Synthesis and Structure-Activity Relationships of Novel 2′,2′-Difluoro Analogues of Docetaxel

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To investigate the role of the 2′-hydroxy group at the C-13 side chain of docetaxel in the antitumor activity, we prepared several 2′,2′-difluoro derivatives of docetaxel and evaluated their cytotoxicity against mouse leukemia and human tumor cell lines and their microtubule disassembly-inhibitory activity. These analogues were prepared by esterification of protected 10-deacetylbaccatin III (21) with appropriate α,α-difluorinated carboxylic acids (Charts 1 and 2). Among these 2′,2′-difluorodocetaxel derivatives, 2′,2′-difluorodocetaxel (23b) was approximately 3—10 times as active as 2′-fluorodocetaxel (29a) in terms of cytotoxicity. In addition, the 3′-(2-furyl) (23h) and 3′-(2-pyrrolyl) (23p) analogues showed activity comparable or superior to that of docetaxel (2).

Key words docetaxel; paclitaxel; 2′,2′-difluoro analogue; structure-activity relationship; cytotoxicity; microtubule disassembly-inhibitory activity

Paclitaxel (**1**, Taxol®),[1] a diterpene natural product isolated by Wani *et al.* from *Taxus brevifolia*, has shown exceptional efficacy in cancer chemotherapy and has been approved by the Food and Drug Administration (FDA) for the treatment of advanced ovarian and breast cancer in December 1992 and April 1994, respectively. In addition, docetaxel (**2**, Taxotere®),[2] a synthetic paclitaxel analogue, was approved by the FDA for the treatment of breast cancer in May 1996.[3] Both taxoids promote the assembly of microtubules and inhibit the disassembly process of microtubules to tubulin, in contrast to the vinblastine and colchicine type compounds, which prevent microtubule assembly.[4]

However, recent reports[5] on clinical trials of paclitaxel and docetaxel have revealed that both drugs are inactive against colon cancer and induce multidrug resistance (MDR). Therefore, it is very important to develop new anticancer drugs which have different activity spectra from these two drugs. Recent studies on the structure-activity relationships (SARs) of paclitaxel and docetaxel have shown that the 2′-hydroxy group at the C_{13} side chain plays an important role in the antitumor activity.[6] To investigate further this relatively unexplored area, we designed 2′,2′-difluoro derivatives (**3**) (Fig. 1).

Several groups have reported analogues of paclitaxel (**1**) or docetaxel (**2**) in which the phenyl group at the 3′-position has been modified or replaced.[7] We prepared several kinds of 2′,2′-difluoro analogues with a *para*-modified 3′-phenyl or 3′-heteroaromatic group and evaluated their cytotoxicity against mouse leukemia and human tumor cell lines, and their microtubule disassembly-inhibitory activity. In addition, we prepared a 2′-fluorodocetaxel derivative (**29a**)[8] in order to confirm the effect of replacement of the 2′-hydroxy group with the 2′,2′-difluoro moiety.

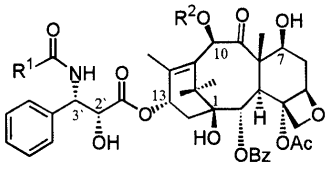
Chemistry

The compounds in this study (Table 1) were synthesized by esterification of protected 10-deacetylbaccatin III (**21**)[9] with the appropriate α,α-difluorinated carboxylic acids (Charts 1, 2).

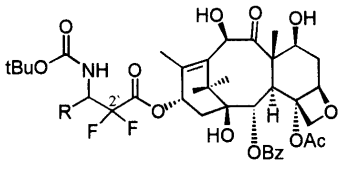
The synthetic routes to the racemic 3-substituted derivatives of 3-(*tert*-butoxycarbonylamino)-2,2-difluoropropionic acid are illustrated in Chart 1.

The 3-phenyl derivative (**8a**) was prepared from compound **5a**, derived by Reformatsky reaction[10] of ethyl bromodifluoroacetate with benzaldehyde (**4a**). The β-hydroxy ester (**5a**) was converted to the β-azide ester (**6a**) by using a standard method. Hydrogenation of **6a** and successive reaction with di-*tert*-butyl dicarbonate gave the β-(Boc–NH–) ester (**7a**). Hydrolysis of **7a** with aqueous lithium hydroxide gave the desired carboxylic acid (**8a**). By using this procedure, compounds **8b** and **8c** were synthesized from **4b** and **4c**, respectively.

The 3-(2-furyl)-substituted derivative (**13a**) was prepared from 3,3-difluoro-2-azetidinone (**10a**), derived by Reformatsky reaction[11] of ethyl bromodifluoroacetate with the *N*-(*p*-methoxyphenyl)imine of 2-furaldehyde (**9a**). Hydrolysis of the β-lactam (**10a**) with aqueous NaOH and successive esterification gave the β-(*p*-methoxyphenylamino) ester (**11a**). Oxidative removal of the *p*-methoxyphenyl (PMP) group with ceric ammonium nitrate (CAN)[12] and successive reaction with di-*tert*-butyl di-



Paclitaxel (**1**: R^1 = Ph, R^2 = Ac)
Docetaxel (**2**: R^1 = tBuO, R^2 = H)



3: R = aryl, heterocycle, or cyclohexyl group

Fig. 1

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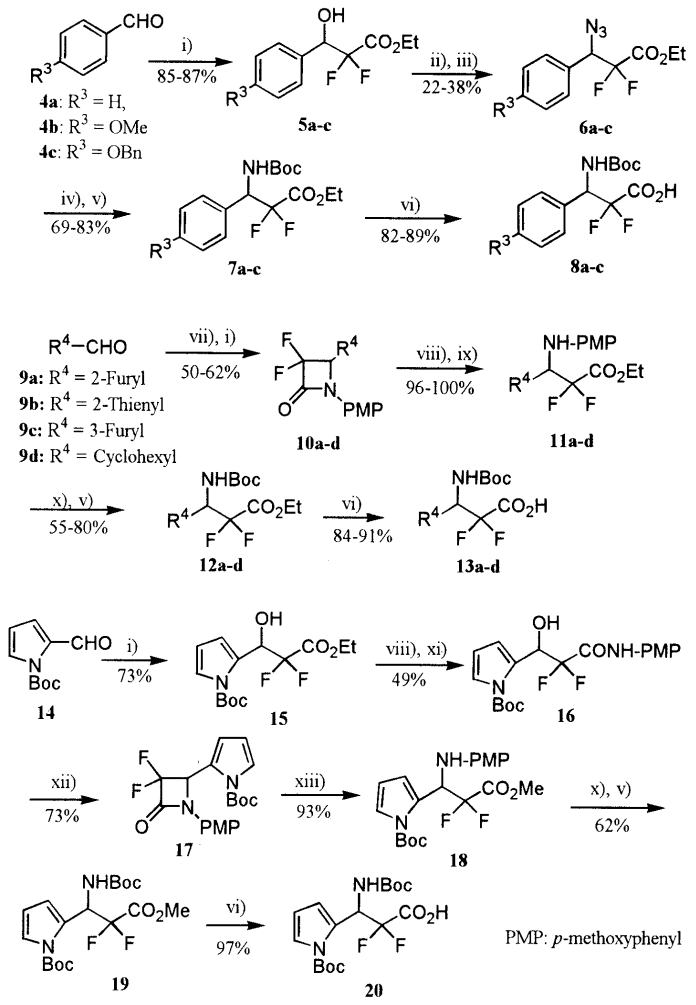
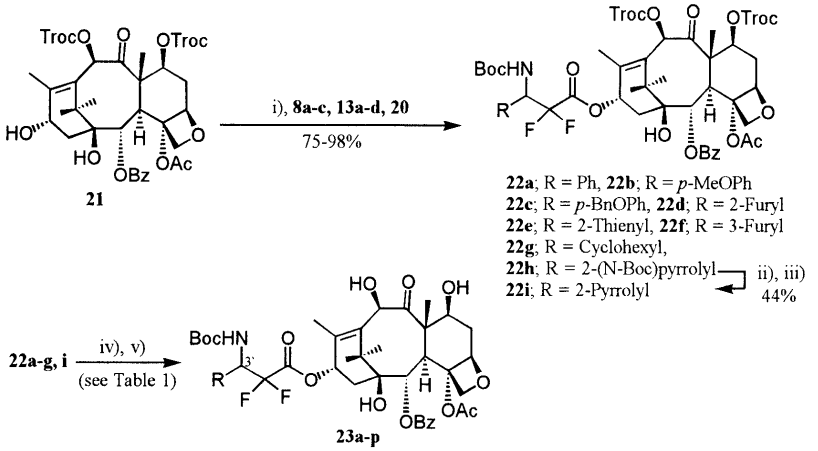


i) Zn, $BrCF_2CO_2Et$; ii) MsCl, Et_3N; iii) NaN_3; iv) H_2, Pd/C or Lindlar catalyst; v) $(Boc)_2O$; vi) LiOH; vii) *p*-anisidine; viii) NaOH aq.; ix) $SOCl_2$, EtOH; x) CAN; xi) *p*-anisidine, BOP-Cl; xii) DEAD, Ph_3P; xiii) NaOMe, MeOH

Chart 1. Preparation of α,α-Difluoronated Carboxylic Acids



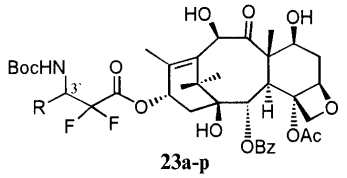
i) DPC, DMAP, toluene; ii) HCO_2H; iii) $(Boc)_2O$; iv) Zn, AcOH, MeOH ; for the preparation of **23e,f**: H_2, Pd/C, v) HPLC separation

Chart 2. Synthesis of 2′,2′-Difluoro Analogues of Docetaxel

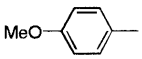
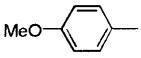
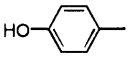
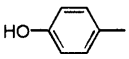
carbonate gave the β-(Boc–NH–) ester (**12a**). Compound **12a** was hydrolyzed to give the carboxylic acid (**13a**) as described for the preparation of **8a**. Compounds **13b—d** were synthesized from **9b—d**, respectively, by the same procedure as that utilized for the preparation of **13a**.

The 3-(*N*-Boc-pyrrole-2-yl) derivative (**20**) was synthesized by a method based on intramolecular Mitsunobu inversion reaction. The β-hydroxy ester (**15**) was prepared from the aldehyde (**14**) by the same method as described for the preparation of **5a**. Condensation of the

Table 1. Physical Properties of 2′,2′-Difluoro Analogues of Docetaxel



23a-p

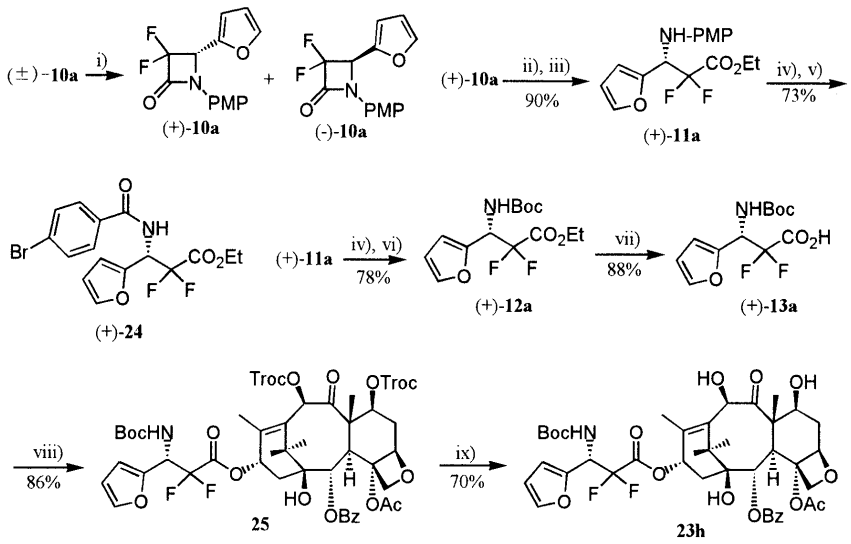
Compound	R	Config. at C-3′[c]	mp (°C)	$[\alpha]_D$ at 25°C[a]	MS *m/z* (MH^+)	Yield (%)[b]	Formula	Analysis (%) Calcd (Found) C	H	N
23a		ND	187—189	−71.2	828	31	$C_{43}H_{51}F_2NO_{13}$ ·1/2H_2O	61.71 (61.64	6.26 6.28	1.67 1.62)
23b		ND	183—186	−46.4	828	29	$C_{43}H_{51}F_2NO_{13}$	62.38 (62.25	6.21 6.38	1.69 1.57)
23c		ND	189—192	−56.4	858	41	$C_{44}H_{53}F_2NO_{14}$ ·H_2O	60.33 (60.57	6.33 6.20	1.60 1.54)
23d		ND	190—193	−30.6	858	38	$C_{44}H_{53}F_2NO_{14}$ ·1/2H_2O	60.96 (60.95	6.28 6.16	1.61 1.63)
23e		ND	193—198	−37.2	844	37	$C_{43}H_{51}F_2NO_{14}$ ·H_2O	59.92 (60.10	6.20 6.07	1.62 1.47)
23f		ND	190—195	−45.2	844	37	$C_{43}H_{51}F_2NO_{14}$ ·H_2O	59.92 (60.93	6.20 6.34	1.62 1.49)
23g		*R*	190—192	−36.2	818	36	$C_{41}H_{49}F_2NO_{14}$ ·1/2H_2O	59.55 (59.37	6.09 6.11	1.69 1.57)
23h		*S*	188—191	−22.7	818	34	$C_{41}H_{49}F_2NO_{14}$ ·H_2O	58.92 (58.70	6.15 6.04	1.68 1.82)
23i		ND	189—193	−76.9	834	44	$C_{41}H_{49}F_2NO_{13}S$ ·1/2H_2O	58.42 (58.40	5.98 5.99	1.66 1.56)
23j		ND	191—195	−38.1	834	37	$C_{41}H_{49}F_2NO_{13}S$ ·1/2H_2O	58.42 (58.37	5.98 6.01	1.66 1.84)
23k		ND	183—186	−54.4	818	40	$C_{41}H_{49}F_2NO_{14}$ ·1/2H_2O	59.55 (59.44	6.09 6.08	1.69 1.55)
23l		ND	185—190	−38.2	818	37	$C_{41}H_{49}F_2NO_{14}$ ·1/2H_2O	59.55 (59.39	6.09 6.13	1.69 1.53)
23m		ND	184—188	−28.6	834	36	$C_{43}H_{57}F_2NO_{13}$ ·1/2H_2O	61.27 (61.29	6.93 6.90	1.66 1.46)
23n		ND	187—192	−49.5	834	41	$C_{43}H_{57}F_2NO_{13}$ ·1/2H_2O	61.27 (61.50	6.93 6.72	1.66 1.66)
23o		ND	189—193	−61.4	817	25	$C_{41}H_{50}F_2O_{13}$ ·1/2H_2O	59.62 (59.85	6.22 6.30	3.39 3.37)
23p		ND	189—193	−21.7	817	39	$C_{41}H_{50}F_2N_2O_{13}$ ·1/2H_2O	59.62 (59.39	6.22 6.35	3.39 3.19)

