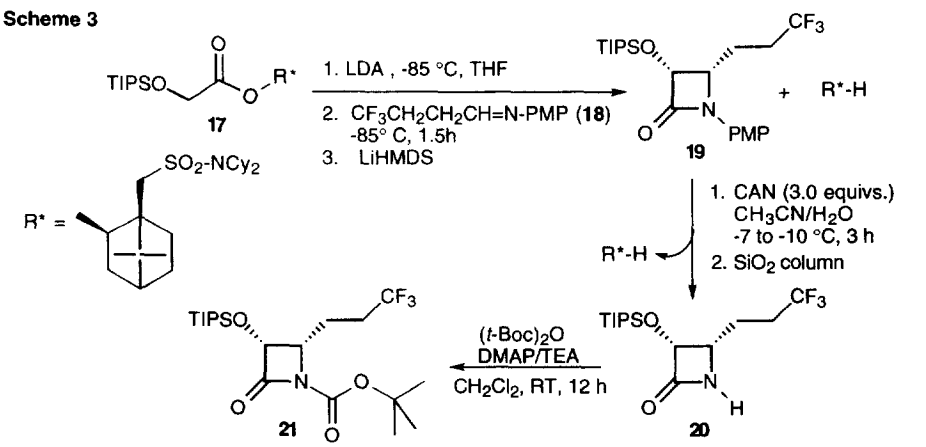
We have found that (3*R*,4*S*)-1-acyl-3-TIPSO-β-lactams can be used for coupling with protected baccatins without any problem, i.e., the conversion of very bulky TIPS to EE is unnecessary, when our coupling protocol is employed that uses C-13 *O*-metalated baccatin derivatives.[23,24] Accordingly, we examined a shorter route to β-lactam **12** using *N*-TMS-(4-fluorophenyl)aldimine (**14**) (TMS = trimethylsilyl) that was readily prepared from 4-fluorobenzaldehyde and lithium hexamethyldisilazide (LiHMDS) in the chiral ester enolate – imine cyclocondensation process (Scheme 2). The reaction of **9** with **14** under the same conditions as those mentioned above proceeded smoothly to give **12** with 96% ee (chiral HPLC) in >99% yield. Then, **12** was converted to the corresponding (3*R*,4*S*)-1-*t*-Boc-3-TIPSO-4-(4-fluorophenyl)azetidin-2-one (**15**) in 94% yield. In the same manner, (3*R*,4*S*)-1-(4-fluorobenzoyl)-3-TIPSO-4-(4-fluorophenyl)azetidin-2-one (**16**) was obtained by reacting **12** with 4-fluorobenzoyl chloride in the presence of triethylamine in 56% yield (Scheme 2).

Scheme 2



In a similar manner, we synthesized (3*R*,4*S*)-1-*t*-Boc-3-TIPSO-4-(3,3,3-trifluoropropyl)azetidin-2-one (**21**) (Scheme 3). It turned out that TIPSO-acetate with the Whitesell chiral auxiliary,[27] i.e., (-)-*trans*-2-phenylcyclohexanol, gave only low enantioselectivity (23% ee). Thus, we examined TIPSO-acetate with the Oppolzer chiral auxiliary,[28] i.e., (-)-10-dicyclohexylsulfamoyl-D-isoborneol, for the reaction with *N*-PMP-3,3,3-trifluoropropylaldimine (**18**), which afforded (3*R*,4*S*)-1-PMP-β-lactam **19** with 93% ee. Since it was very difficult to separate **19** from the chiral auxiliary by flash column chromatography due to almost identical R_f values, the crude product (1:1 mixture of **19** and the chiral auxiliary by ^1H NMR) was carried to the next deprotection step. The deprotection of PMP with CAN in the same manner as described above afforded β-lactam **20** in 67% yield, where the chiral auxiliary was easily recovered. The β-lactam **20** was then reacted with di-*tert*-butyl dicarbonate in the presence of DMAP and TEA to give 1-*t*-Boc-β-lactam **21** in nearly quantitative yield.

Scheme 3

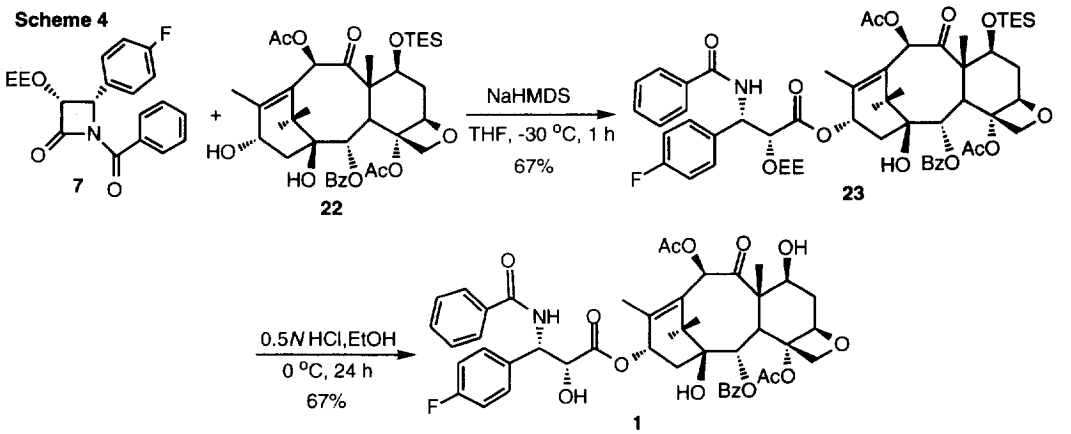


The (3*R*,4*S*)-1-acyl-β-lactams **7**, **8**, **15**, **16**, and **21** with high enantiomeric purity thus obtained were used for coupling with 7-protected baccatin III and 7,10-diprotected 10-deacetylbaccatin III to synthesize the corresponding fluorine-containing analogs of paclitaxel and docetaxel.

Syntheses of fluorine-containing taxoids through coupling of 1-acyl-β-lactams with baccatin III derivatives

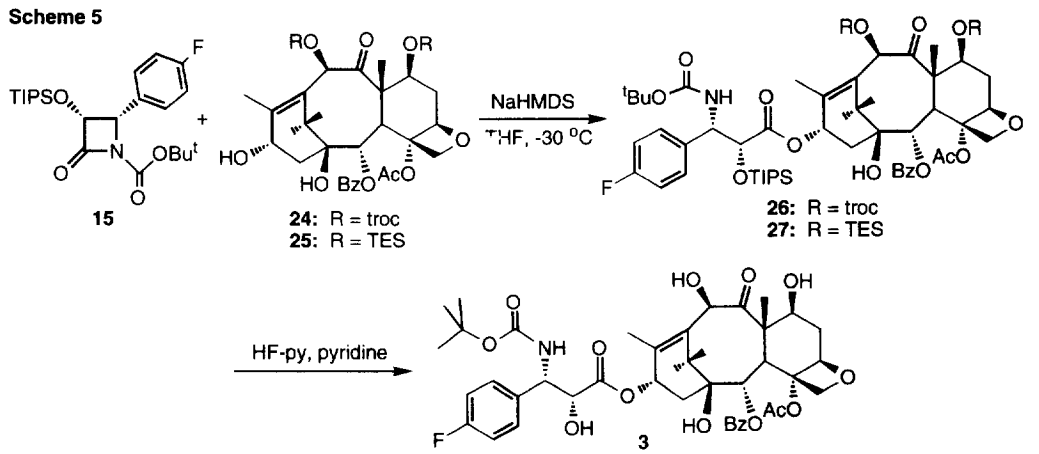
3'-(4-Fluorophenyl)paclitaxel (**1**) was synthesized through the coupling of 1-benzoyl-β-lactam **7** and 7-TES-baccatin III (**22**) using the protocol developed in our laboratories[11,23,24] as shown in Scheme 4. Reaction of **7** with **22** in the presence of sodium hexamethyldisilazide (NaHMDS) at -30 °C for 1 h gave the coupling product **23** in 67% yield (89% based on 75% conversion). Deprotection of 2'-EE and 7-TES groups with 0.5*N* hydrochloric acid in ethanol at 0 °C for 24 h afforded **1** in 67% yield.

Scheme 4



In a similar manner, 3'-(4-fluorophenyl)docetaxel (**3**) was synthesized through the coupling of 1-*t*-Boc-β-lactam **15** with 7,10-di-troc-10-deacetylbaccatin III (**24**) (troc = 2,2,2-trichloroethoxycarbonyl) as shown in Scheme 5. The coupling of **15** with **24** in the presence of NaHMDS gave fully protected 3'-(4-fluorophenyl)-docetaxel derivative **26** in 56% yield. Deprotection of 2'-TIPS by HF/pyridine (85% yield) and of 7,10-di(troc) by Zn/HCl (76% yield) afforded **3**.

