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Trifluoromethyl- and difluoromethyl-β-lactams as useful building blocks for the synthesis of fluorinated amino acids, dipeptides, and fluoro-taxoids

Larisa Kuznetsova, Ioana Maria Ungureanu, Antonella Pepe, Ilaria Zanardi, Xinyuan Wu, Iwao Ojima*

Department of Chemistry, State University of New York at Stony Brook, Graduate Chemistry Bldg. 739, Stony Brook, NY 11794-3400, USA

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Abstract

Enantiopure 1-acyl-3-hydroxyl-4-CF_2H-azetidin-2-ones and 1-acyl-3-hydroxy-4-CF_3-azetidin-2-ones serve as versatile intermediates for the syntheses of CF_2- and CF_3-containing α-hydroxy-β-amino acids, dipeptides, and taxoid anticancer agents. Both enantiomers of 3-hydroxy-4-CF_2H-β-lactams can be obtained in high yields through the diethylaminosulfur trifluoride (DAST) reaction of the corresponding enantiopure 4-formyl-β-lactam that is prepared through [2 + 2] cycloaddition of acetoxyketene to a 3-methyl-2-butenaldimine, followed by enzymatic optical resolution and ozonolysis. (+)-3-Hydroxy-4-CF_3-β-lactams and (−)-3-hydroxy-4-CF_3-β-lactams can also be readily obtained in enantiopure form through [2 + 2] cycloaddition of a CF_3-imine with a ketene, followed by enzymatic optical resolution. Practical processes for the preparations of these enantiopure 3-hydroxy-4-R_f-β-lactams as well as their synthetic applications are described.

Keywords: Fluorine-containing; β-Lactam; α-Hydroxy-β-amino acid; Dipeptide; Taxoid; Enzymatic optical resolution; Enantiopure; Trifluoromethyl; Difluoromethyl

1. Introduction

α-Hydroxy-β-amino acids are structural patterns present in a large number of biologically active compounds such as paclitaxel (antitumor agent) [1–3], bestatin [4–6] (inhibitor of aminopeptidases; immunological response modifier), microginin [7] (ACE inhibitor; KNI inhibitors), and kinostatins (HIV-1 protease inhibitors) [8,9] (Fig. 1). Accordingly, in the past decade extensive studies have been performed for the development of efficient methods for the synthesis of enantiopure α-hydroxy-β-amino acids [10–30].

It has been shown that the introduction of fluorine(s), difluoromethyl, or trifluoromethyl group to bioactive molecules very often brings about substantially improved pharmacological properties because of increased membrane permeability, enhanced hydrophobic binding, stability against metabolic oxidation, etc. [31,32]. The introduction of fluorine(s) into the bioactive molecules as marker(s) also provide a unique and valuable tool for ^{19}F NMR studies, *in vitro* and *in vivo*, of protein structures and drug-protein interactions by taking advantage of the fact that fluorine is virtually absent in the living tissue [33–35]. Therefore, fluorine-containing α-hydroxy-β-amino acids are expected to serve as important and useful bioactive compounds for medicinal chemistry and chemical biology. However, only a limited number of methods for the synthesis of enantiopure fluorine-containing α-hydroxy-β-amino acids have been reported to date [32,36–40].

As a part of our continuing efforts on the development and expansion of the β-Lactam Synthon Method (β-LSM), we became interested in applying the β-LSM to the syntheses of fluorine-containing α-hydroxy-β-amino acids and their congeners for obvious reasons mentioned above. To this end, we have to develop first efficient method(s) for the synthesis of the corresponding enantiopure *N*-acyl-β-lactams.

Besides the utility of fluorine-containing β-lactams as versatile synthetic intermediates, they may have intrinsic importance as a pharmacophore of various therapeutic agents since the β-lactam skeleton is found in numerous pharmacologically active molecules possessing antibacterial [41], antifungal [42], antitumor [43] and plasma cholesterol lowering [44,45] activities.

* Corresponding author. Tel.: +1-631-632-7947; fax: +1-631-632-7942.
E-mail address: iojima@notes.cc.sunysb.edu (I. Ojima).

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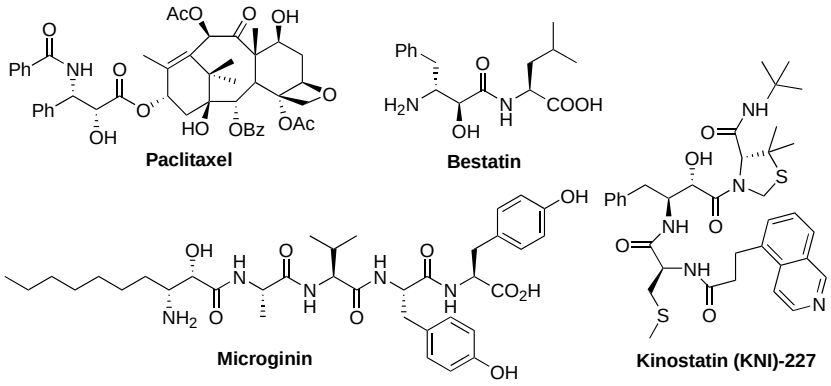
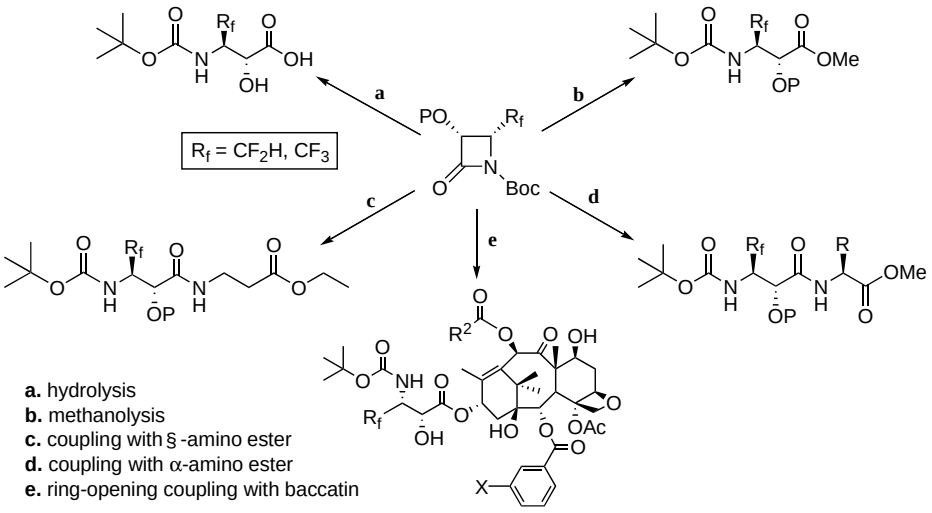


Fig. 1. Examples of bioactive compounds containing α hydroxy-β-amino acid unit.



Scheme 1.

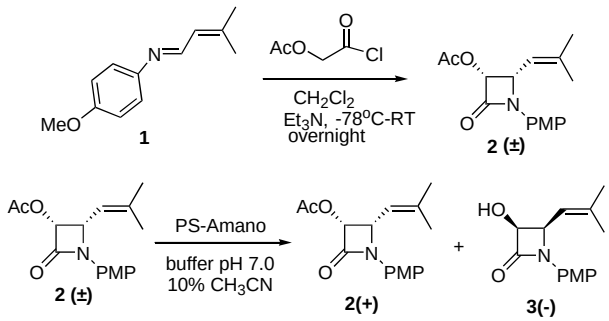
We describe here the practical processes for the preparation of enantiopure *N*-acyl-3-hydroxyl-4-R_f-β-lactams ($R_f = CF_2H$, CF_3) and their applications for the syntheses of the corresponding R_f-containing α-hydroxy-β-amino acids, dipeptides, and taxoids. Scheme 1 illustrates representative transformations of *N*-*t*-Boc-3-PO-4-R_f-β-lactams (P = hydroxyl protecting group).

2. Results and discussion

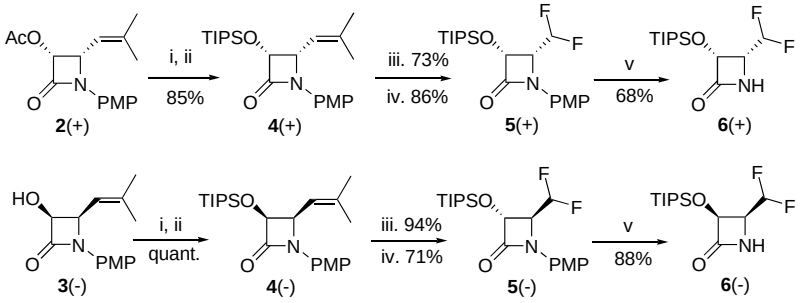
2.1. Synthesis of enantiopure 3-hydroxy-4-CF_2H-β-lactams

The enantioselective synthesis of (3*R*,4*S*)-3-TIPSO-4-(2-methyl-1-propenyl)azetidin-2-one was previously reported by our laboratory using chiral enolate–imine cyclocondensation [46]. In the present work, we investigated the efficacy of enzymatic optical resolution of racemic *cis*-3-AcO-4-(2-methyl-1-propenyl)azetidin-2-ones using the commercially available ''PS-Amano'' lipase, which was successfully employed by Sih and co-workers for the optical resolution of *cis*-3-AcO-4-phenylazetidin-2-ones [47].

First, racemic *cis*-1-PMP-3-AcO-4-(2-methyl-1-propenyl)-azetidin-2-one (**2**) (PMP = *p*-methoxyphenyl) was synthesized through [2 + 2] ketene-imine cycloaddition in 10–20 g scale [48]. Acetoxyketene generated in situ from acetoxyacetyl chloride and triethylamine was reacted with *N*-PMP-3-methyl-2-butenaldimine (**1**) to give racemic cis-β-lactam **2** in good yield (Scheme 2). Then, the enzymatic optical resolution of β-lactam **2** was carried out using the ''PS-Amano'' lipase in a buffer solution at 50 °C and pH 7 to



Scheme 2.



i) KOH, THF, 0 °C; ii) TIPSCl, Et_3N, DMAP; iii) O_3, MeOH/CH_2Cl_2, -78 °C; iv)DAST,CH_2Cl_2; v) CAN, H_2O/CH_3CN, -15 °C.

Scheme 3.