a) Degrees. Chloroform was used as the solvent. *b*) Yields are those obtained from the deprotection step to the final product, including HPLC separation. *c*) ND: Not determined.

carboxylic acid derived from **15** with *p*-anisidine gave the amide (**16**). Intramolecular cyclization of **16** in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) (Mitsunobu reaction) afforded the β-lactam (**17**).[13] Compound **17** was treated with sodium methoxide to give the methyl ester (**18**). Conversion of **18** to the carboxylic acid (**20**) was carried out by the procedure utilized for the preparation of **13a** from **11a**.

The synthetic routes to the novel 2′,2′-difluoro derivatives of docetaxel obtained in this study (Table 1) are illustrated in Chart 2.

Protected compounds (**22a—h**) were prepared by esterification of the appropriate racemic carboxylic acid (Chart 1) with **21** mediated by dipyridyl carbonate[14] (DPC) according to Greene *et al.*[15] Hydrolysis of the 3′-(*N*-Boc-pyrrole-2-yl) derivative (**22h**) with formic acid



i) Chiral HPLC column; ii) NaOH aq.; iii) $SOCl_2$, EtOH; iv) CAN; v) *p*-Br-BzCl, Et_3N; vi) $(Boc)_2O$; vii) LiOH; viii) **21**, DPC, DMAP, toluene; ix) Zn, AcOH, MeOH

Chart 3. Determination of the Absolute Configuration of **23h**

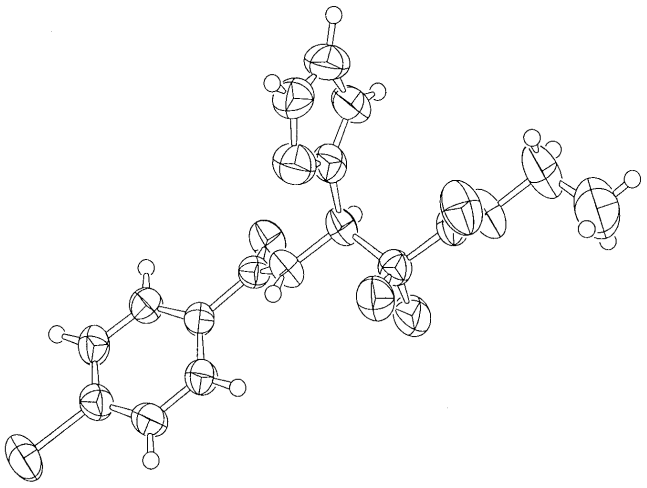


Fig. 2. Crystal Structure of (+)-**24**

and successive reaction with di-*tert*-butyl dicarbonate gave the 3′-(2-pyrrolyl) derivative (**22i**). Deprotection[16] of the coupling product (**22a**) with activated Zn and succesive separation by preparative HPLC provided **23a** and **23b**. In a similar manner, **23c**, **d** and **23g**—**p** were prepared from compounds **22b**, **22d**—**g**, **22i**. 3′-(*p*-Hydroxyphenyl) analogues (**23e**, **23f**) were obtained by removal of the benzyl group at C-3′ and the Troc groups at C-7 and C-10 on compound **22c** followed by HPLC.

The configuration at C-3′ of **23g** and **23h** was determined as follows (Chart 3):

Racemic **10a** was separated on a chiral HPLC column[17] to give (+)-**10a** and (−)-**10a**, then (+)-**10a** was converted to (+)-**11a** as described for the preparation of the racemate (**11a**). Removal of the PMP group and successive reaction with *p*-bromobenzoyl chloride gave (+)-**24**. The absolute configuration of (+)-**24** was determined to be S by X-ray analysis, as shown in Fig. 2. Next, (+)-**13a** was synthesized from (+)-**11a** by the same procedure as that utilized for the preparation of the racemate (**13a**). Esterification of (+)-**13a** with **21** mediated by DPC, followed by deprotection with Zn gave (3′*S*)-**23h** as a single product. Accordingly, we determined that the configuration at C-3′ of **23h** is the same as in paclitaxel (**1**) and docetaxel (**2**).

The synthetic routes to the 2′-fluorodocetaxel derivatives are illustrated in Chart 4. The racemic *cis* 3-fluoroazetidinone (**26**)[18] was converted to the *threo* carboxylic acid (**28**) by the same method as described for the preparation of racemate (**13a**). Esterification of **28** with **21** mediated by DPC, followed by deprotection of the coupling product with activated Zn provided, after preparative HPLC separation, (2′*R*,3′*S*)-**29a** (natural configuration) and (2′*S*,3′*R*)-**29b**.

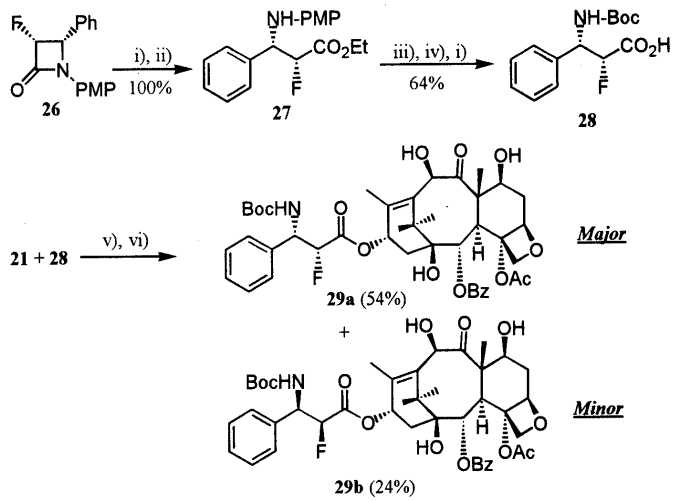
The absolute stereochemistry of the major and minor diastereomers was confirmed by nuclear Overhauser effect (NOE) experiments according to a known method.[19]

Biological Activity and Discussion

Biological activities of the novel 2′,2′-difluoro analogues of docetaxel (**23a**—**p**) were evaluated in two assay systems, *i.e.*, *in vitro* cytotoxicity against five cell lines (P388, PC-6, PC-12, SBC-3, SBC-3/ADM) and microtubule disassembly-inhibitory activity.

In order to obtain more meaningful relative activities, paclitaxel (**1**), docetaxel (**2**), and 2′-fluorodocetaxel (**29a**) were tested at the same time. The results are presented in Table 2.

The configuration at C-3′ of 2′,2′-difluoro analogues appreciably influenced the cytotoxicity. For example, the 3′-phenyl analogue (**23a**) was inactive. On the other hand, the stereoisomer (**23b**) was about 4—16 times less active than **2** against P388, PC-6, and SBC-3, but retained the same activity as **2** against PC-12 and exhibited approximately 2 times greater activity than **2** against SBC-3/ADM. The influence of the configuration at C-3′ in all the other 2′,2′-difluoro analogues was similar. In view of the antitumor activity of **23h** with *S* configuration, it is presumed that the configuration at C-3′ of compounds **23b**, **23d**, **23e**, **23j**, **23l**, and **23p**, which exhibited higher activity than the other stereoisomers, is the same as in



i) LiOH aq.; ii) $SOCl_2$, EtOH; iii) CAN; iv) $(Boc)_2O$; v) DPC, DMAP, toluene; vi) Zn, AcOH, MeOH then HPLC separation

Chart 4. Synthesis of 2′-Fluoro Analogue of Docetaxel (**29a**)

Table 2. Cytotoxicity and Microtubule Disassembly-Inhibitory Activity of 2′,2′-Difluoro Analogues

Compound	Cytotoxicity GI_{50} (ng/ml)[a]					Tubulin[b] IC_{50}/IC_{50} (**1**)
	P388	PC-6	PC-12	SBC-3	SBC-3/ADM	
Paclitaxel (**1**)	25.3	4.64	172	2.14	789	1
Decetaxel (**2**)	5.30	1.72	49.7	0.494	280	0.44
29a[c]	74.4	41.3	542	67.8	>1000	3.6
23a	>1000	>1000	>1000	>1000	>1000	ND
23b	21.0	18.0	58.8	8.33	161	1.8
23c	>1000	>1000	>1000	>1000	>1000	ND
23d	25.1	15.8	92.9	9.55	254	1.9
23e	17.2	4.10	83.6	2.03	92.9	0.58
23f	365	107	>1000	60.2	>1000	ND
23g	288	140	345	86.4	>1000	6.7
23h	5.21	1.43	9.28	0.825	53.3	0.57
23i	>1000	>1000	>1000	774	>1000	ND
23j	6.58	3.90	15.5	2.24	76.0	1.7
23k	>1000	>1000	>1000	712	>1000	ND
23l	10.4	4.10	24.8	2.12	59.2	0.86
22m	>1000	>1000	>1000	>1000	>1000	ND
23n	>1000	>1000	>1000	>1000	>1000	ND
23o	>1000	344	>1000	166	>1000	ND
23p	9.53	1.10	40.0	0.264	197	1.4

a) Concentration that inhibited the growth of cells by 50% on 72 h continuous exposure for five cell lines [mouse leukemia (P388), human lung cancer cell lines (PC-6, PC-12, SBC-3), and an adriamycin-resistant cancer cell line (SBC-3/ADM)]. *b*) IC_{50} represents the concentration of an agent leading to 50% inhibition of the rate of microtubule disassembly. IC_{50} (**1**) is the IC_{50} value of paclitaxel [2.6 μM (mean)] in the same assay. *c*) (2′*S*,3′*R*)-**29b** was completely inactive.

paclitaxel (**1**) and docetaxel (**2**). On the other hand, replacement of the 3′-phenyl group by saturated cyclohexyl moieties (**23m**, **23n**) resulted in a significant decrease of activities. Consequently, the configuration of **23m** and **23n** requires confirmation.

2′,2′-Difluorodocetaxel (**23b**) was twice as active as 2′-fluorodocetaxel (**29a**) in microtubule disassembly-inhibitory activity and showed about 3—9 times greater cytotoxicity than **29a**.

The *p*-methoxy (**23d**) and *p*-hydroxyphenyl (**23e**) analogues exhibited comparable or superior activity to **2** against SBC-3/ADM, but were less active against the other cells. The microtubule disassembly-inhibitory activity of **23e** was of the same order as that of docetaxel (**2**), while **23d** was less active than paclitaxel (**1**).

The 3′-(2-furyl) (**23h**), 3′-(2-thienyl) (**23j**), and 3′-(3-furyl) (**23l**) analogues were approximately 2—5 times more active than **2** against PC-12 and SBC-3/ADM. The 3′-(2-pyrrolyl) analogue (**23p**) was approximately as active as **2**, except against P388. Overall, the 3′-(2-furyl) analogue (**23h**) showed the most potent cytotoxicity and microtubule disassembly-inhibitory activity among these 2′,2′-difluoro docetaxel derivatives.

