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# Synthesis of 10b-fluorinated analogues of protubonine A and its 11a-epimer *via* fluorocyclisation of tryptophan-containing dipeptides

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Synthesis of 10b-fluorinated analogues of protubonine A and its 11a-epimer was accomplished using fluorocyclisation of tryptophan-containing dipeptides with *N*-fluoro-2,4,6-trimethylpyridinium triflate to 3a-fluoropyrrolo[2,3-*b*]indoles as a key step. Acetylation of the indole nitrogen and the following diketopiperazine formation gave the 10b-fluorinated analogues of protubonine A and its 11a-epimer.

## Introduction

Organofluorine compounds have fascinated medicinal chemists ever since 9α-fluorocortisol was reported to have much higher biological activity than cortisol.[1] An extensive number of fluorine-containing pharmaceuticals have been developed to date,[2] some of which have become blockbusters.[3] The growing interest in organofluorine compounds in medicinal chemistry stemmed from the unique properties of fluorine atom(s). Fluorine has the highest electronegativity and the smallest Van der Waals radius next to hydrogen.[2a,4] The C–F bond is far stronger than C–H, C–O and C–X (X = Cl, Br and I) bonds.[2a,4] Therefore, incorporation of fluorine atom(s) into bioactive molecules often produces dramatic changes in their chemical, physical and pharmacological properties.[2a,5] For example, when a hydrogen in molecules is replaced with a fluorine, the fluorinated molecules often have different reactivity from the parent fluorine-free ones, although the replacement has little effect on recognition of the molecules by proteins.[2a,5] Replacement of a hydroxy group with a fluorine can also be utilised for producing isosteric analogues.[2a,5] Introduction of multiple fluorine atoms often increases lipophilicity.[2a,5]

Protubonine A is a pyrroloindole alkaloid with a diketopiperazine (DKP) structure, which was isolated by Ahn and Oh in 2011 from an ethyl acetate extract of the marine-derived fungus *Aspergillus sp.* SF-5044 (Fig. 1).[6] The absolute configuration of protubonine A was originally determined to be 3*S*,5a*R*,10b*R*,11a*R*, as shown in Fig. 1 as **1**.[6] Interestingly, **1** has an unnatural (*R*)-configuration in the tryptophan moiety and would be derived biosynthetically from D-tryptophan and L-leucine. Since D-amino acids reportedly play important roles in exhibiting various biological functions,[7] we were interested in the potential biochemical importance of this rare pyrroloindole alkaloid having an (*R*)-configuration.[8]

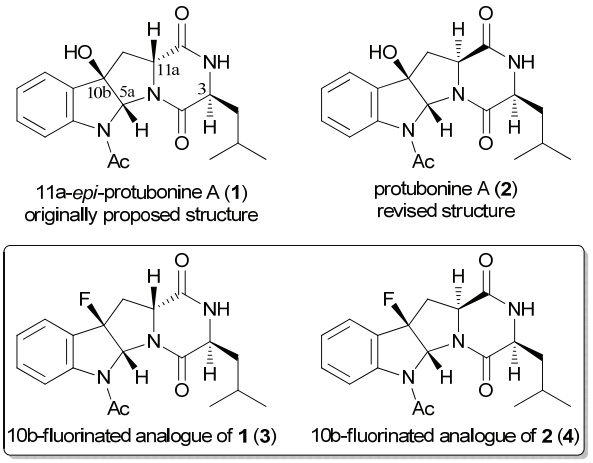
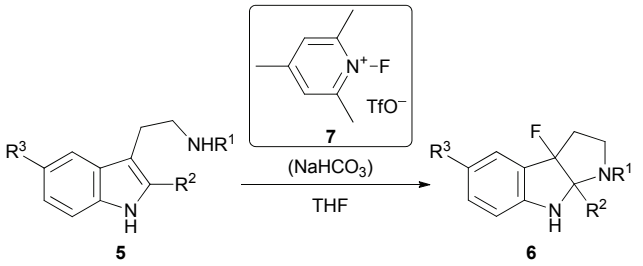



**Fig. 1** Structures of 11a-*epi*-protubonine A (**1**), protubonine A (**2**) and their fluorinated analogues **3** and **4**.

As a part of our studies on the design, synthesis and biological evaluation of fluorine-containing bioactive compounds,[9] we recently reported a versatile procedure for a fluorocyclisation reaction of tryptamines **5** with *N*-fluoro-2,4,6-trimethylpyridinium triflate (**7**), obtaining the corresponding 3a-fluoropyrrolo[2,3-*b*]indoles **6** (Scheme 1).[10] Since the replacement of the 10b-hydroxy group of **1** with a fluorine would generate a useful analogue for understanding the biochemical behaviour of **1**, we envisaged application of our

