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Direct and Diastereoselective Alkylation and Aldol Reactions of α -Bromo- α -fluoro- β -lactams

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Abstract



Herein, we describe the development of a method for the direct alkylation and aldol reaction of α -bromo- α -fluoro- β -lactams. This method provides facile access to a wide range of 3-alkyl- and 3-hydroxyalkyl-fluoro- β -lactams in good yields under mild conditions. The products were obtained with complete diastereoselectivity with regards to the relative configuration of the β -lactam ring at C3 and C4 positions. The reaction conditions were tolerant of a broad range of electrophiles, which highlights the overall scope and utility of this procedure.

Introduction

Fluorinated compounds have recently been highlighted as important chemical scaffolds in both medicinal chemistry and agrochemical research.¹ The incorporation of a fluorine atom at a suitable position within a target molecule can lead to unique changes in the overall properties of the target molecule, such as increased lipophilicity, modified bioavailability, and improved metabolic stability. These changes are effectively facilitated by the chemical properties of the fluorine atom,² and the significance of design strategies using fluorine in this way is exemplified by the fact that almost 20% of all pharmaceuticals³ and 30% of all agrochemicals⁴ contain fluorine(s). The development of synthetic methods allowing for the incorporation of fluorine atoms into target molecules is therefore of particular importance, and extensive research efforts have already been deployed in this area.⁵

 β -Lactams are a particularly well known structural class of bioactive compounds, with activities reported not only in antibiotics but also in the inhibition of a diverse



Figure 1. Bioactive 3-alkylated or 3-hydroxyalkylated β -lactams

range of enzymes.⁶ For example, thienamycin (1) has been used as a carbapenem-type antibiotic, whereas ezetimibe (2) has been used as a cholesterol absorption inhibitor (Figure 1). Ezetimibe (2), in particular, has been used clinically for the treatment of hypercholesteremia and theoretical structure activity relationships have also been developed in this context for a related series of azetidin-2-ones.⁷ Interestingly, β -lactams of this type typically possess a characteristic 3-alkylated substructure on the β -lactam ring. The design of synthetic strategies allowing for the functionalization of the fluoro-β-lactam scaffold is therefore of special importance. With this in mind, our recent research efforts have been focused on the development of methods for the synthesis of 3-alkyl-3-fluoroazetidin-2-ones. To date, there have been a significant number of reports in the literature describing the development of methods for the construction of 3-alkyl β -lactams, including the direct alkylation of β -lactams via the condensation of the corresponding β -lactam enolates with electrophiles,⁸ as well as the direct Lewis acid-mediated arylation and allylation of β-lactams with different nucleophiles.9

Furthermore, a variety of substituted β -lactam compounds have been prepared using a Staudinger ketene-imine [2+2] cycloaddition reaction.¹⁰ Among them, the enolate-alkyl halide condensation is the simplest and most powerful method in this particular reaction class. Although a variety of different methods have been reported for the construction of β -lactam and α -monofluoro- β -lactam compounds,¹¹ to the best of our knowledge, there have only been two reports in the literature concerning the direct alkylation of fluoro- β -lactam.¹² The first of these reports described the synthesis of diastereomerically pure 3-alkylated β-lactams via the deprotonation of 3-fluoroazetidin-2-one with LDA followed by the trapping of the resulting enolate with an electrophile, such as an alkyl halide or carbonyl compound.^{12a} Unfortunately, the practical application of this approach was severely limited by the requirement for particularly low temperature conditions (i.e., -100 to -90 °C) during the lithiation of 3-fluoroazetidin-2-one. Furthermore, with the exception of the methylated product, the yields were invariably low and only a limited number of electrophiles were used. In the second of these two reports, the radical chain reaction of 3-fluoro-3-iodo-B-lactam with olefins was used for the construction of 3-alkylated β -lactams. In this particular case, the substrate scope was limited. Furthermore, the alkylated products contained an alkyl iodide moiety, and an additional step involving the use of toxic Bu₃SnH was



required to furnish the desired products, further limiting the practical application of this method.^{12b} Although an electrophilic fluorination of azetidinone through of β -lactam enolate has been also reported, the reaction example was with only one substrate and there was no information of the scope and limitation.¹³ We recently reported the synthesis of α -bromo- α -fluoro- β -lactam (3) via a Reformatsky-type reaction and the subsequent functionalization of 3 under Kumada coupling reaction conditions using a variety of aryl Grignard reagents (Scheme 1).^{14,15} Although this method allowed for the successful arylation of 3, it remained difficult to alkylate 3 using this method. During the course of our ongoing work towards the synthesis of functionalized β -lactam systems, we recently observed that the lithium enolate of 3 could be readily generated using a halogen-lithium exchange reaction. Herein, we wish to report the alkylation of 3 according to a condensation reaction between its corresponding enolate and a range of

alkyl halides.

Result and discussion

Scheme 2. Halogen-metal exchange reaction of **3a** using several metal reagents



The halogen-metal exchange reaction is a useful method for the generation of carbon nucleophiles under mild conditions.^{8c,d,16} The lithiation of (3R,4S)/(3S,4R)-1-benzyl-3-bromo-3-fluoro-4-phenylazetidin-2-one (**3a**) was initially conducted using 1.5 equiv of *n*-BuLi at -78 °C followed by treatment with 2 equiv of methyl iodide. Following the addition of the electrophile, the reaction temperature was slowly raised to 0 °C, affording the desired product (**4a**) diastereoselectively in quantitative yield (Scheme 2).¹⁷ The insertion of other metals, such as samarium and zinc, into **3a** was also examined. Unfortunately, however, the use of SmI₂ failed to promote the metal insertion and the starting material **3a** was recovered in 82% yield.

Table 1. Direct alkylation of 3a with various alkyl halides

Bn O	1) <i>n</i> -Bu THF	Li (1.5 equiv), –78 °C	Bn O	Bn O	`
	r 2) Elec _78 °	trophile (2 equiv), °C \rightarrow 0 °C, 3 h		F Ph F	_
(3R,4S)/(3S,4R)	-3a		(3R,4S)/(3S,4F	R) -4 ° ∖(3R,4S)/(3S,4R)- 5	•/
E	ntry	Electrophile	Products	Yield (%) ^b	
	1	CH ₃ I	4a	quant. (77°)	
	2	Br	4b	78	
	3	Ph	4c	96	
	4	Br	4d	61	
	5	TMS	4e	91	
	6	Br	4f	43	
	7	Ph Br	4g	89	
	8	TMS—OTf	4h	60 (60 ^c)	
	9	MeOH	5	76	

a: Compound **4h** is (3*S*,4*S*)/(3*R*,4*R*).

b^{: 19}F NMR yields.

ċ Isolated yield.

Although zinc was successfully inserted into **3a**, only a diastereomeric mixture of the hydrogen substituted products **5** and **6** was obtained in a combined yield of 83%, with none of the desired product **4a** detected. Further screening of the conditions revealed that the reaction could be performed with several different alkyl lithium reagents without any reduction in the product yield.¹⁸ Thus, with the optimal reaction conditions in hand, we proceeded to explore the scope and limitations of this reaction using several

different alkyl halides (Table 1). Allyl, cinnamyl, propargyl, TMS-protected propargyl and benzyl groups were well tolerated under the optimized reaction conditions, providing the desired products in good yields (Table 1, entries 2-5 and 7). In contrast, the yield of the 3-phenylpropargylated product **4f** was relatively low (Table 1, entry 6). Interestingly, the reaction also worked well when TMSOTf was used as the electrophile to give the desired product in moderate yield (Table 1, entry 8). It is noteworthy that the *C*-silylated product was observed in this particular case with none of the *O*-silylated product detected. The treatment of lithiated **3a** with methanol afforded the corresponding protonated product **5** (Table 1, entry 9). In all of these reactions, excellent levels of diastereoselectivity were achieved to form the (3R, 4S)/(3S, 4R)-isomers exclusively.

The condensation reaction between the enolate of **3** and methyl iodide was evaluated with a series of different α -bromo- α -fluoro- β -lactams (**3**) (Table 2). The results revealed that substrates bearing bulky substituents on the nitrogen atom of **3** proceeded smoothly through the reaction (Table 2, entries 1-4). In contrast, the substrate bearing a methyl group on the nitrogen atom **3e** did not give the desired product **7e** when the reaction was conducted under the optimized conditions (Table 2, entry 5) and only gave the desired product in moderate yield when the lithiation reaction of **3e** was performed

at -100 °C (Table 2, entry 6). On the basis of these results, it was assumed that the lithium enolate of **3e** could potentially be thermally unstable. Interestingly, the introduction of a methoxy or a fluorine substituent at the *para*-position of the R² phenyl ring did not affect the yield of products, suggesting that the scope of this reaction could be readily expanded into a series of β -lactams containing differentially substituted phenyl groups at the R² positions. It is important to note that the reactions occurred with complete diastereoselectivity in all cases to give a mixture of the (3R.4S)/(3S.4R)-isomers.

Table 2. Direct methylation of several	a-bromo-a-fluoro-	β-lactams (3)
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R ¹ R ² ''' H (3 <i>R</i> ,4 <i>S</i>)	0 1) <i>n</i> -B THF 2) Mel F -78 /(3 <i>S</i> ,4 <i>R</i>)- 3	uLi (1.5 equiv), –7 = (2 equiv), °C → 0 °C, 3 h	$\overset{8 \ \circ C}{\longrightarrow} \begin{array}{c} R^{1} \\ R^{2} \\ R^{2} \\ H \\ R^{2} \\ R^{2}$	-7	
Entry	R ¹	R ²		Products	Yield (%) ^a
1	Bn	Ph	3a	4a	Quant. (77 ^b)
2	PMB	Ph	3b	7b	Quant. (93 ^b)
3	Benzhydryl	Ph	3с	7c	92
4	<i>tert</i> -Bu	Ph	3d	7d	87 (72 ^b)
5	Ме	Ph	3e	7e	0

6^c Ph Me 3e 7e 4-MeO-C₆H₄ 7f Bn 3f $4-F-C_6H_4$ Bn 3g 7g

a: 19F NMR yields.

b: Isolated yields.

c: The lithiation of **3e** was carried out at -100 °C.