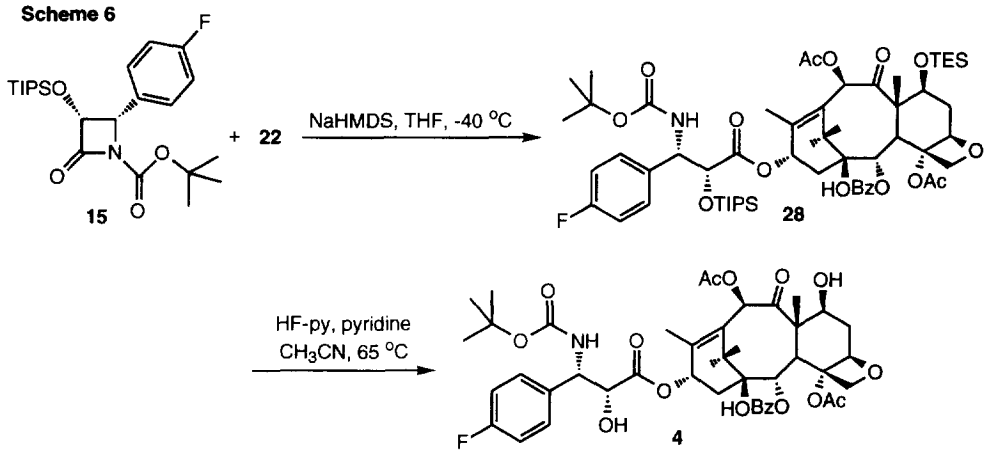
Scheme 5



In order to improve the overall yield, we examined the coupling of **15** with 7,10-di-TES-10-deacetylbaccatin III (**25**) under the same coupling conditions. It has turned out that this coupling is much more efficient, giving 2'-TIPS-7,10-diTES-3'-(4-fluorophenyl)docetaxel (**27**) in nearly quantitative yield. Deprotection of silicon protecting groups using HF/pyridine also proceeded smoothly to afford 3'-(4-fluorophenyl)docetaxel (**3**) in 90% yield (Scheme 5).

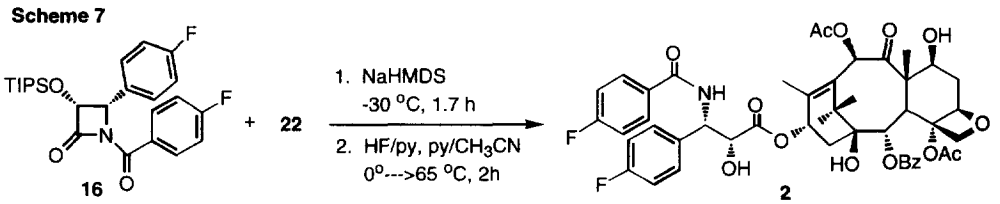
Synthesis of the 3'-(4-fluorophenyl)-10-acetyldocetaxel (**4**) was accomplished in two steps in a similar manner (Scheme 6). 1-*t*-Boc-β-Lactam (**8**) was coupled with 7-TES-baccatin III (**22**) in the presence of NaHMDS to give protected fluoro-docetaxel analog **28** in 54% yield. Subsequent deprotection of **28** using HF/pyridine afforded **4** in 91% yield.

Scheme 6



The synthesis of the difluoro-analog of paclitaxel **2** was attempted in a similar fashion as shown in Scheme 7. However, the coupling reaction of 7-TES-baccatin III (**22**) with 1-(4-benzoyl)-4-(4-fluorophenyl)-β-lactam **16** resulted in the formation of a rather messy product mixture. This product mixture was subjected to HF/pyridine deprotection in the hope of facilitating isolation of the desired product. The desired 3'-*N*-(4-fluorobenzoyl)-3'-(4-fluorophenyl)paclitaxel (**2**) was isolated in only 12% yield in two-steps.

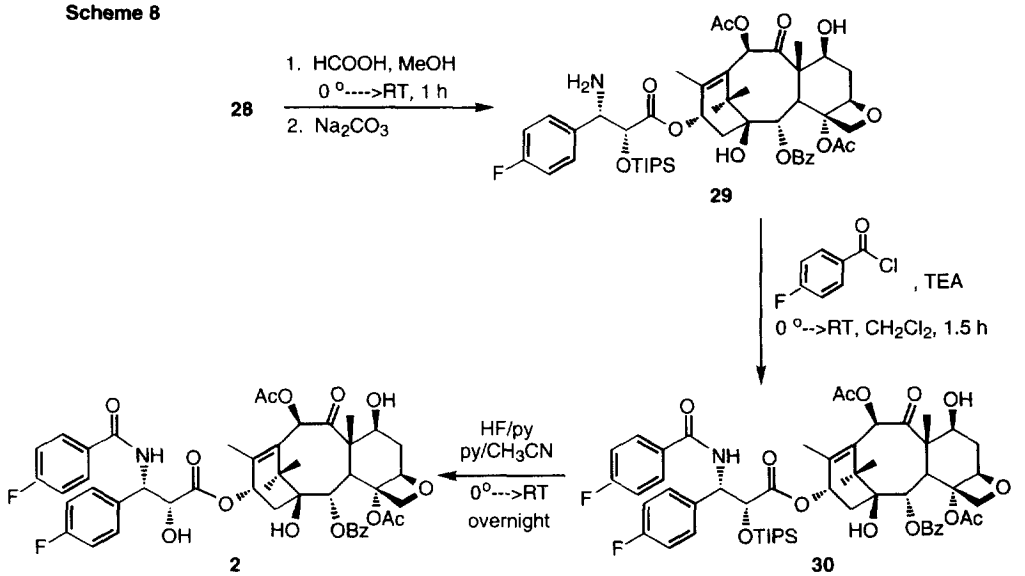
Scheme 7



In order to avoid this unexpected complication, an alternative route to this difluoro-analog **2** was undertaken, which includes the synthesis of 3'-*N*-debenzoyl analog **29**, followed by *N*-acylation with 4-fluorobenzoyl chloride (Scheme 8). The 3'-*N*-*tert*-butoxylcarbonyl group and 7-TES group of 2'-TIPS-3'-(4-fluorophenyl)-7-TES-10-Ac-docetaxel (**28**) (*vide supra*) were removed by formic acid to give 3'-*N*-deacyl derivative **29** in 54% yield. The free C-7 hydroxyl group did not interfere the following *N*-4-fluorobenzoylation

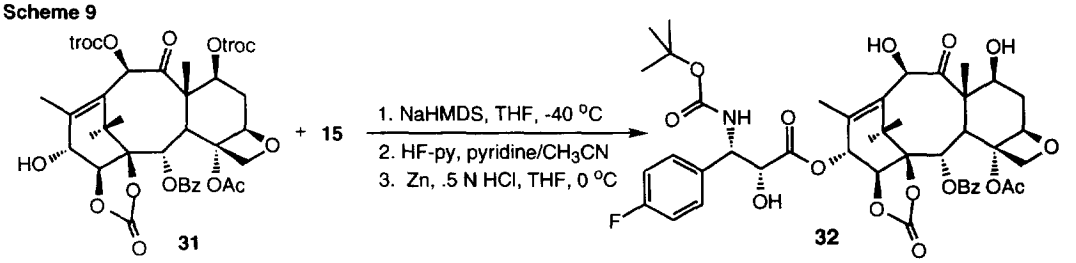
at all. Thus, the reaction of **29** with 4-fluorobenzoyl chloride in the presence of triethylamine gave 2'-TIPS-3'-(4-fluorophenyl)-3'-*N*-(4-fluorobenzoyl)paclitaxel (**30**) in 90% yield. Deprotection of 2'-TIPS group by HF/pyridine gave **2** in 66% yield.

Scheme 8



In addition to baccatin III and 10-deacetylbaccatin III, we also employed a derivative of 14β-hydroxy-10-deacetylbaccatin III[29] for the coupling with a fluorine-containing β-lactam. The coupling reaction between 7,10-di-troc-14-OH-10-deacetylbaccatin III-1,14-carbonate(**31**)[8] and 1-*t*-Boc-β-lactam **15** was carried out under the standard conditions (*vide supra*) to give the fully protected coupling product in 70% yield. Deprotection of TIPS group at C-2' by HF/pyridine and troc groups at C-7 and C-10 by Zn/HCl afforded 3'-(4-fluorophenyl)-14-OH-docetaxel-1,14-carbonate (**32**) in 57% yield (Scheme 9).

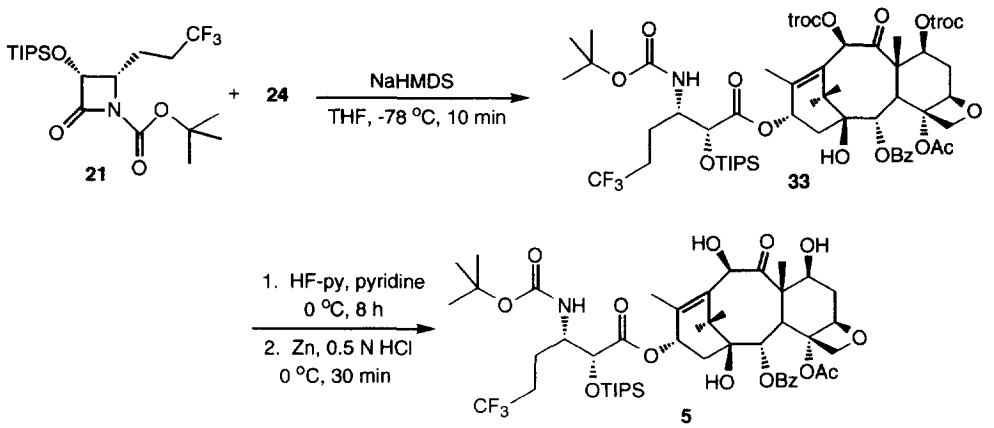
Scheme 9



3'-(3,3,3-Trifluoropropyl)docetaxel (**5**) and 3'-(3,3,3-trifluoropropyl)-10-Ac-docetaxel (**6**) were synthesized in a similar manner using 1-*t*-Boc-β-lactam **21** (Schemes 10 and 11). The coupling reaction of 7,10-di-troc-baccatin III (**24**) with 1-*t*-Boc-β-lactam **21** was carried out at -78 °C in the presence of two equivalents of NaHMDS for 10 min to give 2'-TIPS-3'-(3,3,3-trifluoropropyl)-7,10-di-troc-docetaxel (**33**) in