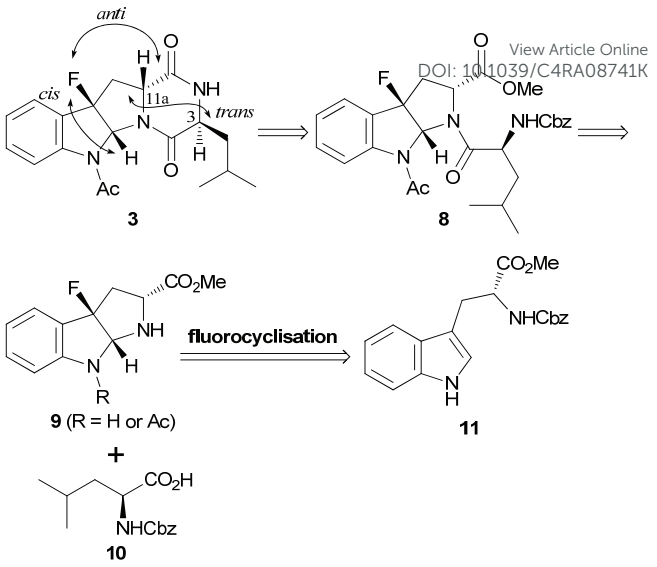
fluorocyclisation reaction to the synthesis of the 10b-fluorinated analogue **3** of **1**. However, unfortunately, after we started our synthesis of **3**, de Lera and co-workers reported that in actuality, protubonine A is represented by **2** and has a 3*S*,5a*R*,10b*R*,11a*S* configuration.[11] In this paper, we report the synthesis of a 10b-fluorinated analogue of originally proposed protubonine A (**3**) and that of the revised one (**4**) *via* fluorocyclisation of tryptophan derivatives with **7** as a key step.




**Scheme 1** Fluorocyclisation reaction of tryptamines **5** with *N*-fluoro-2,4,6-trimethylpyridinium triflate (**7**).

## Results and discussion

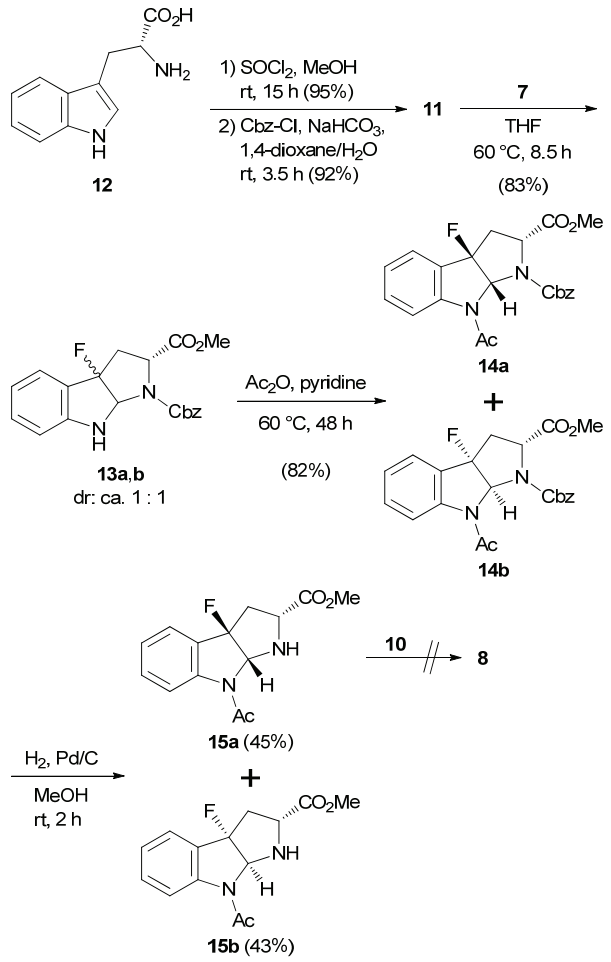
Our simple retrosynthetic analysis is illustrated in Scheme 2. Opening the DKP ring of **3** leads to dipeptide **8**, which includes 3a-fluoropyrrolo[2,3-*b*]indole **9** and *N*-carbobenzyloxy(Cbz)-L-leucine (**10**). The fluoropyrroloindole **9** would be formed by our reported fluorocyclisation of *N*-Cbz-D-tryptophan methyl ester (**11**). Since **3** includes an unnatural D-amino acid, the DKP ring of **3** has a *trans*-relationship between the C-3 and C-11a positions, in contrast to the *cis*-relationship of the generally observed DKP ring in natural products. This suggests that construction of the *trans*-DKP ring of **3** is easier than that of natural *cis*-DKPs.[12] In addition, **8** contains a proline structure in its dipeptide system. It is well-known that the DKP forming reaction of dipeptides containing proline as a C-terminal residue is generally much faster than that of other dipeptides.[12] On the basis of these two considerations, we planned to form the DKP ring at the final stage in our synthesis.[13] Moreover, we were very interested in the stereoselectivity of the fluorocyclisation of **11** relative to the selenocyclisation and bromocyclisation of similar tryptophan derivatives with *N*-(phenylseleno)phthalimide[14] and *N*-bromosuccinimide,[14d,15] respectively.