Kant *et al.* reported that the 2′-hydroxy group of paclitaxel (**1**) may be necessary to achieve a favorable conformation or may function as a hydrogen bond donor at the receptor site in tubulin.[20] However, it is apparent from our present study that the 2′-hydroxy group is not essential for cytotoxicity. In conclusion, we have found that introduction of a difluoro group at the 2′-position of docetaxel increases the cytotoxicity, especially against a MDR cancer cell line (SBC-3/ADM).

Further SAR studies on new docetaxel analogues bearing a 2′,2′-difluoro moiety at the C-2′ position are under way in our laboratories.

Experimental

All melting points were found using a Yanaco MP-S3 or MP-500D apparatus and are uncorrected. IR spectra were obtained on a Hitachi 270-300 IR spectrophotometer. Mass spectra were recorded on a JEOL JMS-HX-100, AX505W, or JMS-D300 spectrometer. ^{1}H-NMR spectra were taken at 400 MHz with a JEOL JNM-EX400 spectrometer; all values are reported in ppm (δ) downfield from $(CH_3)_4Si$. Elemental analyses were obtained on a Heraeus CHN-O-Rapid or a Perkin-Elmer 2400CHN instrument. Optical rotations were measured with a Horiba SEPA-200 polarimeter. Merck Silica gel (230—400 mesh) was used for column chromatography. Preparative thin-layer chromatography (preparative TLC) was performed by using silica gel (150A 1.0 mm thickness; PLK5F Whatman). Preparative HPLC was performed on a Hitachi L-6000 system liquid chromatograph equipped with an ultraviolet detector and a Capcell Pak C_{18} column (20 mm × 25 cm, 5 μm).

Ethyl 2,2-Difluoro-3-hydroxy-3-phenylpropionate (5a)[21] Zinc dust (1.41 g, 21.6 mmol) was suspended in tetrahydrofuran (THF) (36 ml) and the suspension was heated to reflux. Ethyl bromodifluoroacetate (4.38 g, 21.6 mmol) was then added to the refluxing suspension. Within 1 min, benzaldehyde (**4a**) (1.91 g, 18.0 mmol) was added, and refluxing was continued for 15 min. The reaction mixture was cooled to room temperature and then poured into a mixture of AcOEt, 1 M aqueous sodium hydrogen sulfate, and saturated aqueous sodium bicarbonate. The whole was stirred for 15 min, then the layers were separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (20% AcOEt–*n*-hexane) to give **5a** (3.58 g, 86%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3H, J=7 Hz), 2.73 (br, 1H), 4.30 (q, 2H, J=7 Hz), 5.16 (dd, 1H, J=15, 8 Hz), 7.38—7.45 (m, 5H).

Ethyl 2,2-Difluoro-3-hydroxy-3-(*p*-methoxyphenyl)propionate (**5b**): Following the procedure described for **5a**, the aldehyde **4b** was converted to **5b** (85%) as a colorless oil. Exact MS *m/z*: Calcd for $C_{12}H_{14}F_2O_4$ (M^+): 260.0860. Found: 260.0853. IR (neat): 3482, 1759, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (t, 3H, J=7 Hz), 2.65 (d, 1H, J=5 Hz), 3.81 (s, 3H), 4.30 (q, 2H, J=7 Hz), 5.08—5.15 (m, 1H), 6.91 (d, 2H, J=9 Hz), 7.36 (d, 2H, J=9 Hz).

Ethyl 3-(*p*-Benzyloxyphenyl)-2,2-difluoro-3-hydroxypropionate (**5c**): Following the procedure described for **5a**, the aldehyde **4c** was converted to **5c** (87%) as a colorless crystalline solid. mp 60—62 °C. MS (FD) *m/z*: 336 (M^+). *Anal.* Calcd for $C_{18}H_{18}F_2O_4$: C, 64.28; H, 5.39; F, 11.30. Found: C, 64.08; H, 5.30; F, 11.24. IR (KBr): 3556, 1760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 3H, J=7 Hz), 2.57 (d, 1H, J=5 Hz), 4.30 (q, 2H, J=7 Hz), 5.07 (s, 2H), 5.09—5.15 (m, 1H), 6.97 (m, 2H), 7.31—7.44 (m, 7H).

Ethyl 3-Azido-2,2-difluoro-3-phenylpropionate (6a) Mesyl chloride (839 mg, 7.32 mmol) was added dropwise to a stirred solution of **5a** (1.30 g, 5.65 mmol) and triethylamine (1.02 ml, 7.32 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The reaction mixture was stirred for 306 min, then washed with 10% HCl, water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10% AcOEt–*n*-hexane) to give the mesylate as a colorless oil (1.70 g, 97%). A solution of the above mesylate (1.70 g, 5.51 mmol) and *n*-Bu_4NBr (20 mg) in *N*,*N*-dimethylformamide (DMF) (8 ml) was treated with NaN_3 (735 mg, 11.3 mmol) at room temperature, and the mixture was heated at 65 °C for 40 h. It was poured into ice–water. The aqueous solution was extracted with AcOEt, and the organic layer was washed with water, dried over anhydrous $MgSO_4$ and removed under reduced pressure. The residue was purified by silica gel column chromatography (10% AcOEt–*n*-hexane) to give **6a** (559 mg, 39%) as a colorless oil. MS (FD) *m/z*: 255 (M^+). IR (neat): 2117, 1776, 1759 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3H, J=7 Hz), 4.30 (q, 2H, J=7 Hz), 5.04—5.10 (m, 1H), 7.37—7.45 (m, 5H).

Ethyl 3-Azido-2,2-difluoro-3-(*p*-methoxyphenyl)propionate (**6b**): Following the procedure described for **6a**, compound **5b** was converted to **6b** (22%) as a colorless oil. MS (FD) *m/z*: 285 (M^+). IR (neat): 2115, 1774, 1759 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 3H, J=7 Hz), 3.82 (s, 3H), 4.30 (q, 2H, J=7 Hz), 4.99—5.05 (m, 1H), 6.93 (d, 2H, J=9 Hz), 7.34 (d, 2H, J=9 Hz).

Ethyl 3-Azido-3-(*p*-benzyloxyphenyl)-2,2-difluoropropionate (**6c**): Following the procedure described for **5a**, compound **5c** was converted to **6c** (22%) as a colorless crystalline solid. mp 42—43 °C. MS (FD) *m/z*: 361 (M^+). *Anal.* Calcd for $C_{18}H_{17}F_2N_3O_3$: C, 59.83; H, 4.74; F, 10.51; N, 11.62. Found: C, 59.61; H, 4.85; F, 10.38; N, 11.43. IR (KBr): 2120, 1776, 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3H, J=7 Hz), 4.30 (q, 2H, J=7 Hz), 5.01 (dd, 2H, J=15, 10 Hz), 5.08 (s, 2H), 6.99—7.03 (m, 2H), 7.32—7.44 (m, 7H).

Ethyl 3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-phenylpropionate (7a) A mixture of **6a** (559 mg, 2.19 mmol) and 10% palladium on carbon (100 mg), and AcOEt (10 ml) was shaken in a hydrogen atmosphere at room temperature for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was taken up in THF (10 ml), then $NaHCO_3$ (264 mg, 3.14 mmol) and di-*tert*-butyldicarbonate (691 mg, 3.17 mmol) were added at room temperature. The reaction mixture was stirred at 60 °C for 17 h, diluted with AcOEt, and washed with water, 10% HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$ and removed under reduced pressure. The residue was purified by silica gel column chromatography (10% AcOEt–*n*-hexane) to give **7a** (475 mg, 70%) as a colorless solid. mp 75—76 °C. MS (FD) *m/z*: 329 (M^+). *Anal.* Calcd for $C_{16}H_{21}F_2NO_4$: C, 58.35; H, 6.43; F, 11.53; N, 4.25. Found: C, 58.14; H, 6.37; F, 11.42; N, 4.21. IR (KBr): 3369, 2968, 1761, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, 3H, J=7 Hz), 1.42 (s, 9H), 4.21—4.30 (m, 2H), 5.36—5.44 (m, 2H), 7.35—7.40 (m, 5H).

Ethyl 3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(*p*-methoxyphenyl)propio-nate (**7b**): Following the procedure described for **7a**, compound **6b** was converted to **7b** (83%) as a crystalline solid. mp 107—109 °C. MS (FD) *m/z*: 359 (M^+). *Anal.* Calcd for $C_{17}H_{23}F_2NO5 \cdot 1/10H_2O$: C, 56.53; H, 6.47; F, 10.52; N, 3.88. Found: C, 56.42; H, 6.54; F, 10.28; N, 3.74. IR (KBr): 3376, 2988, 1766, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, 3H, J=7 Hz), 1.42 (s, 9H), 3.80 (s, 3H), 4.21—4.30 (m, 2H), 5.31—5.35 (m, 2H), 6.89 (d, 2H, J=9 Hz), 7.26 (d, 2H, J=9 Hz).

Ethyl 3-(*p*-Benzyloxyphenyl)-3-(*tert*-butoxycarbonylamino)-2,2-difluoropropio-nate (**7c**): A mixture of **6c** (500 mg, 1.38 mmol), Lindlar catalyst (Aldrich, 250 mg), and EtOH (25 ml) was shaken in a hydrogen atmosphere at room temperature for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Following the procedure described for **7a**, the above residue was converted to **7c** (83%) as a colorless solid. mp 76—77 °C. MS (FD) *m/z*: 435 (M^+). *Anal.* Calcd for $C_{23}H_{27}F_2NO_5$: C, 63.43; H, 6.25; F, 8.72; N, 3.22. Found: C, 63.09; H, 6.24; F, 8.61; N, 3.17. IR (KBr): 3353, 2981, 1766, 1699 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 3H, J=7 Hz), 1.42 (s, 9H), 4.19—4.30 (m, 2H), 5.05 (s, 2H), 5.31—5.35 (m, 2H), 6.95—6.97 (m, 2H), 7.27—7.43 (m, 7H).

3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-phenylpropionic Acid (8a) Compound **7a** (450 mg, 1.42 mmol) in EtOH (4 ml) and H_2O (2 ml) was stirred with lithium hydroxide (102 mg, 4.26 mmol) at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, then the residue was taken up in water. The solution was acidified with 1 N HCl at 0 °C and extracted with $CHCl_3$. The organic layer was dried and concentrated to dryness to yield **8a** (337 mg, 82%) as a colorless solid: mp 75—79 °C. MS (FAB) *m/z*: 302 (MH^+). *Anal.* Calcd for $C_{14}H_{17}F_2NO_4 \cdot 1/5H_2O$: C, 55.15; H, 5.75; F, 12.46; N, 4.59. Found: C, 55.03; H, 5.69; F, 12.41; N, 4.79. IR (KBr): 2981, 1753, 1685 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.37 (s, 9H), 5.22—5.32 (m, 1H), 7.32—7.51 (m, 5H), 8.09 (d, 1H, J=10 Hz).

3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(*p*-methoxyphenyl)propionic Acid (**8b**): Following the procedure described for **8a**, compound **7b** was converted to **8b** (88%) as a crystalline solid. mp 114—115 °C. MS (FD) *m/z* 331 (M^+). *Anal.* Calcd for $C_{15}H_{19}F_2NO_5 \cdot 1/6H_2O$: C, 53.89; H, 5.82; F, 11.36; N, 4.19. Found: C, 54.09; H, 5.52; F, 11.07; N, 4.23. IR (KBr): 3352, 2988, 1754, 1644, 1616 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.37 (s, 9H), 3.75 (s, 3H), 5.16—5.27 (m, 1H), 6.90 (d, 2H, J=9 Hz), 7.36 (d, 2H, J=9 Hz), 7.99 (d, 1H, J=10 Hz).

3-(*p*-Benzyloxyphenyl)-3-(*tert*-butoxycarbonylamino)-2,2-difluoropropionic Acid (**8c**): Following the procedure described for **8a**, compound **7c** was converted to **8c** (89%) as a colorless oil. MS (FD) *m/z*: 407 (M^+). *Anal.* Calcd for $C_{21}H_{23}F_2NO_5$: C, 61.91; H, 5.69; F, 9.33; N, 3.44. Found: C, 61.82; H, 5.79; F, 9.08; N, 3.31. IR (neat): 3033, 1752, 1643, 1612 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (s, 9H), 5.08 (s, 2H), 5.16—5.26 (m, 1H), 6.96—6.98 (m, 2H), 7.31—7.44 (m, 7H), 7.98 (d, 1H, J=10 Hz).