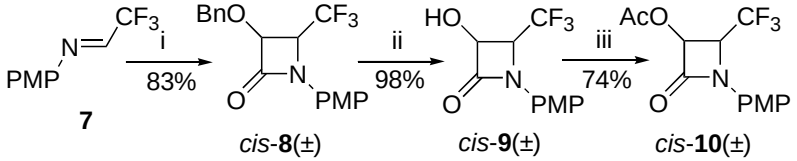
afford kinetically resolved (3*R*,4*S*)-3-AcO-β-lactam **2**(+) (>99% ee) and (3*S*,4*R*)-3-hydroxy-β-lactam **3**(−) (96–99% ee) with extremely high enantiopurity [49] (Scheme 2).

Since the acetyl group would not be tolerated in the diethylaminosulfur trifluoride (DAST) reaction, which was planned to introduce difluoromethyl group later in the synthesis [50], the protecting group of the 3-hydroxyl moiety of β-lactam **2** was changed to triisopropylsilyl (TIPS). The resulting (3*R*,4*S*)-1-PMP-3-TIPSO-4-(2-methyl-1-propenyl)azetidin-2-one (**4**(+)) was subjected to ozonolysis to give (3*R*,4*S*)-1-PMP-3-TIPSO-4-formylazetidin-2-one, which was immediately reacted with DAST to afford the corresponding 4-difluoromethylazetidin-2-one (**5**(+)) in high yield. Finally the PMP group was removed using cerium ammonium nitrate (CAN) to give enantiopure (3*R*,4*R*)-3-TIPSO-4-difluoromethylazetidin-2-one (**6**(+)) (Scheme 3). In a similar manner, (3*S*,4*S*)-3-hydroxy-β-lactam 3(−) was converted to enantiopure (3*S*,4*S*)-3-TIPSO-4-difluoromethylazetidin-2-one (**6**(−)) (Scheme 3).

2.2. Synthesis of enantiopure 3-hydroxy-4-CF_3-β-lactams

For the synthesis of 4-trifluoromethyl-β-lactams we employed a different strategy, i.e., introducing the trifluoromethyl moiety from the very beginning at the imine stage for the [2 + 2] ketene-imine cycloaddition. Because of the reduced nucleophilicity of the nitrogen of *N*-PMP-trifluoroacetaldimine (**7**) the reaction was found to require much higher temperature than those of usual aldimines to achieve a high conversion. We found that 40 °C is the optimal temperature for this reaction. It was also found that acetoxyketene that should have been generated in situ did not react with CF_3-imine **7** well, for some reason. Accordingly, it was necessary to use benzyloxyacetyl chloride as the ketene precursor for the reaction with CF_3-imine **7**. The use of benzyloxyketene for the reaction with CF_3-imines has been reported by us [48,51] and others [40]. Thus, the [2 + 2] ketene-imine cycloaddition proceeded smoothly at 40 °C to give racemic *cis*-3-benzyloxy-4-trifluoromethylazetidin-2-one **8**(±) in moderate yield. The β-lactam **8**(±) was converted to the corresponding *cis*-3-acetoxy-β-lactam **10**(±) through hydrogenolysis, followed by acetylation in good overall yield (Scheme 4).

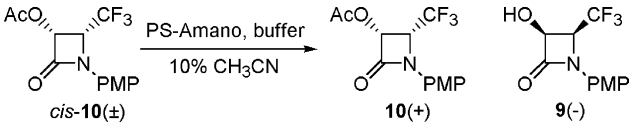
The enzymatic optical resolution of the racemic 3-AcO-4-CF_3-β-lactam **10**(±) under the same conditions as those described for the resolution of racemic β-lactam **2**(±) (PS-Amano, 50 °C, pH 7) gave kinetically resolved (3*R*,4*R*)-3-AcO-4-CF_3-β-lactam **10**(+) in high yield (42%/50% in theory). However, the corresponding (3*S*,4*S*)-3-hydroxy-4-CF_3-β-lactam **9**(−) was not isolated at all, presumably due to the further hydrolysis of the β-lactam ring of this product under these conditions. Changing the pH to 6 (slower reaction) or 8 (faster reaction) did not solve this problem. Fortunately, we found that this over-reaction was controllable by lowering the reaction temperature. Thus, reaction at 0–5 °C at pH 7 for 12 h gave β-lactam **9**(−) with 97% ee in good yield (36%/50% in theory) in addition to β-lactam **10**(+). The results are summarized in Table 1. 3-AcO-4-CF_3-β-lactam **10**(+) and 3-hydroxy-4-CF_3-β-lactam **9**(−), thus obtained, were converted the corresponding



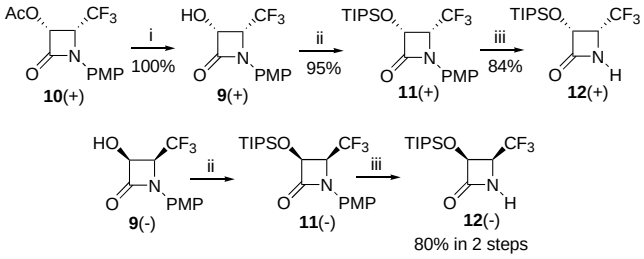
i) $PhCH_2OCH_2COCl$, Et_3N, CH_2Cl_2, 40 °C; ii) H_2, Pd/C, MeOH, 45°C; iii) Ac_2O, DMAP, Py, CH_2Cl_2

Scheme 4.

Table 1
Enzymatic optical resolution of racemic *cis*-3-AcO-4-CF_3-b-lactam **10**(±)



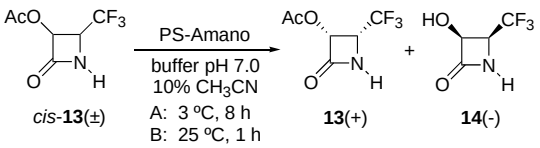
β-Lactam	pH	Temperature (°C)	Time	**10**(+)		**9**(−)	
				Yield (%)	ee (%)	Yield (%)	ee (%)
cis-**10**(±)	7	50	4 days	42	100	–	–
cis-**10**(±)	7	0–5	12 h	45	99.9	36	97



Scheme 5.

(3*R*,4*R*)-3-TIPSO-4-CF_3-β-lactam **12**(+) and (3*S*,4*S*)-3-TIPSO-4-CF_3-β-lactam **12**(−) in a manner similar to that described for the preparation of 3-TIPSO-4-CF_2H-β-lactams **6**(+) and **6**(−) (*vide supra*) (Scheme 5).

We also investigated another route to enantiopure β-lactams **12**(+) and **12**(−) as well as an efficient route to enantiopure 3-hydroxy-4-CF_3-azetidin-2-one (**14**(−)) through enzymatic optical resolution of racemic cis-3-acetoxy-4-CF_3-azetidin-2-one (**13**(±)), which was readily obtained by the removal of the PMP group from racemic β-lactam **10**(±) with CAN. Gratifyingly, we found that the enzymatic resolution of β-lactam **13**(±) using the ''PS-Amano'' lipase proceeded much faster than that of *N*-PMP-β-lactam **10**(±), i.e., the 50% conversion was reached in 8 h at 3 °C to give (+)-3-AcO-4-CF_3-β-lactam **13**(+) as well as (−)-3-hydroxy-4-CF_3-azetidin-2-one (**14**(−)) without the ring-opening over-reaction (Scheme 6). It was further found that (−)-β-lactam (**14**(−)) was stable even at 25 °C under the reaction conditions. This makes a sharp contrast to the labile nature of the corresponding

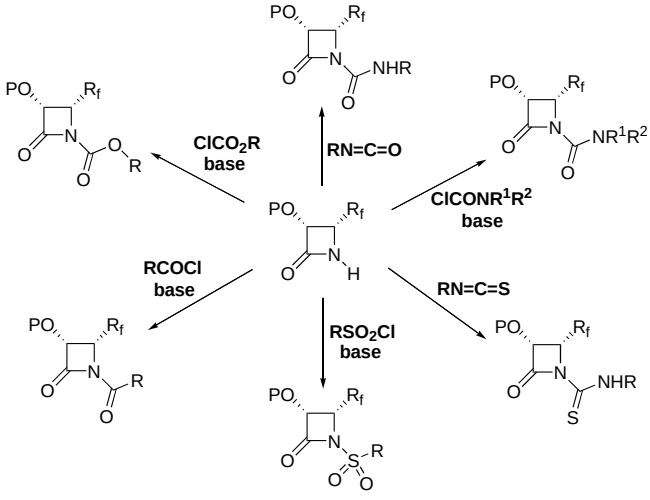


Scheme 6.

(−)-*N*-PMP-(−)-β-lactam **9**(−) (*vide supra*). Thus, the reaction of β-lactam **13**(+) with the ''PS-Amano'' lipase at 25 °C and pH 7 reached the 50% conversion in 3 h to afford 3-AcO-β-lactam **13**(+) and 3-hydroxy-β-lactam **14**(−) in excellent yields (Scheme 6).

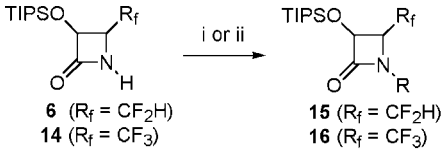
2.3. Synthesis of enantiopure 1-acyl-3-hydroxy-4-R_f-β-lactams

As it has been well documented [52], the β-Lactam Synthon Method is exploiting the unique nature of this four-membered cyclic amide with ring strain for its facile ring-opening reactions [53]. When the nitrogen of this strained cyclic amide is acylated (including carbalkoxy, carbamoyl, thiocarbamoyl, and sulfonyl groups besides the standard acyl groups), the resulting β-lactam ring becomes highly activated for nucleophilic attacks. We and others have been successfully exploiting this unique feature of *N*-acyl-β-lactams in organic syntheses and medicinal chemistry [53]. Scheme 7 illustrates readily available possible *N*-acyl-β-lactams through *N*-acylation of NH-free 3-PO-4-R_f-β-lactams (P = hydroxyl protecting group).



Scheme 7.

