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Synthetic studies of 3-(3-fluorooxindol-3-yl)-L-alanine

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Dedicated to the memory of Professor Toshio Satoh of Tokushima Bunri University who made many lasting contributions to the field of medicinal chemistry.

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ABSTRACT

Oxidative fluorination of several protected tryptophans **8b**–**g** with Selectfluor™ proceeded smoothly in aqueous media to give a diastereomeric mixture of the corresponding 3-fluorooxindoles **9b**–**g**. Attempted deprotection of the 3-fluorooxindoles **9b**–**g** under various conditions did not afford 3-(3-fluorooxindol-3-yl)-L-alanine (**6**). Reaction of the suitably protected tryptophan derivative **16** with Selectfluor™ produced the fluorinated product **17**. Simultaneous cleavage of all protective groups of **17** under acidic conditions successfully gave the target compound **6** in excellent yield.

1. Introduction

The oxindole structure **1** is often found in natural products and is also formed during the metabolism of tryptophan (Fig. 1) [1,2]. Oxindoles have been recognized as probes for investigation of biological processes and leads for drug discovery [3,4]. Among many examples of oxindoles, 3-hydroxyoxindoles have significance in that these frequently occur in natural products and are important structures in medicinal chemistry. Many 3-hydroxyoxindoles have useful biological and pharmacological activities [2,4]. For example, the compounds TMC-95A–D (**3a**–**d**) having a multifunctional 3-hydroxyoxindole structure inhibit the proteolytic activity of proteasome. This is a protease complex that is targeted in the design of new drugs for many diseases including cancer and autoimmune diseases [5]. 3-Oxindol-3-yl-L-alanine (**4**) is a tryptophan metabolite and was found to be a potent competitive inhibitor of both tryptophan synthase and tryptophanase [6]. It should be noted that the (2*S*,4*S*)-isomer of 3-(3-hydroxyoxindol-3-yl)-L-alanine (**5**) inhibits only tryptophan synthase and the (2*S*,4*R*)-isomer inhibits only tryptophanase [7]. Identification of this stereochemistry dependent-biological activity is possible with the 3-hydoxylated structure **5** since epimerization is blocked by the 3-substituent. Similar studies with other oxindoles such as the simple oxindole structure **4** is difficult because of epimerization at the C-4 stereogenic center [6,7].

To provide tools for investigating the relationship between biological activity and absolute configuration of epimerizable substrates, we have been studying the design, synthesis, and biological evaluation of chiral fluorinated bioorganic molecules that possess a fluorine atom at the stereogenic center [8]. Since replacement of a hydrogen of a prototype molecule with a fluorine results in minimal steric alterations, many fluorinated biomolecules and medicinal agents interact with recognition sites of enzyme and receptors in a manner similar to the fluorine-free molecules [9]. This adds to the value of these probes of stereochemistry vs. reactivity. Of course, introduction of fluorine atoms into bioactive molecules often brings about enhanced, additional and/or altered biological activities. In one example, we earlier replaced the labile proton at the stereogenic center of the epimerizable biomolecule thalidomide [10] with a fluorine atom to give a non-epimerizable analog [8a]. Substitution of a hydroxyl group of prototype molecules with fluorine can also provide the

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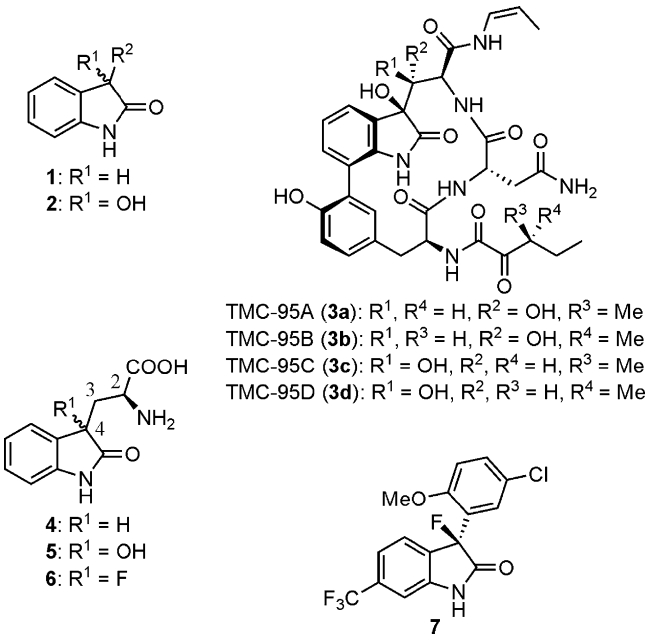


Fig. 1. Structures of oxindoles **1**–**7**

isosteric analogs because of similar electronic character and ability as hydrogen bond acceptor of fluorine to hydroxyl group [9]. In addition, apart from a hydroxyl group, a fluorine moiety is not subjected to further metabolization. For example, Prestwich et al. reported the substitution of one hydroxyl group of lysophosphatidic acids (LPA, 1- or 2-acyl-*sn*-glycerol-3 phosphate) with fluorine in order to prevent the acyl migration and evaluate the inherent biological activities of LPA under the acyl migration-free conditions [11].

As a part of our synthetic studies of chiral fluorinated bioorganic molecules, we earlier attempted the synthesis of 3-(3-fluorooxindol-3-yl)-L-alanine (**6**). The non-epimerizable compound **6** should be a suitable model to study the relationship between the stereochemistry and the biological activities of **4**. Introduction of fluorinated amino acids such as **6** into peptides often changes the original conformation and biological properties [12]. Moreover, clinical application of BMS-204532 (Maxipost, **7**) as a potassium channel opener [13] further encouraged us to pursue the synthesis the fluorinated tryptophan analog **6** as a potential building block for drug development.