**Scheme 2** Retrosynthetic analysis of the 10b-fluorinated analogue **3** of 11a-*epi*-protubonine A.

Our synthesis commenced from D-tryptophan (**12**) shown in Scheme 3. Protected tryptophan **11** was prepared in excellent yield by esterification of **12** with thionyl chloride in anhydrous methanol, followed by protection of the primary amino group with benzyl chloroformate in the presence of sodium bicarbonate. Fluorocyclisation of **11** according to our reported procedure,[10] which employed 1.5 equiv. of **7** in anhydrous THF at 60 °C for 8.5 h, yielded an inseparable mixture of diastereomeric fluoropyrroloindoles **13a** and **13b** in an 83% yield. Unfortunately, no diastereoselectivity (dr: ca. 1:1) was observed. Acetylation of the mixture of **13a** and **13b** with acetic anhydride ($Ac_2O$) and pyridine was rather slow and required 2 days at 60 °C to produce fully protected fluoropyrroloindoles **14a** and **14b** in an 82% yield. Although separation of **14a** and **14b** by silica gel column chromatography proved difficult, small amounts of pure **14a** and **14b** were isolated to estimate their stereochemistries by $^1$H NMR spectroscopic analysis (Fig. 2). Taniguchi and Hino reported that the $^1$H chemical shifts of ester methyl protons of **16a** and **16b** were quite different.[16] Owing to the shielding effect of the indole ring, the ester methyl protons of **16a**, having an *anti* relationship between the H-3a and $CO_2Me$ group, appeared at a higher field ($\delta_H$ 3.11 ppm) compared with the ester methyl protons of **16b** ($\delta_H$ 3.63 and 3.72 ppm) that have a *syn* relationship. Thus, the stereochemistry of **14a** and **14b** was assigned by comparing the chemical shifts of the ester methyl protons of the two isomers. The product having the ester methyl protons appeared at a higher field ($\delta_H$ 3.09 ppm) is to be the *anti*-isomer **14a**, whereas another product having them appeared at a lower field ($\delta_H$ 3.43 and 3.78 ppm) is to be the *syn*-isomer **14b**. Removal of the Cbz groups of the mixture of **14a** and **14b** with hydrogen gas and a Pd/C catalyst gave 8-acetylfluoropyrroloindoles **15a** and **15b** in 45% and 43% yields, respectively. However, condensation of either **15a** or **15b** with **10**, in the presence of coupling agents

such as *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate and *O*-(6-chlorobenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate, resulted in the recovery of the starting material. Hydrogenation of a mixture of **13a** and **13b** to remove their Cbz groups was unsuccessful, producing a complex mixture.




**Scheme 3** Attempted synthesis of dipeptide **8**.

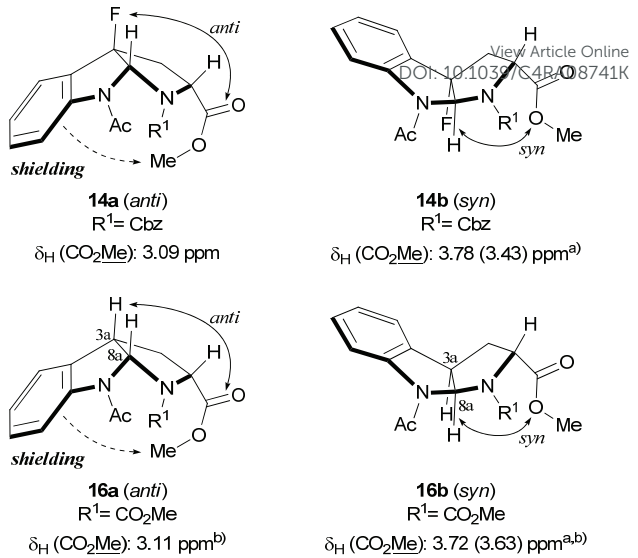



**Fig. 2** Estimation of stereochemistry of fluoropyrroloindoles **14a**,**b**. a) Two methyl signals were observed because of the presence of the rotamers, b) ref. 16.

We subsequently attempted fluorocyclisation of dipeptide **18** as an alternative route to **3** (Scheme 4). Condensation of D-tryptophan methyl ester (**17**) with **10** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole (HOBt) and *N*-methylmorpholine (NMM) produced **18** in an 83% yield. Since **18** has a bulky leucine moiety at the nucleophilic nitrogen atom, we were concerned that the reactivity of **18** for fluorocyclisation might decrease. Fortunately, fluorocyclisation of **18** with 1.5 equiv. of **7** at 60 °C proceeded smoothly, generating a mixture of the corresponding fluoropyrroloindoles **20a** and **20b** in an 84% yield. Again, no diastereoselectivity (dr: ca. 1:1) was observed. In contrast to the high stereoselectivity of the selenocyclisation[14] and bromocyclisation[14d,15] of tryptophan derivatives, the fluorocyclisation of **18** showed no stereoselection. This unfortunate result can be rationalized by the formation of indolenine intermediates such as **19**.[14a] Owing to the difficulty of the separation of **20a** and **20b**, we attempted separation and determination of their stereochemistry after acetylation. Treatment of the mixture of **20a** and **20b** with $Ac_2O$ and pyridine at 60 °C for 42 h afforded an inseparable mixture of **8** and **21** (**8**:**21** = ca. 2:1) in a 65% yield and a substantial amount (<22%) of unreacted **20b**. This suggested a significant difference in the reactivity of **20a** and **20b**. When acetylation of the mixture of **20a** and **20b** was stopped after 3 h, ca. 17:1 mixture of **8** and **21** was obtained in a 45% yield, and **20b** was recovered in a 47% yield. Acetylation of pure **20b** was accomplished by a longer reaction (50 h) to generate pure **21** in a 52% yield accompanied with a 41% recovery of the starting material **20b**. The stereochemistry of **8** and **21** was determined by a comparison of the $^1$H NMR spectra of both isomers. Since the ester methyl protons of **8** appeared at a higher field ($\delta_H$ 3.21 ppm) compared with those of **21** ($\delta_H$ 3.70 and 3.83 ppm), **8** was determined to be the *anti*-isomer and **21** the *syn*-isomer. When **8** was treated with Pd/C under a hydrogen atmosphere,