Table 2
Syntheses of *N*-acyl-3-TIPSO-4-R_f-β-lactams



i) RCl or R_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C; ii) LiHMDS 1eq, RCl (1.2 equiv.), THF, -78°C

Entry	NH-β-lactam	Configuration	R_f	Condition	*N*-Acyl-β-lactam	R	Yield (%)
1	**6**(−)	3*S*,4*S*	CF_2H	i	**15a**(−)	*t*-Boc	80
2	**6**(−)	3*S*,4*S*	CF_2H	i	**15b**(−)	Cbz	60
3	**6**(−)	3*S*,4*S*	CF_2H	i	**15c**(−)	Tosyl	66
4	**6**(−)	3*S*,4*S*	CF_2H	i	**15d**(−)	4-F-Bz	54
5	**14**(+)	3*R*,4*R*	CF_3	i	**16a**(+)	*t*-Boc	87
6	**14**(+)	3*R*,4*R*	CF_3	ii	**16b**(+)	Cbz	60
7	**14**(+)	3*R*,4*R*	CF_3	ii	**16c**(+)	Tosyl	15

Table 2 lists a series of *N*-acyl-3-TIPSO-3-R_f-β-lactams **15** ($R_f = CF_2H$) and **16** ($R_f = CF_3$) prepared through acylation, including carbalkoxylation and sulfonylation, of 3-TIPSO-4-CF_2H-azetidin-2-one (**6**(−)) and 3-TIPSO-4-CF_3-azetidin-2-one (**12**(+)) as examples (*t*-Boc = *t*-butoxycarbonyl; Cbz = carbobenzoxy; Ts = p-toluenesulfonyl; yields are not optimized).

2.4. Synthesis of enantiopure CF_2H- and CF_3-containing α-hydroxy-β-amino acid methyl esters

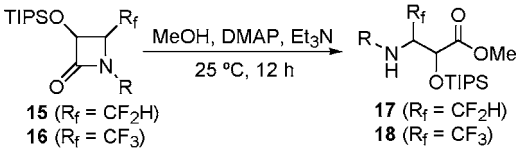
Enantiopure α-hydroxy-β-amino acid methyl esters bearing a CF_2H group or a CF_3 group at the C-3 position, **17** ($R_f = CF_2H$) or **18** ($R_f = CF_3$), were readily synthesized through a facile methanolysis of *N*-acyl-3-TIPSO-4-R_f-β-lactams, **15** or **16**, in the presence of triethylamine and a catalytic amount of 4-(*N,N*-dimethylamino)pyridine (DMAP) at ambient temperature in good to quantitative yields. Results are summarized in Table 3 (yields are not optimized).

2.5. Synthesis of CF_2H- and CF_3-containing dipeptides through ring-opening coupling of *N*-acyl-β-lactams with amino acid esters

We carried out the ring-opening coupling of (3*S*,4*S*)- and (3*R*,4*R*)-*N*-acyl-β-lactams, **15** and **16**, with various (*S*)-α-amino acid methyl esters, glycine methyl ester, and β-alanine ethyl ester, which were generated *in situ* from the corresponding hydrochlorides in dichloromethane in the presence of *N*-methylmorpholine (NMM). Since these coupling reactions do not need any peptide coupling reagents such *N,N*-dicyclohexylcarbodiimide (DCC) and *N,N*-diisopropylcarbodiimide (DIC), the ''atom economy [54] is extremely high. The reactions gave the corresponding R_f-containing dipeptides, **19–22**, in good to quantitative yields. Results are summarized in Table 4.

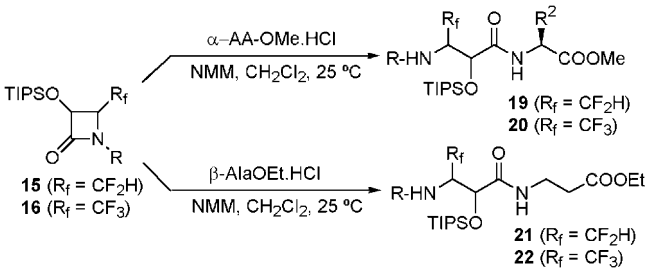
As Table 4 shows, the rate and yield of the coupling reaction highly depends on the bulkiness of amino acid esters. *N*-Tosyl-4-CF_2H-β-lactam **15c** (entries 4-7) and *N*-(4-F-benzoyl)-4-CF_2H-β-lactam **15d** (entry 8) are highly

Table 3
Syntheses of CF_2H- and CF_3-containing α-hydroxy-β-amino acid methyl esters



Entry	β-Lactam	Configuration	R_f	R	β-R_f-α-TIPSO-β-amino ester	Configuration	Yield (%)
1	**15a**(−)	3*S*,4*S*	CF_2H	*t*-Boc	**17a**(−)	2*S*,3*S*	98
2	**15b**(−)	3*S*,4*S*	CF_2H	Cbz	**17b**(−)	2*S*,3*S*	78
3	**15c**(−)	3*S*,4*S*	CF_2H	Tosyl	**17c**(−)	2*S*,3*S*	87
4	**16a**(+)	3*R*,4*R*	CF_3	*t*-Boc	**18a**(+)	2*R*,3*R*	70
5	**16b**(+)	3*R*,4*R*	CF_3	Cbz	**18b**(+)	2*R*,3*R*	58
6	**16c**(+)	3*R*,4*R*	CF_3	Tosyl	**18c**(+)	2*R*,3*R*	100

Table 4
Ring-opening coupling of *N*-acyl-β-lactams with amino acid esters



Entry	β-Lactam	Configuration	R_f	R	Amino ester	Reaction time (h)	Dipeptide	Isolated yield (%)
1	**15a**(−)	3*S*,4*S*	CF_2H	*t*-Boc	(*S*)-Phe-OMe	24	**19a**	No reaction
2	**15a**(−)	3*S*,4*S*	CF_2H	*t*-Boc	Gly-OMe	18	**19b**	62
3	**15a**(−)	3*S*,4*S*	CF_2H	*t*-Boc	β-Ala-OEt	18	**21a**	50
4	**15c**(−)	3*S*,4*S*	CF_2H	Tosyl	(*S*)-Val-OMe	12	**19c**	82
5	**15c**(−)	3*S*,4*S*	CF_2H	Tosyl	(*S*)-Leu-OMe	12	**19d**	94
6	**15c**(−)	3*S*,4*S*	CF_2H	Tosyl	(*S*)-Met-OMe	12	**19e**	89
7	**15c**(−)	3*S*,4*S*	CF_2H	Tosyl	(*S*)-Phe-OMe	12	**19f**	83
8	**15d**(−)	3*S*,4*S*	CF_2H	4-F-Bz	(*S*)-Phe-OMe	12	**19g**	100
9	**16b**(+)	3*R*,4*R*	CF_3	Cbz	(*S*)-Phe-OMe	96	**20a**	65
10	**16b**(+)	3*R*,4*R*	CF_3	Cbz	β-Ala-OEt	48	**22b**	65

reactive, giving the corresponding dipeptides in high yields regardless of the bulkiness of the amino acid esters used. *N*-*t*-Boc-4-CF_2H-β-lactam **15a** and *N*-Cbz-4-CF_3-β-lactam **16b** are modestly reactive. Thus, the reactions of these β-lactams are very sensitive to the bulkiness of the amino acid esters employed. In a publication from our laboratory, we have reported that the bulkiness of the hydroxyl group of *N*-acyl-3-hydroxy-4-substituted-β-lactams imposes significant effects on the reactivity of the β-lactam in the ring-opening coupling with α-amino acid esters, i.e., the *N*-*t*-Boc-β-lactams with free hydroxyl group at C-3 is the most reactive, followed by *t*-Boc group as the hydroxyl protecting group, and TIPS group is the worst [55]. Accordingly, it is surely anticipated that the reactivity of these *N*-acyl-4-R_f-β-lactams would increase substantially by using a free hydroxyl group or a less bulky acyl group than TIPS, such as acetyl, Cbz and *t*-Boc, as the hydroxyl protection group at C3.

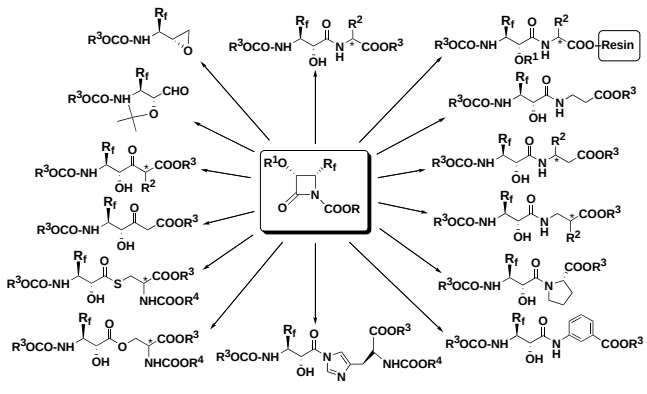
On the basis of the results presented in Table 4 as well as our previous works [55,56], we can readily envision the versatile utility of the *N*-acyl-3-PO-4-R_f-lactams (P = hydroxyl protecting group) for the syntheses of R_f-containing dipeptides, depsipeptides, peptidomimetics, and key synthetic building blocks for R_f-containing hydroxyethylene, dihyroxylethylene, and hydroxyethylamine dipeptide isosteres. Scheme 8 exemplifies the possible transformations of *N*-*t*-Boc-3-PO-4-R_f-lactams.

2.6. Synthesis of CF_2H- and CF_3-containing taxoid anticancer agents through ring-opening coupling of *N*-acyl-β-lactams with baccatins

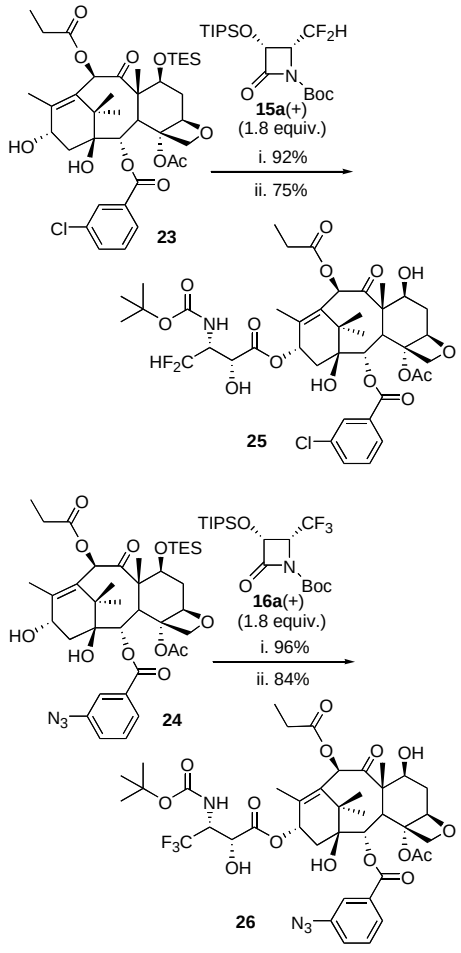
As a part of our continuing work on the synthesis and structure-activity relationship study (SAR) of fluoro-taxoid anticancer agents [50,57], we applied the ring-opening coupling of (3*R*,4*R*)-*N*-*t*-Boc-3-TIPSO-4-R_f-β-lactams, **15a** and **16a**, with baccatins for the syntheses of two new fluoro-taxoids.