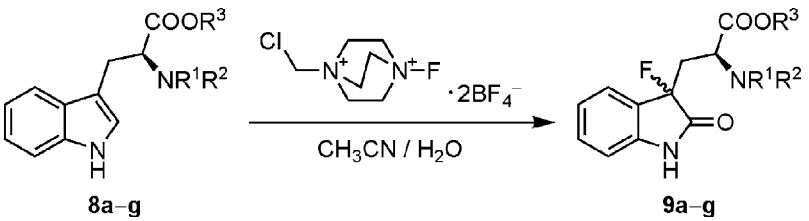
2. Results and discussion

We have previously reported the synthesis of 3-fluorooxindole **9a** from N^{α}-acetyl-L-tryptophan methyl ester (**8a**) by electrophilic fluorination with Selectfluor™ (Table 1, entry 1) [14]. However, we were unable to find conditions to convert **9a** to the free amino acid **6**. We report here the results of fluorination of oxindole substrates **8** with varying protecting groups on the fluorination reaction as well as defining substrates that allow facile deprotection to the amino acid (Table 1). In initial attempts, treatment of N^{α}-(*tert*-butoxycarbonyl)-L-tryptophan methyl ester (**8b**) with 3 equiv. of Selectfluor™ [15] in acetonitrile/water (1/1) produced a diastereomeric mixture of the corresponding 3-fluorooxindole **9b** (entry 2). However, the yield of **9b** was quite low. Fluorination of the other tryptophan derivatives **8c** and **8d** having the same urethane protective groups gave the corresponding 3-fluorooxindoles **9c** and **9d**, again in rather low yields (entries 3 and 4). It should be noted that substantial amounts of the 3a-fluoropyrrolo[2.3-*b*]indole derivatives **10** were formed as side products during the fluorination of **8b**–**d**. The formation of the cyclized compounds **10** was presumably due to the rather nucleophilic character of the N_b-acyloxy moiety of **8b**–**d** compared to the N_b-acyl moiety of **8a**. Indeed, Hino et al. reported that such cyclization occurs readily during electrophilic attack at the 3-position of N_b-alkoxycarbonyl protected tryptamines [16].

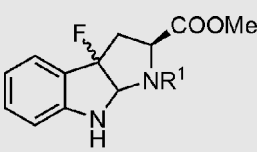
Based on these results, we explored the use of the tryptophans having N_b-acyl protective groups, such as acetyl or trifluoroacetyl, which would be less nucleophilic than N_b-acyloxy groups. Indeed, when N_b-acyl protected tryptophans **8e** and **8f** were submitted to the same fluorination procedure, 3-fluorooxindoles **9e** and **9f** were obtained in 70% and 53% yields, respectively (entries 5 and 6), without detectable formation of **10**. The tryptophan derivative **8g** with the α-amino group being fully protected was also fluorinated to give the corresponding 3-fluorooxindole **9g** in good yield (entry 7).

Although we have succeeded in the fluorination of **8b**–**g**, stereoselectivity of the reaction was rather poor with the

Table 1
Synthesis of 3-fluorooxindoles **9a**–**g** from protected tryptophans **8a**–**g**[a]



Entry	Indole **8**	R^1	R^2	R^3	3-Fluorooxindole	Yield (%)
1	**8a**[b]	Ac	H	Me	**9a**	70
2	**8b**	Boc	H	Me	**9b**	15
3	**8c**	Cbz	H	Me	**9c**	40
4	**8d**	Fmoc	H	Me	**9d**	42
5	**8e**	CF_3CO	H	Me	**9e**	70
6	**8f**	Ac	H	Bu^t	**9f**	53
7	**8g**	Boc	Boc	Me	**9g**	71



10

[a] Experimental conditions: three equivalent of Selectfluor™ was added to a solution of **8** in CH_3CN/H_2O (=1/1) and the mixture was stirred at room temperature overnight.
[b] Ref. [14].

Table 2
Deprotection of the carboxyl groups of fluorooxindoles **9b**,**c**,**f**,**g**

9b,**c**,**f**,**g** **11b**,**c**,**f**,**g**

Entry	3-Fluorooxindole	R^1	R^2	R^3	Conditions	Product (yield)
1	**9b**[a]	Boc	H	Me	0.2N NaOH/MeOH	**11b** (72%)
2	**9c**[a]	Cbz	H	Me	0.2N NaOH/MeOH	**11c** (77%)
3	**9g**[a]	Boc	Boc	Me	0.2N NaOH/MeOH	Decomposition
4	**9f**[b]	Ac	H	Bu^t	HBr/AcOH	**11f** (48%)

[a] Diastereomeric mixture was used.
[b] Less polar isomer was used.

diastereomeric excess of 4–46%. Separation of the diastereomers of 3-fluorooxindoles **9d–g** was carried out readily using silica gel column chromatography. In order to determine the absolute configurations, we attempted to get single crystals of **9d**,**e**,**g**. However, no crystals suitable for X-ray analysis were obtained.

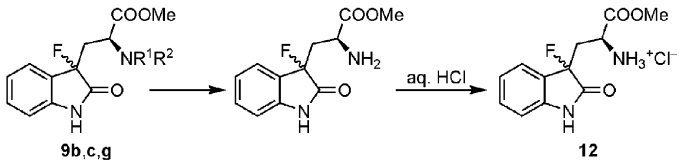
We then examined stepwise deprotection of 3-fluorooxindoles. Saponification of the diastereomeric mixture of **9b** and **9c** in aqueous NaOH/MeOH gave the corresponding carboxylic acids **11b** and **11c** in 72% and 77% yields, respectively (Table 2, entries 1 and 2). However, reaction of **9g** under the same conditions led to decomposition (entry 3). This may result from lactam ring cleavage that occurs instead of the hydrolysis of the ester moiety, the reactivity of which would be lowered due to the sterically hindered neighboring N^{α},N^{α}-di-*tert*-butoxycarbonylamino group. Treatment of **9f** with HBr/AcOH also produced the corresponding carboxylic acid **11f** in 48% yield (entry 4).