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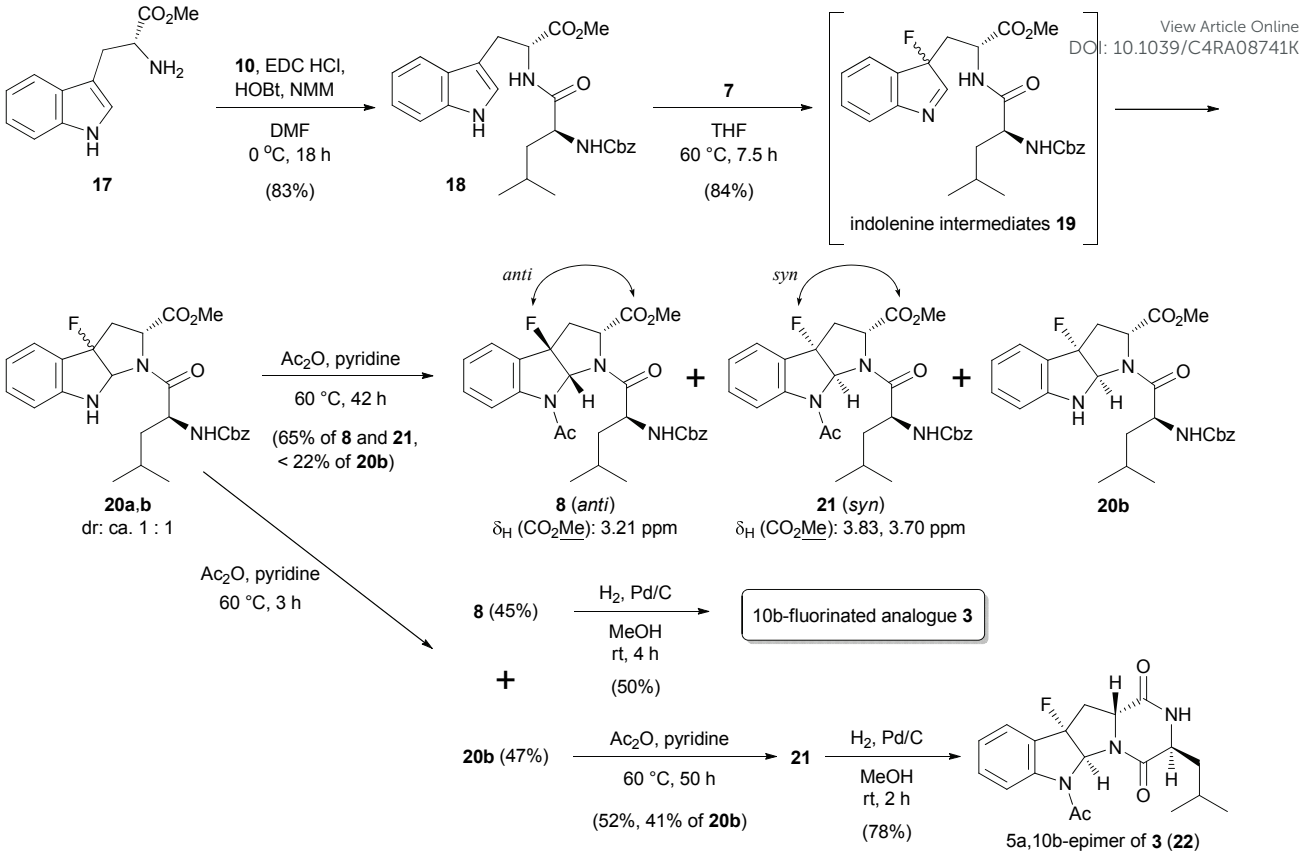


**Scheme 4** Synthesis of 10b-fluorinated analogue **3** and 5a,10b-epimer **22**.

deprotection and subsequent DKP formation occurred smoothly after 4 h as expected, yielding the desired 10b-fluorinated analogue **3** in a 50% yield. On the other hand, a similar reaction of **21** was faster, requiring only 2 h to generate the 5a,10b-epimer of **3** (**22**) in a higher yield (78%).

Finally, we applied the procedure to synthesise **4** (Scheme 5). Fluorocyclisation of *N*-Cbz-L-Leu-L-Trp-OMe (**23**)[17] with **7** gave the corresponding fluoropyrroloindoles **24a** and **24b** (**24a**:**24b** = ca. 1:1) in a 77% yield. Acetylation of the mixture of **24a** and **24b** for 4 h generated ca. 30:1 mixture of **25a** and **25b** in a 49% yield, and **24b** was recovered in a 43% yield. Recrystallisation of the mixture of **25a** and **25b** from hexane and dichloromethane gave **25a** in pure form. Recovered **24b** was acetylated again for 50 h to give pure **25b** (52%) accompanied with a 22% recovery of **24b**. The stereochemistry of **25a** and **25b** was determined by the $^1$H NMR spectroscopic analysis. Catalytic hydrogenation of **25b** fortunately produced the desired 10b-fluorinated analogue **4** in an 87% yield. A similar reaction of **25a** required longer reaction time (5 h) to generate the 5a,10b-epimer **26** in an 86% yield.

## Conclusions

We succeeded in synthesising the 10b-fluorinated analogue of originally proposed protubonine A (**3**) and that of the revised one (**4**) using our fluorocyclisation as a key step. Treatment of **18** with **7** at 60 °C generated **20a** and **20b** in high yields, although no stereoselectivity was observed. Acetylation of **20a** and **20b** produced **8** and **21**, respectively. The stereochemistry of **8** and **21** was easily determined by $^1$H NMR spectroscopic analysis. Deprotection and following *trans*-DKP formation of **8** and **21** under hydrogenation conditions proceeded smoothly to produce **3** and its 5a,10b-epimer **22**, respectively. Synthesis of **4** and its 5a,10b-epimer **26** was accomplished by similar synthetic procedure. A difference in reactivity between the diastereomers was observed both during acetylation and the subsequent DKP formation.