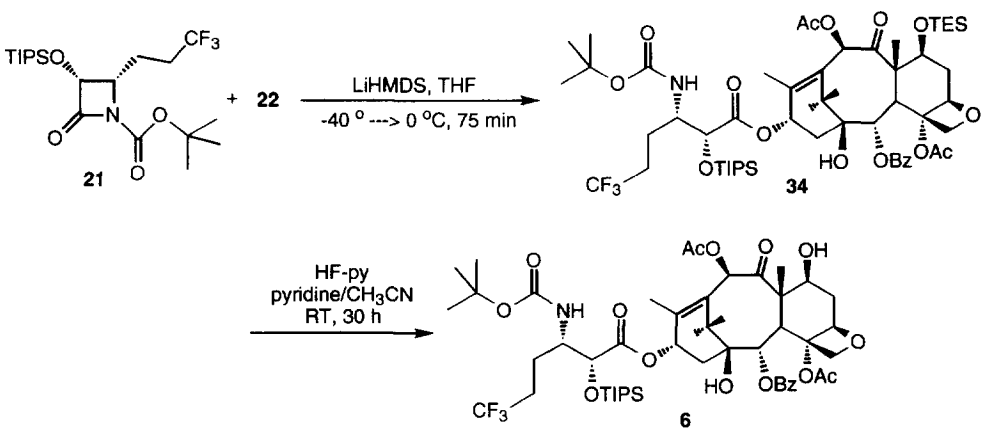
81% yield. Deprotection of TIPS group at C-2' and troc group at C-7 and C-10 by Zn/HCl afforded 3'-(3,3,3-trifluoropropyl)docetaxel (**5**) in 48% yield (in two steps) (Scheme 10).

Scheme 10



The coupling reaction between 1-*t*-Boc-β-lactam **21** and 7-TES-baccatin III (**22**) proceeded under the standard conditions (*vide supra*) to give 2'-TIPS-3'-(3,3,3-trifluoropropyl)-10-Ac-docetaxel (**33**) in 81% yield. Subsequent desilylation of TIPS and TES groups at C-2' and C-7 with HF/pyridine at room temperature afforded (3,3,3-trifluoropropyl)-10-Ac-docetaxel (**6**) in 80% yield (Scheme 11).

Scheme 11



Preliminary bioassay results on the *in vitro* cytotoxicities of these new fluorine-containing taxoids indicate that 3'-(4-fluorophenyl)docetaxel (**3**) and 3'-(4-fluorophenyl)-10-Ac-docetaxel (**4**) possess strong activities against human ovarian, non-small cell lung, colon, and breast cancer cell lines, which are better than paclitaxel. Difluoro-analog of paclitaxel **2**, 3'-trifluoropropyldocetaxel analogs, **5** and **6**, are also cytotoxic, but considerably weaker than paclitaxel. Molecular modeling and conformational study based on NMR strongly

suggest that fluorine of the 3'-(4-fluorophenyl) group in **3** and **4** significantly contributes to the formation of "hydrophobic cluster" conformation in protic solvents. The results on the medicinal chemistry and conformational analyses will be published elsewhere in the near future.

EXPERIMENTAL SECTION

General Methods. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1600 series spectrophotometer. ^{1}H, ^{13}C, ^{19}F and 2D NMR spectra were measured with a Bruker AC 250 or a General Electric QE-300 spectrometer using tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Thin layer chromatography was performed on Merck DC-alufolien with Kieselgel 60F-254. Column chromatography was carried out on Silica gel 60 (230-400 mesh ASTM, Merck). Chiral HPLC analysis for the determination of enantiomeric excess, was carried out with a Waters HPLC assembly consisting of a Waters M45 solvent delivery system, a Waters Model 680 gradient controller, and a Waters M440 detector (at 254 nm), equipped with a Spectra Physics Model SP4270 integrator using a chiral column J. T. Baker DAICEL - CHIRACEL OD employing hexane/2-propanol (13/1) as the solvent system with a flow rate of 0.2 mL/min.

Materials. 10-Deacetylbaccatin III was obtained from Rhône-Poulenc Rorer. 7-*O*-Triethylsilylbaccatin III and 7,10-*O,O*-bis(trichloroethoxycarbonyl)-10-*O*-deacetylbaccatin III were either prepared by literature methods[30,31] or obtained from Rhône-Poulenc Rorer. 7,10-Bis(triethylsilyl)baccatin III[32] and 7,10-*O,O*-bis-(trichloroethoxylcarbonyl)-10-*O*--deacetyl-14β-hydroxybaccatin III-1,14-carbonate[8] were prepared by the literature method. (-)-10-Dicyclohexylsulfamoyl-D-isoborneol was purchased from Aldrich Chemical Co. (-)-*trans*-2-Phenylcylohexanol was prepared by the literature method.[27] (-)-10-Dicyclohexylsulfamoyl-D-isobornyl triisopropylsilyloxyacetate[33] and (-)-*trans*-2-phenylcylohexyl triisopropylsilyloxyacetate[23] were prepared by the literature methods. 4,4,4-Trifluorobutanal was obtained from F-Tech, Inc.

(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-(triisopropylsilyloxy)-4-(4-fluorophenyl)azetidin-2-one (11): To a solution of diisopropylamine (2.35 mL, 1.6 mmol) in 30 mL of THF was added 2.5*M* *n*-butyllithium (6.76 mL, 1.6 mmol) in hexane at 0°C. The solution was stirred for 1 h at 0 °C and then cooled to -78 °C. To the mixture was added TIPSO-acetate **9**[23] (5.07 g, 1.3 mmol) in 30 mL of THF by cannula over a period of 2 h. After the mixture was cooled to -85 °C, *N*-PMP-imine **10** (4.92 g, 1.7 mmol) in 30 mL of THF was added over a period of 3 h. The mixture was stirred overnight and then allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the reaction mixture was extracted with ether. The extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude solid product was purified by column chromatography on silica gel using EtOAc/hexane (1/5) as the eluant to give 1-PMP-β-lactam **11** (3.46 g, 53% yield) as a yellow solid: mp 123-123.5 °C; $[\alpha]_D^{20}$ +82.5° (c 0.72, $CHCl_3$); IR ($CHCl_3$) 2974, 2868, 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82-0.98 (m, 21 H), 3.76 (s, 3 H), 5.14 (d, J = 4.9 Hz, 1 H), 5.25 (d, J = 4.9 Hz, 1 H), 6.80 (d, J = 8.8, 2 H), 7.05 (t, J = 8.8 Hz, 2 H), 7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 11.8, 17.4, 17.5, 55.4, 62.7, 77.8, 114.4, 115.1, 115.2, 118.7, 130.0, 130.1, 130.8, 156.3, 161.3, 165.5. Anal. Calcd for $C_{25}H_{34}NO_3SiF$: C, 67.69; H, 7.72; N, 3.16. Found: C, 67.77; H, 7.83; N, 3.19.

(3*R*,4*S*)-3-(triisopropylsilyloxy)-4-(fluorophenyl)azetidin-2-one (12): ***(Method A)*** To a solution of 1-PMP-β-lactam **11** (3.46 g,7.89 mmol) in 330 mL of acetonitrile at -15 °C, was added dropwise a solution of cerium(IV) ammonium nitrate (12.95 g, 23.6 mmol) in 110 mL of water over a period of 4 h. After 1 h at -15 °C, the reaction mixture was diluted with EtOAc and successively washed with 5% $NaHCO_3$, 10% Na_2SO_3 and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1/4) as the eluant to give β-lactam **12** (2.07 g, 78% yield) as a dark brown oil.
(Method B) To a solution of diisopropylamine (1.16 mL, 8.3 mmol) in 15 ml of THF was added 2.5*M* *n*-butyllithium in hexane (3.33 mL, 1.6 mmol) at 0°C. The solution was stirred for 30 min at 0°C and then cooled to -78 °C. To the mixture was added TIPSO-acetate **9** (2.5 g, 6.4 mmol) in 20 ml of THF by cannula over a period of 2 h. The mixture was then cooled to -85 °C and *N*-TMS-imine **14** (1.61 g, 8.3 mmol) in 30 mL of THF was added over a period of 3 h. The mixture was stirred overnight and then allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the reaction mixture was extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using 1/5 EtOAc/hexane (1/5) to afford 2.1 g (100%) of β-lactam **12** as a pale yellow oil.
12: $[\alpha]_D^{20}$ +54.88° (c 0.82, $CHCl_3$); IR ($CHCl_3$) 3411, 2946, 2894, 1771, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84-1.01 (m, 21 H), 4.78 (d, J = 4.6 Hz, 1 H), 5.13 (dd, J = 4.6,4.4 Hz), 6.78 (bs, 1 H), 7.02 (t, J = 8.6 Hz, 2 H), 7.29 (dd, J = 8.6, 5.5

Hz); ^{13}C NMR ($CDCl_3$) δ 11.7, 17.4, 17.5, 59.0, 79.8, 114.7, 115.0, 129.8, 129.82, 132.1, 164.7, 170.2. Anal Calcd for $C_{18}H_{28}NO_2SiF$: C, 64.06; H, 8.36; N, 4.15. Found: C, 63.84; H, 8.18; N, 4.05.

(3*R*,4*S*)-3-(1-Ethoxyethoxy)-4-(4-fluorophenyl)azetidin-2-one (13): To a solution of 3-TIPSO-β-lactam **12** (1.09 g, 5.63 mmol) in 35 mL of THF, was added 1*M* *n*-Bu_4NF. (6.76 mL, 6.76 mmol) in THF at room temperature. After stirring overnight, the solvent was evaporated and the crude oil was purified by chromatography on silica gel using EtOAc/hexane (4/1) as the eluant to afford (3*R*,4*S*)-3-hydroxy-4-(4-fluorophenyl)azetidin-2-one (590 mg, 60% yield) as a white solid, which was used without further purification in the next step: ^{1}H NMR (CD_3OD) δ 4.83 (d, J = 4.7 Hz, 1 H), 5.03 (d, J = 4.7 Hz, 1 H), 7.09 (t, J = 8.8 Hz, 2 H), 7.32 (dd, J = 5.5, 8.8 Hz, 2 H); IR (KBr disk) 3334, 3291, 2927, 1774, 1240 cm^{-1}.