The relative configuration of products was determined on the basis of the coupling constant between the C4 hydrogen and C3 fluorine atoms of **4** using ¹⁹F NMR spectroscopy. The (3R,4S)/(3S,4R)-isomer **5** had a hydrogen–fluorine coupling constant of 4.3 Hz, whereas the (3S,4S)/(3R,4R)-isomer **6** provided a larger hydrogen–fluorine coupling constant of 10.7 Hz. Furthermore, the NOESY spectra of the two isomers provided conclusive conformation of the relative configuration, with strong NOE correlations observed between the protons at the C3 and C4 positions in the (3R,4S)/(3S,4R)-isomer **5**. All of the (3R,4S)/(3S,4R)-isomer products possessed a small hydrogen–fluorine coupling constant of approximately 4 Hz. The relative configurations of the other substituted products were tentatively assumed by analogy. The facial selectivity associated with the introduction of the alkyl group has been attributed to the desire of the system to avoid the phenyl ring lying on the same convex face of the β -lac-



Figure 2. The plausible stereo-induction model of the alkylation reaction

E⁺

tam substrate (Figure 2).

An aldol reaction is one of the most common strategies for the introduction of hydroxylalkyl groups to the α -position of carbonyl compounds.¹⁹ In a further expansion of the scope of our current methodology, we investigated the introduction of a 3-hydroxyalkyl side chain to the β -lactam with the aim of generating structural motifs similar to those found in the important antibiotic thienamycin. When benzaldehyde was used as an electrophile under the optimized reaction conditions, its aldol reaction with lithiated 3a gave the desired product as a mixture of diastereoisomers (8a and 9a) in good yield (Table 3, entry 1). Interestingly, as well as in the case of the alkylation of $\mathbf{3}$, the stereocenter at the C3 position of the β -lactam was constructed with complete diastereoselectivity with respect to the relative configurations of the C3 and C4 positions. The scope of this aldol reaction was explored using a variety of different carbonyl compounds, and the results have been listed in Table 3. The results revealed that a wide range of aromatic aldehydes and ketone proceeded smoothly through the

aldol reaction to afford the corresponding products in good yields (Table 3, entries 1-6). In contrast to the results reported by Welch et al,^{12a} good levels of stereoselectivity were observed at the C1' position of the side chain. Furthermore, aliphatic aldehydes and ketones were well tolerated under the current reaction conditions and afforded the corresponding products in good yield (Table 3, entries 7-12). Unfortunately, however, these substrates did not experience the same level of stereocontrol at the newly formed C1' position, with the diastereoselective outcomes in these cases being similar to those reported by Welch et al.^{12a}

Table 3. Aldol reaction of 3a with various carbonyl compounds

Bn
$$O$$

Ph'' Br H F 1 n -BuLi (1.5 equiv), $-78 \degree C$
THF 2) Carbonyl compound (1 equiv), $Ph'' H$ F R^4
 $-78 \degree C \rightarrow -30 \degree C$ $(3S,4S)/(3S,4R)-3a$ $(3S,4S)/(3R,4R)-8+9$

					Diastereoratio ^a	Yield
Entry	R ⁴	R⁵	Time (h)	Products	of 8 : 9	(%) ^b
1	Ph	н	18	8a+9a	82:18	85 (79 [°])
2	4-MeO-C ₆ H ₄	Н	22	8b+9b	78:22	77
3	4-CI-C ₆ H ₄	н	18	8c+9c	80:20	72
4	1-naphthyl	Н	20	8d+9d	79:21	83

5	2-naphthyl	Н	23	8e+9e	80:20	78
6	Ph	Ме	17	8f+9f	81:19	92
7 ^d	Ме	н	17	8g+9g	56:44	65
8	iso-Pro	н	20	8h+9h	51:49	76
9	cyclohexyl	н	18	8i+9i	52:48	89
10	<i>tert-</i> Bu	Н	23	8j+9j	67:33	74
11	Ме	Et	18	8k+9k	57:43	73
12	Ме	Ме	22	81		76

a: From ¹⁹F NMR spectra of crude mixture.

b: 19F NMR yields.

c: Isolated yield.

d: Exess of acetaldehyde was used (ca. 3 equiv).

Conclusions

We have developed a mild and efficient method for the direct alkylation and aldol reaction of α -bromo- α -fluoro- β -lactams 3, with both reactions occurring with complete diastereoselectivity with respect to the relative configurations at the C3 and C4 positions. The current alkylation reaction has been shown to be particularly versatile and tolerant of a range of different electrophiles, providing the desired alkylated fluoro- β -lactam products in good yields. When aromatic aldehydes and ketone were used as the electrophiles in the aldol reaction, high levels of diastereoselectivity were observed at the C1' position of the side chain of the fluoro- β -lactam products. In contrast, however, the use of aliphatic aldehydes and ketones as the electrophiles resulted in low levels of diastereoselectivity at the same position. This method has provided effective access to 3-alkylated and 3-hydroxyalkylated α -fluoro- β -lactams, with potential applications in a number of different areas of research.

Experimental Section

NMR spectra were obtained from a solution in CDCl₃ using 600 and 400 MHz for ¹H, 150 and 100 MHz for ¹³C and 564 and 90 MHz for ¹⁹F. Chemical shifts of ¹H NMR and ¹³C NMR are reported in ppm from tetramethylsilane (TMS) as an internal standard. Chemical shifts of ¹⁹F NMR are reported in ppm from benzotrifluoride as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet doublet, br = broad, brs = broad-singlet, m = multiplet), coupling constants (Hz). High-resolution mass spectroscopy (HRMS) experiments were measured on a double-focusing mass spectrometer with an ionization mode of EI or positive FAB as indicated for each

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compound. Infrared (IR) spectra were recorded in KBr tablets or thin films on either KBr disks. Melting points were measured uncorrected.

Anhydrous THF and diethyl ether (Et₂O) were distilled over benzophenone ketyl sodium just before use. All commercially available materials were used as received without further purification. All experiments were carried out under argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted.

Synthesis of α -bromo- α -fluoro- β -lactam (3) by the Reformatsky-type reaction

Ethyl dibromofluoroacetate (1.5 mmol) was added to a solution of the corresponding imine (1 mmol) in Et₂O (4 mL) at 0 °C. Then 1.0 M Et₂Zn in hexane (1.5 mL, 1.5 mmol) was slowly added to the mixture at 0 °C, and the resulting mixture was stirred at same temperature for 1 h. The mixture was quenched with saturated aqueous NaHCO₃, and was filtered through Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt : hexane) to afford the corresponding α -bromo- α -fluoro- β -lactam **3a-3g**.

(3R,4S)/(3S,4R)-1-Benzyl-3-bromo-3-fluoro-4-phenylazetidin-2-one **3a** Compound **3a** was obtained as a colorless solid in 70% yield (7.052 g), after column chromatography (AcOEt : hexane = 1:9). This reaction was conducted in 30 mmol scale. Mp 81.5-82.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 3.93 (1H, d, *J* = 14.9 Hz), 4.77 (1H, d, *J* = 10.3 Hz), 4.97 (1H, d, *J* = 14.9 Hz), 7.12-7.15 (2H, m), 7.19-7.22 (2H, m), 7.31-7.34 (3H, m), 7.44-7.46 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 44.9, 69.4 (d, *J* = 25 Hz), 106.2 (d, *J* = 299 Hz), 127.8, 128.3, 128.5, 128.7, 129.0, 129.7, 132.2, 133.3, 161.0 (d, *J* = 26 Hz); ¹⁹F NMR (CDCl₃, 564 MHz) δ: -54.9 (1F, d, *J* = 10.3 Hz); MS *m*/*z* = 333 (M⁺); HRMS (*pos*-FAB, Gly.) Calcd. for C₁₆H₁₄BrFNO: 334.0243 ([M+H]⁺), Found: 334.0237 ([M+H]⁺, 100%), 336.0227 (96); IR (KBr) cm⁻¹: 1787, 1204.

(3R, 4S)/(3S, 4R)-3-Bromo-3-fluoro-1-(4-methoxybenzyl)-4-phenylazetidin-2-one
3b
Compound 3b was obtained as a colorless solid in 75% yield (2.715 g), after column chromatography (AcOEt : hexane = 1:4). This reaction was conducted in 10 mmol scale.
Mp 102.0-103.5 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 3.80 (3H, s), 3.88 (1H, d, J= 14.8 Hz), 4.75 (1H, d, J= 10.5 Hz), 4.91 (1H, d, J= 14.8 Hz), 6.84 (2H, d, J= 8.6 Hz), 7.05 (2H, d, J = 8.6 Hz), 7.19-7.22 (2H, m), 7.66-46 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 44.3 (d, J= 2 Hz), 55.3, 69.2 (d, J= 26 Hz), 106.2 (d, J= 300 Hz), 114.3, 125.3, 127.8, 128.7, 129.6, 129.9, 132.3, 159.5, 161.0 (d, J= 26 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -55.0 (1F, d, J= 10.5 Hz); MS m/z = 363 (M+); HRMS (pos FAB, NBA) Calcd. for C₁₇H₁₆BrFNO₂: 364.0348 ([M+H]+), Found: 364.0346 ([M+H]+, 100%), 366.0321 (90); IR (KBr) cm⁻¹: 1793,

1248.

(3R, 4S)/(3S, 4R)-1-Benzhydryl-3-bromo-3-fluoro-4-phenylazetidin-2-one **3c** Compound **3c** was obtained as a colorless solid in 35% yield (287 mg), after recrystallization from hexane. This reaction was conducted in 2 mmol scale. Mp 113.5-114.0 °C; ¹H NMR (CDCl₃, 600 MHz) δ: 4.97 (1H, d, J = 11.3 Hz), 5.53 (1H, s), 7.18-7.20 (2H, m), 7.23-7.25 (2H, m), 7.28-7.40 (11H, m); ¹³C NMR (CDCl₃, 150 MHz) δ: 62.9 (d, J = 2 Hz), 71.0 (d, J = 25 Hz), 105.6 (d, J = 297 Hz), 128.1, 128.2, 128.2, 128.5, 128.6, 128.7, 128.9, 129.6, 132.7, 132.7, 136.9, 137.6, 161.3 (d, J = 26 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -54.9 (1F, d, J = 11.3 Hz); MS m/z = 409 (M+); HRMS (pos FAB, NBA) Calcd. for C₂₂H₁₈BrFNO: 410.0556 ([M+H]⁺, 99.6%), 412.0660 (100); IR (KBr) cm⁻¹: 1784.