## Experimental

### General





 

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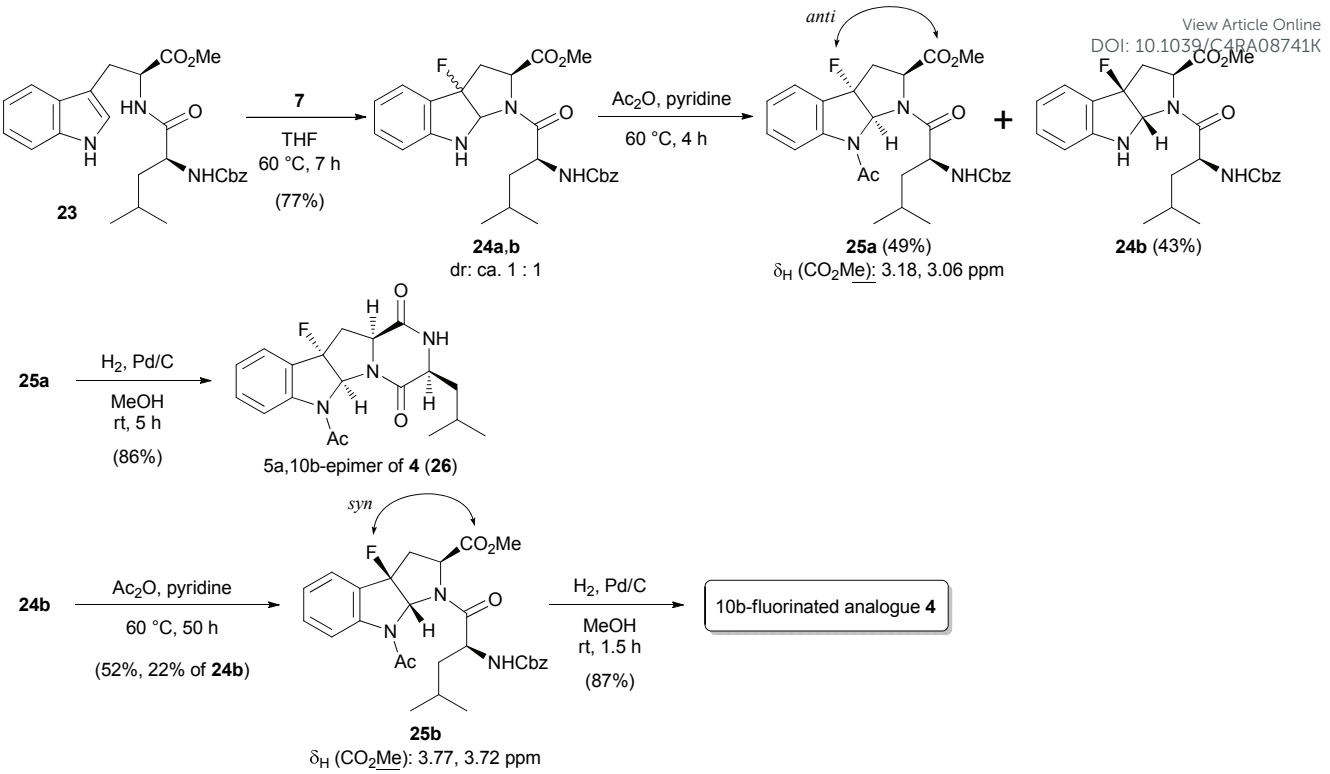


**Scheme 5** Synthesis of 10b-fluorinated analogue **4** and 5a,10b-epimer **26**.

Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were determined using a JASCO P-2100 polarimeter. Infrared (IR) spectra were recorded using a JEOL FT/IR-460Plus spectrometer. All NMR spectra were recorded using a JEOL ECX-400P or JEOL ECA-500II spectrometers. Proton ($^1$H) NMR spectra were recorded at 400 or 500 MHz. Carbon-13 ($^{13}$C) NMR spectra were recorded using the broadband proton decoupling at 100 or 126 MHz. Fluorine-19 ($^{19}$F) NMR spectra were recorded at 376 or 470 MHz. All chemical shifts, δ, are stated in units of parts per million (ppm), relative to a standard. For $^1$H NMR, the reference point is TMS (= 0.00 ppm). For $^{13}$C NMR, the reference point is $CDCl_3$ (= 77.0 ppm). For $^{19}$F NMR, the reference point is $CFCl_3$ (= 0.00 ppm). High and low resolution electron ionization (EI) mass spectra were recorded using a JEOL JMS-GCmate II spectrometer. Values are reported as a ratio of mass to charge (*m*/*z*). Column chromatography was performed on Nacalai Tesque Silica Gel 60 $PF_{254}$ (0.005–0.050 mm), Kanto chemical silica gel 60N (0.040–0.050 mm) or Merck 9385 silica gel 60 (0.040–0.063 mm). Thin layer chromatography was performed on Merck 5715 silica gel 60 $F_{254}$ or Merck 5554 silica gel 60 $F_{254}$.

***N*-Benzyloxycarbonyl-D-tryptophan methyl ester (11).**

D-Tryptophan (1.22 g, 6.00 mmol) was dissolved in anhydrous MeOH (20 mL) and thionyl chloride (1.30 mL, 18.0 mmol) was added to the solution at 0 °C. After stirring at room temperature for 15 h, the mixture was concentrated under reduced pressure. The residue was purified by recrystallization from MeOH/$Et_2O$ to give D-tryptophan methyl ester hydrochloride (1.45 g, 95%) as a colourless crystalline solid.