Thus, the reactions of (3*R*,4*R*)-*N*-*t*-Boc-3-TIPSO-4-CF_2H-β-lactam **15a** and (3*R*,4*R*)-*N*-*t*-Boc-3-TIPSO-4-CF_3-β-lactam **16a** with 2-debenzoyl-2-(3-chlorobenzoyl)-10-deacetyl-10-propanyl-baccatin (**23**) and with 2-debenzoyl-2-(3-azidobenzoyl)-10-deacetyl-10-propanoylbaccatin (**24**), respectively, were carried out in the presence of LiHMDS as the base in THF at −40 °C. The subsequent removal of the silyl protecting groups by HF/pyridine gave the corresponding new fluoro-taxoids **25** and **26** in fairly good overall yields (Scheme 9).

Cytotoxicity of the two new fluoro-taxoids were evaluated *in vitro* against two human breast cancer cell lines and the corresponding drug-resistant cell lines. The IC_{50} values were determined through 72 h exposure of the fluoro-taxoids to



Scheme 8.



i) LiHMDS, THF, -40° C; ii) HF/Py, Py/CH_3CN, 25 ıC.

Scheme 9.

the cancer cells by means of the method developed by Skehan et al. [58]. As Table 5 shows, the new fluoro-taxoids, **25** and **26**, possess more than two orders of magnitude higher cytotoxicity than paclitaxel against the drug-resistant cell lines, MCF7-R and LCC6-MDR, and several times higher potency than paclitaxel against the drug-sensitive cell lines, MCF7-S and LCC6-WT. Thus, these two fluro-taxoids are highly promising additions to the arsenal of the ''second-generation taxoid anticancer agents'', and warrant further evaluations *in vivo*.

In conclusion, practical methods for the syntheses of enantiopure *N*-acyl-3-hydroxy-4-R_f-β-lactams ($R_f = CF_2H$, CF_3) have been successfully developed by means of [2 + 2] ketene-imine cycloaddition, followed by enzymatic optical resolution, *N*-acylation (including carbamoylation and sulfonylation as well), and other manipulations. Facile methanolysis of these enantiopure *N*-acyl-3-hydroxy-4-R_f-β-lactams gave the corresponding R_f-containing α-hydroxy-β-amino acid methyl esters in good to quantitative yields. Ring-opening coupling of these β-lactams with amino acid esters and baccatins afforded the corresponding R_f-containing dipeptides and taxoids, respectively in good overall yields. The two new fluoro-taxoids synthesized exhibited excellent cytotoxicity against human breast cancer cell lines, especially against the drug-resistant cell lines, MCF7-R and LCC6-MDR, which were two orders of magnitude more potent than paclitaxel. On the basis of the results described above, we can easily envision the wide applicability of enantiopure *N*-acyl-3-hydroxy-4-R_f-β-lactams for the syntheses of R_f-containing bioactive compounds. Further studies on the applications of fluorine-containing β-lactams coupled with the β-Lactam Synthon Method (β-LSM) are actively underway in these laboratories.

3. Experimental

3.1. General method

NMR spectra were recorded on a Bruker AC-250 NMR spectrometer or a Varian 300 NMR spectrometer or Varian 400 NMR spectrometer using tetramethylsilane as the internal standard. Melting points were measured on a Thomas Hoover Capillary melting point apparatus. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and column chromatography was carried on silica gel 60 (Merck; 230–400 mesh ASTM). 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), using a DAICEL-CHIRACEL OD chiral column (25 cm × 0.46 cm i.d.), employing hexan/2-propanol (99.5/0.5, v/v) as the solvent system with a flow rate of

Table 5
In vitro cytotoxicity (IC_{50} nM)[a] of fluoro-taxoids

Taxoid	MCF7-S (breast)	MCF7-R (breast)	R/S[b]	LCC6-WT (breast)	LCC6-MDR (breast)	R/S[b]	H460 (ovarian)	HT-29 (colon)
Paclitaxel	1.8	484	269	3.4	216	64	5.5	3.6
25	0.6	6.4	11	0.6	3.1	5.2	0.3	0.5
26	0.4	2.6	6.5	1.2	1.6	1.3	0.2	0.4

[a] The concentration of compound which inhibits 50% (IC_{50}) of the growth of the human tumor cell line after 72 h drug exposure.
[b] R/S = drug-resistance factor = IC_{50} (drug-resistant cell line)/IC_{50} (drug-sensitive cell line).

1.0 ml/min. HPLC analysis for determination of isomeric ratio was carried out with the same Water HPLC assembly using 5 μ Spherical Silica column employing hexane/2-propanol/dichloromethane (15/1/1, v/v/v) as the solvent system with a flow rate 1.0 ml/min, or hexane/2-propanol/dichloromethane (10/1/1, v/v/v) as the solvent system with a flow rate 1.4 ml/min. Elemental analysis were performed at M-H-W Laboratory, Phoenix, AZ. High resolution mass spectra were obtained from the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign, Urbana, IL.

3.2. Materials

The chemicals were purchased from Aldrich and Sigma and purified before use by standard methods. Tetrahydrofuran was freshly distilled under nitrogen from sodium metal and benzophenone. Dichloromethane was distilled immediately prior to use under nitrogen from calcium hydride. 1-(4-Methoxyphenyl)-3-acetoxy-4-(2-methyl-1-propenyl)azetidin-2-one (**2**(±)) [48], 1-(4-methoxyphenyl)-3-triisopropylsiloxy-4-formylazetidin-2-one (**5**(+)) [50], 1-(4-methoxyphenyl)-3-benzyloxy-4-trifluoromethylazetidin-2-one (**10**(±)) [51,59], 1-(4-methoxyphenyl)-3-hydroxy-4-trifluoromethylazetidin-2-one (**9**(±)) [51], 2-debenzoyl-2-(3-chlorobenzoyl)-7-triethylsilyl-10-deacetyl-10-propanoylbaccatin III (**23**) [60], and 2-debenzoyl-2-(3-azidobenzoyl)-7-triethylsilyl-10-deacetyl-10-propanoylbaccatin III (**24**) [60] were prepared by the previously reported methods.

3.3. (3S,4R)-1-(4-Methoxyphenyl)-3-acetoxy-4-(2-methyl-1-propenyl)azetidin-2-one (*2*)

To 90.2 mg of racemic 1-(4-methoxyphenyl)-3-acetoxy-4-(2-methyl-1-propenyl)azetidin-2-one (**2**(±)) suspended in 3.6 ml of 0.2 M sodium phosphate buffer (pH = 7.5) and 0.4 ml of acetonitrile was added 80 mg of the ''PS Amano'' lipase, and the mixture was vigorously stirred at 50 °C. After 22 h, the ^{1}H NMR showed the conversion of the reaction was 50%. The reaction mixture was filtered through Celite and extracted with CH_2Cl_2 (10 ml 3×). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (hexanes/EtOAc = 4/1) to give (3*R*,4*S*)-1-(4-methoxyphenyl)-3-acetoxy-4-(2-methyl-1-propenyl)azetidin-2-one (**2**(+)) (42.1 mg, 47% yield, 96.6% ee) and (3*S*,4*R*)-1-(4-methoxyphenyl)-3-hydroxy-4-(2-methyl-1-propenyl)-azetidin-2-one (**3**(−)) (37.1 g, 47% yield, 99.8% ee).

The enantiopurity of the β-lactams was determined by chiral HPLC at the OH-β-lactam stage using a DAICEL-CHIRACEL OD chiral column (25 cm × 0.46 cm i.d.), employing hexane/2-propanol (97/3, v/v) as the solvent system with a flow rate of 1.0 ml/min.

When this process was carried out in a large scale using 18.13 g of racemic 3-AcO-β-lactam (**2**(+)), under the same conditions except for the longer reaction time (40 h) and less amount of the ''PS-Amano'' lipase (10 g), 8.104 g (45%/50% in theory) of (3*R*,4*S*)-3-AcO-β-lactam **2**(+) (>99% ee) and 5.344 g (34%/50% in theory) of (3*R*,4*S*)-3-hydroxy-β-lactam **3**(−) (96% ee) were obtained.

3.4. 1-(4-Methoxyphenyl)-3-acetoxy-4-trifluoromethylazetidin-2-one (*10*(±))

To a solution of (500 mg, 4.1 mmol) 4-dimethylaminopyridine (DMAP), 3.4 ml of pyridine, and (3.42 g, 13.1 mmol) of racemic 3-hydroxy-β-lactam **9**(±) in 6 ml of CH_2Cl_2, was added dropwise (2.24 ml, 23.76 mmol) acetic anhydride. The mixture was stirred overnight at RT. The reaction mixture was then poured into a mixture of 140 ml 6N HCl, 210 ml of ice, and 430 ml ether. The organic layer was washed with 2N HCl and the combined aqueous layers extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 2.9 g (74%) of the product **10** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H), 3.97 (s, 3H), 4.74 (q, $J = 5.1$ Hz, 1H), 6.17 (d, $J = 5.4$ Hz, 1H), 6.09 (d, $J = 9.0$ Hz, 2H), 6.39 (d, $J = 9.0$ Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.6 (d, $J = 6.2$ Hz).

3.5. (3R,4R)-1-(4-Methoxyphenyl)-3-acetoxy-4-trifluoromethylazetidin-2-one (*10*(+))

A solution of (431 mg, 1.42 mmol) 3-acetoxy-β-lactam in 4 ml of CH_3CN and 20 ml of buffer solution at pH7 (653 mg, 4.8 mmol of KH_2PO_4 and 540 mg, 3.1 mmol of K_2HPO_4) was added 431 mg of PS-Amano at 3 °C. The reaction was monitored by NMR to reach a 1:1 ratio of products. After the reaction mixture was filtrated and extracted with ethyl ether several times, dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography to give 194 mg of **10**(+) as white solid in 45% (50% in theory) yeild: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (3H, s), 3.97 (3H, s), 4.74 (1H, q, $J = 5.1$ Hz), 6.17 (1H, d, $J = 5.4$ Hz), 6.09 (2H, d, $J = 9.0$ Hz), 6.39 (2H, d, $J = 9.0$ Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.6 (d, $J = 6.2$ Hz), MS (FAB^+, m/z): Calcd. for $C_{13}H_{12}F_3NO_4H^+$, 304.07; Found, 303.9%.