(3R, 4S)/(3S, 4R)- 3-Bromo-1-tert-butyl-3-fluoro-4-phenylazetidin-2-one **3d** Compound **3d** was obtained as a colorless solid in 51% yield (459 mg), after recrystallization from Et₂O/hexane. This reaction was conducted in 3 mmol scale. Mp 120.0-121.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 1.34 (9H, s), 4.98 (1H, d, J = 11.9 Hz), 7.33-7.36 (2H, m), 7.42-7.45 (3H, m); ¹³C NMR (CDCl₃, 150 MHz) δ: 28.0, 55.7 (d, J = 1 Hz), 69.8 (d, J = 25 Hz), 105.4 (d, J = 294 Hz), 127.8, 128.3, 128.4, 135.1 (d, J = 1 Hz), 161.0 (d, J = 25 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -56.0 (1F, d, J = 11.9 Hz); MS m/z = 299 (M⁺); HRMS (pos FAB, NBA) Calcd. for C₁₃H₁₆BrFNO: 300.0399 ([M+H]⁺), Found: 300.0404 ([M+H]⁺, 100%), 302.0387 (99.6); IR (KBr) cm⁻¹: 1778.

(3R, 4S)/(3S, 4R)-3-Bromo-3-fluoro-1-methyl-4-phenylazetidin-2-one 3e Compound 3e was obtained as a colorless solid in 47% yield (362 mg), after recrystallization from hexane. This reaction was conducted in 3 mmol scale. Mp 79.0-81.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 2.94 (3H, s), 4.96 (1H, d, J= 10.0 Hz), 7.23-7.26 (2H, m), 7.45-7.50 (3H, m);
¹³C NMR (CDCl₃, 150 MHz) δ: 27.5 (d, J= 2 Hz), 71.8 (d, J= 25 Hz), 106.7 (d, J= 300 Hz), 127.7, 128.9, 129.8, 132.4, 161.4 (d, J= 26 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -54.9 (1F, d, J= 10.0 Hz); MS m/z = 257 (M⁺); HRMS (EI) Calcd. for C₁₀H₉BrFNO: 256.9852 (M⁺), Found: 256.9858 (M⁺, 99.1%), 258.9836 (100); IR (KBr) cm⁻¹: 1790.

(3R,4S)/(3S,4R)-1-Benzyl-3-bromo-3-fluoro-4-(4-methoxyphenyl)azetidin-2-one **3f**

Compound **3f** was obtained as a colorless solid in 56% yield (821 mg), after recrystallization from Et₂O-hexane. This reaction was conducted in 4 mmol scale. Mp 78.0-79.0 °C; ¹H NMR (CDCl₃, 600 MHz) δ: 3.85 (3H, s), 3.89 (1H, d, *J* = 14.8 Hz), 4.72 (1H, d, *J* = 10.2 Hz), 4.93 (1H, d, *J* = 14.8 Hz), 6.94-6.95 (2H, d, *J* = 8.6 Hz), 7.12-7.14 (4H, m), 7.31-7.33 (3H, m); ¹³C NMR (CDCl₃, 150 MHz) δ: 44.7 (d, *J* = 2 Hz), 55.3, 69.2 (d, *J* = 25 Hz), 106.9 (d, *J* = 299 Hz), 114.2, 124.0, 128.4, 128.6, 129.0, 129.4, 133.5, 160.7, 161.2 (d, *J* = 26 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -55.0 (1F, d, *J* = 10.2 Hz); MS *m/z* = 363 (M+); HRMS (*pos*-FAB, NBA) Calcd. for C₁₇H₁₆BrFNO₂: 364.0348 ([M+H]+), Found:

364.0346 ([M+H]+, 38.0%), 366.0326 (37.8); IR (KBr) cm⁻¹: 1783.

(3R,4S)/(3S,4R)-1-Benzyl-3-bromo-3-fluoro-4-(4-fluorophenyl)azetidin-2-one

3g

Compound **3g** was obtained as a colorless solid in 66% yield (929 mg), after column chromatography (AcOEt : hexane = 1:9). Mp 42.0-43.0 °C; ¹H NMR (CDCl₃, 600 MHz) δ : 3.92 (1H, d, J= 14.9 Hz), 4.75 (1H, d, J= 10.3 Hz), 4.94 (1H, d, J= 14.9 Hz), 7.11-7.14 (4H, m), 7.17-7.19 (2H, m), 7.32-7.34 (3H, m); ¹³C NMR (CDCl₃, 150 MHz) δ : 44.9, 68.9 (d, J= 25 Hz), 106.3 (d, J= 299 Hz), 116.0 (d, J= 22 Hz), 128.1 (d, J= 3 Hz), 128.5, 128.6, 129.1, 129.8 (d, J= 9 Hz), 133.3, 161.0 (d, J= 26 Hz), 163.5 (d, J= 251 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -48.3 (1F, m), -55.1 (1F, d, J= 10.3 Hz); MS m/z = 351 (M+); HRMS (*pos*-FAB, NBA) Calcd. for C₁₆H₁₃BrF₂NO: 352.0149 ([M+H]+), Found: 352.0140 ([M+H]+, 48.8%), 354.0135 (43.6); IR (KBr) cm⁻¹: 1792.

Alkylation of α -bromo- α -fluoro- β -lactam

To a solution of the corresponding α -bromo- α -fluoro- β -lactam **3a**-**3g** (0.5 mmol) in 5 mL of THF at -78 °C was slowly added a solution of 1.65M *n*-BuLi (0.45 mL, 0.75 mmol). After 10 min., 1.0 mmol of the appropriate alkylating agent was added at same temperature, and then the reaction mixture was allowed to warm gradually to 0 °C. The resulting mixture was stirred for 3 h, and was quenched with 10% aqueous HCl, followed by extraction with ethyl acetate. The extraction was washed with brine and

dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt : hexane) to afford the corresponding 3-alkylated-3-fluoroazetidin-2-one. The product yields were determined by ¹⁹F NMR spectroscopy from the crude mixture, because of it was difficult to separate the alkylated product. The spectra data were obtained from the pure fraction of chromatography.

(3R, 4S)/(3S, 4R)-1-Benzyl-3-fluoro-3-methyl-4-phenylazetidin-2-one **4a** Compound **4a** was obtained as a colorless liquid in 77% yield (103 mg), after column chromatography (AcOEt : hexane = 1:4). ¹H NMR (CDCl₃, 400 MHz) δ: 1.65 (3H, d, J = 22.3 Hz), 3.87 (1H, dd, J = 14.9, 2.4 Hz), 4.33 (1H, d, J = 3.6 Hz), 4.90 (1H, d, J = 14.9 Hz), 7.11-7.14 (2H, m), 7.24-7.40 (8H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 18.2 (d, J = 25 Hz), 43.9 (d, J = 2 Hz), 66.9 (d, J = 23 Hz), 100.5 (d, J = 223 Hz), 127.9, 127.9, 128.4, 128.6, 128.8, 128.9, 132.5, 134.4, 166.1 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -101.0 (1F, q, J = 22.3 Hz); MS m/z = 269 (M⁺); HRMS (EI) Calcd. for C₁₇H₁₆FNO: 269.1216 (M⁺), Found: 269.1213 (M⁺); IR (neat) cm⁻¹: 1764.

(3R, 4S)/(3S, 4R)-3-Allyl-1-benzyl-3-fluoro-4-phenylazetidin-2-one **4b** Compound **4b** was obtained as a colorless liquid in 78% yield. ¹H NMR (CDCl₃, 600 MHz) δ: 2.61-2.69 (1H, m), 2.75-2.81 (1H, m), 3.87 (1H, dd, J=14.8, 2.4 Hz), 4.43 (1H, d, J= 3.8 Hz), 4.89 (1H, d,

 $J = 14.8 \text{ Hz}, 5.15 (1\text{H}, \text{d}, J = 10.3 \text{ Hz}), 5.20 (1\text{H}, \text{d}, J = 17.1 \text{ Hz}), 5.72-5.79 (1\text{H}, \text{m}), 7.12-7.14 (2\text{H}, \text{m}), 7.23-7.24 (2\text{H}, \text{m}), 7.29-7.31 (3\text{H}, \text{m}), 7.37-7.39 (3\text{H}, \text{m}); ^{13}\text{C} \text{ NMR} (CDCl_3, 150 \text{ MHz}) \delta: 36.6 (\text{d}, J = 24 \text{ Hz}), 44.1, 64.6 (\text{d}, J = 23 \text{ Hz}), 101.7 (\text{d}, J = 229 \text{ Hz}), 120.5, 128.0, 128.1, 128.6, 128.7, 128.9, 128.9, 129.7 (\text{d}, J = 7 \text{ Hz}), 132.6, 134.5, 165.5 (\text{d}, J = 24 \text{ Hz}); ^{19}\text{F} \text{NMR} (CDCl_3, 564 \text{ MHz}) \delta: -106.0 (1\text{F}, \text{dd}, J = 24.6, 14.2 \text{ Hz}); \text{MS } m/z = 295 (\text{M}+); \text{HRMS} (\text{EI}) \text{ Calcd. for } C_{19}\text{H}_{18}\text{FNO}: 295.1372 (\text{M}+), \text{ Found: } 295.1375 (\text{M}+); \text{IR} (\text{neat}) \text{ cm}^{-1}: 1768.$

(3R, 4S)/(3S, 4R)-1-Benzyl-3-cinnamyl-3-fluoro-4-phenylazetidin-2-one **4c** Compound **4c** was obtained as a colorless solid in 96% yield. Mp 102.0-103.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ : 2.80-2.95 (2H, m), 3.85 (1H, dd, J = 14.6, 2.4 Hz), 4.50 (1H, d, J = 3.9 Hz), 4.92 (1H, d, J = 14.6 Hz), 6.12 (1H, dt, J = 15.8, 7.3 Hz), 6.56 (1H, d, J = 15.8 Hz), 7.04-7.39 (15H, m); ¹³C NMR (CDCl₃, 150 MHz) δ : 35.5 (d, J = 25 Hz), 43.9 (d, J = 2 Hz), 64.1 (d, J = 23 Hz), 102.1 (d, J = 226 Hz), 120.4 (d, J = 9 Hz), 126.2, 127.6, 127.7, 127.9 (d, J = 1Hz), 128.2, 128.4, 128.5, 128.6, 128.8, 132.2, 134.0, 135.3, 136.3, 165.2 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -104.5 (1F, t, J = 17.0 Hz); MS m/z = 371 (M+); HRMS (EI) Calcd. for C₂₅H₂₂FNO: 371.1685 (M+), Found: 371.1685 (M+); IR (neat) cm⁻¹: 1758. (3R, 4S)/(3S, 4R)-1-Benzyl-3-fluoro-4-phenyl-3-(prop-2-yn-1-yl)azetidin-2-one **4d** Compound **4d** was obtained as a colorless liquid in 61% yield. ¹H NMR (CDCl₃, 600