Having established conditions to achieve ester hydrolysis, we then addressed the final stage of the synthesis, i.e., N^{α}-deprotection of **11b**,**c** and **11f** thus prepared. Although various conditions were applied for these compounds, we encountered difficulty in isolation of the target molecule **6** from the organic and inorganic salts mixture. Attempted simultaneous removal of all protecting groups of **9d** and **9e** under saponificative conditions (piperidine and/or potassium carbonate) were unsuccessful.

Faced with these difficulties, we also attempted the alternative strategy that involves initial N^{α}-deprotection followed by ester hydrolysis. Removal of the Cbz groups of **9c** occurred under hydrogenative or acidic conditions to produce the desired compound **12** although as mixtures with some inseparable products (Table 3, entries 1 and 2). *N*-Deprotection of **9d** and **9e** under basic conditions (piperidine and potassium carbonate) gave a complicated mixture of mostly decomposition products. Finally, treatment of **9b**,**g** with HBr/AcOH gave the corresponding free amine, which was successfully isolated as HCl salt **12** in excellent yield (entries 3 and 4). However, in spite of extensive efforts, hydrolysis of the methyl ester **12** under acidic conditions either did not proceed or gave decomposition products under drastic conditions. Saponification of **12** did not yield the desired product **6**, instead producing mixtures of non-fluorinated compounds.

After these extensive investigations and taking into consideration all aspects of reaction conditions and isolation procedures, we eventually focused on N^{α},N^{α}-di-(*tert*-butoxycarbonyl)-L-tryptophan *tert*-butyl ester (**16**) as a likely suitable precursor to the target structure. Condensation of N^{α}-(*tert*-butoxycarbonyl)-L-tryptophan (**13**) with *tert*-butanol in the presence of DCC (*N*,*N*′-dicyclohexylcarbodiimide) gave *tert*-butyl ester **14** in 43% yield with ee of 46% (Scheme 1). Protection of the indole nitrogen of **14** with benzyl chloroformate [17] followed by treatment with di-*tert*-butyl carbonate gave the fully protected tryptophan derivative **15** in moderate yield. Catalytic hydrogenation of **15** gave the fluorination precursor **16** in good yield. Compound **16** was then allowed to react with Selectfluor™ in the usual manner to produce a diastereomeric mixture of the corresponding fluorooxindole **17** in 51% yield. Finally, treatment of **17** with HBr/AcOH successfully produced the target compound **6** as HBr salt in excellent yield, although as a mixture of diastereomers.

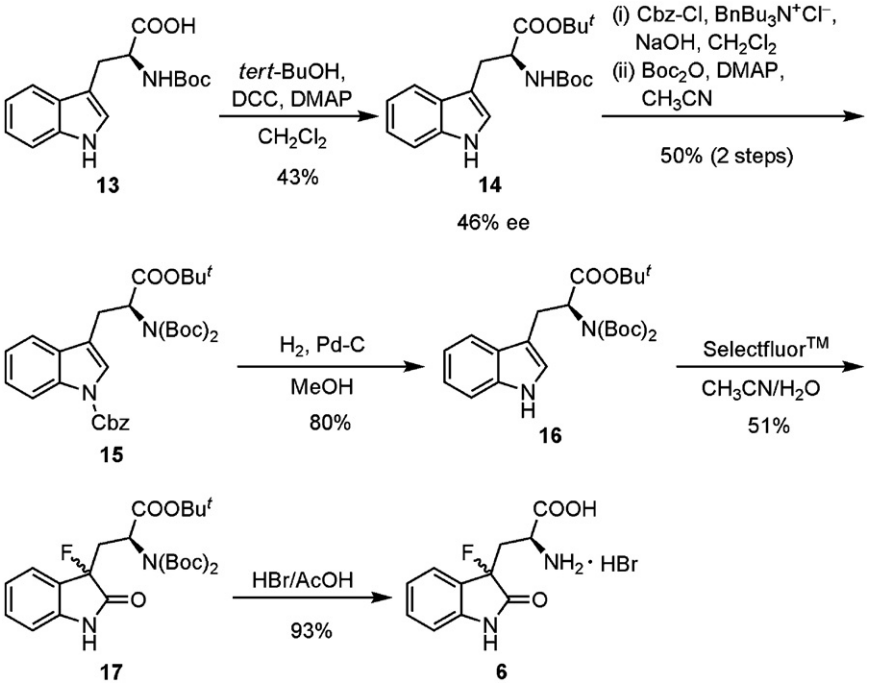
Table 3
Deprotection of the α-amino groups of fluorooxindoles **9b**,**c**,**g**



9b,**c**,**g** **12**

Entry	3-Fluorooxindole	R^1	R^2	Conditions	Yield (%)
1	**9c**[a]	Cbz	H	HBr/AcOH	Mixture[b]
2	**9c**[a]	Cbz	H	Pd–C, $HCOO^-NH_4^+$, MeOH	Mixture[b]
3	**9b**[a]	Boc	H	HBr/AcOH	99%
4	**9g**[a]	Boc	Boc	HBr/AcOH	94%

[a] Diastereomeric mixture was used.
[b] Inseparable mixture with unidentified products.



Scheme 1. Synthesis of **6**.

3. Conclusion

We have synthesized 3-(3-fluorooxindol-3-yl)-L-alanine (**6**) by fluorination of the suitably protected tryptophan derivative **16** with Selectfluor™ followed by simultaneous deprotection under acidic conditions. Having available this new fluorinated amino acid in unprotected form will allow several new applications. In order to evaluate the potential of **6** as a biological tool and precursor for drug development, diastereomeric and enantiomeric separations of **6** are currently underway. Use of the strategy presented here to prepare derivatives suitable for peptide incorporation will also be studied.