3.6. (3R,4R)-1-(4-Methoxyphenyl)-3-hydroxy-4-trifluoromethylazetidin-2-one (*9*(+))

To a solution of β-lactam **10** (1.19 g, 3.94 mmol) in 79 ml of THF was added 1 M aqueous solution of potassium hydroxide (11.8 ml, 11.8 mmol) and the mixture was stirred for 1.5 h at 3 °C. The reaction was quenched with aqueous saturated NH_4Cl solution (30 ml), and the aqueous layer was extracted with EtOAc (60 ml 3×). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a white solid (982 mg,

95% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.43 (bd) 3.80 (3H, s), 4.62 (1H, dq, $J = 5.4$ Hz), 5.27 (1H, d, $J = 5.4$ Hz), 6.88 (2H, d, $J = 9.0$ Hz), 7.40 (2H, d, $J = 9.0$ Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.9 (d, $J = 6.2$ Hz), MS (FAB^+, m/z): Calcd. for $C_{11}H_{10}F_3NO_3H^+$, 262.06; Found, 261.98.

3.7. (3R,4R)-1-(4-Methoxyphenyl)-3-triisopropylsiloxy-4-trifluoromethylazetidin-2-one (**11**)

To a solution of 982 mg (3.8 mmol) of **9**, 2.4 ml (15.2 mmol) of triethylamine, and 100 mg of DMAP in 76 ml CH_2Cl_2, was added 1.6 ml (7.5 mmol) of TIPSCl at room temperature. The reaction mixture was stirred for 18 h and quenched with water. The reaction mixture was diluted with 300 ml EtOAc and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel to yield **11** (1.59 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04–1.42 (21H, m) 3.79 (3H, s), 4.58 (1H, q, $J = 5.4$ Hz), 5.27 (1H, d, $J = 4.8$ Hz), 6.87 (2H, d, $J = 9.0$ Hz), 7.40 (2H, d, $J = 9.0$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.1, 17.9, 18.0, 55.7, 58.3 (q, $J = 31.8$ Hz, CF_3), 76.3, 114.7, 119.5, 130.1, 157.3, 165.6; ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.7 (d, $J = 6.2$ Hz), MS (FAB^+, m/z): Calcd. for $C_{20}H_{30}F_3NO_3Si{\cdot}H^+$, 418.19; Found, 418.09.

3.8. (3R,4R)-3-Triisopropylsiloxy-4-trifluoromethyl-azetidin-2-one (**12**)

To a solution (825 mg, 1.96 mmol) of (+)-*cis*-l-(4-methoxyhenyl)-3-TIPS-4-trifluoromethyl-azetidin-2-one **11** (825 mg, 1.96 mmol) in 60 ml of acetonitrile at −10 °C was slowly added a solution of cerium ammonium nitrate (4.3 g, 7.9 mmol) in 60 ml of water over a 2 h period. The mixture was stirred for additional 30 min at −10 °C and diluted with 20 ml of ether. The aqueous layer was extracted with two 20 ml portions of ether, and the combined organic layers were washed with water and saturated Na_2SO_3 to afford **12** (519 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13–1.26 (21H, m), 4.17 (1H, q, $J = 5.1$ Hz), 5.87 (1H, dd, $J = 1.5$, 4.7 Hz) 6.70 (1H, bs); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.1, 17.7, 17.8, 55.2 (q, $J = 32.7$ Hz, CF_3), 76.9, 165.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −72.2 (d, $J = 7.3$ Hz).

3.9. 3-Acetoxy-4-trifluoromethylazetidin-2-one (**13**(±))

To a solution of 3-AcO-4-trifluoromethylazetidin-2-one (2.8 g, 9.2 mmol) in 385 ml of acetonitrile at −10 °C was slowly added a solution of cerium ammonium nitrate (19.2 g, 35 mmol) in 386 ml of water over a period of 2 h. The mixture was stirred for addition 30 min at −10 °C and diluted with 20 ml of ether. The aqueous layer was extracted with two 20 ml portions of ether, and the combined organic layers were washed with water and saturated Na_2SO_3 to afford **13**(±) (519 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (3H, s), 4.35 (1H, q, $J = 6.0$ Hz), 6.05 (1H, dd, $J = 1.5$, 4.5 Hz), 7.37 (1H, bs).

3.10. (3R,4R)-3-Acetoxy-4-trifluoromethylazetidin-2-one (**13**(+))

To a solution of (400 mg, 1.42 mmol) 3-acetoxy-β-lactam **13**(±) in 4 ml of CH_3CN and 20 ml of buffer solution at pH7 (653 mg, 4.8 mmol of KH_2PO_4 and 540 mg, 3.1 mmol of K_2HPO_4) was added 431 mg of PS-Amano at 3 °C. The reaction was monitored by NMR. The reaction mixture was filtrated and extracted with ethyl ether several times, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel to give **13**(+) as a white solid in 45% (50% in theory) yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (3H, s), 4.35 (1H, q, $J = 6.0$ Hz), 6.05 (1H, dd, $J = 1.5$, 4.5 Hz), 7.37 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 53.5 (q, $J = 31, 63$ Hz), 73.8, 125.0 (q, $J = 277$, 553 Hz), 164.7, 169.0, MS (FAB^+, m/z): Calcd. for $C_6H_6F_3NO_3H^+$, 198.03; Found, 197.97.

3.11. (3R,4R)-3-Hydroxy-4-trifluoromethylazetidin-2-one (**14**(+))

Yield 43% (50% in theory); ^{1}H NMR (400 MHz, CD_3COCD_3): δ 4.32 (1H, m), 5.24 (1H, m), 5.75 (1H, d, $J = 8.0$ Hz), 7.92 (1H, bs); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 54.3 (q, $J = 31$, 63 Hz), 77.5, 125.0 (q, $J = 277$, 553 Hz), 169.2.

3.12. (3S,4S)-1-(tert-Butoxycarbonyl)-3-triisopropylsiloxy-4-difluoromethylazetidin-2-one (**15a**(−))

To a solution of NH-β-lactam **6**(−) (1.0 g, 3.4 mmol), di-*tert*-butyldicarbonate (890 mg, 4.08 mmol), and DMAP (207 mg, 1.7 mmol) in 20 ml of dichloromethane triethylamine (1.42 ml, 10.2 mmol) was added dropwise at room temperature. The mixture was stirred for 3 h and the reaction was quenched with a saturated solution of NH_4Cl. The aqueous layer was extracted with dichloromethane the combined organic layers were treated with brine and $MgSO_4$. After evaporation of the solvent *in vacuo*, the crude product was purified on a silica gel column with hexane ethyl acetate (6:1) to afford the **15a** as white solid (1.08 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (21H, m), 1.5 (9H, s), 4.30 (1H, m), 5.15 (1H, dd, $J = 0.9$, 6.3 Hz), 6.04 (1H, ddd, $J = 55$, 54, 5 Hz, CF_2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0, 17.8, 28.1, 57.6 (dd, $J = 21$, 30 Hz), 76.3, (d, $J = 4.5$ Hz, CF_2H), 84.5, 113.8 (t, $J = 242$ Hz, CF_2H), 147.8, 165.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −122.0 (ddd, $J = 295$, 52, 9 Hz), −127.0 (ddd, $J = 298$, 55, 9 Hz).

3.13. (3S,4S)-1-Benzyloxycarbonyl-3-triisopropylsiloxy-4-difluoromethyazetidin-2-one (**15b**(−))

Yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (21H, m), 1.5 (s, 9H), 4.30 (1H, m), 5.15 (1H, d, $J = 0.6$ Hz), 5.28 (2H, m), 6.04 (ddd, $J = 55, 54, 5$ Hz, 1H, CF_2H). 7.4 (5H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0, 17.8, 57.6 (dd, $J = 21$, 30 Hz), 68.9, (t, $J = 179$ Hz, CF_2H), 84.5, 113.8 (t, $J = 244$ Hz, CF_2H), 122.6, 122.2, 128.3, 128.6, 128.7, 128.8, 128.9, 129.0, 134.8, 140.1, 164.5.

3.14. (3S,4S)-1-(4-Methylbenzenesulfonyl)-3-triisopropylsiloxy-4-difluoromethyazetidin-2-one (**15c**(−))

Yield 66%; $[\alpha]_D{}^{20} - 85.7°$ (c 0.84, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 (2H, d, $J = 8.4$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 5.83 (1H, ddd, $J = 4.8, 54$ Hz), 5.22 (1H, d, $J = 6$ Hz), 4.51–4.46 (1H, m), 2.43 (3H, s), 1.15–1.01 (21H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz): 163.9, 145.81, 135.5, 130.1, 128, 113.4 (dd, $J = 244$ Hz), 76.8, 60 (dd, $J = 20.6$, 29.8 Hz), 22, 17.8, 12; ^{19}F NMR (282 MHz, $CDCl_3$): δ −121.9 (ddd, 1F, $J = 6.2, 51.9, 295.6$ Hz),−125.2 (ddd, 1F, $J = 9.3, 55, 296.9$ Hz). HRMS (FAB$^+$, *m/z*): Calcd. for $C_{20}H_{31}F_2NO_4SSi{\cdot}H^+$, 448.1784. Found: 448.1794.

3.15. (3S,4S)-1-(4-Fluorobenzoyl)-3-triisopropylsiloxy-4-difluoromethyazetidin-2-one (**15d**(−))

Yield 54%; $[\alpha]_D{}^{20} - 53.4°$ (c 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.24–1.07 (21H, m), 4.75–4.64 (1H, m), 5.21 (1H, d, $J = 6$ Hz), 6.16 (1H, ddd, $J = 5$, 55 Hz), 7.26–7.06 (2H, m), 7.99 (2H, dd, $J = 5, 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 12, 17.8, 22, 60 (dd, $J = 20.6$, 29.8 Hz), 76.8, 113.4 (dd, $J = 244$ Hz), 128, 130.1, 135.5, 145.81, 162.9, 163.5; ^{19}F NMR (282 MHz, $CDCl_3$): −103.9 (sl, 1F), −122.9 (ddd, 1F, $J = 12.1, 54.8, 298.9$ Hz), −127.7 (ddd, 1F, $J = 5.9, 54.8, 298.9$ Hz). HRMS (FAB$^+$, *m/z*): Calcd. for $C_{20}H_{28}F_3NO_3Si{\cdot}H^+$, 416.1864. Found: 416.1872.