To a solution of D-tryptophan methyl ester hydrochloride (1.01 g, 3.95 mmol) in 1,4-dioxane/$H_2O$ (1/1, 19 mL) were added $NaHCO_3$ (1.16 g, 13.8 mmol) and benzyl chloroformate (0.560 mL, 3.95 mmol) at room temperature. After stirring for 3.5 h, the mixture was extracted twice with EtOAc. The combined organic layers were washed with 5% aq. HCl, water and brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) to give **11** (1.29 g, 92%) as a pale yellow viscous oil. $[\alpha]_D^{25}$ –46.2 (*c* 1.0 in $CHCl_3$). $\nu_{max}$ (neat)/cm$^{-1}$ 3410, 3360, 3059, 3034, 2952, 2850, 1741, 1709, 1510, 1456, 1438, 1341, 1265, 1215, 1059, 1027, 1011, 741, 699. $\delta_H$ (400 MHz, $CDCl_3$) 3.26 (1H, dd, *J* = 15.1, 5.5 Hz), 3.28 (1H, dd, *J* = 15.1, 5.5 Hz), 3.63 (3H, s), 4.70 (1H, dt, *J* = 7.8, 5.5 Hz), 5.05 (1H, d, *J* = 12.4 Hz), 5.10 (1H, d, *J* = 12.4 Hz), 5.39 (1H, br d, *J* = 7.8 Hz), 6.85 (1H, br d, *J* = 1.4 Hz), 7.07 (1H, td, *J* = 7.3, 1.4 Hz), 7.15 (1H, td, *J* = 7.3, 1.4 Hz), 7.20–7.33 (6H, m), 7.50 (1H, br d, *J* = 7.3 Hz), 8.28 (1H, br s). $\delta_C$ (100 MHz, $CDCl_3$) 27.8 (s), 52.3 (s), 54.4 (s), 66.8 (s), 109.5 (s), 111.2 (s), 118.4 (s), 119.5 (s), 122.0 (s), 122.9 (s), 127.4 (s), 128.0 (s), 128.1 (s), 128.4 (s), 136.0 (s), 136.1 (s), 155.8 (s), 172.4 (s). MS (EI) *m*/*z* 353 ([M+H]$^+$), 352 ([M]$^+$).

HRMS (EI) calcd for $C_{20}H_{20}N_2O_4$ ($[M]^+$): 352.1423, found 352.1424.

**(2*R*,3a*RS*,8a*SR*)-3a-Fluoro-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylic acid 1-benzyl 2-methyl ester (13a and 13b).**

To a solution of **11** (1.06 g, 3.00 mmol) in anhydrous THF (300 mL) was added **7** (1.30 g, 4.50 mmol) at room temperature. After stirring at 60 °C for 8.5 h, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 4/1) to give an inseparable mixture of **13a** and **13b** (**13a**:**13b** = ca. 1:1, 926 mg, 83%) as a pale yellow viscous oil. Each of **13a** and **13b** was observed as a mixture of two rotamers (**13a**: ca. 7:10 ratio, **13b**: ca. 7:10 ratio) in $^1$H and $^{19}$F NMR. $\delta_H$ (400 MHz, $CDCl_3$) 2.61–3.04 (4H, m), 3.17 (30/17H, s), 3.28 (21/17H, s), 3.60 (30/17H, s), 3.79 (21/17H, s), 4.47 (10/17H, dd, $J$ = 8.7, 4.6 Hz), 4.53 (7/17H, dd, $J$ = 8.7, 4.6 Hz), 4.66–4.87 (2H, m), 5.03–5.30 (5H, m), 5.53 (7/17H, d, $J$ = 17.4 Hz), 5.56 (10/17H, d, $J$ = 17.4 Hz), 5.73 (7/17H, dd, $J$ = 22.0, 3.2 Hz), 5.76 (10/17H, dd, $J$ = 22.0, 3.2 Hz), 6.59–6.69 (2H, m), 6.75–6.85 (2H, m), 7.19–7.41 (14H, m). $\delta_F$ (376 MHz, $CDCl_3$) –139.2 (7/17F, m), –139.7 (7/17F, br t, $J$ = 16.2 Hz), –139.8 (10/17F, m), –141.4 (10/17F, br t, $J$ = 16.6 Hz). MS (EI) $m/z$ 371 ($[M+H]^+$), 370 ($[M]^+$), 350 ($[M–HF]^+$).

**(2*R*,3a*R*,8a*S*)-8-Acetyl-3a-fluoro-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylic acid 1-benzyl 2-methyl ester (14a) and (2*R*,3a*S*,8a*R*)-8-acetyl-3a-fluoro-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylic acid 1-benzyl 2-methyl ester (14b).**

To a solution of a mixture of **13a** and **13b** (**13a**:**13b** = ca. 1:1, 198 mg, 0.535 mmol) in acetic anhydride (2.10 mL) was added pyridine (0.130 mL, 1.60 mmol) at room temperature. After stirring at 60 °C for 48 h, the mixture was diluted with $CHCl_3$. The mixture was then washed sat. aq. $NaHCO_3$, water, 5% aq. citric acid, water and brine. The resulting organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 3/1) to give a mixture of **14a** and **14b** (**14a**:**14b** = ca. 1:1, 180 mg, 82%) as a pale yellow amorphous solid. Each of **14a** and **14b** gave the following data after partial separation by silica gel column chromatography (eluent: hexane/EtOAc = 3/1) and recrystallisation from hexane/$CH_2Cl_2$.