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MHz) δ : 1.92 (1H, m), 2.82-2.93 (2H, m), 3.91 (1H, dd, J= 14.9, 2.4 Hz), 4.71 (1H, d, J= 3.9 Hz), 4.92 (1H, d, J= 14.9 Hz), 7.17-7.18 (2H, m), 7.28-7.30 (5H, m), 7.40-7.41 (3H, m),; ¹³C NMR (CDCl₃, 150 MHz) δ : 22.4 (d, J= 31 Hz), 44.3 (d, J= 1 Hz), 64.5 (d, J= 23 Hz), 72.1 (d, J= 2 Hz), 75.9 (d, J= 14 Hz), 100.4 (d, J= 229 Hz), 128.1, 128.2, 128.7, 128.8, 128.9, 129.1, 132.1, 134.3, 164.3 (d, J= 24 Hz); ¹⁹F NMR (CDCl₃, 564 MHz) δ : -105.0 (1F, m); MS m/z = 293 (M+); HRMS (EI) Calcd. for C₁₉H₁₆FNO: 293.1216 (M+), Found: 293.1223 (M+); IR (neat) cm⁻¹: 3294, 1769.

(3R, 4S)/(3S, 4R)·1-Benzyl·3-fluoro-4-phenyl·3-{3-(trimethylsilyl)prop-2-yn-1-yl)azetidin-2-one **4e** Compound **4e** was obtained as a colorless solid in 91% yield. Mp 85.0-86.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 0.13 (9H, s), 2.78-3.01 (2H, m), 4.01 (1H, dd, J= 14.7, 2.2 Hz), 4.71 (1H, d, J= 4.0 Hz), 4.85 (1H, d, J= 14.7 Hz), 7.13-7.15 (2H, m), 7.26-7.31 (5H, m), 7.37-7.39 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 0.07, 24.1 (d, J= 28 Hz), 44.5 (d, J = 2 Hz), 65.3 (d, J= 23 Hz), 88.9 (d, J= 1 Hz), 98.2 (d, J= 8 Hz), 100.3 (d, J= 229 Hz), 128.1, 128.2 (d, J= 1 Hz), 128.6, 128.7, 128.9, 129.0, 132.2, 134.4, 164.5 (d, J= 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -105.8 (1F, m); MS m/z = 365 (M+); HRMS (EI) Calcd. for C₂₂H₂₄FNOSi: 365.1611 (M+), Found: 365.1620 (M+); IR (KBr) cm⁻¹: 1774. (3R, 4S)/(3S, 4R)-1-Benzyl-3-fluoro-4-phenyl-3-(3-phenylprop-2-yn-1-yl)azetidin-2-one **4f**

Compound **4f** was obtained as a colorless liquid in 43% yield. ¹H NMR (CDCl₃, 600 MHz)

δ: 3.06-3.17 (2H, m), 3.93 (1H, dd, J= 14.9, 2.5 Hz), 4.80 (1H, d, J= 4.0 Hz), 4.93 (1H, d, J= 14.9 Hz), 7.05-7.17 (5H, m), 7.28-7.34 (7H, m), 7.38-7.41 (3H, m),; ¹³C NMR (CDCl₃, 150 MHz) δ: 23.2 (d, J= 31 Hz), 44.1 (d, J= 1 Hz), 64.6 (d, J= 23 Hz), 81.3 (d, J= 15 Hz), 83.8 (d, J= 2 Hz), 100.9 (d, J= 227 Hz), 128.2 (d, J= 1 Hz), 128.3, 128.4, 128.5, 128.7, 128.8, 129.1, 131.9, 132.1, 134.1, 164.4 (d, J= 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -104.5 (1F, m); MS m/z = 369 (M⁺); HRMS (EI) Calcd. for C₂₅H₂₀FNO: 369.1529 (M⁺), Found: 369.1527 (M⁺); IR (neat) cm⁻¹: 1771.

(3R, 4S)/(3S, 4R)-1, 3-Dibenzyl-3-fluoro-4-phenylazetidin-2-one **4g** Compound **4g** was obtained as a colorless solid in 89% yield. Mp 112.5-113.5 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 3.19-3.35 (2H, m), 3.77 (1H, dd, J = 15.0, 2.5 Hz), 4.43 (1H, d, J = 4.4 Hz), 4.83 (1H, d, J = 15.0 Hz), 6.68-6.70 (2H, m), 7.06-7.08 (2H, m), 7.13-7.21 (3H, m), 7.26-7.34 (8H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 37.9 (d, J = 25 Hz), 43.7 (d, J = 2 Hz), 63.4 (d, J = 23 Hz), 102.7 (d, J = 226 Hz), 127.4, 127.6, 127.9, 128.5, 128.6, 128.7, 128.7, 130.3, 132.2, 133.0, 133.1, 133.8, 165.5 (d, J = 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -102.3 (1F, m); MS m/z = 345 (M+); HRMS (EI) Calcd. for C₂₃H₂₀FNO: 345.1529 (M+), Found: 345.1528 (M+); IR (KBr) cm⁻¹: 1769.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-4-phenyl-3-(trimethylsilyl)azetidin-2-one 4h Compound 4h was obtained as a colorless solid in 60% yield (98 mg), after column chromatography (AcOEt : hexane = 1:9). Mp 114.0-116.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ : 0.10 (9H, s), 3.85 (1H, dd, J= 14.4, 2.8 Hz), 4.43 (1H, d, J= 5.3 Hz), 4.87 (1H, d, J= 14.4 Hz), 7.14-7.16 (2H, m), 7.24-7.31 (5H, m), 7.36-7.42 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ : -4.4 (d, J= 3 Hz), 44.4 (d, J= 1 Hz), 61.5 (d, J= 22 Hz), 100.5 (d, J= 230 Hz), 127.9 (d, J= 1 Hz), 128.0, 128.5, 128.6, 128.7, 128.9, 133.2 (d, J= 2 Hz), 134.6, 166.0 (d, J= 19 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -135.7 (1F, d, J= 5.3 Hz); MS m/z= 327 (M⁺); HRMS (*pos* FAB, NBA) Calcd. for C₁₉H₂₃FNOSi: 328.1533 ([M+H]⁺), Found: 328.1537 ([M+H]⁺); IR (KBr) cm⁻¹: 1741.

(3R, 4S)/(3S, 4R)-1-Benzyl-3-fluoro-4-phenylazetidin-2-one **5** Compound **5** was obtained as a colorless liquid in 76% yield. ¹H NMR (CDCl₃, 400 MHz) δ : 3.89 (1H, dd, J = 14.8, 2.5 Hz), 4.64 (1H, dd, J = 4.6, 4.3 Hz), 4.86 (1H, d, J = 14.8 Hz), 5.54 (1H, dd, J = 55.0, 4.6 Hz), 7.12-7.14 (2H, m), 7.25-7.32 (5H, m), 7.38-7.41 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ : 44.2 (d, J = 2 Hz), 60.6 (d, J = 23 Hz), 92.4 (d, J = 227 Hz), 127.9, 128.1 (d, J = 1 Hz), 128.4, 128.5, 128.7, 128.9, 131.8 (d, J = 1 Hz), 134.1, 163.6 (d, J = 22 Hz); ¹⁹F NMR (CDCl₃, 564 MHz) δ : -136.8 (1F, d, J = 55.0 Hz); MS m/z = 255 (M⁺); HRMS (EI) Calcd. for C₁₆H₁₄FNO: 255.1059 (M⁺), Found: 255.1053 (M⁺); IR (neat) cm⁻¹: 1768. (*3R*, 4S)/(3S, 4R)-3-Fluoro-1-(4-methoxybenzyl)-3-methyl-4-phenylazetidin-2-one **7b** Compound **7b** was obtained as a colorless liquid in 93% yield (140 mg), after column

chromatography (AcOEt : hexane = 1:4). ¹H NMR (CDCl₃, 400 MHz) δ : 1.63 (3H, d, J= 22.2 Hz), 3.79-3.84 (4H, m), 4.31 (1H, d, J= 3.8 Hz), 4.84 (1H, d, J= 14.7 Hz), 6.83 (2H, d, J = 8.5 Hz), 7.04 (2H, d, J = 8.5 Hz), 7.24-7.26 (2H, m), 7.38-7.40 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ : 18.2 (d, J= 25 Hz), 43.4 (d, J= 2 Hz), 55.1, 66.7 (d, J= 23 Hz), 100.3 (d, J= 222 Hz), 114.1, 126.3, 127.8 (d, J= 1 Hz), 128.5, 128.7, 129.6, 132.5, 159.1, 165.9 (d, J= 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -101.1 (1F, q, J= 22.2 Hz); MS m/z = 299 (M+); HRMS (EI) Calcd. for C₁₈H₁₈FNO₂: 299.1322 (M+), Found: 299.1323 (M+); IR (neat) cm⁻¹: 1768.