3.16. (3R,4R)-1-(tert-Butoxycarbonyl)-3-triisopropylsiloxy-4-trifluoromethylazetidin-2-one (**16a**(+))

Yield 87%; $[\alpha]_D{}^{20} + 66.2°$ (c 1.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12–1.22 (21H, m), 1.52 (9H, s), 4.48 (1H, q, $J = 5.7$ Hz), 5.20 (1H, d, $J = 6.0$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0, 17.7, 17.8, 28.1, 57.3 (q, $J = 32.9$ Hz, CF_3), 76.4, 85.0, 164.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −70.0 (d, $J = 6.2$ Hz). HRMS (FAB$^+$, *m/z*): Calcd. for $C_{18}H_{32}F_3NO_4Si{\cdot}H^+$, 412.2126. Found: 412.2128.

3.17. (3R,4R)-1-Benzyloxycarbonyl-3-triisopropylsiloxy-4-trifluoromethylazetidin-2-one (**16b**(+))

To a solution of *N*-H-β-lactam **14**(+) (322 mg, 1.03 mmol) in 5 ml of THF under nitrogen atmosphere at −78 °C was added dropwise 1 M solution of LiHMDS (2 ml, 2 mmol). The reaction mixture was allowed to stir for 30 min then of CbzCl (0.155 ml, 1.03 mmol) was added. After 1 h the reaction was quenched with water and extracted with ethyl acetate three times. The crude material was purified by flash chromatography on silica gel to give 274 mg **16b**(+) in 60% yield as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.23 (21H, m), 4.55 (1H, q, $J = 4.8$ Hz), 5.28 (3H, m), 7.34 (5H, m).

3.18. (3R,4R)-1-(4-Methylbenzenesulfonyl)-3-triisopropylsiloxy-4-trifluoromethylazetidin-2-one (**16c**(+))

Yield 15%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87–1.12 (21H, m), 3.66 (3H, s), 4.46 (1H, q, $J = 5.2$ Hz), 5.14 (1H, d, $J = 5.1$ Hz), 6.75 (2H, d, $J = 9$ Hz), 6.28 (2H, d, $J = 9$ Hz).

3.19. (2S,3S)-3-(N-tert-Butoxycarbonylamino)-4,4-difluoro-2-triisopropylsiloxybutanoic acid methyl ester (**17a**(−))

A mixture of *t*-Boc-β-lactam **15a**(−) (37 mg, 0.094 mmol), triethylamine (21 μl, 0.15 mmol) and a catalytic amount of DMAP (8 mg, 0.065 mmol) in methanol (1 ml) was stirred for 30 h. Methanol was evaporated and the crude product was purified by flash chromatography on silica gel to afford **17a**(−) as colorless oil (39 mg, 98% yield); $[\alpha]_D{}^{20}+21.8°$ (c 1.375, $CHCl_3$); IR (neat): *v* 3440, 2940, 2867, 1760, 1720, 1490; ^{1}H, NMR (400 MHz, $CDCl_3$): δ 1.10 (21H, m), 1.40 (9H, s), 3.70 (3H, s), 4.3 (1H, bd, $J = 10$ Hz), 4.66 (1H, s), 5.07 (1H, bd, $J = 10$ Hz), 5.82 (1H, dt, $J = 56$, 4 Hz, CF_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 18.2, 28.5, 52.6, 55.7 (t, $J = 24$ Hz, C-3), 70.5, 80.6, 114.2 (t, $J = 243$ Hz, CF_2H), 155.3, 171.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.4 (ddd, $J = 287$, 56, 9 Hz), −130.0 (ddd, $J = 284$, 56, 9 Hz). HRMS (FAB$^+$, *m/z*): Calcd. for $C_{19}H_{37}F_2NO_5Si{\cdot}H^+$, 426.2482. Found: 426.2492.

3.20. (2S,3S)-3-(N-Benzyloxycarbonylamino)-4,4-difluoro-2-triisopropylsiloxybutanoic acid methyl ester (**17b**(−))

Yield 78%; colorless oil; IR (neat): *v* 3440, 3353, 2940, 2867, 1760–1710; ^{1}H, NMR (400 MHz, $CDCl_3$): δ 1.10 (21H, m), 3.69 (3H, s), 4.38 (1H, m), 4.68 (1H, s), 5.10 (1H, d, $J = 12$ Hz), 5.14 (1H, d, $J = 12$ Hz), 5.35 (1H, d, $J = 10$ Hz), 5.87 (1H, dt, $J = 56$, 4.4 Hz, CF_2H), 7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.7, 18.2, 52.6, 56.2 (t, $J = 24$ Hz, C-3), 67.6, 70.4, 114.0 (t, $J = 243$ Hz, CF_2H), 128.4, 128.6, 128.7,136.1, 155.9, 171.0.

3.21. (2R,3R)-3-(N-4-Methylbenzenesulfonylamino)-4,4-difluoro-2-triisopropylsiloxybutanoic acid methyl ester (**17c**(−))

Yield 87%, colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.18–1.06 (21H, m), 2.48 (3H, s), 3.67 (3H, s), 4.02–3.86

(1H, m), 4.64 (1H, sl), 5.49 (1H, d, $J = 9.3$ Hz), 5.88 (1H, dd, $J = 3.9$, 55.5 Hz), 7.36 (2H, d, $J = 8.1$ Hz), 7.82 (2H, d, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): 12.3, 17.8, 21.5, 52.4, 57.7 (dd, $J = 23$ Hz), 69.8, 113.5 (dd, $J = 245.8$ Hz), 127.2, 129.6, 137.4, 143.7, 170.6; ^{19}F NMR (282 MHz, $CDCl_3$): −125.3 (ddd, 1F, $J = 8.5$, 53.6, 284 Hz),−129.0 (ddd, 1F, $J = 18.4$, 55, 287 Hz).

*3.22. (2R,3R)-3-N-tert-Butoxycarbonylamino-4,4,4-trifluoro-2-triisopropylsiloxybutanoic acid methyl ester (**18a**(+))*

Yield 70% yield; colorless oil; $[\alpha]_D^{20}$ −23.6° (c 1.99, $CHCl_3$); IR (neat): *v* 3446, 2947, 2869, 1766, 1732, 1496, 1161; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11–1.38 (21H, m), 1.50 (9H, s), 3.79 (3H, s), 4.69 (1H, q, $J = 8.1$ Hz), 4.86 (1H, s), 5.26 (1H, d, $J = 10.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 18.0, 28.3, 52.7, 55.1 (q, $J = 29.6$ Hz, CF_3), 70.2, 81.0, 122.9, 125.8, 155.1, 170.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.4 (d, $J = 7.3$ Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{19}H_{36}F_3NO_5Si{\cdot}H^+$, 444.2388. Found: 444.2393.

*3.23. (2R,3R)-3-N-Benzyloxycarbonylamino-4,4,4-trifluoro-2-triisopropylsiloxybutanoic acid methyl ester (**18b**(+))*

Yield 58% yield; colorless oil; $[\alpha]_D^{20}$ −19.4° (c 1.08, $CHCl_3$); IR (neat): *v* 3442, 2947, 2867, 1762, 1730, 1500, 1163; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04–1.17 (21H, m), 3.68 (3H, s), 4.69 (1H, q, $J = 8.2$ Hz), 4.81 (1H, s), 5.12 (2H, s), 5.45 (1H, d, $J = 9.6$ Hz), 7.30–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 18.0, 52.7, 55.3 (q, $J = 30.4$ Hz), 67.8, 70.1, 128.3, 128.5, 128. 8, 136.1, 155.9, 170.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ −73.5 (d, $J = 7.1$ Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{22}H_{34}F_3NO_5Si{\cdot}H^+$, 478.2231. Found: 478.2235.

*3.24. (2R,3R)-3-(N-4-Methylbenzenesulfonylamino)-4,4,4-trifluoro-2-triisopropylsiloxybutanoic acid methyl ester (**18c**(+))*

100% yield; colorless oil; $[\alpha]_D^{20}$+53.4° (c 0.88, $CHCl_3$); IR (neat): *v* 3440, 2945, 2867, 1768, 1514, 1249, 1139; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04–1.27 (21H, m), 3.79 (3H, s), 4.58 (1H, q, $J = 5.4$ Hz), 5.27 (1H, d, $J = 5.2$ Hz), 6.87 (2H, d, $J = 7.0$ Hz), 7.40 (2H, d, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 17.7, 17.8, 29.9, 55.7, 58.5 (q, $J = 31.9$ Hz), 76.3, 114.6, 119.4, 130.0, 157.2, 165.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.7 (d, $J = 5.6$ Hz).

*3.25. [(2S,3S)-3-tert-Butoxycarbonylamino-4,4-difluoro-2-triisopropylsiloxybutanoyl]glycine methyl ester (**19b**)*

To the solution of β-lactam **15a**(−) (40 mg, 0.1 mmol) and glycine methyl ester (16 mg, 0.13 mmol) in 1 ml of CH_2Cl_2 was added dropwise *N*-methylmorpholine (16 μl, 0.15 mmol) at ambient temperature. The mixture was stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, and concentrated in *vacuo* to afford 30 mg of **19b** in 62% yield as colorless oil: $[\alpha]_D^{20}$ −12.84° (c 1.635, $CHCl_3$); IR (neat): *v* 3417, 2947, 2869, 1760–1693; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (18H, s), 1.12 (3H, m), 1.20 (9H, s), 3.78 (3H, s), 4.00 (1H, dd, $J = 18$, 5 Hz), 4.10 (1H, dd $J = 18$, 5 Hz) 4.33 (1H, m), 4.40 (1H, d, $J = 4$ Hz), 5.70 (1H, d, $J = 10$ Hz), 5.93 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 18.2, 28.5, 41.2, 52.7, 55.2 (t, $J = 21$ Hz), 71.5, 80.4, 113.8 (t, $J = 243$ Hz, CF_2H), 155.2, 169.6, 171.5; ^{19}F NMR (282 MHz, $CDCl_3$): −126.6 (ddd, $J = 286$, 55, 9 Hz), −128.6 (ddd, $J = 286$, 55, 18 Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{21}H_{40}F_2N_2O_6Si{\cdot}H^+$, 483.2697. Found: 483.2703.