4. Experimental

4.1. General

Melting points were measured with a Yanaco micro-melting point apparatus and are uncorrected. Spectroscopic measurements were carried out with the following instruments: optical rotations, JASCO DIP-1000 digital polarimeter; IR spectra, JEOL FT/IR-460Plus; mass spectra (MS), JEOL JMS-GCmate; high resolution mass spectra (HRMS), JEOL JMS-AX 505; ^{1}H NMR spectra, JEOL ECX-400P (400 MHz) in $CDCl_3$ or CD_3OD with TMS (=0.00 ppm) as an internal standard; ^{19}F NMR spectra, JEOL ECX-400P (376 MHz) in $CDCl_3$ or CD_3OD with $CFCl_3$ (=0.00 ppm) as an internal standard. Column chromatography and thin layer chromatography were performed on Kanto chemical silica gel 60N (0.040–0.050 mm) or Merck 9385 silica gel 60 (0.040–0.063 mm) and on Merck 5715, respectively.

4.2. General procedure for the synthesis of the protected 3-(3-fluorooxindol-3-yl)alanine

Selectfluor™ (755 mg, 2.13 mmol) was added to a solution of N^{α}-trifluoroacetyl-L-tryptophan methyl ester (**8e**) (223 mg, 0.710 mmol) in a mixture of acetonitrile and water (1:1, 14 mL) at room temperature. After stirring overnight, the mixture was concentrated and extracted with EtOAc. The organic layer was then dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/$CHCl_3$/EtOAc = 5/1/1) to give the less polar isomer (80.5 mg, 0.231 mmol, 33%) and the more polar isomer (90.3 mg, 0.259 mmol, 37%) of (2*S*)-2-(trifluoroacetylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid methyl ester (**9e**). Diastereomeric excess (de) was determined to be 12% from the ^{1}H NMR of crude mixture. Less polar isomer: colorless solid; mp 122–123 °C; $[\alpha]_D^{28}$ −12.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν 3291, 1755, 1737, 1703, 1628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (1H, ddd, *J* = 24.2, 15.1, 4.1 Hz), 3.05 (1H, dt, *J* = 15.1, 6.9 Hz), 3.81 (3H, s), 4.77 (1H, ddd, *J* = 8.2, 6.9, 4.1 Hz), 6.91 (1H, d, *J* = 7.8 Hz), 7.17 (1H, dd, *J* = 7.8, 7.3 Hz), 7.39 (1H, ddt, *J* = 7.8, 2.3, 1.4 Hz), 7.44 (1H, d, *J* = 7.3 Hz), 8.10 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.48 (3F, s), −156.16 (1F, d, *J* = 23.8 Hz); MS (EI) *m*/*z*: 348 (M^+), 289 (M^+−COOMe), 269 (M^+−COOMe–HF); HRMS (EI) calcd. for $C_{14}H_{12}F_4N_2O_4$ (M^+): 348.0733; found 348.0714. More polar isomer: colorless solid; mp 129–130 °C; $[\alpha]_D^{28}$ +15.8 (*c* 1.1, $CHCl_3$); IR (KBr) 3388, 3301, 1754, 1726, 1710, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (1H, ddd, *J* = 22.4, 15.1, 7.3 Hz), 2.90 (1H, dt, *J* = 15.1, 5.0 Hz), 3.72 (3H, s), 4.87 (1H, dt, *J* = 7.3, 5.0 Hz), 6.91 (1H, d, *J* = 7.8 Hz), 7.14 (1H, dd, *J* = 7.8, 7.3 Hz), 7.38 (1H, ddt, *J* = 7.8, 1.8, 0.9 Hz), 7.44 (1H, d, *J* = 7.3 Hz), 7.65 (1H, br d, *J* = 6.9 Hz), 7.92 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.54 (3F, s), −153.89 (1F, dd, *J* = 22.4, 15.1 Hz); MS (EI) *m*/*z*: 348 (M^+), 289 (M^+−COOMe), 269 (M^+−COOMe–HF); HRMS (EI) calcd. for $C_{14}H_{12}F_4N_2O_4$ (M^+): 348.0733; found 348.0705.

4.2.1. (2S)-2-(tert-Butoxycarbonylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid methyl ester (9b)

Yield: 15% (as a diastereomeric mixture). De was determined to be 4% from the ^{1}H NMR of crude mixture: pale yellow oil; IR (neat) ν 3246, 1736, 1718, 1697, 1686, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (9H, s), 1.41 (9H, s), 2.57–2.79 (4H, m), 3.66 (3H, s), 3.71 (3H, s), 4.27 (1H, m), 4.53 (1H, dd, *J* = 12.8, 7.8 Hz), 5.14 (1H, br

d, J = 7.8 Hz), 5.25 (1H, br d, J = 7.8 Hz), 6.88 (1H, d, J = 7.8 Hz), 6.90 (1H, d, J = 7.8 Hz), 7.11 (1H, t, J = 7.3 Hz), 7.13 (1H, t, J = 7.3 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.45–7.48 (2H, m), 8.06 (1H, br s), 8.18 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.05 (1/6F, br s), −152.30 (5/6F, br s), −152.55 (5/6F, br t, J = 14.7 Hz), −152.69 (1/6F, br s); MS (EI) m/z: 352 (M^+), 296 ($M^+-C_4H_8$).