(3R, 4S)/(3S, 4R)-1-Benzhdryl-3-fluoro-3-methyl-4-phenylazetidin-2-one **7c** Compound **7c** was obtained as a colorless solid in 92% yield. Mp 138.0-140.0 °C; ¹H NMR (CDCl₃, 600 MHz) δ: 1.70 (3H, d, J = 22.3 Hz), 4.48 (1H, d, J = 3.8 Hz), 5.69 (1H, s), 7.16-7.35 (15H, m); ¹³C NMR (CDCl₃, 150 MHz) δ: 18.4 (d, J = 26 Hz), 62.0 (d, J = 2 Hz), 68.8 (d, J = 22 Hz), 99.5 (d, J = 223 Hz), 127.8, 127.9, 128.2, 128.3, 128.4, 128.5 (d, J = 2 Hz), 128.5, 128.6, 128.8, 133.1, 137.7, 138.2, 166.6 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -100.7 (1F, q, J = 22 Hz); MS m/z = 345 (M⁺); HRMS (*pos*-FAB, Gly.) Calcd. for C₂₃H₂₁FNO: 346.1607 ([M+H]⁺), Found: 346.1606 ([M+H]⁺); IR (KBr) cm⁻¹: 1752. (3R, 4S)/(3S, 4R)-1-tert-Butyl-3-fluoro-3-methyl-4-phenylazetidin-2-one **7d** Compound **7d** was obtained as a colorless solid in 72% yield (84 mg), after column chromatography (AcOEt : hexane = 1:4). Mp 70.0-71.0 °C; ¹H NMR (CDCl₃, 600 MHz) δ: 1.28 (9H, s), 1.66 (3H, d, J = 22.0 Hz), 4.55 (1H, d, J = 3.0 Hz), 7.34-7.40 (5H, m); ¹³C NMR (CDCl₃, 150 MHz) δ: 18.3 (d, J = 26 Hz), 28.2, 54.6 (d, J = 1 Hz), 67.5 (d, J = 22 Hz), 97.9 (d, J = 224 Hz), 128.1 (d, J = 2 Hz), 128.4, 128.8, 135.3, 166.4 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -101.8 (1F, qd, J = 22.0, 3.0 Hz); MS *m*/*z* = 235 (M⁺); HRMS (*pos*-FAB, Gly.) Calcd. for C₁₄H₁₉FNO: 236.1451 ([M+H]⁺), Found: 236.1453 ([M+H]⁺); IR (KBr) cm⁻¹: 2937, 1748.

(3R, 4S)/(3S, 4R)-3-Fluoro-1, 3-dimethyl-4-phenylazetidin-2-one **7e** Compound **7e** was obtained as a colorless liquid in 68% yield. ¹H NMR (CDCl₃, 400 MHz) δ: 1.72 (3H, d, J= 22.5 Hz), 2.85 (3H, d, J = 1.6 Hz), 4.50 (1H, d, J = 3.6 Hz), 7.27-7.30 (2H, m), 7.40-7.43 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 18.3 (d, J = 26 Hz), 26.5 (d, J = 2 Hz), 69.4 (d, J = 23 Hz), 100.8 (d, J = 222 Hz), 127.6 (d, J = 1 Hz), 128.6, 128.9, 132.5 (d, J = 1 Hz), 134.6, 166.3 (d, J = 25 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -100.6 (1F, q, J = 22.5 Hz); MS m/z = 193 (M⁺); HRMS (EI) Calcd. for C₁₁H₁₂FNO: 193.0903 (M⁺), Found: 193.0895 (M⁺); IR (neat) cm⁻¹: 1769.

(3R, 4S)/(3S, 4R)-1-Benzyl-3-fluoro-4-(4-methoxyphenyl)-3-methylazetidin-2-one
7f
Compound 7f was obtained as a colorless liquid in 82% yield. ¹H NMR (CDCl₃, 400 MHz)
δ: 1.63 (3H, d, J = 22.3 Hz), 3.82-3.86 (4H, m), 4.29 (1H, d, J = 3.7 Hz), 4.87 (1H, d, J =

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14.8 Hz), 6.92 (2H, d, J= 8.5 Hz), 7.11-7.13 (2H, m), 7.17 (2H, d, J= 8.5 Hz), 7.30-7.31 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ : 18.1 (d, J= 26 Hz), 43.7 (d, J= 2 Hz), 55.2, 66.5 (d, J= 23 Hz), 100.4 (d, J= 222 Hz), 113.9, 124.2 (m), 127.8, 128.3, 128.7, 129.2 (d, J= 1 Hz), 134.4, 159.9, 166.0 (d, J= 25 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -101.2 (1F, q, J= 22.3 Hz); MS m/z = 299 (M+); HRMS (EI) Calcd. for C₁₈H₁₈FNO₂: 299.1322 (M+), Found: 299.1312 (M+); IR (neat) cm⁻¹: 1768.

(3R, 4S)/(3S, 4R)-1-Benzyl-3-fluoro-4-(4-fluorophenyl)-3-methylazetidin-2-one **7g** Compound **7g** was obtained as a colorless liquid in 84% yield. ¹H NMR (CDCl₃, 400 MHz) δ : 1.65 (3H, d, J= 22.4 Hz), 3.87 (1H, dd, J= 14.8, 2.4 Hz), 4.31 (1H, d, J= 3.8 Hz), 4.86 (1H, d, J= 14.8 Hz), 7.05-7.13 (4H, m), 7.19-7.23 (2H, m), 7.30-7.32 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ : 18.0 (d, J= 26 Hz), 44.0 (d, J= 2 Hz), 66.3 (d, J= 23 Hz), 100.4 (d, J= 223 Hz), 115.6 (d, J= 22 Hz), 127.9, 128.3, 128.8, 129.6 (d, J= 1 Hz), 129.7 (d, J= 1 Hz), 134.2, 162.9 (d, J= 245 Hz), 165.8 (d, J= 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -50.0 (1F, m), -100.9 (1F, q, J= 22.4 Hz); MS m/z= 287 (M+); HRMS (EI) Calcd. for C₁₇H₁₅F₂NO: 287.1122 (M+), Found: 287.1124 (M+); IR (neat) cm⁻¹: 1769.

Insertion of zinc metal into α -bromo- α -fluoro- β -lactam

To the suspension of zinc metal (0.6 mmol) in 5 mL of THF was added TMSCl (0.1 mmol), and then the resulting mixture was heated at 50 °C. After 30 min., the mixture was cooled to room temperature and the α -bromo- α -fluoro- β -lactam **3a** (0.5 mmol) was added. The reaction mixture was refluxed for 1 h, and the heating was stoped before methyl iodide (1 mmol) was added. The whole mixture was refluxed for 3 h, and was quenched with 10% aqueous HCl, followed by extraction with ethyl acetate. The extraction was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt : hexane) to afford the hydrogen substituted product (**5** and **6**) without the formation of the methylated product

4a.

1-Benzyl-3-fluoro-4-phenylazetidin-2-one (**5** and **6**) Compound (3R,4S/(3S,4R)-**5** and (3S,4S)/(3R,4R)-**6** was obtained as a colorless liquid in 83% yield (RS/SR : SS/RR = 68 : 15). (3S,4S)/(3R,4R)-Isomer **6**: ¹H NMR (CDCl₃, 600 MHz) δ: 3.89 (1H, d, J = 15.0 Hz), 4.48 (1H, dd, J = 10.7, 1.3 Hz), 4.88 (1H, d, J = 15.0 Hz), 5.24 (1H, ddd, J = 54.4, 1.3, 0.6 Hz), 7.12-7.14 (2H, m), 7.19-7.26 (2H, m), 7.29-7.33 (3H, m), 7.39-7.42 (3H, m); ¹³C NMR (CDCl₃, 150 MHz) δ: 44.5, 62.5 (d, J = 24 Hz), 97.9 (d, J = 226 Hz), 126.8, 128.1, 128.6, 128.9, 129.2, 129.3, 134.2, 134.3, 163.6 (d, J = 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -127.2 (1F, dd, J = 54.4, 10.7 Hz); MS m/z = 255 (M⁺); HRMS (EI) Calcd. for C₁₆H₁₄FNO: 255.1059 (M⁺), Found: 255.1060 (M⁺); IR (neat) cm⁻¹: 1770.

Aldol reaction of α -bromo- α -fluoro- β -lactam

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To a solution of the α -bromo- α -fluoro- β -lactam **3a** (0.5 mmol) in 5 mL of THF at -78 °C was slowly added a solution of 1.65M *n*-BuLi (0.45 mL, 0.75 mmol). After 10 min., 0.5 mmol of the appropriate carbonyl compound was added at same temperature, and then the reaction mixture was allowed to warm gradually to -30 °C. The resulting mixture was stirred for appropriate time, and was quenched with 10% aqueous HCl, followed by extraction with ethyl acetate. The extraction was washed with brine and dried over MgSO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography (AcOEt hexane) afford the corresponding to 3-hydroxyalkylated-3-fluoroazetidin-2-one (8 and 9). The product yields were determined by ¹⁹F NMR spectroscopy from the crude mixture, because of it was difficult to separate the aldol products. The spectra data were obtained from the pure fraction of chromatography. Furthermore, separable diastereomixtures showed the data of each isomer, whereas inseparable diastereomixtures showed the date of both isomers. (3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-{hydroxy(phenyl)methyl}-4-phenylazetidin-2-one 8a and **9a** Compound **8a** and **9a** was obtained as a colorless solid in 79% yield (143 mg, **8a/9a** = 82/18). Major isomer **8a**: Mp 152.0-153.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 2.95 (1H, d, J = 4.6 Hz), 3.92 (1H, dd, J = 15.2, 2.4 Hz), 4.76 (1H, d, J = 4.5 Hz), 4.92 (1H, d, J = 4.5 Hz), 4.

= 15.2 Hz), 5.22 (1H, dd, J= 9.0, 4.6 Hz), 6.89-6.91 (2H, m), 7.06-7.09 (2H, m), 7.23-7.27