*3.26. [(2S,3S)-4,4-Difluoro-3-(4-methylbenzenesulfonylamino)-2-triisopropylsiloxybutanoyl]-(S)-valine methyl ester (**19c**)*

Yield 82%; colorless oil ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.12–0.85 (27H, m), 2.19–2.13 (1H, m), 2.41 (3H, s), 3.72 (3H, s), 3.87–3.79 (1H, m), 4.15–3.91 (1H, m), 4.47–4.43 (1H, m), 5.87 (1H, dd, $J = 1.6$, 54.8 Hz), 6.62 (1H, d, $J = 8.4$ Hz), 7.28–7.23 (3H, m), 7.79 (2H, d, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 11.9,14.3, 17.8, 18.6, 21.6, 31, 52.2, 56.9 (dd, $J = 25$ Hz), 60.4, 69.9, 113.1 (dd, $J = 244.8$ Hz), 127.2, 129.5, 137.7, 143.5, 170.6, 171.1; ^{19}F NMR (282 MHz, $CDCl_3$): −126.2 to −126.5 (m, 2F). HRMS (FAB^+, *m/z*): Calcd. for $C_{26}H_{44}F_2N_2O_6SSi{\cdot}H^+$, 579.2730. Found: 579.2723.

*3.27. [(2S,3S)-4,4-Difluoro-3-(4-methylbenzenesulfonylamino)-2-triisopropylsiloxybutanoyl]-(S)-leucine methyl ester (**19d**)*

Yield 94%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03–089 (28H, m), 1.65–1.52 (2H, m), 2.4 (3H, s), 3.71 (3H, s), 3.85–3.81 (1H, m), 4.12–4.08 (1H, m), 4.58–4.51 (1H, m), 5.85 (1H, dd, $J = 54.4$ Hz), 7.07 (1H, d, $J = 8.4$ Hz), 7.29 (2H, d, $J = 8.4$ Hz), 7.79 (2H, d, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.9, 17.8, 21.6, 21.9, 22.7, 24.8, 41.4, 50.4, 52.3, 57.2 (dd, $J = 21.3$ Hz), 69.8, 113 (dd, $J = 245.6$ Hz), 127.2, 129.5, 137.7, 143.5, 170.4, 172.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.4 to −126.7 (m, 2F). HRMS (FAB^+, *m/z*): Calcd. for $C_{27}H_{46}F_2N_2O_6SSi{\cdot}H^+$, 593.2887. Found: 593.2900.

*3.28. [(2S,3S)-4,4-Difluoro-3-(4-methylbenzenesulfonylamino)-2-triisopropylsiloxybutanoyl]-(S)-methionine methyl ester (**19e**)*

Yield 89%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08–0.89 (21H, m), 2.06 (3H, s), 2.14–1.97 (2H, m), 2.4 (3H, s), 2.49–2.42 (2H, m), 3.74 (3H, s), 3.88–3.82 (1H, m),

4.14–4.11 (1H, m), 4.72–4.66 (1H, m), 5.88 (1H, dd, $J = 1.6$, 54.4 Hz), 6.53 (1H, d, $J = 9.6$ Hz), 7.29 (2H, d, $J = 8.4$ Hz), 7.4 (1H, d, $J = 8$ Hz), 7.79 (2H, d, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$, 100.5 MHz): δ 12, 15.4, 17.8, 21.6, 29.6, 31.3, 51.1, 52.6, 57.1 (dd, $J = 20.6$ Hz), 69.9, 113.1 (dd, $J = 245.5$ Hz), 127.2, 129.5, 137.7, 143.6, 170.5, 171.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.4 to −126.7 (m, 2F). HRMS (FAB^+, *m/z*): Calcd. for $C_{26}H_{44}F_2N_2O_6S_2Si{\cdot}H^+$, 611.2451. Found: 611.2451.

*3.29. (2S,3S)-2-[4,4-Difluoro-3-(4-methylbenzenesulfonylamino)-2-triisopropylsiloxybutanoyl]-(S)-phenylalanine methyl ester (**19f**)*

Yield 83%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.94–0.89 (21H, m), 3.39 (3H, s), 2.97 (1H, dd, $J = 5.6$, 14 Hz), 3.16 (1H, dd, $J = 5.6$, 14 Hz), 3.68 (3H, s), 3.84–3.76 (1H, m), 4.11 (1H, d, $J = 5.2$ Hz), 4.92–4.87 (1H, m), 5.69 (1H, ddd, $J = 1.6$, 54.4 Hz), 6.53 (1H, d, $J = 9.2$ Hz), 7.1–7.07 (3H, m), 7.29–7.22 (5H, m), 7.79 (2H, d, $J = 8.4$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.9, 17.7, 21.5, 37.9, 52.2, 57.1 (dd, $J = 20.6$ Hz), 69.8, 112.9 (dd, $J = 245.6$ Hz), 127.1, 127.2, 128.6, 128.9, 129.5, 135.1, 137.7, 143.5, 170.2, 170.8; ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.9 to −126.3 (m, 2F). HRMS (FAB^+, *m/z*): Calcd. for $C_{30}H_{44}F_2N_2O_6SSi{\cdot}H^+$, 627.2730. Found: 627.2747.

*3.30. [(2S,3S)-4,4-Difluoro-3-(4-fluorobenzoylamino)-2-triisopropylsiloxybutanoyl]-(S)-phenylalanine methyl ester (**19g**)*

Yield 100%; colorless oil; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.98–0.86 (21H, m), 3.05 (dd, $J = 5.3$, 14 Hz), 3.16 (dd, $J = 5.2$, 14 Hz), 3.71 (3H, s), 4.76 (d, 1H, $J = 5$ Hz), 4.39 (1H, d, $J = 5$ Hz), 4.99–4.84 (2H, m), 5.92 (1H, dd, $J = 55$ Hz), 7.15–7.07 (3H, m), 7.32–7.22 (5H, m), 7.75 (1H, d, $J = 7.5$ Hz), 7.92–7.87 (2H, m); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 6.7, 12.6, 24.5, 32.6, 47.09, 47.8 (dd, $J = 20.1$ Hz), 108.3 (dd, $J = 243$ Hz), 65.3, 110.5 (d, $J = 15.7$ Hz), 113, 122.2, 123.6, 124.4, 124.5 (d, $J = 9.5$ Hz), 129.9, 159.8 (d, $J = 251.6$ Hz), 163.1(d, $J = 326$ Hz), 165.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.8 (sl, 1F), −126.5 to −126.9 (m, 2F). HRMS (FAB^+, *m/z*): Calcd. for $C_{30}H_{41}F_3N_2O_5Si{\cdot}H^+$, 595.2810. Found: 595.2811.

*3.31. [(2R,3R)-3-(N-Benzyloxycarbonylamino)-4,4,4-trifluoro-2-triisopropylsiloxybutanoyl]-(S)-phenylalanine methyl ester (**20a**)*

Yield 65%; colorless oil; $[\alpha]_D^{20}$+6.8° (c 1.76, $CHCl_3$); IR (neat): *v* 3404, 2947, 2867, 1730, 1500, 1143; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (21H, m), 3.08 (1H, dd, $J = 7.2$ Hz), 3.19 (1H, dd, $J = 5.2$ Hz), 3.71 (3H, s), 4.47 (1H, d, $J = 3.2$ Hz), 4.62 (1H, m), 4.83 (1H, q, $J = 6.8$ Hz), 5.08 (1H, d, $J = 12$ Hz), 5.15 (1H, d, $J = 12$ Hz), 6.12 (1H, d, $J = 10$ Hz), 7.10 (2H, d, $J = 6.4$ Hz), 7.33 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5, 17.9, 18.0, 38.2, 52.1, 53.4, 55.7 (q, $J = 29.6$ Hz), 67.7, 71.4, 127.4, 128.3, 128.5, 128.7, 128.8, 129.2, 135.8, 136.1, 155.7, 170.8, 171.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −71.7 (d, $J = 9.0$ Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{31}H_{43}F_3N_2O_6Si{\cdot}H^+$, 625.2915. Found: 625.2930.

*3.32. [(2S,3S)-3-N-tert-Butoxycarbonylamino-4,4-difluoro-2-triisopropylsiloxybutanoyl]-β-alanine ethyl ester (**21a**)*

Yield 50%; colorless oil; $[\alpha]_D^{20}$+20.85° (c 0.815, $CHCl_3$); IR (neat): *v* 3427, 2964, 2869, 1760–1693; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.24 (24H, m), 1.43 (9H, s), 2.49 (2H, m), 3.46 (1H, m), 3.58 (1H, m), 4.14 (2H, m) 4.32 (2H, m), 5.76–6.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.5, 18.2, 33.8, 34.6, 55.2 (t, $J = 21$ Hz), 61.0, 71.4, 80.3, 113.9 (t, $J = 243$ Hz, CF_2H), 155.2, 171.2, 172.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.8 (ddd, $J = 286$, 55, 9 Hz), −128.5 (ddd, $J = 286$, 55, 18 Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{23}H_{44}F_2N_2O_6Si.Na^+$, 533.2829. Found: 533.2848.

*3.33. [(2R,3R)-3-N-Benzyloxycarbonylamino-4,4,4-trifluoro-2-triisopropylsiloxybutanoyl]-β-alanine ethyl ester (**22b**)*

Yield 65%; colorless oil; $[\alpha]_D^{20}$-26.9° (c 0.89, $CHCl_3$); IR (neat): *v* 3421, 2947, 2867, 1730, 1500, 1271, 1182, 1141; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (21H, m), 1.24 (t, $J = 7.2$ Hz, 3H), 2.48 (3H, m), 3.46 (1H, m), 3.58 (1H, m), 4.13 (2H, m), 4.44 (1H, d, $J = 3.2$ Hz), 4.60 (1H, m), 5.09 (1H, d, $J = 12$ Hz), 5.17 (1H, d, $J = 12$ Hz), 6.19 (1H, d, $J = 10$ Hz), 7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 14.3, 18.0, 33.7, 34.6, 55.7 (q, $J = 28.9$ Hz), 61.0, 67.7, 71.5, 128.3, 128.5, 128.7, 136.1, 155.7, 170.8, 172.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −71.7 (d, $J = 7.3$ Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{26}H_{41}F_3N_2O_6Si{\cdot}H^+$, 563.2759. Found: 563.2772.