4.2.2. (2S)-2-(Benzyloxycarbonylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid methyl ester (**9c**)

Yield = 40% (as a diastereomeric mixture). De was determined to be 16% from the ^{1}H NMR of crude mixture: pale yellow oil; IR (neat) ν 3310, 1739, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58–2.85 (4H, m), 3.66 (3H, s), 3.72 (3H, s), 4.26 (1H, dt, J = 9.6, 4.1 Hz), 4.59 (1H, dt, J = 7.8, 5.0 Hz), 4.94 (1H, d, J = 12.4 Hz), 5.03 (1H, d, J = 12.4 Hz), 5.05 (1H, d, J = 12.4 Hz), 5.09 (1H, d, J = 12.4 Hz), 5.39 (1H, br d, J = 9.2 Hz), 5.52 (1H, br d, J = 8.2 Hz), 6.65 (1H, d, J = 7.8 Hz), 6.85 (1H, d, J = 7.8 Hz), 7.09 (1H, t, J = 7.8 Hz), 7.11 (1H, m), 7.26–7.45 (14H, m), 7.81 (1H, br s), 7.98 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.11 (1F, t, J = 16.9 Hz), −152.39 (1F, br t, J = 10.9 Hz); MS (EI) m/z: 386 (M^+), 327 (M^+−COOMe).

4.2.3. (2S)-2-(9-Fluorenylmethoxycarbonylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid methyl ester (**9d**)

De was determined to be 8% from the ^{1}H NMR of crude mixture.

Less polar isomer: yield = 16%; pale pink solid; mp 81–82 °C; $[\alpha]_D^{29}$ −26.2 (c 1.0, $CHCl_3$); IR (KBr) ν 3298, 2954, 1739, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71–2.75 (2H, m), 3.73 (3H, s), 4.18 (1H, br t, J = 6.4 Hz), 4.28 (1H, br q, J = 7.8 Hz), 4.32 (1H, br s), 4.33 (1H, br s), 5.39 (1H, br d, J = 9.2 Hz), 6.77 (1H, d, J = 7.8 Hz), 7.11 (1H, br t, J = 7.3 Hz), 7.12 (1H, br s), 7.30–7.44 (6H, m), 7.59 (1H, d, J = 7.8 Hz), 7.62 (1H, d, J = 7.8 Hz), 7.76–7.81 (2H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.21 (1F, br t, J = 11.7 Hz); MS (EI) m/z: 474 (M^+), 456 (M^+-H_2O); HRMS (EI) calcd. for $C_{27}H_{23}FN_2O_5$ (M^+): 474.1591; found 474.1629.

More polar isomer: yield = 26%; pale yellow solid; mp 80–81 °C; $[\alpha]_D^{29}$ −41.4 (c 1.1, $CHCl_3$); IR (KBr) 3307, 2954, 1742, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (1H, ddd, J = 16.9, 15.1, 7.8 Hz), 2.82 (1H, ddd, J = 17.4, 15.1, 4.6 Hz), 3.69 (3H, s), 4.19 (1H, br t, J = 6.9 Hz), 4.32 (1H, br s), 4.33 (1H, br s), 4.61 (1H, ddd, J = 7.8, 7.3, 4.6 Hz), 5.55 (1H, br d, J = 8.3 Hz), 6.85 (1H, d, J = 7.3 Hz), 7.07 (1H, t, J = 7.3 Hz), 7.28–7.46 (7H, m), 7.58 (2H, d, J = 6.9 Hz), 7.77 (2H, d, J = 7.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.30 (1F, t, J = 17.1 Hz); MS (EI) m/z: 456 (M^+–H_2O); HRMS (EI) calcd. for $C_{27}H_{23}FN_2O_5$ (M^+): 474.1591; found 474.1618.

4.2.4. (2S)-2-(Acetylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid tert-butyl ester (**9f**)

De was determined to be 46% from the ^{1}H NMR of crude mixture.

Less polar isomer: yield = 35%; pale red oil; $[\alpha]_D^{28}$ −13.4 (c 1.0, $CHCl_3$); IR (neat) ν 3284, 2981, 1739, 1658, 1625 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.83 (3H, s), 2.53 (1H, ddd, J = 16.0, 14.6, 9.2 Hz), 2.68 (1H, ddd, J = 20.1, 14.6, 4.1 Hz), 4.72 (1H, ddd, J = 9.2, 7.8, 4.1 Hz), 6.11 (1H, br d, J = 7.8 Hz), 6.88 (1H, d, J = 7.8 Hz), 7.11 (1H, t, J = 7.8 Hz), 7.33 (1H, ddt, J = 7.8, 1.8, 1.4 Hz), 7.46 (1H, d, J = 7.8 Hz), 7.84 (2/3H, br s), 7.95 (1/3H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −152.43 (1F, t, J = 18.0 Hz); MS (EI) m/z: 336 (M^+), 280 ($M^+-C_4H_8$), 235 (M^+−COOBu^t); HRMS (EI) calcd. for $C_{17}H_{21}FN_2O_4$ (M^+): 336.1485; found 336.1460.

More polar isomer: yield = 18%; pale red oil; $[\alpha]_D^{29}$ −4.4 (c 1.0, $CHCl_3$); IR (neat) ν 3285, 2979, 1736, 1660, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (9H, s), 1.95 (3H, s), 2.67 (1H, d, J = 12.8 Hz), 2.68 (1H, d, J = 12.8 Hz), 4.43 (1H, dt, J = 7.6, 6.9 Hz), 6.30 (1H, br d, J = 9.2 Hz), 6.87 (1H, d, J = 7.8 Hz), 7.13 (1H, dd, J = 7.8, 7.3 Hz), 7.35 (1H, t, J = 7.8 Hz), 7.45 (1H, d, J = 7.3 Hz), 8.23 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −151.97 (1F, t, J = 13.0 Hz); MS (EI) m/z: 336 (M^+), 280 ($M^+-C_4H_8$), 235 (M^+−COOBu^t); HRMS (EI) calcd. for $C_{17}H_{21}FN_2O_4$ (M^+): 336.1485; found 336.1493.

4.2.5. (2S)-2-[Bis(tert-butoxycarbonyl)amino]-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid methyl ester (**9g**)

Yield = 71% (as a diastereomeric mixture). De was determined to be 12% from the ^{1}H NMR of crude mixture. Each diastereomer gave the following data after partial separation.