3,3-Difluoro-4-(2-furyl)-1-(*p*-methoxyphenyl)-2-azetidinone (10a) Powdered Na_2SO_4 (5.0 g) was added to a stirred solution of *p*-anisidine (2.56 g, 20.8 mmol) and 2-furaldehyde (**9a**) (2.33 g, 20.8 mmol) in benzene (20 ml) at room temperature. After 30 min, the reaction mixture was filtered through a sintered glass disk, then the filtrate was concentrated under reduced pressure to give 4-methoxy-*N*-[(2-furyl)methylidene]aniline (4.5 g, 100%). Zinc dust (1.30 g, 19.9 mmol) was suspended in THF (15 ml) and the suspension was heated to reflux. Ethyl bromodifluoroacetate (2.42 g, 11.9 mmol) was then added neat to the refluxing suspension. Within 1 min, the above imine (2.00 g, 9.94 mmol) was added, and refluxing was continued for 30 min. The reaction mixture was cooled to room temperature and then poured into a mixture of AcOEt and 1 N HCl. The whole was stirred for 5 min, then the organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% AcOEt–*n*-hexane) to give **10a** (1.54 g, 55%) as a crystalline solid. mp 94—95 °C. MS (FD) *m/z*: 279 (M^+). *Anal.* Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.21; H, 3.97; F, 13.60; N, 5.02. Found: C, 60.01; H, 3.83; F, 13.48; N, 4.97. IR (KBr): 1768 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (s, 3H), 5.41 (dd, 1H, J=6, 2 Hz), 6.44 (dd, 1H, J=3, 1.5 Hz), 6.56 (d, 1H, J=3 Hz), 6.83—6.86 (m, 2H), 7.27—7.32 (m, 2H), 7.50 (d, 1H, J=1.5 Hz).

3,3-Difluoro-1-(*p*-methoxyphenyl)-4-(2-thienyl)-2-azetidinone (**10b**): Following the procedure described for **10a**, compound **9b** was converted to **10b** (63%) as a crystalline solid. mp 86—87 °C. MS (FD) *m/z*: 295 (M^+). *Anal.* Calcd for $C_{14}H_{11}F_2NO_2S$: C, 56.94; H, 3.75; F, 12.87; N, 4.74; S, 10.86. Found: C, 56.68; H, 3.75; F, 13.17; N, 4.60; S, 10.99. IR (KBr): 1766 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.76 (s, 3H), 5.63 (dd, 1H, J=6, 1 Hz), 6.82—6.85 (m, 2H), 7.08 (dd, 1H, J=5, 3.5 Hz), 7.20 (d, 1H, J=3.5 Hz), 7.29—7.34 (m, 2H), 7.42 (d, 1H, J=5 Hz).

3,3-Difluoro-4-(3-furyl)-1-(*p*-methoxyphenyl)-2-azetidinone (**10c**): Following the procedure described for **10a**, compound **9c** was converted to **10c** (73%) as a crystalline solid. mp 100—101 °C. MS (FD) *m/z*: 279 (M^+). *Anal.* Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.21; H, 3.97; F, 13.60; N, 5.02. Found: C, 60.39; H, 3.70; F, 13.83; N, 4.87. IR (KBr): 1770 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (s, 3H), 5.35 (dd, 1H, J=7, 2 Hz), 6.41 (s, 1H), 6.83—6.87 (m, 2H), 7.32—7.35 (m, 2H), 7.47 (s, 1H), 7.60 (s, 1H).

4-Cyclohexyl-3,3-difluoro-1-(*p*-methoxyphenyl)-2-azetidinone (**10d**): Following the procedure described for **10a**, compound **9d** was converted to **10d** (56%) as a crystalline solid. mp 80—82 °C. MS (FD) *m/z*: 295 (M^+). *Anal.* Calcd for $C_{16}H_{19}F_2NO_2$: C, 65.07; H, 6.48; F, 12.87; N, 4.74. Found: C, 64.93; H, 6.57; F, 12.73; N, 4.69. IR (KBr): 1772 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.21 (m, 5H), 1.67—1.74 (m, 5H), 1.97—1.99 (m, 1H), 3.81 (s, 3H), 4.24—4.29 (m, 1H), 6.90 (m, 2H), 7.34 (m, 2H).

Ethyl 2,2-Difluoro-3-(2-furyl)-3-(*p*-methoxyphenylamino)propionate (11a) A stirred solution of **10a** (1.00 g, 3.58 mmol) in THF (10 ml) was treated with 1 M aqueous NaOH solution (4 ml). After 1 h, THF was evaporated off and the remaining solution was lyophilized to give a fluffy sodium salt. Thionyl chloride (0.65 ml, 8.91 mmol) was added dropwise to a solution of the above sodium salt in EtOH (40 ml) at 0 °C. The reaction mixture was stirred at 80 °C for 15 h, then poured into ice/water and AcOEt, and the organic layer was washed with saturated aqueous sodium bicarbonate, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized (*n*-hexane) to give **11a** (1.12 g, 96%) as a light yellow solid. mp 46—48 °C. MS (FD) *m/z* 325 (M^+). *Anal.* Calcd for $C_{16}H_{17}F_2NO_4 \cdot 1/10H_2O$: C, 58.75; H, 5.30; F, 11.62; N, 4.28. Found: C, 58.57; H, 5.11; F, 11.86; N, 4.15. IR (KBr): 3368, 1748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 3H, J=7 Hz), 3.72 (s, 3H), 3.96 (d, 1H, J=11 Hz), 4.31 (q, 2H, J=7 Hz), 5.07—5.16 (m, 1H), 6.34 (dd, 1H, J=3, 2 Hz), 6.38 (d, 1H, J=3 Hz), 6.68 (m, 2H), 6.75 (m, 2H), 7.40 (d, 1H, J=2 Hz).

Ethyl 2,2-Difluoro-3-(*p*-methoxyphenylamino)-3-(2-thienyl)propionate (**11b**): Following the procedure described for **11a**, compound **10b** was converted to **11b** (97%) as a yellow oil. Exact MS *m/z* Calcd for $C_{16}H_{17}F_2NO_3S$ (M^+): 341.0897. Found: 341.0940. IR (neat): 3359, 1770 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, 3H, J=7 Hz), 3.72 (s, 3H), 3.93 (br, 1H), 4.30 (q, 2H, J=7 Hz), 5.29 (dd, 1H, J=19, 7 Hz), 6.63—6.67 (m, 2H), 6.72—6.76 (m, 2H), 6.99 (dd, 1H, J=5 Hz, 3 Hz), 7.10 (d, 1H, J=3 Hz), 7.28 (d, 1H, J=5 Hz).

Ethyl 2,2-Difluoro-3-(3-furyl)-3-(*p*-methoxyphenylamino)propionate (**11c**): Following the procedure described for **11a**, compound **10c** was converted to **11c** (100%) as a light yellow solid. mp 69—71 °C. MS (FD) *m/z* 325 (M^+). *Anal.* Calcd for $C_{16}H_{17}F_2NO_4 \cdot 1/10H_2O$: C, 58.75; H, 5.30; F, 11.62; N, 4.28. Found: C, 58.74; H, 5.17; F, 11.50; N, 4.24. IR (KBr): 3340, 1768 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3H, J=7 Hz), 3.73 (s, 3H), 4.29 (q, 2H, J=7 Hz), 4.97—5.06 (m, 1H), 6.42 (s, 1H), 6.64—6.66 (m, 2H), 6.74—6.77 (m, 2H), 7.39 (s, 1H), 7.44 (s, 1H).

Ethyl 3-Cyclohexy-2,2-difluoro-3-(*p*-methoxyphenylamino)propionate (**11d**): Following the procedure described for **11a**, compound **10d** was converted to **11d** (97%) as a light yellow solid. mp 69—71 °C. MS (FD) *m/z*: 341 (M^+). *Anal.* Calcd for $C_{18}H_{25}F_2NO_3$: C, 63.32; H, 7.38; F, 11.13; N, 4.10. Found: C, 63.39; H, 7.44; F, 11.12; N, 3.98. IR (KBr): 3420, 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.06—1.29 (m, 5H), 1.18 (t, 3H, J=7 Hz), 1.62—1.90 (m, 6H), 3.42 (br, 1H), 3.73 (s, 3H), 3.81—3.88 (m, 1H), 4.08—4.17 (m, 2H), 6.59 (m, 2H), 6.74 (m, 2H).

Ethyl 3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)propionate (12a) A stirred solution of 11a (500 mg, 1.54 mmol) in CH_3CN (15 ml) at 0 °C was treated with a solution of CAN (2.53 g, 4.61 mmol) in H_2O (8 ml). The resulting mixture was stirred at room temperature for 30 min, then treated with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with five portions of AcOEt. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% AcOEt–*n*-hexane) to give the amine (257 mg, 76%) as a yellow oil. A solution of the above amine in THF (10 ml) was treated with di-*tert*-butyldicarbonate (384 mg, 1.76 mmol) at room temperature, then the reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was diluted with AcOEt and washed with water, 10% HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% AcOEt–*n*-hexane) to give **12a** (370 mg, 100%) as a colorless solid. mp 29—30 °C. MS (FAB) *m/z* 320 (MH^+). *Anal.* Calcd for $C_{14}H_{19}F_2NO_5$: C, 52.66; H, 6.00; F, 11.90; N, 4.39. Found: C, 52.64; H, 5.79; F, 11.97; N, 4.14. IR (KBr): 3304, 1768, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (t, 3H, J=7 Hz), 1.44 (s, 9H), 4.30 (q, 2H, J=7 Hz), 5.29 (br d, 1H, J=10 Hz), 5.50—5.59 (m, 1H), 6.36—6.39 (m, 2H), 7.41 (d, 1H, J=2 Hz).

Ethyl 3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-thienyl)propionate (**12b**): Following the procedure described for **12a**, compound **11b** was converted to **12b** (81%) as a colorless solid. mp 61—62 °C. MS (FAB) *m/z*: 336 (MH^+). *Anal.* Calcd for $C_{14}H_{19}F_2NO_4S$: C, 50.14; H, 5.71; F, 11.33; N, 4.18; S, 9.56. Found: C, 50.14; H, 5.69; F, 11.28; N, 4.14; S, 9.43. IR (KBr): 3378, 2977, 1759, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 3H, J=7 Hz), 1.44 (s, 9H), 4.28 (q, 2H, J=7 Hz), 5.66—5.75 (m, 1H), 7.00 (dd, 1H, J=5, 4 Hz), 7.11 (d, 1H, J=4 Hz), 7.32 (d, 1H, J=5 Hz).

Ethyl 3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(3-furyl)propionate (**12c**): Following the procedure described for **12a**, compound **11c** was converted to **12c** (98%) as a colorless solid. mp 66—67 °C. MS (FAB) *m/z*: 320 (MH^+). *Anal.* Calcd for $C_{14}H_{19}F_2NO_5$: C, 52.66; H, 6.00; F, 11.90; N, 4.39. Found: C, 52.51; H, 5.92; F, 11.78; N, 4.31. IR (KBr): 3372, 2987, 1756, 1709 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (t, 3H, J=7 Hz), 1.44 (s, 9H), 4.27 (q, 2H, J=7 Hz), 5.06 (br d, 1H, J=9 Hz), 5.37—5.46 (m, 1H), 6.42 (s, 1H), 7.41 (d, 1H, J=2 Hz), 7.47 (s, 1H).

Ethyl 3-(*tert*-Butoxycarbonylamino)-3-cyclohexyl-2,2-difluoropropionate (**12d**): Following the procedure described for **12a**, compound **11d** was converted to **12d** (86%) as a colorless solid. mp 59—61 °C. MS (FD) *m/z*: 335 (M^+). *Anal.* Calcd for $C_{16}H_{27}F_2NO_4$: C, 57.30; H, 8.11; F, 11.33; N, 4.18. Found: C, 57.12; H, 8.23; F, 11.01; N, 4.00. IR (KBr): 1770, 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.02—1.81 (m, 5H), 1.34 (t, 3H, J=7 Hz), 1.43 (s, 9H), 1.63—1.83 (m, 6H), 4.11—4.27 (m, 1H), 4.27 (q, 2H, J=7 Hz), 4.69 (br d, 1H, J=10.5 Hz).

3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)propionic Acid (13a) Following the procedure described for **8a**, compound **12a** was converted to **13a** (90%) as a colorless oil. MS (FAB) *m/z* 292 (MH^+). IR (neat): 3370, 1752, 1656 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (s, 9H), 5.36—5.46 (m, 1H), 6.45 (d, 1H, J=3 Hz), 6.49 (d, 1H, J=3 Hz), 7.65 (s, 1H), 7.95 (d, 1H, J=10 Hz).

3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-thienyl)propionic Acid (**13b**): Following the procedure described for **8a**, compound **12b** was converted to **13b** (91%) as a colorless oil. MS (FAB) *m/z*: 308 (MH^+). IR (neat): 3315, 1750, 1648 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (s, 9H), 5.49—5.58 (m, 1H), 7.03 (dd, 1H, J=5, 3 Hz), 7.20 (d, 1 H, J=3 Hz), 7.50 (d, 1H, J=5 Hz), 8.09 (br d, 1H, J=9 Hz).