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(6H, m), 7.32-7.35 (3H, m), 7.43-7.45 (2H, m); ¹³ C NMR (CDCl ₃ , 100 MHz) δ : 44.2 (d, J =
1 Hz), 61.5 (d, J = 23 Hz), 71.1 (d, J = 28 Hz), 103.4 (d, J = 226 Hz), 126.7 (d, J = 2 Hz),
127.7, 127.7 (d, <i>J</i> = 1 Hz), 128.1, 128.3, 128.3, 128.5, 128.6, 131.9, 133.9, 137.1, 165.1 (d,
$J = 23$ Hz); ¹⁹ F NMR (CDCl ₃ , 564 MHz) δ : -111.5 (1F, m); MS $m/z = 361$ (M+); HRMS
(pos FAB, Gly.) Calcd. for C ₂₃ H ₂₁ FNO ₂ : 362.1556 ([M+H]+), Found: 362.1557 ([M+H]+);
IR (KBr) cm ⁻¹ : 3373, 1749. Minor isomer 9a : Mp 156.0-156.5 °C; ¹ H NMR (CDCl ₃ , 400
MHz) δ: 2.53 (1H, dd, J= 2.8, 1.3 Hz), 3.72 (1H, dd, J= 15.0, 2.7 Hz), 4.63 (1H, d, J= 4.4
Hz), 4.75 (1H, d, J=15.0 Hz), 5.32 (1H, dd, J=11.5, 2.8 Hz), 6.44-6.46 (2H, m), 7.06-7.09
(2H, m), 7.14-7.23 (3H, m), 7.35-7.40 (6H, m), 7.55-7.58 (2H, m); ¹³ C NMR (CDCl ₃ , 100
MHz) δ : 43.6 (d, J = 2 Hz), 60.6 (d, J = 23 Hz), 72.7 (d, J = 26 Hz), 104.4 (d, J = 227 Hz),
127.1 (d, $J = 1$ Hz), 127.4, 127.7, 128.0 (d, $J = 1$ Hz), 128.5, 128.6 (d, $J = 1$ Hz), 128.6,
128.7, 132.2 (d, $J = 1$ Hz), 133.2, 135.4, 135.5, 164.0 (d, $J = 24$ Hz); ¹⁹ F NMR (CDCl ₃ , 90
MHz) δ : -110.3 (1F, m); MS m/z = 361 (M+); HRMS (pos-FAB, Gly.) Calcd. for
C ₂₃ H ₂₁ FNO ₂ : 362.1556 ([M+H] ⁺), Found: 362.1553 ([M+H] ⁺); IR (KBr) cm ⁻¹ : 3488, 1752.
$(3S,4S)/(3R,4R)-1$ -Benzyl-3-fluoro-3-{hydroxy(4-methoxyphenyl)methyl}-4-phenylazeti-
din-2-one 8b and 9b Compound 8b and 9b was obtained as a colorless solid in 77% yield
(8b/9b = 78/22). Major isomer 8b : Mp 156.0-157.0 °C; ¹ H NMR (CDCl ₃ , 400 MHz) δ: 3.03
(1H, d, J= 4.5 Hz), 3.80 (3H, s), 3.89 (1H, dd, J= 15.2, 2.5 Hz), 4.73 (1H, d, J= 4.4 Hz),

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4.91 (1H, d, $J = 15.2$ Hz), 5.15 (1H, dd, $J = 9.2$, 4.5 Hz), 6.85-6.87 (2H, d, $J = 8.5$ Hz),
$6.96-6.98$ (2H, m), $7.02-7.05$ (2H, m), $7.24-7.28$ (6H, m), $7.34-7.36$ (2H, d, $J=8.5$ Hz); ${}^{13}C$
NMR (CDCl ₃ , 100 MHz) δ : 44.1 (d, J = 2 Hz), 55.2, 61.5 (d, J = 22 Hz), 71.0 (d, J = 28 Hz),
103.5 (d, J = 227 Hz), 113.7, 127.7, 127.8 (d, J = 1 Hz), 128.1 (d, J = 2 Hz), 128.1, 128.4,
128.6, 128.6, 129.1 (d, $J = 1$ Hz), 132.0 (d, $J = 1$ Hz), 133.8, 159.7, 165.1 (d, $J = 23$ Hz);
¹⁹ F NMR (CDCl ₃ , 90 MHz) δ : –111.5 (1F, m); MS m/z = 391 (M ⁺); HRMS (EI) Calcd. for
C ₂₄ H ₂₂ FNO ₃ : 391.1584 (M ⁺), Found: 391.1584 (M ⁺); IR (KBr) cm ⁻¹ : 3399, 1752. Minor
isomer 9b : Mp 156.0-157.0 °C; ¹ H NMR (CDCl ₃ , 400 MHz) δ: 2.75 (1H, bs), 3.70 (1H, dd,
<i>J</i> = 15.2, 2.6 Hz), 3.86 (3H,s), 4.64 (1H, d, <i>J</i> = 4.2 Hz), 4.76 (1H, d, <i>J</i> = 15.2 Hz), 5.27 (1H,
d, $J = 11.0$ Hz), 6.49-6.51 (2H, m), 6.88-6.91 (2H, d, $J = 8.7$ Hz), 7.07-7.11 (2H, m),
7.16-7.19 (1H, m), 7.23-7.26 (3H, m), 7.37-7.39 (3H, m), 7.46-7.48 (2H, d, J = 8.7 Hz); ¹³ C
NMR (CDCl ₃ , 100 MHz) δ : 43.6 (d, J = 2 Hz), 55.2, 60.5 (d, J = 23 Hz), 72.2 (d, J = 25 Hz),
104.5 (d, J = 227 Hz), 113.9, 127.4, 127.5, 127.7, 128.0 (d, J = 1 Hz), 128.3 (d, J = 1 Hz),
128.4, 128.6, 128.7, 132.3 (d, $J = 1$ Hz), 133.3, 159.7, 164.0 (d, $J = 23$ Hz); ¹⁹ F NMR
(CDCl ₃ , 90 MHz) δ : -110.0 (1F, m); MS $m/z = 391$ (M+); HRMS (EI) Calcd. for
C ₂₄ H ₂₂ FNO ₃ : 391.1584 (M+), Found: 391.1590 (M+); IR (KBr) cm ⁻¹ : 3483, 1753.
$(3S, 4S)/(3R, 4R)$ -1-Benzyl-3-{ $(4$ -chlorophenyl)hydroxymethyl}-3-fluoro-4-phenylazetidin-
2-one 8c and 9c Compound 8c and 9c was obtained as a colorless solid in 72% yield (8c/9c

= 80/20). Major isomer 8c: Mp 168.0-174.0 °C; ¹H NMR (CDCl₃, 400 MHz) & 3.56 (1H, bs), 3.89 (1H, dd, J = 15.1, 2.4 Hz), 4.70 (1H, d, J = 4.6 Hz), 4.89 (1H, d, J = 15.1 Hz), 5.19 (1H, d, J = 8.3 Hz), 6.89-6.92 (2H, m), 7.06-7.09 (2H, m), 7.25-7.29 (8H, m), 7.34-7.36 (2H, m); ¹³C NMR (CDCl₃, 100 MHz) δ : 44.2 (d, J = 2 Hz), 61.5 (d, J = 23 Hz), 70.2 (d, J = 28 Hz), 103.2 (d, J = 227 Hz), 127.7 (d, J = 1 Hz), 127.8, 128.1, 128.1 (d, J = 2Hz), 128.4, 128.4, 128.6, 128.6, 131.6 (d, *J* = 2 Hz), 133.7, 134.2, 135.8 165.0 (d, *J* = 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -111.3 (1F, m); MS m/z = 395 (M+); HRMS (*pos*-FAB, Gly.) Calcd. for C₂₃H₂₀ClFNO₂: 396.1167 ([M+H]⁺), Found: 396.1167 ([M+H]⁺); IR (KBr) cm⁻¹: 3372, 1751. Minor isomer **9c**: Mp 146.0-147.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 2.59 (1H, bs), 3.68 (1H, dd, J = 14.9, 2.3 Hz), 4.56 (1H, d, J = 4.0 Hz), 4.74 (1H, d, J = 14.9 Hz), 5.29 (1H, d, J = 11.1 Hz), 6.50-6.52 (2H, m), 7.13-7.17 (2H, m), 7.20-7.26 (4H, m), 7.13-7.17 (2H, m), 7.20-7.26 (4H, m), 7.20-7.26 (m), 7.30-7.32 (2H, m), 7.39-7.40 (3H, m), 7.46-7.48 (2H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 43.7 (d, J = 2 Hz), 60.3 (d, J = 23 Hz), 72.0 (d, J = 26 Hz), 104.2 (d, J = 228 Hz), 127.7, 127.8, 128.0 (d, J = 1 Hz), 128.4 (d, J = 1 Hz), 128.6, 128.6, 128.7, 128.9, 131.9 (d, J = 1Hz), 133.1, 133.8 (d, J = 8 Hz), 134.5, 163.6 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -110.0 (1F, m); MS m/z = 395 (M⁺); HRMS (pos FAB, Gly.) Calcd. for C₂₃H₂₀ClFNO₂: 396.1167 ([M+H]⁺), Found: 396.1167 ([M+H]⁺); IR (KBr) cm⁻¹: 3483, 1751.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-{hydroxy(naphthalen-1-yl)methyl}-4-phenylazeti-

din-2-one 8d and 9d Compound 8d and 9d was obtained as a colorless solid in 83% yield
(8d/9d = 79/21). Major isomer 8d : Mp 201.0-202.0 °C; ¹ H NMR (CDCl ₃ , 400 MHz) δ: 3.11
(1H, d, J= 4.8 Hz), 3.83 (1H, dd, J= 15.6, 2.6 Hz), 4.81 (1H, d, J= 4.4 Hz), 4.88 (1H, d, J
= 15.6 Hz), 6.12 (1H, dd, <i>J</i> = 7.9, 4.8 Hz), 6.88-6.91 (2H, m), 7.01-7.03 (2H, m), 7.15-7.26
(6H, m), 7.45-7.54 (3H, m), 7.84-7.89 (3H, m), 8.05-8.07 (1H, m); ¹³ C NMR (CDCl ₃ , 100
MHz) δ: 44.0 (d, J= 2 Hz), 61.7 (d, J= 23 Hz), 67.6 (d, J= 29 Hz), 104.1 (d, J= 229 Hz),
123.0 (d, J = 3 Hz), 124.8 (d, J = 1 Hz), 125.1, 125.7, 126.4, 127.6, 127.9, 128.1 (d, J = 1
Hz), 128.4, 128.5, 128.6, 128.7, 129.3, 131.3, 131.8 (d, $J = 1$ Hz), 133.2 (d, $J = 2$ Hz),
133.5, 133.7, 164.9 (d, J = 23 Hz); ¹⁹ F NMR (CDCl ₃ , 90 MHz) δ : –110.4 (1F, m); MS m/z =
411 (M+); HRMS (EI) Calcd. for C ₂₇ H ₂₂ FNO ₂ : 411.1635 (M+), Found: 411.1634 (M+); IR
(KBr) cm ⁻¹ : 3370, 1743. Minor isomer 9d : Mp 199.0-203.0 °C; ¹ H NMR (CDCl ₃ , 400 MHz)
δ: 2.71 (1H, bd, J= 3.5 Hz), 3.67 (1H, dd, J= 15.2, 2.6 Hz), 4.74 (1H, d, J= 15.2 Hz), 4.78
(1H, d, J = 4.1 Hz), 5.29 (1H, dd, J = 12.5, 3.4 Hz), 6.49-6.51 (2H, m), 7.07-7.10 (2H, m),
7.16-7.18 (3H, m), 7.36-7.38 (3H, m), 7.43-7.46 (1H, m), 7.52-7.55 (2H, m), 7.87-7.91 (3H,
m), 8.14-8.17 (1H, m); ¹³ C NMR (CDCl ₃ , 100 MHz) δ : 43.7 (d, J = 2 Hz), 61.4 (d, J = 23
Hz), 69.3 (d, $J = 25$ Hz), 103.9 (d, $J = 230$ Hz), 123.5, 124.8 (d, $J = 1$ Hz), 125.1, 125.6 (d,
<i>J</i> = 3 Hz), 125.9, 126.3, 127.5, 127.7, 128.0 (d, <i>J</i> = 1 Hz), 128.5, 128.6, 128.8 129.4, 130.7,
131.7 (d, $J = 4$ Hz), 132.2 (d, $J = 1$ Hz), 133.5, 133.6, 163.8 (d, $J = 24$ Hz); ¹⁹ F NMR