Less polar isomer: colorless solid; mp 151–152 °C; $[\alpha]_D^{29}$ −62.1 (c 1.0, $CHCl_3$); IR (KBr) ν 3230, 2983, 1742, 1733, 1702, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (18H, s), 2.90 (1H, ddd, J = 15.1, 11.0, 9.6 Hz), 3.02 (1H, ddd, J = 21.3, 15.1, 3.2 Hz), 3.70 (3H, s), 5.23 (1H, dd, J = 9.6, 3.2 Hz), 6.85 (1H, d, J = 7.8 Hz), 7.08 (1H, t, J = 7.8 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.52 (1H, br s), 7.53 (1H, d, J = 7.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −153.15 (1F, br m); MS (EI) m/z: 452 (M^+), 396 ($M^+-C_4H_8$); HRMS (EI) calcd. for $C_{22}H_{29}FN_2O_7$ (M^+): 452.1959; found 452.1985.

More polar isomer: colorless solid; mp 140–141 °C; $[\alpha]_D^{29}$ −39.7 (c 1.0, $CHCl_3$); IR (KBr) ν 3275, 2985, 1777, 1739, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (18H, s), 2.90 (1H, dt, J = 15.1, 8.7 Hz), 3.08 (1H, ddd, J = 21.6, 15.1, 3.7 Hz), 3.69 (3H, s), 5.24 (1H, dd, J = 8.7, 3.7 Hz), 6.86 (1H, d, J = 7.8 Hz), 7.10 (1H, dd, J = 7.8, 7.3 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.41 (1H, d, J = 7.3 Hz), 7.60 (1/2H, br s), 7.64 (1/2H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −154.39 (1F, br dd, J = 21.6, 8.7 Hz); MS (EI) m/z: 452 (M^+), 396 ($M^+-C_4H_8$); HRMS (EI) calcd. for $C_{22}H_{29}FN_2O_7$ (M^+): 452.1959; found 452.1967.

4.3. General procedure for saponification of the protected 3-(3-fluorooxindol-3-yl)alanine methyl ester **9b** and **9c**

To a solution of 3-fluorooxindole **9b** (23 mg, 0.0653 mmol) in methanol (0.45 mL) was added 0.2N aqueous NaOH (0.49 mL, 0.1 mmol) at 0 °C. The mixture was stirred for 20 min at 0 °C and for 40 min at room temperature. The mixture was then concentrated and extracted with ether. The aqueous layer was acidified (pH ∼ 2) with 5% aqueous $KHSO_4$ at 0 °C. The solution was saturated with NaCl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solution was concentrated to give a diastereomeric mixture of (2*S*)-2-(*tert*-butoxycarbonylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid (**11b**) as a colorless solid (16 mg, 0.0473 mmol, 72%).

IR (KBr) ν 3700–2900 (br), 2980, 2932, 1728, 1624 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.28 (5H, br s), 1.34 (4H, br s), 1.39 (9H, s), 2.27–2.82 (4H, m), 3.60 (1/3H, m), 3.65 (2/3H, m), 3.95 (1/3H, m), 4.01 (2/3H, dd, J = 11.0, 1.8 Hz), 6.87 (1H, d, J = 7.3 Hz), 6.88 (1H, d, J = 7.8 Hz), 7.05 (1H, dt, J = 7.8, 0.9 Hz), 7.10 (1H, t, J = 7.3 Hz), 7.24 (1H, dt, J = 7.8, 0.9 Hz), 7.34–7.38 (2H, m), 7.46 (1H, d, J = 7.3 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −150.31 (1/11F, m), −151.05 (5/11F, m), −151.47 (16/11F, m); MS (EI) m/z: 318 (M^+–HF).

4.3.1. (2S)-2-(Benzyloxycarbonylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid (**11c**)

Diastereomeric mixture: colorless solid; IR (KBr) ν 3700–3000 (br), 2924, 1725, 1624 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 2.36 (1H, dt, J = 14.2, 10.5 Hz), 2.50–2.84 (3H, m), 4.02 (1/2H, dd, J = 10.5, 2.7 Hz), 4.09 (1/2H, dd, J = 10.5, 2.7 Hz), 4.19 (3/4H, dd, J = 10.5, 2.7 Hz), 4.26 (1/4H, dd, J = 10.5, 2.7 Hz), 4.89 (2H, s), 5.02 (2H, s), 6.83 (1H, d, J = 7.8 Hz), 6.84 (1/2H, d, J = 7.8 Hz), 6.86 (1/2H, d, J = 8.2 Hz), 6.99 (1/2H, t, J = 7.3 Hz), 7.02 (1H, t, J = 7.8 Hz), 7.07 (1/2H, t, J = 7.3 Hz), 7.17–7.46 (14H, m); ^{19}F NMR (376 MHz, CD_3OD) δ −150.29 (2/5F, m), −152.07 (1/4F, m), −152.63 (27/20F, m); MS (EI) m/z: 352 (M^+−HF).

4.4. (2S)-2-(Acetylamino)-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid (11f)

To a solution of the less polar isomer of 3-fluorooxindole **9f** (20 mg, 0.0595 mmol) in acetic acid (0.75 mL) was added 33% HBr/AcOH (0.75 mL) at 0 °C. The mixture was stirred for 20 min at room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The aqueous layer was acidified (pH ~ 1) with 10% aqueous HCl at 0 °C. The solution was saturated with NaCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by recrystallization from *n*-hexane/$CHCl_3$/EtOH to give **11f** as a pale brown solid (8 mg, 0.0285 mmol, 48%).