To a solution of 3-OH-β-lactam (460 mg, 2.53 mmol) thus obtained in 30 mL of THF was added ethyl vinyl ether (0.485 mL, 5.06 mmol) at 0 °C. After stirring for 2 h at 0°C, the reaction mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2CO_3, filtered and concentrated to yield 3-EEO-β-lactam **13** (660 mg, 100%) as a white solid (1:1 mixture of two diastereomers): mp 95-96 °C; ^{1}H NMR ($CDCl_3$) δ 0.95-1.12 (m, 6 H), [3.25 (dq, J = 7.0, 9.4 Hz), 3.28-3.36 (m), 3.67 (dq, J = 7.0, 9.4 Hz] (2 H), [4.70 (q, J = 5.4 Hz), 4.80 (q, J = 5.4 Hz)] (1 H), 5.10-5.18 (m, 2 H), 6.2 (bs, 1 H), 7.02-7.05 (m, 2H), 7.27-7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.9, (19.8, 20.1), (57.7, 58.4), (60.4, 62.1), (78.3, 79.4), (98.9, 99.3), (114.8, 114.9), (115.1, 115.2), (129.3, 129.4), (129.6, 129.7), (131.9, 132.1), (160.9, 164.2), (169.2, 169.6); IR (KBr) 3214, 2983, 2933, 1753, 1718, 1456 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N0_3F$: C, 61.65; H, 6.37; N, 5.53. Found: C, 61.49; H, 6.52; N, 5.54.

(3*R*,4*S*)-1-Benzoyl-3-(1-ethoxyethoxy)-4-(4-fluorophenyl)azetidin-2-one (7): To a solution of 3-EEO-β-lactam **13** (250 mg, 0.987 mmol), 5 mg of DMAP (5 mg), and triethylamine (680 μL) in 10 mL of CH_2Cl_2, was added dropwise benzoyl chloride (171 μL, 1.48 mmol) at 0 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2CO_3 and concentrated. The oily crude product was purified by column chromatography on silica gel using EtOAc/hexane (1/4) as the eluant to afford 1-benzoyl-β-lactam **7** (235 mg, 70% yield) as an off-white solid (1:1 mixture of diastereomers): mp 64-66 °C; IR (KBr disk) 3001, 2978, 1795, 1719, 1466, 1296 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ [1.04 (d, J = 5.4 Hz), 1.14 (d, J = 5.4 Hz)] (3 H), 1.12-1.18 (m, 3 H), 3.29-3.75 (m, 2 H), [4.58 (q, J = 5.4 Hz), 4.77 (q, J = 5.4 Hz)] (1 H), 5.27 (dd, J = 7.1, 2.1 Hz, 1 H), 5.43-5.6 (m, 1 H), 7.05-8.05 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ (14.8, 14.9), (19.9, 20.0), (59.1, 59.9), (60.2, 60.9), 62.33, (74.7, 75.7), (99.3, 99.7), (115.0, 115.1), 115.3, 128.1, (129.44, 129.6), (129.7, 129.8), (131.7, 133.4), 160.98, (164.3, 164.8), (165.7, 165.8). Anal Calcd for $C_{20}H_{21}NO_4F$: C, 67.03; H, 5.91; N, 3.91. Found: C, 67.20; H, 6.02; N, 3.92.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(1-ethoxyethoxy)-4-(4-fluorophenyl)azetidin-2-one (8): To a solution of 3-EEO-β-lactam **13** (250 mg, 0.987 mmol), DMAP (5 mg), and triethylamine (680 μL) in 10 mL of CH_2Cl_2 was added dropwise di-*tert*-butyl dicarbonate (322 mg, 1.48 mmol) in 5 mL of CH_2Cl_2 at 0 °C. The mixture was stirred overnight at room temperature. The reaction mixture was washed several times with brine, dried over anhydrous Na_2CO_3 and concentrated. The crude solid product was purified by column chromatography on silica gel using EtOAc/hexane (1/5) as the eluant to yield 1-*t*-Boc-β-lactam **8** (290 mg, 83% yield) as a white solid (1:1 mixture of diastereomers): mp 79-80 °C; IR ($CHCl_3$) 3011, 2982, 1808, 1726, 1236 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ [0.94 (d, J = 5.3 Hz), 0.95 (d, J = 5.3 Hz)] (3 H), 1.08-1.12 (m, 3 H), 1.35 (s, 9 H), 3.20-3.34 (m, 2 H), [4.50 (q, J = 5.1 Hz), 4.67 (q, J = 5.1 Hz)] (1 H), 5.05 (dd, J = 5.7, 3.9 Hz, 1 H), 5.17 (d, J = 5.7 Hz, 1 H), 7.0-7.06 (m, 2 H), 7.2-7.3 (m, 2 H). Anal. Calcd for $C_{18}H_{24}N0_5F$: C, 61.18; H, 6.85; N, 3.96. Found: C, 61.07; H, 7.11; N, 3.83.

***N*-Trimethylsilyl-4-fluorobenzaldimine (14):** To hexamethyldisilazane (14.8 mL, 0.07 mol) was added 2.5*M* *n*-BuLi in hexane (25.8 mL, 0.07 mol) at 0 °C with stirring. The solvent was then removed *in vacuo* to afford a white slurry. To this slurry, 4-fluorobenzaldehyde (6.89 mL, 0.064 mol) was added at room temperature and the mixture was stirred for 30 min. The resulting yellow residue was distilled to afford *N*-TMS-4-fluoro-benzaldimine **14** (5.6 g, 45%) as a clear yellow oil: bp 57-60 °C/0.25 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H), 7.13 (t, J = 8.5 Hz, 2H), 7.81 (dd, J = 8.5, 5.4 Hz, 2H), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -1.17, 115.4, 115.7, 130.3, 130.5, 135.2, 162.7, 166.7.

(3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-(triisopropylsilyloxy)-4-(4-fluorophenyl)azetidin-2-one (15): To a solution of 3-TIPSO-β-lactam **12** (990 mg, 2.96 mmol), DMAP (14 mg, 0.11 mmol), and triethylamine (1.5 mL, 15 mmol) in 20 mL of CH_2Cl_2, was added dropwise a solution of di-*tert*-butyldicarbonate (645 mg, 2.96 mmol) in 5 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred overnight at room temperature, and water was added. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1/3) as the eluant to give 1-*t*-Boc-β-lactam **15** (1.22 g, 94% yield) a colorless oil: $[\alpha]_D^{20}$ +65.5° (c 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (bs, 21 H), 1.40 (s, 9 H), 5.05 (d, J = 5.5 Hz, 1 H), 5.15 (d, J = 5.5 Hz, 1 H), 7.04 (t, J = 8.7 Hz, 2 H), 7.29 (dd, J = 5.4, 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.7, 17.3, 17.4, 27.9, 61.7, 77.7, 83.3, 114.8, 115.1, 129.8, 129.9, 147.8, 161.2, 164.5, 165.9. Anal. Calcd for $C_{23}H_{36}NO_4F$: C, 63.13; H, 8.29; N 3.2. Found: C, 63.25; H, 8.06; N, 3.24.

(3*R*,4*S*)-1-(4-Fluorobenzoyl)-3-triisopropylsilyloxy-4-(4-fluorophenyl)azetidin-2-one (16): To a solution of 3-TIPSO-β-lactam **12** (119 mg, 0.352 mmol), DMAP (5 mg), triethylamine (200 μL) in 10 mL of CH_2Cl_2, was added dropwise 4-

fluorobenzoyl chloride (50 μL, 0.33 mmol) at 0 °C. The reaction mixture was washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2CO_3 and concentrated. The oily crude product was purified by column chromatography on silica gel using EtOAc/hexane (1/4) as the eluant to afford (90 mg, 56%) of 1-benzoyl-β-lactam **16** as a colorless oil: $[\alpha]D^{20}$ +102.5° (c .4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (bs, 21 H), 5.23 (d, J = 6.1 Hz, 1 H), 5.39 (d, J = 6.1 Hz, 1 H), 7.05 (t, J = 8.5 Hz, 2 H), 7.14 (t, J = 8.5 Hz, 2 H), 7.37 (dd, J = 8.5, 5.4 Hz, 2 H), 8.09 (dd, J = 8.5, 5.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.7, 17.4, 60.5, 76.5, 115.0, 115.3, 115.6, 128.0, 129.6, 130.0, 130.1, 132.6, 132.7, 160.9, 164.9, 165.0, 168.0; ^{19}F NMR ($CDCl_3$) δ -104.28, -114.32. Anal. Calcd for $C_{25}H_{31}NO_3F_2Si$: C, 65.33; H, 6.8; N, 3.05. Found: C, 65.30; H, 6.90; N, 3.01, .

***N*-(4-Methoxyphenyl)-4,4,4-trifluorobutanaldimine (18):** A mixture of *p*-anisidine (472 mg, 3.83 mmol) recrystallized from ethanol and anhydrous Na_2SO_4 was dissolved in 2 mL of CH_2Cl_2. The solution was stirred for 5 min, and freshly distilled 4,4,4-trifluorobutanal (482 mg, 3.83 mmol) was added dropwise at room temperature. The reaction mixture was stirred for about 20 min at room temperature during which period its color was darkened. An aliquot was taken and checked by ^1H NMR for confirming the formation of *N*-PMP-imine **18**. The *N*-PMP-imine **18** thus obtained was used for β-lactam synthesis without further purification.