 $(CDCl_3, 90 \text{ MHz}) \delta$: -111.6 (1F, m); MS m/z = 411 (M+); HRMS (EI) Calcd. for C₂₇H₂₂FNO₂: 411.1635 (M⁺), Found: 411.1638 (M⁺); IR (KBr) cm⁻¹: 3419, 1750. (3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-{hydroxy(naphthalen-2-yl)methyl}-4-phenylazetidin-2-one 8e and 9e Compound 8e and 9e was obtained as a colorless solid in 78% yield (**8e/9e** = 80/20). Major isomer **8e**: Mp 164.0-165.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 3.34 (1H, d, J= 4.7 Hz), 3.88 (1H, dd, J= 15.2, 2.4 Hz), 4.81 (1H, d, J= 4.6 Hz), 4.90 (1H, d, J = 15.2 Hz), 5.37 (1H, dd, J= 8.5, 4.7 Hz), 6.92-6.97 (4H, m), 7.07-7.11 (2H, m), 7.16-7.25 (4H, m), 7.48-7.55 (3H, m), 7.79-7.84 (3H, m), 7.91 (1H, s); ¹³C NMR (CDCl₃, 100 MHz) δ: 44.0 (d, J = 2 Hz), 61.5 (d, J = 23 Hz), 71.4 (d, J = 28 Hz), 103.4 (d, J = 227 Hz), 124.4 (d, J=2 Hz), 126.1, 126.1, 127.5, 127.5, 127.8 (d, J=1 Hz), 127.9, 128.0, 128.0, 128.3, 128.4, 128.5, 131.7 (d, J = 2 Hz), 132.8, 133.2, 133.6, 134.5 (d, J = 1 Hz), 164.9 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -111.2 (1F, m); MS *m*/*z* = 411 (M⁺); HRMS (EI) Calcd. for C₂₇H₂₂FNO₂: 411.1635 (M⁺), Found: 411.1631 (M⁺); IR (KBr) cm⁻¹: 3362, 1747. Minor isomer **9e**: Mp 173.0-173.5 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 2.72 (1H, bs), 3.62 (1H, dd, J = 15.3, 2.6 Hz), 4.69 (2H, m), 5.51 (1H, d, J = 10.9 Hz), 6.13-6.15 (2H, m), 6.44-6.48 (2H, m), 6.83-6.87 (1H, m), 7.26-7.29 (2H, m), 7.36-7.41 (3H, m), 7.52-7.67 (3H, m), 7.84-7.91 (3H, m), 8.04 (1H, s); ¹³C NMR (CDCl₃, 100 MHz) δ : 43.5 (d, J = 2 Hz), 60.3 (d, J = 23 Hz), 72.7 (d, J = 25 Hz), 104.5 (d, J = 227 Hz), 124.7, 126.2 (d, J = 1 Hz), 126.3, 126.4, 127.2,

 127.3, 127.7, 128.0 (d, J = 1 Hz), 128.0, 128.3, 128.4, 128.6, 128.8, 132.2 (d, J = 1 Hz), 132.8, 132.9, 133.1, 133.4, 163.9 (d, J = 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -109.4 (1F, m); MS m/z = 411 (M⁺); HRMS (EI) Calcd. for C₂₇H₂₂FNO₂: 411.1635 (M⁺), Found: 411.1637 (M⁺); IR (KBr) cm⁻¹: 3445, 1748.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(1-hydroxy-1-phenylethyl)-4-phenylazetidin-2-one 8f and 9f Compound 8f and 9f was obtained as a colorless solid in 92% yield (8f/9f = 81/19). Major isomer **8f**: Mp 180.0-181.5 °C; ¹H NMR (CDCl₃, 400 MHz) & 1.85 (3H, d, J = 2.5 Hz, 2.51 (1 H, bs), 3.93 (1 H, dd, J = 15.2, 2.4 Hz), 4.64 (1 H, d, J = 4.8 Hz), 4.93 (1 H, d)d, J = 15.2 Hz), 6.67-6.69 (2H, m), 7.12-7.33 (11H, m), 7.48-7.51 (2H, m); ¹³C NMR $(CDCl_3, 100 \text{ MHz}) \delta: 24.8 \text{ (d, } J = 4 \text{ Hz}), 44.1, 61.9 \text{ (d, } J = 23 \text{ Hz}), 73.7 \text{ (d, } J = 25 \text{ Hz}), 105.3$ (d, J=231 Hz), 125.7, 125.7, 127.6, 127.7, 128.1, 128.1, 128.2, 128.3, 128.6, 132.1, 134.1, 141.7, 165.1 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -112.3 (1F, m); MS m/z = 375(M⁺); HRMS (pos FAB, Gly.) Calcd. for C₂₄H₂₃FNO₂: 376.1713 ([M+H]⁺), Found: 376.1719 ([M+H]⁺); IR (KBr) cm⁻¹: 3433, 1747. Minor isomer **9f**: Mp 152.0-153.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 1.83 (3H, d, J = 2.2 Hz), 2.30 (1H, bs), 3.72 (1H, dd, J = 15.1, 2.8 Hz), 4.50 (1H, d, J = 4.4 Hz), 4.72 (1H, d, J = 15.1 Hz), 6.38-6.39 (2H, m), 7.01-7.39 (11H, m), 7.67-7.69 (2H, m); ¹³C NMR (CDCl₃, 150 MHz) δ : 25.3 (d, J = 4 Hz), 43.6 (d, J = 2 Hz), 61.6 (d, J = 23 Hz), 74.9 (d, J = 24 Hz), 105.8 (d, J = 228 Hz), 126.5, 127.5, 127.9,

128.0, 128.2 (d, J= 1 Hz), 128.5, 128.5, 128.5, 128.7, 132.6 (d, J= 2 Hz), 133.2, 140.1 (d, J= 4 Hz), 164.1 (d, J= 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -115.4 (1F, m); MS m/z = 375 (M+); HRMS (*pos*-FAB, Gly.) Calcd. for C₂₄H₂₃FNO₂: 376.1713 ([M+H]+), Found: 376.1714 ([M+H]+); IR (KBr) cm⁻¹: 3386, 1737.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(1-hydroxyethyl)-4-phenylazetidin-2-one 8g and 9g Compound 8g and 9g was obtained as a colorless solid in 65% yield (8g/9g = 56/44). This reaction was conducted in 1 mmol scale. Both isomers 8g and 9g: Mp 87.0-88.0 °C; 1H NMR (CDCl₃, 400 MHz) δ : 1.27 (1.7H, dd, J = 6.6, 1.1 Hz), 1.33 (1.3H, dd, J = 6.3, 1.3 Hz), 2.27 (0.56H, d, J = 4.3 Hz), 2.32 (0.44H, d, J = 7.0 Hz), 4.13-4.25both isomers (1H, m), 4.64 $(0.56H, d, J = 3.9 Hz), 4.76 (0.44H, d, J = 4.1 Hz), 4.91_{both isomers} (1H, d, J_{one isomer} = 14.6, J_{one i$ J_{the other isomer} = 14.9 Hz), 7.14-7.17_{both} isomers (2H, m), 7.26-7.32_{both} isomers (5H, m), 7.36-7.41_{both isomers} (3H, m); 13 C NMR (CDCl₃, 150 MHz) δ : 16.8 (d, J = 6.1 Hz), 17.4 (d, J= 2.3 Hz), 44.2, 61.7 (d, J = 23 Hz), 62.5 (d, J = 23 Hz), 66.4 (d, J = 28 Hz), 67.2 (d, J = 26Hz), 103.8 (d, J= 228 Hz), 103.9 (d, J= 227 Hz), 128.0, 128.1, 128.5, 128.6, 128.6, 128.7, 128.8, 128.8, 128.9, 132.4, 132.5, 134.2, 164.6 (d, J = 24 Hz), 165.1 (d, J = 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -114.8 (0.56F, d, J = 14.0 Hz), -118.3 (0.44F, d, J = 11.0 Hz); MS m/z = 299 (M⁺); HRMS (pos FAB, Gly.) Calcd. for C₁₈H₁₉FNO₂: 300.1400 ([M+H]⁺), Found: 300.1397 ([M+H]+); IR (KBr) cm⁻¹: 3453, 1758.

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(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(1-hydroxy-2-methylpropyl)-4-phenylazetidin-2-one **8h** and **9h** Compound **8h** and **9h** was obtained as a colorless solid in 76% yield (**8h/9h** = 51/49). Both isomers 8h and 9h: Mp 115.0-116.0 °C; ¹H NMR (CDCl₃, 600 MHz) δ: 0.93-1.02both isomers (6H, m), 1.96-2.04 both isomers (1H, m), 2.21-2.22 (0.51H, m), 2.37-2.38 (0.49H, m), 3.71 (0.49H, ddd, 17.0, 6.4, 5.6 Hz), 3.86-3.91 (1.51H, m), 4.60 (0.44H, d, J= 4.1 Hz), 4.82 (0.51H, d, J = 4.6 Hz), 4.86-4.90both isomers (1H, d, Jone isomer = 15.2, Jthe other isomer = 14.8 Hz), 7.13-7.16both isomers (2H, m), 7.25-7.31both isomers (5H, m), 7.37-7.39both isomers (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ : 17.3 (d, J = 2 Hz), 17.9 (d, J = 1 Hz), 19.5 (d, J = 3 Hz), 19.7 (d, J = 2 Hz), 29.9 (d, J = 3 Hz), 29.9, 44.1 (d, J = 2 Hz), 62.8 (d, J = 22 Hz), 63.8 (d, J = 23 Hz), 73.9 (d, J = 26 Hz), 76.5 (d, J = 25 Hz), 103.7 (d, J = 230 Hz), 104.2 (d, J = 230 Hz), 104228 Hz), 127.8, 127.9, 128.3, 128.4, 128.5, 128.5, 128.6, 128.7, 128.7, 128.8, 128.8, 129.0, 131.9 (d, J = 1 Hz), 132.3 (d, J = 1 Hz), 134.1, 134.2, 164.8 (d, J = 24 Hz), 165.3 (d, J = 23Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -114.9 (0.51F, d, *J* = 4.0 Hz), -117.5 (0.49F, d, *J* = 17.0 Hz); MS m/z = 327 (M⁺); HRMS (*pos*-FAB, Gly.) Calcd. for C₂₀H₂₃FNO₂: 328.1713 ([M+H]+), Found: 328.1710 ([M+H]+); IR (KBr) cm⁻¹: 3409, 1748.