3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(3-furyl)propionic Acid (**13c**): Following the procedure described for **8a**, compound **12c** was converted to **13c** (91%) as a colorless solid. mp 78—82 °C. MS (FAB) *m/z* 292 (MH^+). *Anal.* Calcd for $C_{12}H_{15}F_2NO_5$: C, 49.49; H, 5.19; F,

13.05; N, 4.81. Found: C, 49.37; H, 4.96; F, 12.85; N, 4.78. IR (KBr): 3344, 2941, 1757, 1670 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (s, 9H), 5.23—5.33 (m, 1H), 6.60 (s, 1H), 7.61 (s, 1H), 7.71 (s, 1H), 7.80 (d, 1H, J=10 Hz).

3-(*tert*-Butoxycarbonylamino)-3-cyclohexyl-2,2-difluoropropionic Acid (**13d**): Following the procedure described for **8a**, compound **12d** was converted to **13d** (84%) as a colorless solid. mp 139—142 °C. MS (FD) *m/z*: 307 (M^+). *Anal.* Calcd for $C_{14}H_{23}F_2NO_4$: C, 54.71; H, 7.54; F, 12.36; N, 4.56. Found: C, 54.56; H, 7.62; F, 12.29; N, 4.46. IR (KBr): 3311, 2937, 1743, 1643 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.02—1.40 (m, 5H), 1.44 (s, 9H), 1.65—1.84 (m, 6H), 4.14—4.20 (m, 1H), 4.86 (d, 1H, J=10.5 Hz).

Ethyl 3-[(1-*tert*-Butoxycarbonyl)pyrrole-2-yl]-2,2-difluoro-3-hydroxypropionate (15) Following the procedure described for **5a**, the aldehyde (**14**) was converted to **15** (73%) as a colorless oil. Exact MS *m/z*: Calcd for $C_{14}H_{19}F_2NO_5$ (M^+): 319.1231. Found: 319.1268. IR (neat): 3515, 2987, 1774, 1747 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (t, 3H, J=7 Hz), 1.61 (s, 9H), 4.35 (q, 2H, J=7 Hz), 5.08 (d, 1H, J=9 Hz), 5.43—5.52 (m, 1H), 6.16 (t, 1H, J=3.5 Hz), 6.43 (br s, 1H), 7.25 (dd, 1H, J=3.5, 2 Hz).

***N*-(*p*-Methoxyphenyl)-3-[(1-*tert*-butoxycarbonyl)pyrrole-2-yl]-2,2-difluoro-3-hydroxypropionamide (16)** A 1 M aqueous NaOH solution (18.6 ml) was added to a stirred solution of **15** (5.95 g, 18.6 mmol) in EtOH (50 ml). After 30 min, the EtOH was evaporated off and the remaining solution was lyophilized to give a fluffy sodium salt. A solution of the above salt and *p*-anisidine (2.98 g, 24.1 mmol) in CH_2Cl_2 (150 ml) was treated with diisopropylethylamine (4.19 ml, 24.1 mmol), followed by the addition of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) (6.14 g, 24.1 mmol). The raction mixture was stirred at room temperature for 2 h, then partitioned between CH_2Cl_2 and dilute aqueous HCl. The combined organic layer was dried over anhydrous $MgSO_4$ and removed under reduced pressure. The residue was purified by silica gel column chromatography (20% AcOEt–*n*-hexane) to give **16** (3.58 g, 49%) as a yellow oil. Exact MS *m/z*: Calcd for $C_{19}H_{22}N_2F_2O_5$ (M^+): 396.1496. Found: 396.1483. IR (neat): 3353, 2973, 1739, 1699 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (s, 9H), 3.80 (s, 3H), 5.00 (d, 1H, J=7 Hz), 5.66—5.74 (m, 1H), 6.17 (t, 1H, J=3 Hz), 6.49 (br s, 1H), 6.87—6.90 (m, 2H), 7.25 (d, 1H, J=2 Hz), 7.47—7.49 (m, 2H), 8.12 (br, 1H).

4-[(1-*tert*-Butoxycarbonyl)pyrrole-2-yl]-3,3-difluoro-1-(*p*-methoxyphenyl)-2-azetidinone (17) A solution of DEAD (1.57 g, 9.03 mmol) in dry THF (15 ml) was added to a stirred solution of **16** (3.58 g, 9.03 mmol) and Ph_3P (2.37 g, 9.03 mmol) in dry THF (35 ml) under argon at room temperature. After 10 min, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (20% AcOEt–*n*-hexane) to give **17** (2.50 g, 73%) as a colorless solid. mp 89—91 °C. MS (FD) *m/z*: 378 (M^+). *Anal.* Calcd for $C_{19}H_{20}F_2N_2O_4$: C, 60.31; H, 5.33; F, 10.04; N, 7.40. Found: C, 60.25; H, 5.31; F, 9.92; N, 7.39. IR (KBr): 1776, 1744 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (s, 9H), 3.80 (s, 3H), 6.03—6.05 (m, 2H), 6.12 (t, 1H, J=3 Hz), 6.87—6.89 (m, 2H), 7.30 (br s, 1H), 7.38—7.40 (m, 2H).

Methyl 3-[(1-*tert*-Butoxycarbonyl)pyrrole-2-yl]-2,2-difluoro-3-(*p*-methoxyphe-nyl)propionate (18) Sodium methoxide (195 mg, 3.60 mmol) was added to a stirred solution of **17** (1.13 g, 3.00 mmol) in MeOH (30 ml) at room temperature. After 20 min, the reaction mixture was partitioned between AcOEt and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and removed under reduced pressure. The residue was purified by silica gel column chromatography (20% AcOEt–*n*-hexane) to give **18** (1.14 g, 97%) as a light yellow solid. mp 88—91 °C. MS (FAB) *m/z*: 410 (MH^+). *Anal.* Calcd for $C_{20}H_{24}F_2N_2O_5$: C, 58.53; H, 5.89; F, 9.26; N, 6.83. Found: C, 58.26; H, 5.94; F, 9.23; N, 6.67. IR (KBr): 3384, 1762, 1746 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (s, 9H), 3.71 (s, 3H), 3.84 (s, 3H), 4.00 (br, 1H), 6.13 (t, 1H, J=3.5 Hz), 6.25—6.30 (m, 1H), 6.34 (br s, 1H), 6.66—6.68 (m, 2H), 6.72—6.75 (m, 2H), 7.27 (dd, 1H, J=3.5, 2 Hz).

Methyl 3-(*tert*-Butoxycarbonylamino)-3-[(1-*tert*-butoxycarbonyl)pyrrole-2-yl]-2,2-difluoropropionate (19) Following the procedure described for **12a**, compound **18** was converted to **19** (62%) as a colorless solid. mp 124—125 °C. MS (FD) *m/z*: 404 (M^+). *Anal.* Calcd for $C_{18}H_{26}F_2N_2O_6$: C, 53.46; H, 6.48; F, 9.40; N, 6.93. Found: C, 53.19; H, 6.54; F, 9.28; N, 6.85. IR (KBr): 3328, 1766, 1740, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (s, 9H), 1.62 (s, 9H), 3.84 (s, 3H), 6.15 (t, 1H, J=3.5 Hz), 5.55 (br, 1H), 6.28—6.35 (m, 1H), 6.34 (br s, 1H), 7.30 (br s, 1H).

3-(*tert*-Butoxycarbonylamino)-3-[(1-*tert*-butoxycarbonyl)pyrrole-2-yl]-2,2-difluoropropionic Acid (20) Following the procedure described for **8a**, compound **19** was converted to **20** (97%) as a colorless solid. mp 135—137 °C (dec.). MS (FD) *m/z*: 390 (M^+). *Anal.* Calcd for $C_{17}H_{24}F_2N_2O_6$: C, 52.30; H, 6.20; F, 9.73; N, 7.17. Found: C, 52.25; H, 6.35; F, 9.65; N, 7.09. IR (KBr): 3320, 1748, 1648 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (s, 9H), 1.56 (s, 9H), 6.17 (t, 1H, J=3 Hz), 6.35—6.43 (m, 1H), 6.58 (br s, 1H), 7.26 (br s, 1H), 7.74 (d, 1H, J=10 Hz).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-phenylpropionyl]-10-deacetylbaccatin III (22a). (General Esterification Procedure) A solution of **8a** (201 mg, 0.667 mmol) in toluene (2 ml) was added to a stirred solution of 7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetylbaccatin III (**21**) (201 mg, 0.167 mmol), DPC (144 mg, 0.667 mmol), and 4-(dimethylamino)pyridine (44.5 mg, 0.334 mmol) in toluene (3 ml) at room temperature. The mixture was heated to 80 °C with stirring for 60 h, then cooled, diluted with AcOEt, washed with aqueous 1 N HCl, water, saturated aqueous sodium bicarbonate, and brine, dried (sodium sulfate), and concentrated under reduced pressure. The residue was purified by preparative TLC (5% acetone–$CHCl_3$) to give **22a** (138 mg, 71%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.23, 1.24 (each s, 3H), 1.41, 1.43 (each s, 9H), 1.84 (s, 3H), 2.22, 2.32 (each s, 3H), 2.60—2.63 (m, 1H), 3.85—3.89 (m, 1H), 4.12—4.16 (m, 1H), 4.30—4.33 (m, 1H), 4.59, 4.90 (each d, 2H, J=12 Hz), 4.77 (s, 2H), 4.93—4.95 (m, 1H), 5.53—5.57 (m, 4H), 5.67 (d, 1H, J=7 Hz), 6.05, 6.17 (each t, 1H, J=8 Hz), 6.20, 6.21 (each s, 1H), 7.31—8.09 (m, 10H).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-(*p*-methoxyphenyl)propionyl]-10-deacetylbaccatin III (**22b**): Following the procedure described for **22a**, **8b** was converted to **22b** (75%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.22, 1.24 (each s, 3H), 1.40, 1.42 (each s, 9H), 1.87 (s, 3H), 2.02—2.08 (m, 1H), 2.25, 2.34 (each s, 3H), 2.58—2.65 (m, 1H), 3.78, 3.79 (each s, 3H), 3.88 (t, 1H, J=7 Hz), 4.13—4.16 (m, 1H), 4.31—4.33 (m, 1H), 4.59, 4.60 (each d, 1H, J=12 Hz), 4.77 (s, 2H), 4.90 (d, 1H, J=12 Hz), 4.95 (d, 1H, J=12 Hz), 5.35 (br, 1H), 5.41 (br, 1H), 5.53—5.57 (m, 1H), 5.68 (d, 1H, J=6 Hz), 6.07, 6.17 (each t, 1H, J=8 Hz), 6.20, 6.21 (each s, 1H), 6.90—6.93 (m, 2H), 7.28—7.31 (m, 2H), 7.48—8.09 (m, 5H).

13-*O*-[3-(*p*-Benzyloxyphenyl)-3-(*tert*-butoxycarbonylamino)-2,2-difluoro-propionyl]-7,10-bis-*O*-(2,2,2-trichloroethoxycarbonyl)-10-deacetylbaccatin III (**22c**): Following the procedure described for **22a**, **8c** was converted to **22c** (89%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.22, 1.24 (each s, 3H), 1.40, 1.42 (each s, 9H), 1.85 (s, 3H), 1.86 (s, 3H), 2.02—2.08 (m, 1H), 2.19—2.33 (m, 1H), 2.24, 2.33 (each s, 3H), 2.58—2.65 (m, 1H), 3.86—3.90 (m, 1H), 4.13—4.16 (m, 1H), 4.31—4.33 (m, 1H), 4.57—4.61 (m, 1H), 4.77 (s, 2H), 4.87—4.91 (m, 1H), 4.95 (d, 1H, J=9 Hz), 5.05, 5.06 (each s, 2H), 5.36—5.42 (m, 2H), 5.53—5.58 (m, 1H), 5.68 (d, 1H, J=7 Hz), 6.06, 6.16 (each t, 1H, J=8 Hz), 6.21, 6.22 (each s, 1H), 6.98—7.01 (m, 2H), 7.28—7.42, 7.47—7.62, 8.06—8.08 (each m, 12H).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)propionyl]-10-deacetylbaccatin III (**22d**): Following the procedure described for **22a**, **13a** was converted to **22d** (98%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (s, 3H), 1.25, 1.26 (each s, 3H), 1.43, 1.45 (each s, 9H), 1.85 (s, 3H), 1.94, 1.97 (each s, 3H), 2.02—2.09 (m, 1H), 2.28, 2.35 (each s, 3H), 2.25—2.30 (m, 1H), 2.62—2.64 (m, 1H), 3.91 (m, 1H), 4.11—4.17 (m, 1H), 4.33 (d, 1H, J=9 Hz), 4.59 (d, 1H, J=12 Hz), 4.77, 4.78 (each s, 2H), 4.90 (d, 1H, J=12 Hz), 4.94—4.97 (m, 1H), 5.35 (d, 1H, J=9 Hz), 5.55—5.60 (m, 2H), 5.69 (d, 1H, J=7 Hz), 6.17, 6.26 (each t, 1H, J=8 Hz), 6.24 (s, 1H), 6.39—6.41 (m, 1H), 6.43—6.44 (m, 1H), 7.44—8.10 (m, 6H).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-(2-thienyl)propionyl]-10-deacetylbaccatin III (**22e**): Following the procedure described for **22a**, **13b** was converted to **22e** (95%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (s, 3H), 1.23, 1.24 (each s, 3H),1.42, 1.45 (each s, 9H), 1.85 (s, 3H), 1.90 (s, 3H), 2.02—2.09 (m, 1H), 2.29, 2.36 (each s, 3H), 2.23—2.36 (m, 2H), 2.59—2.66 (m, 1H), 3.88—3.92 (m, 1H), 4.13—4.16 (m, 1H), 4.32 (d, 1H, J=9 Hz), 4.58—4.61 (m, 1H), 4.77 (s, 2H), 4.91 (d, 1H, J=12 Hz), 4.96 (d, 1H, J=10 Hz), 5.29, 5.40 (each d, 1H, J=9 Hz), 5.54—5.59 (m, 1H), 5.69 (d, 1H, J=7 Hz), 5.74—5.80 (m, 1H), 6.14, 6.23 (each t, 1H, J=8 Hz), 6.21, 6.22 (each s, 1H), 7.02—7.05 (m, 1H), 7.15 (d, 1H, J=3.5 Hz), 7.34—7.36 (m, 1H), 7.49—7.53, 7.62—7.66, 8.05—8.09 (each m, 5H).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-(3-furyl)propionyl]-10-deacetylbaccatin III