(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(3,3,3-trifluoropropyl)azetidin-2-one (20): A solution of *N*-PMP-imine **18** in CH_2Cl_2 thus obtained was cooled to -78 °C and added slowly to the lithium enolate solution of **17** at -87 °C over a period of 90 min via cannula. After completion of the transfer, the mixture was stirred at -87 °C for 3 h and 1*M* LiHMDS (2.04 mL, 2.04 mmol) in THF was added. The reaction mixture was stirred at -87 °C for 2h and then allowed to gradually warm to room temperature. The mixture was stirred for an additional 2 h at room temperature. The reaction was quenched with a saturated aqueous NH_4Cl (50 mL). The reaction mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography with hexane/EtOAc (9/1) of the crude product yielded 830 mg of a 1:1 mixture of β-lactam and the chiral auxiliary, (-)-10-dicyclohexylsulfamoyl-D-isoborneol (^1H NMR). The chiral HPLC analysis showed that the enantiomeric purity of this sample was 93% ee. A 1 : 1 mixture of the (3*R*,4*S*)-1-PMP-3-TIPSO-4-(4-fluorophenyl)azetidin-2-one (**19**) and the chiral auxiliary (796 mg) was dissolved in acetonitrile (30 mL) and cooled to -8 °C. A solution of cerium(IV) ammonium nitrate (1.47 g, 2.68 mmol) in an acetonitrile/water mixture (30 mL/55 mL) was added dropwise to the mixture over a period of 25-30 min, by carefully maintaining the temperature between -8 to -10 °C. The reaction was monitored by TLC and upon completion (3 h), the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 40 mL). The organic extracts were washed with 5% Na_2CO_3 (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were washed with 10% Na_2SO_3 (until the aqueous layer remained colorless), 5% Na_2CO_3 (50 mL), and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography of the crude product using hexane/EtOAc (4/1) as the eluant gave β-lactam **20** (202 mg, 67% yield) as a yellow oil: $[\alpha]_D^{20}$ +39.89° (c 2.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.01-1.23 (m, 21H), 1.80-2.05 (m, 2H), 2.12-2.32 (m, 2H), 3.73-3.84 (m, 1H), 4.98 (dd, J = 4.8, 2.5 Hz, 1H), 6.91 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 11.97, 17.72, 22.98, 30.19 (q, $^2J_{C\text{-}F}$ = 29.4 Hz, $\underline{C}H_2CF_3$), 54.34, 77.87, 126.91 (q, J = 279.2 Hz, $CH_2\underline{C}F_3$), 169.80. IR (KBr disk) 3261, 2943, 2873, 1761, 1283 cm^{-1}. Anal. Cald. for $C_{15}H_{28}NO_2SiF_3$: C, 53.07; H, 8.31; N, 4.13. Found: C, 52.89; H, 8.17; N, 4.02.

(3*R*,4*S*)-1-*tert*-Butyloxycarbonyl-3-triisopropylsilyloxy-4-(3,3,3-trifluoropropyl)azetidin-2-one (21): A mixture of β-lactam **20** (202 mg, 0.6 mmol) in CH_2Cl_2 (10 mL), a catalytic amount of DMAP, and triethylamine (181 mg, 1.79 mmol) was cooled with an ice-bath and di-*tert*-butyl dicarbonate (338 mg, 1.58 mmol) in CH_2Cl_2 (2 mL) was added. After stirring for 4 h (monitored by TLC), CH_2Cl_2 (20 mL) was added to the mixture. The reaction mixture was washed with 1% HCl (15 mL), saturated $NaHCO_3$ (15 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the resulting crude product was purified by flash column chromatography on silica gel using hexane/EtOAc (4/1) as the eluant to afford 1-*t*-Boc-β-lactam **21** (260 mg, 99%) as a yellow oil: $[\alpha]_D^{20}$ +60.77° (c 2.7, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.05-1.28 (m, 21H), 1.50 (s, 9H), 2.10-2.19 (m, 2H), 2.21-2.38 (m, 2H), 4.05-4.18 (m, 1H), 5.00 (d, J = 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 11.98, 17.57, 21.29, 27.98, 30.33 (q, $^2J_{C\text{-}F}$ = 24.6 Hz, $\underline{C}H_2CF_3$), 57.15, 76.35, 83.71, 126.83 (q, J = 232.1 Hz, $CH_2\underline{C}F_3$), 148.41, 165.41. IR (KBr disk) 2943, 2867, 1809, 1722, 1456, 1342, 1315, 1152 cm^{-1}. Anal. Cald. for $C_{20}H_{36}O_4NSiF_3$: C, 54.65; H, 8.25; N, 3.19. Found: C, 54.70; H, 8.07; N, 3.11.

3'-Desphenyl-3'-(4-fluorophenyl)paclitaxel (1): To a solution of 1-benzoyl-β-lactam **7** (115 mg, 0.32 mmol) and 7-TES-baccatin III (**22**) (150 mg, 0.214 mmol) in 10 mL of THF was added 1*M* NaHMDS (0.214 mL, 0.214 mmol) in THF at -30 °C. The reaction was monitored by TLC and quenched after 1 h by the addition of brine at -30 °C. The aqueous layer was extracted with CH_2Cl_2. The extracts were washed with brine, dried over anhydrous Na_2CO_3, and concentrated. The oily crude product was purified by column chromatography on silica gel using EtOAc/hexane (1/2) as the eluant to give 2'-EE-3'-desphenyl-3'-(4-fluorophenyl)-7-TES-paclitaxel (**23**) (150 mg, 67% yield; 89% yield based on 75% conversion) as a white solid, and 36 mg of the chiral auxiliary **22** was recovered. The EE and TES protecting groups were then removed by reacting **23** (60 mg, 0.057 mmol) in 3 mL of THF and 2 mL of 0.5*N* HCl at 0°C for 24 h with stirring. The reaction mixture was extracted with CH_2Cl_2. The extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The solid residue was purified by chromatography on silica gel using EtOAc/hexane (1/2) as the eluant to give 3'-(4-fluorophenyl)paclitaxel (**1**) (36 mg, 67% yield) as a white solid:

$[\alpha]_D^{20}$ -46.5° (c 1.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.22 (s, 3 H), 1.67 (s, 3 H), 1.79 (s, 3 H), 1.89 (m, 1 H), 2.22 (s, 3 H), 2.31 (dd, J = 8.9, 14.1 Hz, 1 H), 2.37 (s, 3 H), 2.53 (m, 1 H), 3.79 (d, J = 6.8 Hz, 1 H), 4.19 (d, J = 8.4 Hz, 1 H), 4.30 (d, J = 8.3 Hz, 1 H), 4.38 (dd, J = 10.3, 6.7 Hz, 1 H), 4.75 (d, J = 2.0 Hz, 1 H), 4.93 (d, J = 9.0 Hz, 1 H), 5.66 (d, J = 7.0 Hz, 1H), 5.77 (br d, J = 8.7 Hz, 1 H), 6.23 (bt, J = 8.4 Hz, 1 H), 6.27 (s, 1 H), 7.09 (m, 3 H), 7.49 (m, 8 H), 7.73 (d, J = 7.3 Hz, 2 H), 8.12 (d, J = 7.5 Hz, 2 H); ^{13}C NMR δ 9.6, 15.0, 20.86, 21.72, 22.60, 26.87, 35.66, 43.16, 45.68, 54.27, 58.62, 72.17, 72.27, 73.07, 74.85, 75.52, 78.94, 81.18, 84.34, 115.64, 115.97, 127.04, 128.68, 128.83, 128.97, 129.07, 130.16, 132.01, 133.25, 133.44, 133.71, 133.98, 134.04, 141.77, 160.49, 164.43, 166.97, 170.37, 171.22, 172.43, 203.55. ^{19}F NMR (MeOH) δ -114.65; Anal. Calcd for $C_{47}H_{50}NO_{14}F$: C 64.74, H 5.78, N 1.61. Found: C 64.70, H 5.95, N 1.60.

3'-Desphenyl-3'-(4-fluorophenyl)docetaxel (3): ***(Method A)*** To a solution of 7,10-di(troc)-10-deacetylbaccatin III (**24**) (250 mg, 0.28 mmol) and 1-*t*-Boc-β-lactam **15** (180 mg, 0.41 mmol) in 7 mL THF at -30 °C was added 1*M* NaHMDS (0.44 mL, 0.44 mmol) in THF. After stirring for 80 min, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were washed with saturated aqueous NH_4Cl and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using EtOAc/hexane (1/9) as the eluant to afford 7,10-di(troc)-2'-TIPS-3'-(4-fluorophenyl)docetaxel (**26**) (207 mg, 56% yield) as a white solid.

To a solution of **26** (140 mg, 0.10 mmol) in 9 mL of pyridine at 0 °C was added 1.5 mL of HF/pyridine (70/30). The mixture was stirred at room temperature for 1 h and then heated to 50 °C for 30 min. An additional 1.5 mL of HF/pyridine was added and the reaction mixture was stirred for an additional 41 h, then the reaction was quenched with 3% hydrochloric acid. The reaction mixture was extracted with EtOAc and the extracts were washed with 3% hydrochloric acid and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1:1) as the eluant to afford 7,10-di(troc)-3'-(4-fluorophenyl)docetaxel (**27**) (105 mg, 85% yield) as a white solid: ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.25 (s, 6 H), 1.32 (s, 9 H), 1.84 (s, 3 H), 1.94 (s, 3 H), 2.02 (s, 3 H), 2.36 (s, 3 H), 2.65 (m, 1 H), 3.50 (d, J = 4.6 Hz, 1 H), 3.89 (d, J = 6.8 Hz, 1 H), 4.05-4.13 (m, 1 H), 4.15 (d, J = 8.6 Hz, 1 H), 4.31 (d, J = 8.6 Hz, 1 H), 4.57-4.62 (m, 2 H), 4.77 (s, 2 H), 4.87-4.96 (m, 2 H), 5.25 (d, J = 7.4 Hz, 1 H), 5.41 (d, J = 9.7 Hz, 1 H), 5.51 (dd, J = 9.7, 7.4 Hz, 1 H), 5.68 (d, J = 6.8 Hz, 1 H), 6.23 (s, 2 H), 7.06 (t, J = 8.7 Hz, 2 H), 7.37 (dd, J = 8.7, 5.5 Hz, 2 H), 7.46 (t, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 8.07 (d, J = 7.5 Hz, 2 H).