(3S, 4S)/(3R, 4R)·1·Benzyl·3·{cyclohexyl(hydroxy)methyl}·3·fluoro·4·phenylazetidin·2·
one 8i and 9i Compound 8i and 9i was obtained as a colorless solid in 89% yield (8i/9i = 52/48). Both isomers 8i and 9i: Mp 117.0·122.0 °C; ¹H NMR (CDCl₃, 400 MHz) δ:

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> 1.07-1.21both isomers (5H, m), 1.57-1.99 both isomers (6H, m), 2.23 (0.48H, d, J = 7.2 Hz), 2.36 $(0.52H, d, J = 5.0 Hz), 3.75 (0.52H, ddd, 18.1, 6.4, 5.0 Hz), 3.83 \cdot 3.91 (1.48H, m), 4.59$ (0.52H, d, J = 4.5 Hz), 4.81 (0.48H, d, J = 4.7 Hz), 4.85-4.91_{both} isomers (1H, d, J_{one} isomer = 15.0, Jthe other isomer = 14.8 Hz), 7.13-7.16both isomers (2H, m), 7.26-7.32both isomers (5H, m), 7.36-7.41_{both isomers} (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 25.8, 25.8, 26.0, 26.0, 26.1, 27.5 (d, J = 1 Hz), 28.0 (d, J = 1 Hz), 29.3 (d, J = 3 Hz), 29.6 (d, J = 1 Hz), 39.4 (d, J = 3 Hz), 39.7, 44.0 (d, J = 1 Hz), 44.0 (d, J = 1 Hz), 62.7 (d, J = 22 Hz), 63.6 (d, J = 23 Hz), 73.6 (d, J = 26 Hz), 76.0 (d, J = 25 Hz), 103.6 (d, J = 229 Hz), 104.9 (d, J = 229 Hz), 127.8, 127.9, 128.3, 128.5, 128.5, 128.5 (d, *J* = 1 Hz), 128.6, 128.6 (d, *J* = 1 Hz), 128.7, 128.7, 128.8, 129.0, 132.1 (d, J = 1 Hz), 132.4 (d, J = 1 Hz), 134.1, 134.2, 164.9 (d, J = 24 Hz), 165.4 (d, J = 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ : -114.2 (0.51F, m), -116.6 (0.49F, d, J = 0.51 Hz); 18.1 Hz); MS m/z = 367 (M⁺); HRMS (*pos*-FAB, Gly.) Calcd. for C₂₃H₂₇FNO₂: 368.2026 ([M+H]+), Found: 368.2026 ([M+H]+); IR (KBr) cm⁻¹: 3478, 2927, 2851, 1746.

> (3S, 4S)/(3R, 4R)-1-Benzyl-3-fluoro-3-(1-hydroxy-2,2-dimethylpropyl)-4-phenylazetidin-2-one 8j and 9j Compound 8j and 9j was obtained as a colorless solid in 74% yield (8j/9j = 67/33). Both isomers 8j and 9j: Mp 126.0-127.5 °C; ¹H NMR (CDCl₃, 400 MHz) δ: 0.96-0.98_{both isomers} (9H, m), 2.33 (0.33H, d, J = 7.1 Hz), 2.75 (0.67H, d, J = 4.2 Hz), 3.66
> (0.67H, dd, 24.3, 3.9 Hz), 3.80-3.87 (1.33H, m), 4.59 (0.67H, d, J = 4.4 Hz), 4.86_{both isomers}

(1H, d, J = 14.7 Hz), 4.91 (0.33H, d, J = 4.9 Hz), 7.11-7.16both isomers (2H, m), 7.26-7.30both
$_{\text{isomers}}$ (5H, m), 7.36-7.40 _{both isomers} (3H, m); ¹³ C NMR (CDCl ₃ , 100 MHz) δ : 26.7 (d, J = 3
Hz), 26.8 (d, J = 3 Hz), 35.2 (d, J = 2 Hz), 35.5 (d, J = 2 Hz), 43.9, 43.9, 62.8 (d, J = 22 Hz)
64.7 (d, $J = 23$ Hz), 75.9 (d, $J = 26$ Hz), 79.0 (d, $J = 22$ Hz), 104.4 (d, $J = 235$ Hz), 105.1 (d,
J = 229 Hz), 127.7, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9 (d, $J = 2$ Hz),
129.1, 129.1 (d, <i>J</i> = 2 Hz), 131.7, 132.2, 134.0, 134.2, 165.1 (d, <i>J</i> = 25 Hz), 165.6 (d, <i>J</i> = 23
Hz); ¹⁹ F NMR (CDCl ₃ , 90 MHz) δ: –112.5 (0.33F, m), –119.1 (0.67F, d, <i>J</i> = 24.3.0 Hz); MS
m/z = 341 (M ⁺); HRMS (<i>pos</i> FAB, Gly.) Calcd. for C ₂₁ H ₂₅ FNO ₂ : 342.1869 ([M+H] ⁺),
Found: 342.1877 ([M+H]+); IR (KBr) cm ⁻¹ : 3422, 2959, 1749, 1725.

(3S,4S)/(3R,4R)-1-Benzyl-3-fluoro-3-(2-hydroxybutan-2-yl)-4-phenylazetidin-2-one **8k** and **9k** Compound **8k** and **9k** was obtained as a colorless solid in 73% yield (**8k/9k** = 57/43). This reaction was conducted in 1 mmol scale. Both isomers **8k** and **9k**: Mp 112.5-113.5 °C; ¹H NMR (CDCl₃, 600 MHz) δ: 0.91-0.94 (1.29H, m), 0.94-0.97 (1.71H, m), 1.20 (1.71H, d, *J* = 1.7 Hz), 1.36 (1.29H, d, *J* = 2.0 Hz), 1.57-1.60 (0.86H, m), 1.67-1.73 (0.57H, m), 1.74 (0.43H, bs), 1.79 (0.57H, bs), 1.81-1.87 (0.57H, m), 3.77-3.90_{both} isomers (1H, m), 4.78 (0.57H, d, *J* = 4.5 Hz), 4.81 (0.43H, d, *J* = 4.6 Hz), 4.90-4.93_{both} isomers (1H, d, *J*one isomer = 14.9, *J*the other isomer = 14.9 Hz), 7.15-7.17_{both} isomers (2H, m), 7.26-7.30_{both} isomers (5H, m), 7.36-7.40_{both} isomers (3H, m); ¹³C NMR (CDCl₃, 150 MHz) δ: 6.9 (m), 20.2 (d, *J* = 2 Hz), 20.4 (d, J= 2 Hz), 28.6 (d, J= 2 Hz), 29.2 (d, J= 2 Hz), 44.1 (m), 61.9 (d, J= 22 Hz), 62.2 (d, J= 23 Hz), 73.3 (d, J= 24 Hz), 73.4 (d, J= 24 Hz), 106.2 (d, J= 230 Hz), 106.3 (d, J= 230 Hz), 127.9, 127.9, 128.4 (d, J= 1 Hz), 128.4 (d, J= 1 Hz), 128.6, 128.6, 128.6, 128.6, 128.7, 128.8, 128.9, 132.7 (d, J= 1 Hz), 132.8 (d, J= 1 Hz), 134.3, 134.4, 164.9 (d, J= 24 Hz), 165.0 (d, J= 23 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -114.5 (0.57F, m), -114.8 (0.43F, m); MS m/z = 327 (M⁺); HRMS (pos FAB, Gly.) Calcd. for C₂₀H₂₃FNO₂: 328.1713 ([M+H]⁺), Found: 328.1715 ([M+H]⁺); IR (KBr) cm⁻¹: 3450, 1751.

(3S, 4S)/(3R, 4R)·1·Benzyl·3·fluoro·3·(2·hydroxypropan·2·yl)·4·phenylazetidin·2·one 8I
Compound 8I was obtained as a colorless solid in 76% yield. Mp 173.0·173.5 °C; ¹H NMR
(CDCl₃, 400 MHz) δ: 1.29 (3H, J = 1.5 Hz), 1.38 (3H, J = 1.5 Hz), 1.92 (1H, bs), 3.90 (1H, dd, J = 14.9, 2.4 Hz), 4.78 (1H, d, J = 4.3 Hz), 4.93 (1H, d, J = 14.9 Hz), 7.15·7.18 (2H, m), 7.26·7.31 (5H, m), 7.37·7.39 (3H, m); ¹³C NMR (CDCl₃, 100 MHz) δ: 24.2 (d, J = 3 Hz), 24.5 (d, J = 2 Hz), 44.1 (d, J = 2 Hz), 61.9 (d, J = 23 Hz), 71.1 (d, J = 25 Hz), 105.6 (d, J = 227 Hz), 127.9, 128.1 (d, J = 1 Hz), 128.5, 128.5, 128.6, 128.7, 132.6 (d, J = 1 Hz), 134.2, 164.7 (d, J = 24 Hz); ¹⁹F NMR (CDCl₃, 90 MHz) δ: -114.7 (1F, m); MS m/z = 313 (M+); HRMS (pos FAB, Gly.) Calcd. for C₁₉H₂₁FNO₂: 314.1556 ([M+H]+), Found: 314.1549 ([M+H]+); IR (KBr) cm⁻¹: 3451, 1755.

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Supporting Information

Copies of ¹H and ¹³C NMR spectra for all starting substrates **3a-3g** (α-bromo-α-fluoro-β-lactams) and all products **4a-4h**, **5**, **6**, **7b-g**, **8a-1** and **9a-k** are provided. ¹⁹F NMR spectra for all products **4a-4h**, **5**, **7b-g**, **8a-1** and **9a-k** are provided. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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