$[\alpha]_D^{29}$ −27.0 (*c* 0.5, MeOH); IR (KBr) ν 3650–2900 (br), 2923, 2853, 1733, 1625 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.62 (3H, s), 2.58 (1H, dt, *J* = 14.2, 10.5 Hz), 2.73 (1H, ddd, *J* = 16.4, 14.2, 3.2 Hz), 4.52 (1H, dd, *J* = 10.5, 3.2 Hz), 6.89 (1H, d, *J* = 7.8 Hz), 7.09 (1H, t, *J* = 7.8 Hz), 7.34 (1H, ddt, *J* = 7.8, 1.8, 1.4 Hz), 7.44 (1H, d, *J* = 7.8 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −150.09 (1F, dd, *J* = 16.2, 10.8 Hz); MS (EI) *m*/*z*: 280 (M^+); HRMS (EI) calcd. for $C_{13}H_{13}FN_2O_4$ (M^+): 280.0859; found 280.0860.

4.5. (2S)-2-Amino-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid methyl ester hydrochloride (12)

To a solution of 3-fluorooxindole **9g** (45 mg, 0.0995 mmol) in acetic acid (0.5 mL) was added 25% HBr/AcOH (0.5 mL) at −20 °C. After stirring for 20 min at room temperature, water was added to the solution. The mixture was extracted with ether. The aqueous layer was basified (pH ~ 11) with K_2CO_3 at 0 °C. The solution was saturated with NaCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in ca. 2.5 M HCl/MeOH. The solution was concentrated to give a diastereomeric mixture of **12** as a pale yellow solid (27 mg, 0.0935 mmol, 94%).

IR (KBr) ν 3700–2150 (br), 3423, 1736, 1624 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.54 (1H, ddd, *J* = 27.9, 15.6, 7.3 Hz), 2.62 (1H, ddd, *J* = 34.3, 16.0, 4.6 Hz), 2.92 (1H, ddd, *J* = 16.0, 12.4, 9.2 Hz), 3.01 (1H, ddd, *J* = 16.0, 12.4, 5.0 Hz), 3.79 (3H, s), 3.83 (3H, s), 4.47 (1H, dd, *J* = 7.3, 5.0 Hz), 4.77 (1H, dd, *J* = 9.2, 4.6 Hz), 6.98 (1H, d, *J* = 7.8 Hz), 6.99 (1H, d, *J* = 7.8 Hz), 7.14 (1H, t, *J* = 7.8 Hz), 7.16 (1H, t, *J* = 7.8 Hz), 7.39–7.45 (2H, m), 7.48 (1H, ddd, *J* = 7.8, 1.8, 1.4 Hz), 7.55 (1H, ddd, *J* = 7.8, 1.8, 1.4 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −154.38 (1F, dd, *J* = 27.9, 12.1 Hz), −155.98 (1F, dd, *J* = 34.2, 12.1 Hz).

4.6. (2S)-2-(tert-Butoxycarbonylamino)-3-(indol-3-yl)propionic acid tert-butyl ester (14)

To a solution of (2*S*)-2-(*tert*-butoxycarbonylamino)-3-(indol-3-yl)propionic acid (**13**) (202 mg, 0.664 mmol) in dry CH_2Cl_2 (10 mL) was added *tert*-butanol (77 μL, 0.796 mmol), *N*,*N*′-dicyclohexylcarbodiimide (164 mg, 0.796 mmol), and 4-dimethylaminopyridine (8 mg, 0.0664 mmol) at 0 °C. The mixture was stirred for 20.5 h at room temperature. After filtration with celite, the filtrate was concentrated. The residue was dissolved in EtOAc and washed with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was then dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) to give **14** as a colorless solid (102 mg, 0.283 mmol, 43%).

Mp 180–184 °C; 46% ee (Chiralpak IA, eluent: *n*-hexane/2-propanol = 9/1); $[\alpha]_D^{29}$ +11.2 (*c* 0.24, $CHCl_3$); IR (KBr) ν 3436, 3344, 2977, 1730, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (9H, s), 1.42 (9H, s), 3.23 (1H, dd, *J* = 15.1, 5.5 Hz), 3.27 (1H, dd, *J* = 15.1, 6.0 Hz), 4.54 (1H, ddd, *J* = 7.8, 6.0, 5.5 Hz), 5.06 (1H, br d, *J* = 7.8 Hz), 7.03 (1H, br d, *J* = 2.3 Hz), 7.11 (1H, dt, *J* = 7.8, 0.9 Hz), 7.19 (1H, dt, *J* = 8.2, 0.9 Hz), 7.35 (1H, d, *J* = 8.2 Hz), 7.62 (1H, d, *J* = 7.8 Hz), 8.07 (1H, br s); MS (EI) *m*/*z*: 360 (M^+); HRMS (EI) calcd. for $C_{20}H_{28}N_2O_4$ (M^+): 360.2049; found 360.2060.

4.7. (2S)-2-[Bis(tert-butoxycarbonyl)amino]-3-(1-benzyloxycarbonylindol-3-yl)propionic acid tert-butyl ester (15)

To a solution of **14** (344 mg, 0.954 mmol) in dry CH_2Cl_2 (10 mL) was added benzyl chloroformate (0.125 mL, 1.43 mmol), pulverized NaOH (57.2 mg, 1.43 mmol), and benzyl tri-*n*-butylammonium chloride (29.8 mg, 0.0954 mmol) at 0 °C. The mixture was stirred for 15 h at room temperature. After filtration with celite, the filtrate was concentrated. The residue was dissolved in EtOAc and washed with water and brine. The organic layer was then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 5/1) to give (2*S*)-2-(*tert*-butoxycarbonylamino)-3-(1-benzyloxycarbonylindol-3-yl)propionic acid *tert*-butyl ester (420 mg) as a colorless solid, which was then dissolved in dry acetonitrile (8 mL). 4-Dimethylaminopyridine (51.9 mg, 0.425 mmol) and di-*tert*-butyl dicarbonate (0.305 mL, 1.27 mmol) were added to the solution at 0 °C. After stirring overnight, the mixture was concentrated and dissolved in EtOAc. The solution was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 8/1) to give **15** as a colorless oil (281 mg, 0.473 mmol, 50%).