*3.34. 2-Debenzoyl-2-(3-chlorobenzoyl)-10-propanoyl-3′-dephenyl-3′-difluoromethyldocetaxel (**25**)*

2-(3-Chlorobenzoyl)-7-TES-10-propanoylbaccatin **23** [60] (31 mg, 0.042 mmol) and β-lactam **15a**(+) (23 mg, 0.058 mmol) were dissolved in THF (1 ml, $c = 0.042$ M). The mixture was cooled to −40 °C, and LiHMDS (1 M THF solution, 76 μl) was added. The solution was stirred for 2 h, and the reaction was quenched with 1 ml of NH_4Cl, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The crude was purified on silica gel column to yield 44 mg (92%) of 7-TES-2′-TIPS-**25** as a white solid: ^{1}H

NMR ($CDCl_3$, 300 MHz): δ 0.68 (6H, m, TES), 0.94 (9H, m, TES), 1.15–1.30 (30H, m, H-17, H-16, TIPS, CH_3), 1.32 (9H, s, Boc), 1.68 (3H, s, H-19), 1.90 (1H, m, H-6b), 2.10 (4H, m, H-18, H-14b), 2.30 (1H, m, H-14a), 2.40 (3H, s, 4-OAc), 2.55 (3H, m, H-6a, $COCH_2$), 3.87 (1H, d, $J = 7$ Hz, H-3), 4.16 (1H, d, $J = 8.0$ Hz, H-20b), 4.32 (1H, d, $J = 8.0$ Hz, H-20a), 4.42 (1H, m, H-3′), 4.48 (1H, dd, $J = 7$, 10 Hz H-7), 4.87 (1H, bs, H-2′), 4.95 (1H, bd, $J = 7.0$ Hz, H-5), 5.08 (1H, d, $J = 10$ Hz, NH′), 5.64 (1H, d, $J = 7.0$ Hz, H-2), 5.80 (dt, $J = 6.3$, 56.0 Hz, CF_2H), 6.25 (1H, m, H-13), 6.38 (1H, s, H-10), 7.50 (1H, t, $J = 8.0$ Hz, arom), 7.60 (1H, m, arom), 8.00 (1H, m, arom), 8.16 (1H, m, arom); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 202.0, 172.9, 171.1, 170.3, 166.0, 155.5, 140.6, 135.0, 133.8, 133.7, 131.2, 130.7, 130.3, 128.5, 84.5, 81.3, 80.9, 79.1, 76.7, 75.6, 75.0, 72.5, 72.1, 70.6, (d, $J_{CF} = 6$ Hz), 58.6, 56.0 (t, $J_{CF} = 24$ Hz), 47.0, 43.5, 37.4, 35.4, 28.2, 27.8, 26.5, 22.9, 21.5, 18.2, 18.1, 14.5, 12.9, 10.3, 9.4, 7.0, 5.5; ^{19}F NMR, ($CDCl_3$, 282 MHz): δ −125.0 (ddd, $J = 9.0$, 55, 283 Hz), −128.8 (ddd, $J = 9.0$, 55, 283 Hz).

To a solution of 7-TES-2′-TIPS-**25** (44 mg) in 4 ml of a 1:1 mixture of pyridine and CH_3CN at 0 °C was added 0.5 ml of HF-pyridine. The reaction was allowed to warm to room temperature and stirred for 26 h. The reaction mixture was then quenched with 1 ml of $NaHCO_3$, and extracted with ethyl acetate. The combined organic layers washed with $CuSO_4$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel using hexane/ethyl acetate (1/1) as eluant to afford 18 mg (75% yield) of **25** as a white solid: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (9H, m, H-17, H-16, CH_3), 1.33 (9H, s, Boc), 1.69 (3H, s, H-19), 1.91 (4H, m, H-18, H-6b), 2.30 (2H, m, H-14a, H-14b), 2.43 (3H, s, 4-OAc), 2.55 (3H, m, H-6a, $COCH_2$), 3.48 (1H, d, $J = 5$ Hz, OH-2′), 3.86 (1H, d, $J = 7$ Hz, H-3), 4.16 (1H, d, $J = 8.0$ Hz, H-20b), 4.32 (1H, d, $J = 8.0$ Hz, H-20a), 4.44 (2H, m, H-7, H-3′), 4.66 (1H, dd, $J = 5$ Hz, H-2′), 5.00 (1H, bd, $J = 7.0$ Hz, H-5), 5.08 (1H, d, $J = 10$ Hz, NH′), 5.64 (1H, d, $J = 7.0$ Hz, H-2), 5.80 (dt, $J = 6.3$, 56.0 Hz, CF_2H), 6.25 (1H, m, H-13), 6.38 (1H, s, H-10), 7.50 (1H, t, $J = 8.0$ Hz, arom), 7.60 (1H, m, arom), 8.00 (1H, m, arom), 8.16 (1H, m, arom); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.3, 9.8, 15.1, 22.1, 22.6, 27.8, 28.2, 26.9, 35.6, 35.8, 43.4, 45.9, 54.8 (t, $J_{CF} = 24$ Hz), 58.7, 68.9 ($J_{CF} = 6$ Hz), 72.5, 73.1, 75.6, 75.7, 76.5, 79.4, 81.2, 81.3, 84.7, 114.3 (t, $J_{CF} = 244$ Hz) 128.5, 130.4, 130.6, 131.1, 133.4, 134.0, 135.1, 142.1, 155.3, 166.0, 170.6, 172.6, 174.9, 203 8; ^{19}F NMR, ($CDCl_3$, 282 MHz): δ −126.0 (ddd, $J = 12$, 55, 283 Hz), −128.0 (ddd, $J = 9$, 55, 286 Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{41}H_{52}ClF_2NO_{15}.Na^+$, 894.2886. Found: 894.2922.

In the same manner as described for the synthesis of 25, 7-TES-2′-TIPS-**26** and fluoro-taxoid **26** were obtained. The characterization data of these taxoids are shown below.

*3.35. 2-Debenzoyl-2-(3-azidobenzoyl)-7-triethylsilyl-10-propanoyl-2′-triisopropylsilyl-3′-dephenyl-3′-trifluoromethyldocetaxel (7-TES-2′-TIPS-**26**)*

Yield 96%; white solid; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.60 (6H, m, TES), 0.93 (9H, m, TES), 1.13–1.28 (30H, m, H-17, H-16, TIPS, CH_3), 1.33 (9H, s, Boc), 1.70 (3H, s, H-19), 1.91 (1H, m, H-6b), 2.05 (3H, s, H-18), 2.32 (2H, m, H-14), 2.37 (3H, s, 4-OAc), 2.52 (3H, m, H-6a, $COCH_2$), 3.86 (1H, d, $J = 6.9$ Hz, H-3), 4.18 (1H, d, $J = 8.4$ Hz, H-20b), 4.35 (1H,d, $J = 8.4$ Hz, H-20a), 4.49 (1H, dd, $J = 3.6$, 10.2 Hz, H-7), 4.69 (1H, q, $J = 8.1$ Hz, H-3′), 4.95 (2H, m, H-2′, H-5), 5.19 (1H, d, $J = 10.2$ Hz, NH′), 5.70 (1H, d, $J = 6.9$ Hz, H-2), 6.25 (1H, t, $J = 9.6$ Hz, H-13), 6.50 (1H, s, H-10), 7.22 (1H, dd, $J = 1.5$, 7.8 Hz, arom), 7.50 (1H t, $J = 8.1$ Hz, arom), 7.85 (1H s, arom), 7.91 (1H d, $J = 8.1$ Hz, arom); ^{19}F NMR, ($CDCl_3$, 282 MHz): δ −72.90 (d, $J = 6.2$ Hz).

*3.36. 2-Debenzoyl-2-(3-azidobenzoyl)-10-propanoyl-3′-dephenyl-3′-trifluoromethyldocetaxel (**26**)*

Yield 84%; white solid; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.16 (3H, s, C-16), 1.25 (6H, m, C-17, CH_3), 1.32 (9H, s, Boc), 1.69 (3H, s, H-19), 1.69 (1H, ds, OH), 1.90 (4H, m, H-6b, H-18), 2.32 (2H, m, H-14), 2.39 (3H, s, 4-OAc), 2.56 (4H, m, H-6a, $COCH_2$, OH), 3.55 (1H, bs, OH), 3.84 (1H, d, $J = 6.9$ Hz, H-3), 4.18 (1H, d, $J = 8.7$ Hz, H-20b), 4.34 (1H, d, $J = 8.7$ Hz, H-20a), 4.45 (1H, dd, $J = 3.6$, 10.2 Hz, H-7), 4.72 (1H, s, H-5), 4.78 (1H, q, $J = 8.1$ Hz, H-3′), 4.98 (1H, d, $J = 8.1$, H-2′), 5.30 (1H, d, $J = 10.2$ Hz, NH′), 5.67 (1H, d, $J = 7.2$ Hz, H-2), 6.25 (1H, t, $J = 9.3$ Hz, H-13), 6.32 (1H, s, H-10), 7.24 (1H, d, $J = 8.1$ Hz), 7.50 (1H, t, $J = 7.8$ Hz), 7.84 (1H, s), 7.91 (1H, d, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.0, 9.5, 14.2, 14.8, 21.9, 22.4, 26.6, 27.5, 27.9, 35.3, 35.5, 43.2, 45.6, 53.8 (q, $J_{CF} = 48$ Hz), 58.5, 60.4, 68.1, 72.1, 73.3, 75.2, 75.4, 76.3, 76.6, 79.0, 81.1, 81.2, 84.5, 120.0, 124.5, 126.7, 130.2, 130.7, 133.3, 140.9, 141.6, 154.6, 166.2, 170.3, 171.8, 174.6, 203.5; ^{19}F NMR, ($CDCl_3$, 282 MHz): δ −73.78 (d, $J = 9.3$ Hz). HRMS (FAB^+, *m/z*): Calcd. for $C_{41}H_{51}F_3N_4O_{15}{\cdot}H^+$, 897.3376. Found: 897.3406.

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