To a solution of **27** (108 mg, 0.089 mmol) in 5 mL THF was added 0.5 *N* hydrochloric acid (2.5 mL) and the mixture was stirred until it became a homogenous solution. To this solution was added zinc dust (170 mg) at 0 °C. The suspension was allowed to stir at room temperature for 2.5 h, and then filtered to remove Zn and Zn salt. The reaction mixture was diluted with 75 mL of EtOAc and washed with aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (3:2) as the eluant to afford 3'-(4-fluorophenyl)docetaxel (**3**) (57 mg, 76%) as a white solid.

(Method B) To a solution of 7,10-di-TES-baccatin III (**25**) (102 mg, 0.132 mmol) and 1-*t*-Boc-β-lactam **15** (86 mg, 0.198 mmol) in 7 mL of THF at -40 °C was added 1*M* LiHMDS (0.17 mL) in THF. After stirring for 30 min, the reaction was quenched by adding saturated aqueous NH_4Cl, the reaction mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product through a short silica gel column using EtOAc/hexane (1/2) as the eluant afforded 2'-TIPS-3'-(4-fluorophenyl)-7,10-di-TES-docetaxel (**27**) (155 mg, 98% yield). Compound **27** was dissolved in 5 mL of pyridine and 5 mL of CH_3CN at 0 °C and 1.0 mL of HF/pyridine was added. The mixture was heated to 40 °C for 2 h and the reaction was quenched by adding 5 mL of 1 *N* hydrochloric acid. The aqueous layer was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered an concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel using EtOAc/hexane (2/1) as the eluant afforded 3'-(4-fluorophenyl)docetaxel (**3**) (96 mg, 90% yield) as a white solid:

3: mp. 180-183 °C; $[\alpha]_D^{20}$ -32.7° (c 0.55, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.24 (s, 3 H), 1.34 (s, 9 H), 1.76 (s, 3 H), 1.86 (s, 3 H), 1.88 (m, 1 H), 2.29 (d, J = 8.8 Hz, 2 H), 2.36 (s, 3 H), 2.60 (m, 1 H), 3.41 (d, J = 4.8 Hz, 1 H), 3.92 (d, J = 7.0 Hz, 1 H), 4.13 (d, J = 8.3 Hz, 1 H), 4.21 (bs, 1 H), 4.32 (d, J = 8.3 Hz, 1 H), 4.59 (bs, 1 H), 4.95 (d, J = 7.9 Hz, 1 H), 5.21 (s, 1 H), 5.40 (d, J = 9.4 Hz, 1 H), 5.68 (d, J = 7.0 Hz, 1 H), 6.23 (t, J = 8.8 Hz, 1 H), 7.07 (t, J = 8.5 Hz, 2 H), 7.36 (dd, J = 8.5, 5.3 Hz, 2 H), 7.49 (t, J = 7.3 Hz, 2 H), 7.60 (t, J = 7.3 Hz, 1 H), 8.09 (d, J = 7.3 Hz, 2 H); ^{19}F NMR (MeOH) δ -113.07. Anal. Calcd. for $C_{45}H_{54}NO_{15}F$: C, 62.27; H, 6.27; N, 1.61. Found: C, 61.95; H, 6.49; N, 1.53.

3'-Desphenyl-3'-(4-fluorophenyl)-10-*O*-acetyldocetaxel (4):

To a solution of 7-TES baccatin III (**22**) (200 mg, 0.285 mmol) and 1-*t*-Boc-β-lactam **15** (186 mg, 0.43 mmol) in 9 mL of THF was added 1*N* NaHMDS (0.37 mL, 0.37 mmol) in THF at -35 °C. After stirring 30 min, the reaction was quenched by adding saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product through a short silica gel column using EtOAc/hexane (1:2) as the eluant gave the coupling product, 2'-TIPSO-3'-(4-fluorophenyl)-7-TES-10-Ac-docetaxel (**28**) (175 mg, 54% yield) as a white solid and unreacted **22**.

28: mp. 186.0-187.0 °C; ^1H NMR ($CDCl_3$) δ 0.61 (m, 6 H), 0.96 (m, 30 H), 1.23 (s, 3 H), 1.29 (brs, 12 H), 1.68 (br s, 4 H), 1.82-1.98 (m, 1 H), 2.02 (s, 3 H), 2.18 (s, 3 H), 2.25-2.41 (m, 1 H), 2.46 (br s, 4 H), 3.8 (d, J = 7.0 Hz, 1 H), 4.15 (d, J = 8.4 Hz, 1 H), 4.29 (d, J = 8.4 Hz, 1 H), 4.47 (dd, J = 10.3, 6.5 Hz, 1 H), 4.75 (br s, 1 H), 4.93 (d, J = 8.3 Hz, 1 H), 5.27-5.38 (m, 2 H), 5.69 (d, J = 7.0 Hz, 1 H), 6.25 (t, J = 8.9 Hz, 1 H), 6.45 (s, 1 H), 7.05 (t, J = 8.5 Hz, 2 H), 7.23-7.29 (m, 2 H), 7.45 (t, J = 7.3 Hz, 2 H), 7.56 (J = 7.3 Hz, 1 H), 8.09 (d, J = 7.3 Hz, 2 H).

Compound **28** (153 mg, 0.134 mmol) was dissolved in 6 mL of pyridine and 3 mL of CH_3CN at 0 °C and 1.5 mL of HF/pyridine was added. The mixture was heated to 61 °C for 2 h and quenched by adding 10 mL of 1 *N* hydrochloric acid. The aqueous layer was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude product by column chromatography on silica gel using EtOAc/hexane (2/1) as the eluant afforded 3'-(4-fluorophenyl)-10-acetyldocetaxel (**4**) (111 mg, 91% yield) as a white solid: mp 175-179 °C; $[\alpha]_D^{20}$ -62.96° (c .27, $CHCl_3$); IR ($CDCl_3$) 3425, 1757, 1661, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 1..27 (s, 3 H), 1.33 (s, 9 H), 1.68 (s, 3 H), 1.83 (s, 3 H), 1.80 (s, 3 H), 2.24 (s, 3 H), 2.38 (m, 2 H), 2.54 (m, 2 H), 3.50 (d, J = 5.1 Hz, 1 H), 3.81 (d, J = 6.9 Hz, 1 H), 4.17 and 4.31 (ABq, J = 8.2 Hz, 2 H), 4.41 (m, 1 H), 4.60 (bd, 1 H), 4.94 (d, J = 8.0 Hz, 1 H), 5.27 (bd, 1 H), 5.42 (d, J = 9.0 Hz, 1 H), 5.67 (d, J = 6.9 Hz, 1 H), 7.09 (t, 2 H), 7.37 (dd, 2 H), 7.49 (t, 2 H), 7.61 (t, 1 H), 8.10 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.0, 16.3, 22.3, 23.2, 24.0, 28.2, 29.6, 37.0, 44.6, 47.2, 56.9, 73.5, 73.7, 74.9, 78.0, 78.5, 78.7, 79.0, 80.4, 81.7, 82.6, 85.8, 116.9, 117.2, 129.9, 130.1, 130.5, 131.6, 134.5, 135.9, 143.5, 156.7, 161.8, 165.7, 168.4, 171.6, 172.7, 174.1, 205.0: Anal. Calcd for $C_{47}H_{56}NO_{16}F$: C, 62.04; H, 6.2; N, 1.54. Found: C, 62.14; H, 6.08; N, 1.58.

3'-Desphenyl-3'-(4-fluorophenyl)-3'-*N*-debenzoyl-3'-*N*-(4-fluorobenzoyl)paclitaxel (2): ***(Method A)*** To a solution of 7-TES-baccatin III (**22**) (73 mg, 0.10 mmol) and 1-(4-fluorobenzoyl)-4-(4-fluorophenyl)-β-lactam **16** (74 mg, 0.16 mmol) in 5 mL THF at -30 °C, was added 1*M* NaHMDS (0.175 mL, 0.175 mmol) in THF. After 1.7 h, the reaction was quenched with a saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc and the combined extracts were washed with a saturated aqueous NH_4Cl and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude coupling product was used directly in the subsequent deprotection step without further purification.

To a solution of the crude coupling product in 3 mL of pyridine/acetonitrile (1/1) at 0 °C, was added dropwise 1.2 mL of HF/pyridine (70/30). The reaction mixture was allowed to warm to room temperature and then heated to 65 °C and stirred for 2 h. The reaction was quenched with 2 *N* hydrochloric acid, and the reaction mixture was extracted with EtOAc, washed with 2 *N* hydrochloric acid and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (1:1) as the eluant afforded 3'-(4-fluorophenyl)-3'-*N*-(4-fluorobenzoyl)paclitaxel (**2**) (8 mg, 12% in two steps) as a white solid.