(**22f**): Following the procedure described for **22a**, **13c** was converted to **22f** (93%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (s, 3H), 1.24, 1.25 (each s, 3H), 1.42, 1.45 (each s, 9H), 1.85 (s, 3H), 1.92 (s, 3H), 2.03—2.09 (m, 1H), 2.28, 2.36 (each s, 3H), 2.21—2.32 (m, 2H), 2.59—2.66 (m, 1H), 3.89—3.93 (m, 1H), 4.14—4.17 (m, 1H), 4.33 (d, 1H, J=8 Hz), 4.60 (d, 1H, J=12 Hz), 4.77 (d, 2H, J=4 Hz), 4.91 (d, 1H, J=12 Hz), 4.95—4.97 (m, 1H), 5.12, 5.50 (each m, 1H), 5.55—5.59 (m, 1H), 5.69 (d, 1H, J=7 Hz), 6.14, 6.24 (each t, 1H, J=7 Hz), 6.23 (s, 1H), 6.45 (s, 1H), 7.44, 7.45 (each s, 1H), 7.48 (s, 1H), 7.50—8.09 (m, 5H).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-3-cyclohexyl-2,2-difluoropropionyl]-10-deacetylbaccatin III (**22g**): Following the procedure described for **22a**, **13d** was converted to **22g** (95%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.05—1.89 (m, 11H), 1.20 (s, 3H), 1.27 (s, 3H), 1.37, 1.42 (each s, 9H), 1.86 (s, 3H), 2.05, 2.13 (each s, 3H), 2.26—2.44 (m, 2H), 2.31, 2.37 (each s, 3H), 2.59—2.67 (m, 1H), 3.92—3.94 (m, 1H), 4.14—4.22 (m, 2H), 4.33 (d, 1H, J=8 Hz), 4.58—4.62 (m, 1H), 4.74—4.81 (m, 3H), 4.90 (d, 1H, J=12 Hz), 4.96 (d, 1H, J=9 Hz), 5.56—5.62 (m, 1H), 5.70 (d, 1H, J=7 Hz), 6.14, 6.26 (each t, 1H, J=9 Hz), 6.26, 6.27 (each s, 1H), 7.48—7.52, 7.61—7.65, 8.06—8.11 (each m, 5H).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-3-[(1-*tert*-butoxycarbonyl)pyrrole-2-yl]-2,2-difluoropropionyl]-10-deacetylbaccatin III (**22h**): Following the procedure described for **22a**, **20** was converted to **22h** (86%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (s, 3H), 1.24, 1.25 (each s, 3H), 1.41, 1.44 (each s, 9H), 1.61, 1.63 (each s, 9H), 1.85 (s, 3H), 1.93, 2.04 (each s, 3H), 2.27, 2.37 (each s, 3H), 2.20—2.40 (m, 2H), 2.57—2.64 (m, 1H), 3.90—3.93 (m, 1H), 4.13—4.16 (m, 1H), 4.31—4.34 (m, 1H), 4.58—4.62 (m, 1H), 4.77, 4.78 (each s, 2H), 4.91 (d, 1H, J=12 Hz), 4.96 (d, 1H, J=10 Hz), 5.55—5.60 (m, 2H), 5.69 (d, 1H, J=7 Hz), 6.12—6.17 (m, 1H), 6.16—6.18 (m, 1H), 6.24, 6.25 (each s, 1H), 6.38 (br s, 1H), 6.30—6.39 (m, 1H), 7.28—7.31 (m, 1H), 7.48—7.53, 7.61—7.65, 8.06—8.10 (each m, 5H).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[3-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-(2-pyrrolyl)propionyl]-10-deacetylbaccatin III (**22i**): Compound **22h** (112 mg, 0.0877 mmol) was dissolved in formic acid (5ml) at room temperature. The solution was stirred for 7 h, then poured into $CHCl_3$ and saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure. A solution of the residue in THF (4 ml) was treated with di-*tert*-butyldicarbonate (100 mg, 0.456 mmol) at room temperature. The mixture was stirred at 70 °C for 4 h, then concentrated, and the residue was purified by preparative TLC (30% AcOEt–*n*-hexane) to give **22i** (44.8 mg, 44%) as an amorphous foam. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (s, 3H), 1.24, 1.26 (each s, 3H), 1.44 (s, 9H), 1.85 (s, 6H), 2.27, 2.39 (each s, 3H), 2.20—2.39 (m, 2H), 2.57—2.64 (m, 1H), 3.89 (d, 1H, J=7 Hz), 4.13—4.17 (m, 1H), 4.33 (d, 1H, J=8 Hz), 4.60 (d, 1H, J=12 Hz), 4.76, 4.77 (each s, 2H), 4.91 (d, 1H, J=12 Hz), 4.94—4.99 (m, 1H), 5.27 (br, 1H), 5.51—5.58 (m, 2H), 5.68 (d, 1H, J=7 Hz), 6.13—6.24 (m, 4H), 6.78—6.80 (m, 1H), 7.48—7.52, 7.61—7.65, 8.07—8.08 (each m, 5H), 8.72, 8.77 (each br, 1H)

13-*O*-[(3*R*)- or (3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-phenylpropio-nyl]-10-deacetylbaccatin III (23a, 23b). (General Deprotection Procedure) Activated Zn (116 mg, 1.77 mmol) was added to a solution of **22a** (138 mg, 0.118 mmol) in an acetic acid–methanol-mixture (1 : 1) (8 ml), and the reaction mixture was heated to 60 °C for 15 min. It was cooled to room temperature, diluted with AcOEt, filtered to remove zinc salts, washed with 1 N HCl and saturated aqueous sodium bicarbonate, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a mixture of diastereomers. The crude product was purified by preparative HPLC and lyophilized with 1,4-dioxane to give **23a** (30 mg, 31%) and **23b** (27.4 mg, 29%) each as an amorphous foam. HPLC: Capcell Pak C_{18} (20 mm × 25 cm) (Shiseido Co., Ltd.); solvent, MeOH–H_2O (2 : 1); flow rate, 22.5 mkl/min; retention time, 14.2 min for **23a**, 16 min for **23b**. Compound **23a**: IR (KBr): 3452, 2976, 2936, 1760, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.19 (s, 3H), 1.42 (s, 9H), 1.58 (s, 3H), 1.74 (s, 3H), 1.77—1.86 (m, 1H), 2.54—2.62 (m, 1H), 2.20 (s, 3H), 2.12—2.28 (m, 2H), 3.86 (d, 1H, J=7 Hz), 4.09—4.31 (m, 3H), 4.93 (d, 1H, J=8 Hz), 5.16 (s, 1H), 5.35—5.45 (m, 2H), 5.66 (d, 1H, J=7 Hz), 6.07 (t, 1H, J=9 Hz), 7.30—8.06 (m, 10H). Compound **23b**: IR (KBr): 3452, 2976, 2932, 1760, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.20 (s, 3H), 1.40 (s, 9H), 1.70 (s, 3H), 1.74 (s, 3H), 1.70—1.85 (m, 1H), 2.54—2.62 (m, 1H), 2.28 (s, 3H), 2.19—2.22 (m, 2H), 3.87 (d, 1H, J=7 Hz), 4.17 (d, 1H, J=8 Hz), 4.22—4.26 (m, 1H), 4.30 (d, 1H, J=8 Hz), 4.94 (d, 1H, J=8 Hz), 5.16 (s, 1H), 5.40—5.58 (m, 2H), 5.66 (d, 1H, J=7 Hz), 6.15 (t, 1H, J=9 Hz), 7.30—8.08 (m, 10H).

13-*O*-[(3*R*)- or (3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(*p*-methoxy-phenyl)propionyl]-10-deacetylbaccatin III (**23c**, **23d**): Following the procedure described for **23a** and **23b**, compound **22b** was converted to **23c** (41%) and **23d** (38%). Compound **23c**: IR (KBr): 3456, 2984, 2944, 1764, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.19 (s, 3H), 1.42 (s, 9H), 1.73 (s, 3H), 1.74 (s, 3H), 2.14—2.29 (m, 2H), 2.22 (s, 3H), 2.54—2.62 (m, 1H), 3.78 (s, 3H), 3.88 (d, 1H, J=7 Hz), 4.15 (d, 1H, J=8 Hz), 4.16—4.19 (m, 1H), 4.30 (d, 1H, J=8 Hz), 4.94 (d, 1H, J=8 Hz), 5.17 (s, 1H), 5.37 (br, 2H), 5.67 (d, 1H, J=7 Hz), 6.08 (t, 1H, J=8yHz), 6.90 (d, 2H, J=9 Hz), 7.29 (d, 2H, J=9 Hz), 7.48—8.06 (each m, 5H). Compound **23d**: IR (KBr): 3646, 2984, 2944, 1764, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (s, 3H), 1.20 (s, 3H), 1.40 (s, 9H), 1.73 (s, 3H), 1.74 (s, 3H), 2.22 (d, 2H, J=8 Hz), 2.30 (s, 3H), 2.55—2.62 (m, 1H), 3.77 (s, 3H), 3.88 (d, 1H, J=7 Hz), 4.16 (d, 1H, J=8 Hz), 4.22—4.30 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.94 (d, 1H, J=8 Hz), 5.17 (s, 1H), 5.30—5.49 (m, 1H), 5.47 (d, 1H, J=10 Hz), 5.67 (d, 1H, J=7 Hz), 6.16 (t, 1H, J=8 Hz), 6.91 (d, 2H, J=9 Hz), 7.29 (d, 2H, J=9 Hz), 7.48—8.08 (m, 5H).

13-*O*-[(3*R*)- or (3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(*p*-hydroxy-phenyl)propionyl]-10-deacetylbaccatin III (**23e**, **23f**): Following the procedure described for **23a** and **23b**, the 7,10-bis-*O*-troc groups were removed from **22c**. A mixture of the resulting residue (65.7 mg), 10% palladium on carbon (66 mg), and AcOEt (4 ml) was shaken in a hydrogen atmosphere at room temperature for 8 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The crude product was purified by preparative HPLC and lyophilized with 1,4-dioxane to give **23e** (22 mg, 37%) and **23f** (22 mg, 37%), each as an amorphous foam. Compound **23e**: IR (KBr): 3460, 2984, 1762, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (s, 3H), 1.16 (s, 3H), 1.42 (s, 9H), 1.71 (s, 3H), 1.73 (s, 3H), 2.19—2.23 (m, 2H), 2.30 (s, 3H), 2.52—2.58 (m, 1H), 3.85 (d, 1H, J=7 Hz), 4.17 (d, 1H, J=8 Hz), 4.22—4.25 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.39 (br, 1H), 4.95 (d, 1H, J=8 Hz), 5.21 (s, 1H), 5.39—5.42 (m, 1H), 5.62—5.66 (m, 2H), 6.11 (t, 1H, J=8 Hz), 6.24 (br, 1H), 6.80—6.82 (m, 2H), 7.20—7.22 (m, 2H), 7.48—8.07 (m, 5H). Compound **23f**: IR (KBr): 3448, 2984, 1762, 1720 cm^{-1}. ^{1}H-NMR (CDCl3) δ: 1.10 (s, 3H), 1.18 (s, 3H), 1.43 (s, 9H), 1.73 (s, 3H), 1.84 (s, 3H), 2.12—2.19 (m, 2H), 2.22 (s, 3H), 2.52—2.58 (m, 1H), 3.83 (d, 1H, J=7 Hz), 4.16 (d, 1H, J=8 Hz), 4.17—4.28 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.37 (br, 1H), 4.95 (d, 1H, J=9 Hz), 5.18 (s, 1H), 5.30—5.42 (m, 2H), 5.65 (d, 1H, J=7 Hz), 6.05 (t, 1H, J=8 Hz), 6.08 (br, 1H), 6.80—6.82 (m, 2H), 7.21—7.23 (m, 2H), 7.48—8.06 (m, 5H).