$[\alpha]_D^{29}$ −11.5 (*c* 0.39, $CHCl_3$); IR (neat) ν 2979, 2934, 1737, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (18H, s), 1.48 (9H, s), 3.35 (1H, dd, *J* = 15.1, 10.1 Hz), 3.45 (1H, ddd, *J* = 15.1, 5.0, 0.9 Hz), 5.11 (1H, dd, *J* = 10.1, 5.0 Hz), 5.41 (1H, d, *J* = 11.9 Hz), 5.43 (1H, d, *J* = 11.9 Hz), 7.23 (1H, dt, *J* = 7.6, 1.4 Hz), 7.30 (1H, dt, *J* = 7.8, 0.9 Hz), 7.36–7.48 (6H, m), 7.54 (1H, d, *J* = 7.8 Hz), 8.16 (1H, br s); MS (EI) *m*/*z*: 594 (M^+); HRMS (EI) calcd. for $C_{33}H_{42}N_2O_8$ (M^+): 594.2941; found 594.2933.

4.8. (2S)-2-[Bis(tert-butoxycarbonyl)amino]-3-(indol-3-yl)propionic acid tert-butyl ester (16)

To a solution of **15** (658 mg, 1.11 mmol) in methanol (20 mL) was added 5% palladium on carbon (132 mg) at room temperature. The mixture was stirred for 33 h under hydrogen at room temperature. The palladium on carbon was filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 6/1) to give **16** as a colorless solid (405 mg, 0.879 mmol, 80%).

Mp 110–112 °C; $[\alpha]_D^{27}$ −25.0 (*c* 0.33, $CHCl_3$); IR (KBr) ν 3347, 3327, 2981, 1782, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (18H, s), 1.49 (9H, s), 3.40 (1H, dd, *J* = 15.1, 10.1 Hz), 3.54 (1H, ddd, *J* = 15.1, 5.0, 0.9 Hz), 5.09 (1H, dd, *J* = 10.1, 5.0 Hz), 7.01 (1H, br d, *J* = 2.3 Hz), 7.09 (1H, ddd, *J* = 8.2, 7.3, 0.9 Hz), 7.16 (1H, ddd, *J* = 8.2, 6.9, 0.9 Hz), 7.32 (1H, d, *J* = 8.2 Hz), 7.60 (1H, d, *J* = 7.3 Hz), 8.02 (1H, br s); MS (EI) *m*/*z*: 460 (M^+); HRMS (EI) calcd. for $C_{25}H_{36}N_2O_6$ (M^+): 460.2573; found 460.2596.

4.9. (2S)-2-[Bis(tert-butoxycarbonyl)amino]-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid tert-butyl ester (17)

Fluorination of **16** (2.08 g, 4.52 mmol) in the same manner as that of **8b–g** produced a diastereomeric mixture of **17** (1.13 g, 2.29 mmol, 51%) as a colorless oil after purification by silica gel column chromatography (eluent: hexane/EtOAc = 6/1–4/1). De was determined to be 14% from the ^1H NMR of crude mixture.

IR (neat) ν 3295, 3008, 2981, 2935, 1788, 1739, 1697, 1625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (18H, s), 1.45 (18H, s), 1.46 (18H, s), 2.84–3.07 (4H, m), 4.89 (1H, ddd, J = 9.6, 3.7, 0.9 Hz), 5.03 (1H, dd, J = 9.6, 3.2 Hz), 6.86 (1H, d, J = 7.8 Hz), 6.87 (1H, d, J = 7.3 Hz), 7.06 (1H, t, J = 7.3 Hz), 7.10 (1H, t, J = 7.8 Hz), 7.30 (1H, ddt, J = 7.8, 1.8, 1.4 Hz), 7.34 (1H, tt, J = 7.3, 1.4 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.45 (1H, d, J = 7.3 Hz), 7.98 (1H, br s), 8.17 (1H, br s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −153.08 (1F, dd, J = 20.2, 10.8 Hz), −153.30 (1F, dd, J = 19.3, 8.1 Hz); MS (EI) m/z: 494 (M^+), 438 ($M^+-C_4H_8$).

*4.10. (2S)-2-Amino-3-(3-fluoro-2-oxoindoline-3-yl)propionic acid hydrobromide (**6**)*

To a solution of **17** (25 mg, 0.0506 mmol) in acetic acid (0.5 mL) was added 25% HBr/AcOH (0.5 mL) at 0 °C. The mixture was stirred for 20 min at room temperature and then concentrated in vacuo. The residue was dissolved in water and the residual acetic acid was azeotropically removed under reduced pressure to give a diastereomeric mixture of **6** as a pale brown solid (15 mg, 0.470 mmol, 93%).

IR (KBr) ν 3700–2400 (br), 3430, 1732, 1718, 1625 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.46 (1H, ddd, J = 27.9, 16.0, 8.7 Hz), 2.61 (1H, ddd, J = 37.1, 16.5, 3.7 Hz), 2.91 (1H, ddd, J = 16.3, 11.4, 9.6 Hz), 3.03 (1H, ddd, J = 16.0, 12.8, 3.7 Hz), 4.50 (1H, dd, J = 8.7, 3.7 Hz), 4.76 (1H, dd, J = 9.6, 3.7 Hz), 6.97 (1H, d, J = 7.8 Hz), 6.98 (1H, d, J = 7.8 Hz), 7.14 (1H, t, J = 7.8 Hz), 7.16 (1H, t, J = 7.8 Hz), 7.41 (1H, tt, J = 7.8, 1.4 Hz), 7.43 (1H, tt, J = 7.8, 1.4 Hz), 7.47 (1H, d, J = 7.8 Hz), 7.54 (1H, d, J = 7.8 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ −156.57 (1F, dd, J = 27.9, 13.0 Hz), −156.70 (1F, dd, J = 37.1, 11.4 Hz).

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