**14a**: colourless crystalline solid. Mp 153–154 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ –80.8 ($c$ 1.0 in $CHCl_3$). $\nu_{max}$ (KBr)/cm$^{-1}$ 3033, 3002, 2956, 1761, 1736, 1707, 1675, 1604, 1478, 1467, 1422, 1389, 1361, 1335, 1311, 1285, 1248, 1217, 1197, 1172, 1139, 1094, 1061, 1022, 924, 768, 756, 727, 707. $\delta_H$ (400 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:5 ratio) 2.19 (1/2H, br s), 2.65 (5/2H, br s), 2.90–3.02 (2H, m), 3.09 (3H, br s), 4.75 (1H, br d, $J$ = 6.0 Hz), 5.16 (2H, s), 6.13 (1H, br d, $J$ = 11.5 Hz), 7.16 (1H, t, $J$ = 7.3 Hz), 7.26–7.38 (6H, m), 7.42–7.46 (1H, m), 8.06 (1H, br s). $\delta_C$ (100 MHz, $CDCl_3$, major rotamer) 23.5 (s), 37.1 (br s), 52.2 (s), 59.3 (d, $J$ = 5.8 Hz), 67.9 (s), 80.6 (d, $J$ = 32.6 Hz), 102.2 (d, $J$ = 207.0 Hz), 119.3 (s), 124.3 (s), 124.6 (s), 126.6 (d, $J$ = 21.1 Hz), 127.9 (s), 128.4 (s), 128.6 (s), 132.2 (d, $J$ = 3.8 Hz), 135.4 (s), 144.8 (s), 154.0 (s), 170.0 (s), 170.9 (br s). $\delta_F$ (376 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:5 ratio) –142.7 (1/6F, br s), –143.0 (5/6F, br s). MS (EI) $m/z$ 413 ($[M+H]^+$), 412 ($[M]^+$). HRMS (EI) calcd for $C_{22}H_{21}FN_2O_5$ ($[M]^+$): 412.1434, found 412.1430.

**14b**: colourless needles. Mp 110–112 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ +148.5 ($c$ 1.0 in $CHCl_3$). $\nu_{max}$ (KBr)/cm$^{-1}$ 3063, 3037, 2980, 2952, 1743, 1708, 1676, 1480, 1418, 1385, 1357, 1343, 1291, 1215, 1179, 1044, 974, 917, 785, 761, 742, 699. $\delta_H$ (400 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2.5 ratio) 2.08 (6/7H, br s), 2.63–2.72 (22/7H, m), 3.01 (1H, dd, $J$ = 12.4, 7.3 Hz), 3.43 (15/7H, br s), 3.78 (6/7H, br s), 4.07 (1H, dd, $J$ = 10.1, 7.3 Hz), 4.88 (4/7H, br s), 5.15 (20/21H, s), 5.17 (10/21H, s), 6.09 (1H, br s), 7.22 (1H, t, $J$ = 7.3 Hz), 7.33 (5H, br s), 7.44–7.50 (2H, m), 7.95 (2/7H, br s), 8.11 (5/7H, br s). $\delta_C$ (100 MHz, $CDCl_3$, major rotamer) 23.7 (s), 35.2 (d, $J$ = 26.8 Hz), 52.4 (s), 58.7 (s), 67.8 (s), 80.2 (d, $J$ = 36.4 Hz), 100.8 (d, $J$ = 205.1 Hz), 119.7 (s), 123.9 (s), 124.9 (s), 126.9 (d, $J$ = 20.1 Hz), 128.4 (s), 128.5 (s), 128.7 (s), 132.3 (d, $J$ = 2.9 Hz), 135.0 (s), 143.8 (s), 153.0 (s), 170.8 (s), 171.4 (s). $\delta_F$ (376 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2.5 ratio) –142.0 (2/7F, br s), –142.4 (5/7F, br s). MS (EI) $m/z$ 413 ($[M+H]^+$), 412 ($[M]^+$). HRMS (EI) calcd for $C_{22}H_{21}FN_2O_5$ ($[M]^+$): 412.1434, found 412.1428.

**(2*R*,3a*R*,8a*R*)-8-Acetyl-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (15a) and (2*R*,3a*S*,8a*S*)-8-acetyl-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (15b).**

To a solution of a mixture of **14a** and **14b** (**14a**:**14b** = ca. 1:1, 113 mg, 0.274 mmol) in MeOH (0.6 mL) was added 10% palladium on carbon (23 mg) at room temperature. After stirring under 3–4 atm of hydrogen for 2 h, the mixture was filtered through a small pad of celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 2/3) to give **15a** (34 mg, 45%) and **15b** (33 mg, 43%).

**15a**: pale yellow viscous oil. $[\alpha]_D^{25}$ +19.0 ($c$ 0.93 in $CHCl_3$). $\nu_{max}$ (neat)/cm$^{-1}$ 3344, 3001, 2952, 2853, 1740, 1666, 1606, 1483, 1467, 1436, 1396, 1356, 1317, 1294, 1218, 1144, 1092, 1053, 1021, 944, 914, 850, 836, 760, 736. $\delta_H$ (400 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2 ratio) 2.37 (2H, br s), 2.47 (1H, br s), 2.56–3.01 (3H, m), 3.42 (2H, br s), 3.47 (1H, br s), 4.12–4.18 (1H, m), 5.49 (2/3H, br d, $J$ = 18.8 Hz), 5.68 (1/3H, br d, $J$ = 22.0 Hz), 7.15 (1H, t, $J$ = 7.8 Hz), 7.40 (1H, t, $J$ = 7.8 Hz), 7.49 (1H, br d, $J$ = 7.8 Hz), 8.22 (1H, br d, $J$ = 7.8 Hz). $\delta_C$ (100 MHz, $CDCl_3$, major rotamer) 23.7 (s), 39.9 (d, $J$ = 31.6 Hz), 52.3 (s), 59.3 (s), 83.1 (d, $J$ = 30.7 Hz), 105.2 (d, $J$ = 197.4 Hz), 117.7 (s), 123.8 (s), 124.5 (s), 125.9 (s), 131.6 (d, $J$ = 39.3 Hz), 143.4 (br s), 168.7 (s), 172.3 (s). $\delta_F$ (376 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2 ratio) –136.9 (2/3F, td, $J$ = 18.4, 9.5 Hz), –137.8 (1/3F, td, $J$ = 20.4, 13.5 Hz). MS (EI) $m/z$