(Method B) A mixture of compound **28** (268 mg, 0.236 mmol), 40 mL of HCOOH (88%), and 10 mL of MeOH was stirred for 1 h, and the reaction mixture was neutralized with saturated aqueous Na_2CO_3, and then extracted with EtOAc. The extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel using EtOAc/hexane (2/1) as the eluant afforded 2'-TIPS-3'-(4-fluorophenyl)-3'-*N*-debenzoylpaclixal (**29**) (117 mg, 54% yield).

To a solution of **29** (117 mg, 0.126 mmol) and triethylamine (26 mg, 0.252 mol) in 15 mL of CH_2Cl_2, was added dropwise 4-fluorobenzoyl chloride (20 mg, 0.126 mmol) at 0 °C with stirring. The mixture was allowed to warm to room temperature with stirring and the reaction was quenched with a saturated aqueous $NaHCO_3$ after 1.5 h. The reaction mixture was extracted with EtOAc and the extracts were washed with a saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel using EtOAc/hexane (1/2 to 1/1 gradient) as the eluant afforded 2'-TIPS-3'-(4-fluorophenyl)-3'-*N*-(4-fluorobenzoyl)-paclitaxal (**30**) (119 mg, 90%) as a white solid.

To a solution of **30** (117 mg, 0.11 mmol) in 6 mL of pyridine/acetonitrile (1/1) was added, 1.5 mL of HF/pyridine (70/30) at 0 °C. The solution was warmed to 40 °C for 5 h. The reaction was quenched with 2 *N* hydrochloric acid and the reaction mixture was extracted with EtOAc. The extracts were washed with 2 *N* hydrochloric acid and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (2/1) as the eluant to afford 3'-(4-fluorophenyl)-3'-*N*-(4-fluorobenzoyl)paclitaxal (**2**) (66 mg, 66% yield) as a white solid.

2: mp. 171-174 °C; $[\alpha]_D^{20}$ -42.1° (c 0.19, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.21 (s, 3 H), 1.67 (s, 3 H), 1.78 (s, 3 H), 1.86-1.92 (m, 1 H), 2.21 (s, 3 H), 2.27-2.32 (m, 2 H), 2.35 (s, 3 H), 2.44-2.58 (m, 1 H), 3.78 (d, J = 6.9 Hz, 1 H), 4.17 (d, J = 8.4 Hz, 1 H), 4.29 (d, J = 8.4 Hz, 1 H), 4.37 (dd, J = 10.8, 6.7 Hz, 1 H), 4.74 (d, J = 2.2. Hz, 1 H), 4.91 (d, J = 8.2 Hz, 1 H), 5.65 (d, J = 7.0 Hz, 1 H), 5.74 (d, J = 7.2 Hz, 1 H), 6.18-6.25 (m, 2 H), 6.98-7.11 (m, 5 H), 7.42-7.52 (m, 4 H), 7.60 (t, J = 7.3 Hz, 1 H), 7.69-7.75 (m, 2 H), 8.11 (d, J = 7.3 Hz, 2 H); ^{19}F NMR (MeOH) δ -113.08, -107.30.

3'-Desphenyl-3'-(4-fluorophenyl)-14β-hydroxydocetaxel-1,14-carbonate (32): To a mixture of 7,10-di-troc-10-deacetyl-14-OH-baccatin III-1,14-carbonate (**31**) (163 mg, 0.174 mmol) and 1-*t*-Boc-β-lactam (**15**) (100 mg, .226 mmol) in 7 mL of THF was added 1*M* NaHMDS (0.226 mL) in THF at -40 °C. The mixture was stirred for 30 min and the reaction was quenched by adding saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid product was treated with Zn powder (680 mg) in 2 mL of 0.5*N* hydrochloric acid and 3 mL of THF at 0 °C for 1 h. The reaction mixture was filtered to remove Zn and Zn salt, and the filtrate was diluted with 50 mL of EtOAc. The organic layer was separated and washed with 5% aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using EtOAc/hexane (1/1) as the eluant to afford 3'-(4-fluorophenyl)-14β-hydroxydocetaxel-1,14-carbonate (**32**) (54 mg, 40% overall yield) as a white solid: mp 150-152 °C; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.26 (s, 3 H), 1.36 (s, 9 H), 1.40 (s, 3 H), 1.78 (s, 3 H), 1.88 (s, 3 H), 2.42 (bs, 1 H), 2.56 (m, 1 H), 3.79 (bd, J = 7.5 Hz, 1 H), 4.26 (dd, J = 8.4, 18.3 Hz, 2 H), 4.36 (bs, 2 H), 4.78 (d, J = 7.5 Hz, 1 H), 4.92 (bd, J = 8.5 Hz, 1 H), 5.21 (s, 1 H), 5.30 (m, 1 H), 5.66 (bd, J = 9.0 Hz, 1 H), 6.10 (d, J = 7.4 Hz, 1 H), 7.10 (t, 2 H), 7.4 (m, 3 H), 7.5

(t, 2 H), 7.63 (bt, 1 H), 8.02 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 9.7, 10.0, 22.0, 22.5, 25.6, 28.1, 29.7, 36.6, 41.6, 45.9, 55.4, 57.9, 69.3, 71.6, 74.0, 74.9, 76.1, 79.4, 80.6, 80.1, 84.0, 88.1, 115.6, 116.0, 127.8, 128.3, 128.4, 129.0, 134.2, 135.7, 136.5, 140.9, 151.9, 155.6, 160.4, 164.3, 167.3, 170.6, 171.9, 209.6; ^{19}F NMR ($CDCl_3$) δ -114.65. Anal. Calcd for $C_{44}H_{49}NO_{16}F$: C, 62.33; H, 5.83; N, 1.65. Found: C, 62.07; H, 5.96; N, 1.42.

2'-*O*-Triisopropylsilyl-3'-desphenyl-3'-(3,3,3-trifluoropropyl)-7,10-di-*O*-troc-docetaxel (33): A solution of 1-*t*-Boc-β-lactam **21** (300 mg, 0.68 mmol) and 7,10-di-troc-10-deacetylbaccatin III (**24**) (403 mg, 0.45 mmol) in 15 mL of THF was cooled to -78 °C and 1*M* NaHMDS (1.7 mL, 1.7 mmol) in THF was added dropwise. The mixture was stirred for 10 min at -78 °C and quenched by adding saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with ether and the extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude solid product was purified by flash chromatography on silica gel using EtOAc/hexane (1/4) as the eluant to afford **33** (483 mg, 81% yield) as a white solid: mp 140-141 °C; $[\alpha]_D^{20}$ -35.7° (c 1.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.12 (m, 21H), 1.18 (s, 3H), 1.26 (s, 3H), 1.33 (s, 9H), 1.85 (m, 5H), 2.01 (s, 3H), 2.06 (m, 1H), 2.25 (m, 2H), 2.36 (bs, 5H), 2.62 (m, 1H), 3.93 (d, J = 6.8 Hz, 1H), 4.12 (m, 1H), 4.19 (d, J = 8.3 Hz, 1H), 4.33 (d, J = 8.3 Hz, 1H), 4.46 (m, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.76 (d, J = 4.1 Hz, 2H), 4.91 (d, J = 11.8 Hz, 1H), 4.96 (bd, J = 9.5 Hz, 1H), 5.56 (dd, J = 7.0, 10.5 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.17 (bt, J = 8.5 Hz, 1H), 6.25 (s, 1H), 7.49 (m, 2H), 7.63 (t, J = 7.3 Hz, 1H), 8.09 (d, J = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.68, 12.63, 14.74, 17.98, 18.08, 21.12, 22.19, 25.77, 25.97, 29.66, 30.43 (q, $^2J_{C\text{-}F}$ = 28.9 Hz, $\underline{C}H_2CF_3$), 33.21, 35.32, 43.12, 46.80, 53.05, 56.11, 76.27, 76.36, 77.06, 77.36, 78.55, 79.16, 80.10, 80.76, 83.66, 94.17, 128.68, 129.02, 130.16, 131.47 (q, J = 276.7 Hz, $CH_2\underline{C}F_3$), 131.61, 133.72, 143.08, 153.23, 155.97, 166.79, 169.74, 171.61, 200.76. IR (KBr disk) 2942, 1760, 1722, 1713, 1493, 1451, 1381, 1246, 1147 cm^{-1}. Anal. Cald. for $C_{55}H_{74}O_{18}NSiF_3Cl_6$: C, 49.48; H, 5.59; N, 1.05. Found: C, 49.60; H, 5.76; N, 0.99.

3'-(3,3,3-Trifluoropropyl)docetaxel (5): The fully protected 3'-(3,3,3-trifluoropropyl)docetaxel derivative **33** (324 mg, 0.24 mmol) was dissolved in 5 mL of pyridine. The solution was cooled to 0 °C and HF/pyridine (5 mL) was added dropwise. The reaction was monitored by TLC till completion (about 8 h) and then quenched by the adding saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was extracted with ether. The extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude solid product was purified by flash chromatography on silica gel using EtOAc/hexane (1/2) as the eluant to afford 3'-(3,3,3-trifluoropropyl)-7,10-di-troc-docetaxel (226 mg, 80% yield) as a white solid: mp 143-144 °C; $[\alpha]_D^{20}$ -39.1° (c 0.68, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3H), 1.25 (s, 9H), 1.86 (s, 3H), 1.94 (m, 2H), 2.01 (s, 3H), 2.07 (m, 1H), 2.26 (m, 1H), 2.34 (m, 2H), 2.40 (s, 3H), 2.63 (m, 1H), 3.91 (d, J = 6.8 Hz, 1H), 4.13 (m, 1H), 4.19 (d, J = 8.5 Hz, 1H), 4.27 (bs, 1H), 4.34 (d, J = 8.5 Hz, 1H), 4.46 (bs, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.78 (s, 2H), 4.82 (bs, 1H), 4.89 (d, J = 11.8 Hz, 1H), 4.97 (bd, J = 8.7 Hz, 1H), 5.54 (dd, J = 7.1, 10.5 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.19 (bt, J = 8.9 Hz, 1H), 6.25 (s, 1H), 7.49 (m, 2H), 7.63 (t, J = 7.2 Hz, 1H), 8.09 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 10.68, 14.71, 20.92, 22.26, 24.87, 26.21, 28.09, 29.66, 30.49 (q, $^2J_{C\text{-}F}$ = 28.9 Hz, $\underline{C}H_2CF_3$), 33.24, 35.18, 43.12, 46.88, 51.87, 56.20, 72.44, 74.15, 76.30, 76.38, 77.08, 77.37, 78.54, 79.12, 80.29, 80.79, 83.61, 94.13, 126.69 (q, J = 276.7 Hz, $CH_2\underline{C}F_3$), 128.71, 128.92, 130.15, 133.79, 142.41, 153.15, 153.20, 155.55, 166.83, 170.25, 173.02, 200.67. IR (KBr disk) 3234, 2978, 1760, 1731, 1707, 1249 cm^{-1}. Anal. Cald. for $C_{46}H_{54}O_{18}NSiF_3Cl_6$: C, 46.88; H, 4.62; N, 1.19. Found: C, 46.88; H, 4.76; N, 1.21.