13-*O*-[(3*R*)- and (3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)-propionyl]-10-deacetylbaccatin III (**23g**, **23h**): Following the procedure described for **23a** and **23b**, compound **22d** was converted to **23g** (36%) and **23d** (34%). Compound **23g**: IR (KBr): 3464, 2984, 1764, 1722 cm^{-1}. 1H-NMR ($CDCl_3$) δ: 1.12 (s, 3H), 1.22 (s, 3H), 1.44 (s, 9H), 1.75 (s, 3H), 1.89 (s, 3H), 2.19—2.34 (m, 2H), 2.25 (s, 3H), 2.55—2.62 (m, 1H), 3.91 (d, 1H, J=7 Hz), 4.16 (d, 1H, J=8 Hz), 4.22—4.27 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.94 (d, 1H, J=8 Hz), 5.20 (s, 1H), 5.38 (br d, 1H, J=10 Hz), 5.56—5.64 (m, 1H), 5.68 (d, 1H, J=7 Hz), 6.16 (t, 1H, J=8 Hz), 6.39 (dd, 1H, J=3, 2 Hz), 6.43 (d, 1H, J=3 Hz), 7.43 (d, 1H, J=2 Hz), 7.47—8.08 (m, 5H). Compound **23h**: IR (KBr): 3460, 2984, 1768, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.12 (s, 3H), 1.22 (s, 3H), 1.42 (s, 9H), 1.75 (s, 3H), 1.85 (s, 3H), 2.26-2.31 (m, 2H), 2.31 (s, 3H), 2.55—2.63 (m, 1H), 3.92 (d, 1H, J=7 Hz), 4.17 (d, 1H, J=8 Hz), 4.21—4.26 (m, 1H), 4.32 (d, 1H, J=9 Hz), 4.95 (d, 1H, J=8 Hz), 5.19 (s, 1H), 5.39 (br d, 1H, J=10 Hz), 5.62—5.69 (m, 1H), 5.68 (d, 1H, J=7 Hz), 6.23 (t, 1H, J=8 Hz), 6.39 (dd, 1H, J=3, 2 Hz), 6.43 (d, 1H, J=3 Hz), 7.44 (d, 1H, J=2 Hz), 7.47—8.09 (m, 5H).

13-*O*-[(3*R*)- or (3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-thienyl)-propionyl]-10-deacetylbaccatin III (**23i**, **23j**): Following the procedure described for **23a** and **23b**, compound **22e** was converted to **23i** (44%) and **23j** (37%), respectively. Compound **23i**: IR (KBr): 3452, 2984, 1764, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.20 (s, 3H), 1.44 (s, 9H), 1.74 (s, 3H), 1.83 (s, 3H), 2.26 (s, 3H), 2.19—2.29 (m, 2H), 2.55—2.62 (m, 1H) 3.90 (d, 1H, J=7 Hz), 4.16 (d, 1H, J=8 Hz), 4.21—4.28 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.94 (d, 1H, J=8 Hz), 5.31 (br d, 1H, J=8 Hz), 5.18 (s, 1H), 5.74—5.77 (m, 1H), 5.67 (d, 1H, J=7 Hz), 6.14 (t, 1H, J=8 Hz), 7.02 (dd, 1H, J=5, 4 Hz), 7.15 (d, 1H, J=4 Hz), 7.34 (d, 1H, J=5 Hz), 7.48—8.07 (m, 5H). Compound **23j**: IR (KBr): 3464, 2984, 1766, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (s, 3H), 1.20 (s, 3H), 1.41 (s, 9H), 1.74 (s,3H), 1.80 (s, 3H), 2.25—2.27 (m,

2H), 2.32 (s, 3H), 2.55—2.62 (m, 1H), 3.90 (d, 1H, J=7 Hz), 4.16 (d, 1H, J=8 Hz), 4.17—4.26 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.95 (d, 1H, J=8 Hz), 5.19 (s, 1H), 5.47 (d, 1H, J=10 Hz), 5.74—5.79 (m, 1H), 5.67 (d, 1H, J=7 Hz), 6.20 (t, 1H, J=8 Hz), 7.03 (dd, 1H, J=5, 4 Hz), 7.14 (d, 1H, J=4 Hz), 7.34 (d, 1H, J=5 Hz), 7.48—8.09 (m, 5H).

13-*O*-[(3*R*)- or (3S)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(3-furyl)-propionyl]-10-deacetylbaccatin III (**23k**, **23l**): Following the procedure described for **23a** and **23b**, compound **22f** was converted to **23k** (40%) and **23l** (37%). Compound **23k**: IR (KBr): 3464, 2984, 1764, 1726 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (s, 3H), 1.21 (s, 3H), 1.44 (s, 9H), 1.75 (s, 3H), 1.90 (s, 3H), 2.25 (s, 3H), 2.18—2.33 (m, 2H), 2.55—2.63 (m, 1H), 3.91 (d, 1H, J=7 Hz), 4.17 (d, 1H, J=8 Hz), 4.22—4.29 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.94 (d, 1H, J=8 Hz), 5.13 (br d, 1H, J=8 Hz), 5.20 (s, 1H), 5.41—5.47 (m, 1H), 5.68 (d, 1H, J=7 Hz), 6.14 (t, 1H, J=8 Hz), 6.45 (s, 1H), 7.43 (s, 1H), 7.50 (s, 1H), 7.48—8.07 (m, 5H). Compound **23l**: IR (KBr): 3464, 2984, 1768, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ:1.12 (s, 3H), 1.21 (s, 3H), 1.42 (s, 9H), 1.75 (s, 3H), 1.83 (s, 3H), 2.27—2.32 (m, 2H), 2.32 (s, 3H), 2.55—2.63 (m, 1H), 3.91 (d, 1H, J=7 Hz), 4.17 (d, 1H, J=8 Hz), 4.21—4.28 (m, 1H), 4.32 (d, 1H, J=8 Hz), 4.95 (d, 1H, J=7 Hz), 5.19 (s, 1H), 5.23 (d, 1H, J=10 Hz), 5.41—5.53 (m, 1H), 5.68 (d, 1H, J=7 Hz), 6.21 (t, 1H, J=9 Hz), 6.44 (s, 1H), 7.44 (s, 1H), 7.52 (s, 1H), 7.48—8.09 (m, 5H).

13-*O*-[(3*R*)- or (3*S*)-3-(*tert*-Butoxycarbonylamino)-3-cyclohexyl-2,2-difluoro-propionyl]-10-deacetylbaccatin III (**23m**, **23n**): Following the procedure described for **23a** and **23b**, compound **22g** was converted to **23m** (36%) and **23n** (41%). Compound **23m**: IR (KBr): 3464, 2932, 2856, 1760, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (s, 3H), 1.06—1.88 (m, 11H), 1.23 (s, 3H), 1.42 (s, 9H), 1.76 (s, 3H), 2.04 (s, 3H), 2.28 (s, 3H), 2.20—2.38 (m, 2H), 2.56—2.63 (m, 1H), 3.93 (d, 1H, J=7 Hz), 4.17 (d, 1H, J=8 Hz), 4.14—4.29 (m, 1H), 4.32 (d, 1H, J=8 Hz), 4.75 (d, 1H, J=11 Hz), 4.95 (d, 1H, J=8 Hz), 5.23 (s, 1H), 5.69 (d, 1H, J=7 Hz), 6.13 (t, 1H, J=8 Hz), 7.47—8.08 (m, 5H). Compound **23n**: IR (KBr): 3960, 3456, 2932, 2856, 1764, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (s, 3H), 1.06—1.88 (m, 11H), 1.24 (s, 3H), 1.38 (s, 9H), 1.76 (s, 3H), 1.96 (s, 3H), 2.34 (s, 3H), 2.29—2.31 (m, 2H), 2.56—2.63 (m, 1H), 3.93 (d, 1H, J=7 Hz), 4.18 (d, 1H, J=9 Hz), 4.21—4.28 (m, 1H), 4.32 (d, 1H, J=9 Hz), 4.76 (d, 1H, J=11 Hz), 4.96 (d, 1H, J=9 Hz), 5.22 (s, 1H), 5.69 (d, 1H, J=7 Hz), 6.25 (t, 1H, J=8 Hz), 7.47—8.11 (m, 5H).

13-*O*-[(3*R*)- or (3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-pyrrolyl)-propanoyl]-10-deacetylbaccatin III (**23o**, **23p**): Following the procedure described for **23a** and **23b**, compound **22i** was converted to **23o** (25%) and **23p** (39%). Compound **23o**: IR (KBr): 3428, 2976, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.18 (s, 3H), 1.44 (s, 9H), 1.75 (s, 3H), 1.84 (s, 3H), 2.24 (s, 3H), 2.55—2.63 (m, 1H), 3.90 (d, 1H, J=7 Hz), 4.16 (d, 1H, J=8 Hz), 4.24—4.27 (m, 1H), 4.31 (d, 1H, J=8 Hz), 4.95 (d, 1H, J=8 Hz), 5.20 (s, 1H), 5.24 (d, 1H, J=10 Hz), 5.51—5.60 (m, 1H), 5.67 (d, 1H, J=7 Hz), 6.13 (t, 1H, J=8 Hz), 6.16—6.19 (m, 1H), 6.25 (br s, 1H), 6.77—6.79 (m, 1H), 7.48—8.07 (m, 5H), 8.74 (br, 1H). Compound **23p**: IR (KBr): 3424, 2980, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (s, 3H), 1.19 (s, 3H), 1.46 (s, 9H), 1.76 (s, 6H), 1.88—1.95 (m, 1H), 2.17—2.28 (m, 1H), 2.32 (s, 3H), 2.74—2.81 (m, 1H), 2.88 (br, 1H), 3.93 (d, 1H, J=7 Hz), 4.19 (d, 1H, J=8 Hz), 4.32 (d, 1H, J=8 Hz), 4.24—4.33 (m, 1H), 4.95 (d, 1H, J=8 Hz), 5.25 (s, 1H), 5.26 (br d, 1H, J=10 Hz), 5.51—5.58 (m, 1H), 5.68 (d, 1H, J=7 Hz), 6.14 (br s, 1H), 6.18 (t, 1H, J=8 Hz), 6.22 (br s, 1H), 6.83 (br s, 1H), 7.47—8.08 (m, 5H), 9.07 (br, 1H).

(4*S*)- and (4*R*)-3,3-Difluoro-4-(2-furyl)-1-(*p*-methoxyphenyl)-2-azetidin-one [(+)-**10a**, (−)-**10a**]: Compound (±)-**10a** (25.5 g) was separated by preparative HPLC to give (+)-(4*S*)-**10a** (12.0 g) and (−)-(4*R*)-**10a** (12.3 g), each as colorless crystallites. HPLC: Chiralcel OJ (Daicel Chemical Industries, Ltd.). Compound (+)-**10a**: mp 54—55 °C. $[\alpha]_D^{24}$ +130° (c=2.5, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; F, 13.61; N, 5.02. Found: C, 60.07; H, 3.94; F, 13.87; N, 4.96. Compound (−)-**10a**: mp 54.5—55.5 °C. $[\alpha]_D^{24}$ −132° (c=2.5, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; F, 13.61; N, 5.02. Found: C, 60.14; H, 3.95; F, 13.77; N, 5.00. The ^{1}H-NMR, IR, and FD-MS data agreed with those of the corresponding racemate (**10a**).

Ethyl (3*S*)-2,2-Difluoro-3-(2-furyl)-3-[(*p*-methoxyphenyl)amino]propionate [(+)-**11a**]: Following the procedure described for (±)-**11a**, (+)-**10a** was converted to (+)-**11a** (90%) as a colorless crystalline solid. mp 66—67 °C. $[\alpha]_D^{24}$ +59.0° (c=1.1, EtOH). *Anal.* Calcd for $C_{16}H_{17}F_2NO_4$: C, 59.07; H, 5.27; F, 11.68; N, 4.30. Found: C, 58.98; H, 5.30; F, 11.51; N, 4.31. The data of ^{1}H-NMR, IR, and FD-MS agreed with those of the corresponding racemate (**11a**).

Ethyl (+)-(3*S*)-3-[(*p*-Bromobenzoyl)amino]-2,2-difluoro-3-(2-furyl) propionate (24) A solution of CAN (3.54 g, 6.45 mmol) in H_2O (11 ml) was aded to a solution of (+)-**11a** (700 mg, 2.15 mmol) in CH_3CN (21 ml) at 0 °C. The resulting mixture was stirred at room temperature for 30 min. The mixture was treated with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with five portions of AcOEt. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% AcOEt–*n*-hexane) to give the amine as a yellow oil. A solution of the above amine and triethylamine (0.30 ml, 2.15 mmol) in CH_2Cl_2 (14 ml) was treated with *p*-bromobenzoyl chloride (472 mg, 2.15 mmol) at room temperature, the reaction mixture was stirred for 18 h. It was then washed with water, 10% HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% AcOEt–*n*-hexane) to give (+)-**24** (627 mg, 73%), which was recrystallized from diethyl ether. mp 97—99 °C. MS (FD) m/z: 401 (M^+). $[\alpha]_D^{24}$ +6.8° (c=1.0, EtOH). *Anal.* Calcd for $C_{16}H_{14}BrF_2NO_4$: C, 47.78; H, 3.50; Br, 19.87; F, 9.45; N, 3.48. Found: C, 47.63; H, 3.56; Br, 19.90; F, 9.59; N,3.28. IR (KBr): 3340, 1760, 1656 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (t, 3H, J=7 Hz), 4.31 (q, 2H, J=7 Hz), 6.09 (dt, 1H, J=14, 10 Hz), 6.39 (dd, 1H, J=3.5, 1.5 Hz), 6.47 (d, 1H, J=3.5 Hz), 6.83 (d, 1H, J=10 Hz), 7.43 (d, 1H, J=1.5 Hz), 7.59—7.62 (m, 2H), 7.66—7.69 (m, 2H).

Ethyl (3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)-propionate [(+)-**12a**]: Following the procedure described for (±)-**12a**, (+)-11a was converted to (+)-**12a** (78%) as colorless crystallites. mp 59—60 °C. $[\alpha]_D^{24}$ +38.9° (c=1.2, EtOH). *Anal.* Calcd for $C_{14}H_{19}F_2NO_5$: C, 52.66; H, 6.00; F, 11.90; N, 4.39. Found: C, 52.85; H, 5.98; F, 12.09; N,4.20. The ^{1}H-NMR, IR, and FD-MS data agreed with those of the corresponding racemate (**12a**).

(3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)propionic Acid [(+)-**13a**]: Following the procedure described for (±)-**13a**, (+)-**12a** was converted to (+)-**13a** (78%) as colorless crystallites. mp 74—76 °C. $[\alpha]_D^{24}$ +59.3° (c=1.0, EtOH). *Anal.* Calcd for $C_{12}H_{15}F_2NO_5$: C, 49.49; H, 5.20; F, 13.05; N, 4.80. Found: C, 49.77; H, 5.27; F, 13.34; N,4.71. The ^{1}H-NMR, IR spectra, and FAB-MS data agreed with those of the corresponding racemate (**13a**).

7,10-Bis-*O*-(2,2,2-trichloroethoxycarbonyl)-13-*O*-[(3*S*)-3-(*tert*-butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)propionyl]-10-deacetylbaccatin III (25) Following the procedure described for **22a**, (+)-**13a** was converted to **25** (86%) as an amorphous foam. mp 223—226 °C. $[\alpha]_D^{22}$ −34.5° (c=0.51, $CHCl_3$). MS (FAB) m/z: 1166 (MH^+). *Anal.* Calcd for $C_{47}H_{51}C_{16}F_2NO_{18}$: C, 48.31; H, 4.40; N, 1.20. Found: C, 48.41; H, 4.41; N, 1.23. IR (KBr): 3456, 2976, 1764, 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (s, 3H), 1.26 (s,, 3H), 1.43 (s, 9H), 1.85 (s, 3H), 1.94 (s, 3H), 2.03—2.09 (m, 1H), 2.31—2.34 (m, 2H), 2.35 (s, 3H), 2.59—2.57 (m, 1H), 3.91 (d, 1H, J=7 Hz), 4.15 (d, 1H, J=8 Hz), 4.33 (d, 1H, J=8 Hz), 4.60 (d, 1H, J=11.5 Hz), 4.77 (AB type d, 2H, J=12 Hz), 4.91 (d, 1H, J= 11.5 Hz), 5.36 (d, 1H, J=10 Hz), 5.57 (dd, 1H, J=10, 7 Hz), 5.67 (d, 1H, J=10 Hz), 5.69 (d, 1H, J=7 Hz), 6.24 (s, 1H), 6.26 (t, 1H, J=8 Hz), 6.40 (d, 1H, J=1.5 Hz), 6.43 (d, 1H, J=3.5 Hz), 7.45 (s, 1H), 7.43—8.10 (m, 5H).

13-*O*-[(3*S*)-3-(*tert*-Butoxycarbonylamino)-2,2-difluoro-3-(2-furyl)-propionyl]-10-deacetylbaccatin III (**23h**): Following the procedure described for **23a** and **23b**, compound **25** was converted to **23h** (70%) as a single product. The ^{1}H-NMR, IR, and FAB-MS data, optical rotation, and melting point agreed with those of the corresponding taxoid (**23h**) derived from the racemate (**13a**) and the protected baccatin derivative (**21**).

Ethyl (2,3-*threo*)-2-Fluoro-3-[(*p*-methoxyphenyl)amino]-3-phenylpropionate (27) Following the procedure described for **11a**, **26** was converted to **27** (100%) as a colorless solid. mp 58—60 °C. MS (FAB) m/z 317 (MH^+). *Anal.* Calcd for $C_{18}H_{20}FNO_3$: C, 68.12; H, 6.35; F, 5.99; N, 4.41. Found: C, 68.25; H, 6.27; F, 5.87; N, 4.13. IR (KBr): 3392, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (t, 3H, J=7 Hz), 3.68 (s, 3H), 4.19—4.26 (m, 2H) , 4.93 (dd, 1H, J=27, 3 Hz), 5.14 (dd, 1H, J=48, 3 Hz), 6.54 (d, 2H, J=9 Hz), 6.69 (d, 2H, J=9 Hz), 7.27—7.38 (m, 5H).

(2,3-*Threo*)-3-(*tert*-Butoxycarbonylamino)-2-fluoro-3-phenylpropionic Acid (28) Following the procedure described for **12a** and **8a**, **27** was converted to **28** (64%) as an amorphous foam. Exact MS m/z: Calcd for $C_{14}H_{19}FNO_4$ (M^+): 284.1298. Found: 284.1295. IR (KBr): 3320, 2984, 1728, 1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (s, 9H), 5.14 (d, 1H, J=44 Hz), 5.13 (dd, 1H, J=38, 17 Hz), 7.25—7.40 (m, 5H), 7.69 (d, 1H,

$J=9$ Hz), 13.3 (br, 1H).

13-*O*-[(2*R*,3*S*)- and (2*S*,3*R*)-3-(*tert*-Butoxycarbonylamino)-2-fluoro-3-phenyl-propionyl]-10-deacetylbaccatin III (29a, 29b) The protected fluorodocetaxel (a mixture of diastereomers) was prepared from **28** as described for the preparation of **22a**. Following the procedure described for **23a** and **23b**, the above mixture was converted to **29a** (54%) and **29b** (24%). Compound **29a**: mp 181—184 °C. MS (FAB) *m/z*: 810 (MH^+). $[\alpha]_D^{24}$ −26.5° ($c=0.2$, $CHCl_3$). *Anal.* Calcd for $C_{43}H_{52}FNO_{13}\cdot 2H_2O$: C, 61.05; H, 6.67; N, 1.65. Found: C, 60.99; H, 6.45; N, 1.63. IR (KBr): 452, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (s, 3H), 1.22 (s, 3H), 1.40 (s, 9H), 1.73 (s, 3H), 1.75 (s, 3H), 2.29 (s, 3H), 2.20—2.31 (m, 2H), 2.54—2.62 (m, 1H), 3.90 (d, 1H, $J=7$ Hz), 4.17 (d, 1H, $J=8$ Hz), 4.22—4.28 (m, 1H), 4.30 (d, 1H, $J=8$ Hz), 4.94 (d, 1H, $J=8$ Hz), 5.19 (s, 1H), 5.28 (d, 1H, $J=47$ Hz), 5.42 (dd, 1H, $J=24$, 9 Hz), 5.62 (d, 1H, $J=9$ Hz), 5.67 (d, 1H, $J=7$ Hz), 6.20 (t, 1H, $J=8$ Hz), 7.28—8.08 (m, 10H). Compound **29b**: mp 179—181 °C. MS (FAB) *m/z*: 810 (MH^+). $[\alpha]_D^{24}$ −45.5° ($c=0.3$, $CHCl_3$). *Anal.* Calcd for $C_{43}H_{52}FNO_{13}\cdot 2H_2O$: C, 61.05; H, 6.67; N, 1.65. Found: C, 60.80; H, 6.62; N, 1.45. IR (KBr): 3456, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (s, 3H), 1.22 (s, 3H), 1.39 (s, 9H), 1.74 (s, 3H),1.97 (s, 3H), 2.11 (s, 3H), 2.06—2.22 (m, 2H), 2.55—2.62 (m, 1H), 3.90 (d, 1H, $J=7$ Hz), 4.16 (d, 1H, $J=8$ Hz), 4.22—4.26 (m, 1H), 4.29 (d, 1H, $J=8$ Hz), 4.93 (d, 1H, $J=8$ Hz), 5.22 (s, 1H), 5.22 (d, 1H, $J=48$ Hz), 5.32 (dd, 1H, $J=24$, 9 Hz), 5.54 (br, 1H), 5.66 (d, 1H, $J=7$ Hz), 6.22 (t, 1H, $J=8$ Hz), 7.27—8.06 (m, 10H).

X-ray Crystallographic Analysis of (+)-24a[22] A colorless, needle-shaped crystal of $C_{16}H_{14}BrF_2NO_4$ having approximate dimensions of $0.25\times0.18\times0.18$ mm was grown from diethyl ether. The lattice parameters and intensities were measured on a Philips four-circle X-ray autodiffractometer with monochromated CuK_α radiation using the θ–2θ scan technique. The compound crystallized in orthorhombic space group $P2_12_12_1$ with cell dimensions $a=15.8738$ Å, $b=19.7884$ Å, $c=5.2115$ Å, $V=1637.0$ Å^3. For $Z=4$ and F.W. = 402.19, the calculated density was 1.632 g/cm^3. The structure was solved by the direct method with the program MULTAN 78. The final R value was 0.029. A perspective view of the molecule is shown in Fig. 2.

***In Vitro* Cytotoxicity** Growth inhibition experiments were carried out in 96-well microplates, and the amount of viable cells at the end of the incubation was determined by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay.[23] Thus, 500—5000 cells/well in 150 μl of medium were plated and grown for 24 h (the P388 for 2 h), then a test drug (in 50 μl medium/well) or the medium alone as a control was added, and the cells were incubated for an additional 3 d. After addition of MTT (20 μl, 20 mg/ml in phosphate-buffered saline), the medium was removed and the blue dye formed was dissolved in 150 μl of dimethylsulfoxide (DMSO). The absorbance was measured at 540 nm using a Microplate Reader model 3550 (Bio-Rad, Richmond, California).

Preparation of Tubulin Tubulin was purified from porcine brain extract by two cycles of polymerization and depolymerization, as described by Shelanski *et al.*[24] Brain tissue was homogenized at 4 °C with 5 mM 2-(*N*-morpholino)ethanesulfonic acid (MES), pH 6.5, 0.5 mM $MgSO_4$, 1 mM ethylenebis(oxyethylenenitrilo)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA), 50 mM KCl, 1 mM ATP and PMSF (1 mg per one brain). The homogenate was then centrifuged at $26000\times g$ for 30 min at 4 °C. The supernatant was decanted and centrifuged at $50000\times g$ for 30 min at 4 °C. The supernatant was decanted and mixed with an equal volume of 5 mM MES pH 6.5, 0.5 mM $MgSO_4$, 1 mM EGTA, 50 mM KCl, 1 mM ATP and 8 mM glycerol. It was incubated at 37 °C for 40 min to allow assembly of microtubules and then centrifuged at $105,000\times g$ for 45 min at 25 °C. The pellets were resuspended in 5 mM MES pH 6.5, 0.5 mM $MgSO_4$, 1 mM EGTA, 50 mM KCl, 1 mM GTP and incubated at 4° for 30 min for disassembly of microtubules. After centrifugation at $105,000\times g$ for 60 min at 4 °C, the supernatant was decanted and mixed with an equal volume of 5 mM MES pH 6.5, 0.5 mM $MgSO_4$, 1 mM EGTA, 50 mM KCl, 1 mM ATP and 8 mM alycerol (1 cycle microtubule proteins, 1 cycle MTS). The preparation was stored at −80 °C.

Microtubule Disassembly Assay Immediately before use, a stock solution of 1 cycle MTS was carried through an additional cycle of polymerization and depolymerization to give 2 cycle MTS. The 2 cycle MTS was adjusted to a concentration of 5 mg/ml in 5 mM MES pH 6.5, 0.5 mM $MgSO_4$, 1 mM EGTA, 50 mM KCl, 1 mM GTP. A taxoid in DMSO was added to the 2 cycle MTS solution in a 96-well plate. The plate was incubated at 37 °C for 40 min to allow assembly of microtubules. The polymerization was evaluated by measuring turbidity at 405 nm. Then the temperature was shifted at 4 °C, and after 20 min the cold-reversibility was also evaluated. The depolymerization rate was calculated from the difference in turbidity between before and after the cold treatment. The IC_{50} value indicates the concentration of a taxoid for which the rate is decreased by 50%.

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