To a solution of the di-troc derivative (150 mg, 0.12 mmol), thus obtained, in 0.5 *N* hydrochloric acid – THF (1/1, 8 mL) was added Zn dust (450 mg) at 0 °C. The mixture was stirred for 30 min at 0 °C and then filtered to remove Zn and Zn salt. The filtrate was extracted with ether (10 mL) and the extract was dried over anhydrous $MgSO_4$ and purified by flash chromatography on silica gel using EtOAc/hexane (3/1) as the eluant to afford 3'-(3,3,3-trifluoropropyl)docetaxel (**5**) (64 mg, 60% yield) as a white powder: mp 171-172 °C; $[\alpha]_D^{20}$ -45.9° (c 0.19, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.22 (s, 3H), 1.32 (s, 9H), 1.75 (s, 3H), 1.87 (m, 1H), 1.91 (s, 3H), 1.99 (m, 2H), 2.18 (m, 2H), 2.32 (m, 2H), 2.37 (s, 3H), 2.55 (m, 1H), 3.90 (d, J = 6.9 Hz, 1H), 4.13 (m, 1H), 4.18 (d, J = 8.3 Hz, 1H), 4.26 (m, 2H), 4.32 (d, J = 8.3 Hz, 1H), 4.81 (d, J = 9.8 Hz, 1H), 4.95 (d, J = 8.2 Hz, 1H), 5.24 (s, 1H), 5.67 (d, J = 6.9 Hz, 1H), 6.19 (bt, J = 8.7 Hz, 1H), 7.49 (m, 2H), 7.62 (t, J = 7.3 Hz, 1H), 8.11 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.85, 14.46, 20.64, 22.31, 24.96, 26.35, 28.12, 28.29, 29.67, 30.56 (q, $^2J_{C\text{-}F}$ = 28.9 Hz, $\underline{C}H_2CF_3$), 35.64, 36.98, 43.11, 46.52, 51.84, 57.71, 71.99, 72.56, 72.64, 74.59, 74.87, 77.20, 78.78, 80.27, 81.17, 84.13, 127.14 (q, J = 259.1 Hz, $CH_2\underline{C}F_3$), 128.71, 129.18, 130.18, 133.68, 136.06, 138.39, 155.54, 167.03, 170.14, 173.05, 211.32. IR (KBr disk) 3436, 2978, 1760, 1731, 1702, 1513, 1448, 1366, 1249, 1143 cm^{-1}. Anal. Cald. for $C_{40}H_{52}O_{14}NF_3$: C, 58.04; H, 6.33; N, 1.69. Found: C, 57.97; H, 6.44; N, 1.46.

7-*O*-Triethylsilyl-10-*O*-acetyl-2'-*O*-triisopropylsilyl-3'-(3,3,3-trifluoropropyl)docetaxel (34): A solution of 7-TES-baccatin (**22**) (106 mg, 0.15 mmol) in 8 mL of THF was cooled to -45 °C, and 1*M* LiHMDS (0.17 mL, 0.17 mmol) in THF was added dropwise, and the solution was stirred for 3 min. 1-*t*-Boc-β-lactam **21** (100 mg, 0.23 mmol) was added and the reaction mixture was allowed to slowly warm to 0 °C over a period of 75 min. The reaction was quenched with saturated aqueous NH_4Cl (4 mL), and the reaction mixture was extracted with EtOAc (2 x 25 mL) and the extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent *in vacuo* gave the crude solid product, which was purified by flash chromatography on silica gel using EtOAc/hexane (1/6 to 1/3 gradient) as the eluant to afford fully protected 3'-(3,3,3-trifluoropropyl)-10-Ac-docetaxel derivative (**34**) (140 mg, 81% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 0.58 (m, 6H), 0.92 (t, J = 7.9 Hz, 9H), 1.12 (m, 21H), 1.17 (s, 3H), 1.22 (s, 3H), 1.31 (s, 9H), 1.69 (s, 3H), 1.79 (m, 2H), 1.87 (m, 1H), 2.01 (s, 3H), 2.17 (s, 3H), 2.23 (m, 2H), 2.30 (m, 2H), 2.34 (s, 3H), 2.52 (m, 1H), 3.82 (d, J = 7.0 Hz, 1H), 4.11

(m, 1H), 4.18 (d, J = 8.3 Hz, 1H), 4.31 (d, J = 8.3 Hz, 1H), 4.45 (m, 2H), 4.73 (d, J = 10.3 Hz, 1H), 4.93 (d, J = 8.2 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 6.09 (bt, J = 8.8 Hz, 1H), 6.46 (s, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 8.11 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 5.28, 6.68, 10.01, 12.63, 14.37, 17.99, 18.07, 20.84, 21.17, 22.36, 25.74, 26.27, 28.08, 30.50 (q, $^2J_{C-F}$ = 29.0 Hz, $\underline{C}H_2CF_3$), 35.31, 37.16, 43.25, 46.73, 53.01, 58.41, 71.75, 72.23, 74.48, 74.88, 75.03, 78.68, 80.01, 81.18, 84.19, 126.76 (q, J = 276.29 Hz, $CH_2\underline{C}F_3$), 128.61, 129.22, 130.19, 133.56, 140.54, 155.88, 166.98, 169.25, 169.61, 171.56, 201.78. Anal. Cald. for $C_{57}H_{88}O_{15}NSi_2F_3$: C, 60.03; H, 7.78; N, 1.23. Found: C, 60.16; H, 7.61; N, 1.22.

3'-(3,3,3-Trifluoropropyl)-10-*O*-acetyldocetaxel (6): A solution of the protected fluoro-docetaxel analog **34** (30 mg, 0.026 mmol) in 2 mL of acetonitrile/pyridine (1/1) was cooled to 0 °C, and HF/pyridine (70/30) was added dropwise (0.1 mL/10 mg of reactant). The mixture was stirred at 0 °C for 1 h and then at room temperature overnight. After the disappearance of **24** on TLC analysis, the reaction was quenched with saturated aqueous $CuSO_4$. The reaction mixture was extracted with EtOAc, and the extracts were washed with saturated aqueous $CuSO_4$ (2 x 10 mL) and water (2 x 10 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by purification of the crude product by flash chromatography on silica gel using EtOAc/hexane (2/1) as the eluant afforded 3'-(3,3,3-trifluoropropyl)-10-acetyldocetaxel (**6**) (18 mg, 80% yield) as a white solid: mp 175-177 °C; $[\alpha]_D^{20}$ -68.42° (c 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.24 (s, 3H), 1.31 (s, 9H), 1.68 (s, 3H), 1.86 (m, 1H), 1.88 (s, 3H), 1.94 (m, 2H), 2.20 (m, 2H), 2.24 (s, 3H), 2.35 (m, 2H), 2.37 (s, 3H), 2.56 (m, 1H), 3.80 (d, J = 6.9 Hz, 1H), 4.12 (m, 1H), 4.18 (d, J = 8.5 Hz, 1H), 4.25 (bs, 1H), 4.31 (d, J = 8.5 Hz, 1H), 4.41 (dd, J = 6.7, 10.8 Hz, 1H), 4.78 (d, J = 9.9 Hz, 1H), 4.99 (d, J = 8.3 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H), 6.20 (bt, J = 8.7 Hz, 1H), 6.30 (s, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.61 (t, J = 7.3 Hz, 1H), 8.10 (d, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.52, 14.89, 20.81, 21.82, 22.31, 24.92, 26.64, 28.06, 29.66, 30.47 (q, $^2J_{C-F}$ = 29.4 Hz, $\underline{C}H_2CF_3$), 35.39, 35.57, 43.18, 45.64, 51.79, 58.53, 72.13, 72.42, 72.60, 74.96, 75.55, 79.00, 80.24, 81.12, 84.35, 128.67, 130.17, 131.07 (q, J = 275.94 Hz, $CH_2\underline{C}F_3$), 133.68, 142.14, 155.48, 167.03, 170.04, 171.22, 173.14, 203.61; ^{19}F NMR ($CDCl_3$) δ -66.82 (t, J = 11.3 Hz); IR ($CHCl_3$) 3436, 3013, 2978, 1742, 1719, 1525, 1454, 1372, 1249, 1213, 1149, 1067 cm^{-1}. Anal. Cald. for $C_{42}H_{54}O_{15}NF_3$: C, 57.99; H, 6.26; N, 1.61. Found: C, 58.08; H, 6.09; N, 1.52.

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