 

279 ([M+H]$^+$), 278 ([M]$^+$), 258 ([M–HF]$^+$), 219 ([M–$CO_2$Me]$^+$). HRMS (EI) calcd for $C_{14}H_{15}FN_2O_3$ ([M]$^+$): 278.1067, found 278.1067.

**15b**: colourless viscous oil. $[\alpha]_D^{25}$ +49.3 (*c* 0.67 in $CHCl_3$). $\nu_{max}$ (neat)/cm$^{-1}$ 3330, 2955, 2927, 2853, 1740, 1668, 1605, 1483, 1468, 1393, 1357, 1312, 1287, 1252, 1217, 1199, 1180, 1136, 1092, 1064, 1032, 1013, 957, 916, 820, 799, 762. $\delta_H$ (400 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:4 ratio) 2.35 (12/5H, s), 2.48 (3/5H, s), 2.64–2.81 (2H, m), 3.27 (4/5H, br s), 3.62 (1/5H, br s), 3.78 (3H, s), 3.71–3.88 (1H, m), 5.66 (4/5H, br d, *J* = 18.8 Hz), 5.85 (1/5H, br d, *J* = 19.7 Hz), 7.17 (1H, dd, *J* = 7.8, 7.3 Hz), 7.40–7.53 (2H, m), 8.27 (1H, br d, *J* = 7.8 Hz). $\delta_C$ (100 MHz, $CDCl_3$, major rotamer) 24.0 (s), 42.5 (d, *J* = 30.7 Hz), 52.6 (s), 59.0 (s), 83.3 (d, *J* = 29.7 Hz), 107.0 (d, *J* = 197.9 Hz), 117.4 (s), 124.3 (s), 124.4 (s), 126.9 (d, *J* = 23.0 Hz), 131.9 (s), 143.6 (d, *J* = 2.9 Hz), 169.4 (s), 172.8 (s). $\delta_F$ (376 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:4 ratio) –138.6 – –138.7 (4/5F, br m), –139.5 (1/5F, br s). MS (EI) *m*/*z* 279 ([M+H]$^+$), 278 ([M]$^+$), 258 ([M–HF]$^+$), 219 ([M–$CO_2$Me]$^+$). HRMS (EI) calcd for $C_{14}H_{15}FN_2O_3$ ([M]$^+$): 278.1067, found 278.1070.

***N*-(Benzyloxycarbonyl)-L-leucyl-D-tryptophan methyl ester (18).**

To a solution of D-tryptophan methyl ester (**17**) (1.40 g, 6.40 mmol), obtained by neutralisation of its hydrochloride, and *N*-carbobenzyloxy-L-leucine (2.04 g, 7.70 mmol) in anhydrous DMF (32 mL) were added HOBt (1.04 g, 7.70 mmol), EDC·HCl (1.48 g, 7.70 mmol) and NMM (0.94 mL, 8.30 mmol) at 0 °C. After stirring for 18 h, the mixture was diluted with sat. aq. $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 3/2) to give **18** (2.47 g, 83%) as a colourless crystalline solid. Mp 133–134 °C (from hexane/$CHCl_3$). $[\alpha]_D^{25}$ –51.9 (*c* 0.75 in $CHCl_3$). $\nu_{max}$ (KBr)/cm$^{-1}$ 3410, 3392, 3320, 2957, 2930, 2871, 1755, 1739, 1689, 1656, 1533, 1457, 1439, 1351, 1341, 1321, 1267, 1230, 1217, 1112, 1050, 1022, 743, 698. $\delta_H$ (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* = 6.0 Hz), 0.85 (3H, d, *J* = 6.0 Hz), 1.36–1.45 (1H, m), 1.50–1.60 (2H, m), 3.26 (1H, dd, *J* = 15.1, 5.5 Hz), 3.30 (1H, dd, *J* = 15.1, 5.5 Hz), 3.64 (3H, s), 4.16–4.21 (1H, m), 4.87–4.91 (1H, m), 5.04 (1H, d, *J* = 12.4 Hz), 5.10 (1H, br d, *J* = 7.3 Hz), 5.11 (1H, d, *J* = 12.4 Hz), 6.60 (1H, br d, *J* = 7.3 Hz), 6.90 (1H, br s), 7.09 (1H, ddd, *J* = 7.8, 6.9, 0.9 Hz), 7.16 (1H, ddd, *J* = 8.2, 6.9, 0.9 Hz), 7.30 (2H, dt, *J* = 8.2, 0.9 Hz), 7.31–7.36 (4H, br m), 7.50 (1H, br d, *J* = 7.8 Hz), 7.95 (1H, br s). $\delta_C$ (100 MHz, $CDCl_3$) 21.6 (s), 22.9 (s), 24.6 (s), 27.4 (s), 41.3 (s), 52.4 (s), 52.6 (s), 53.6 (s), 67.0 (s), 109.5 (s), 111.2 (s), 118.4 (s), 119.6 (s), 122.1 (s), 123.0 (s), 127.4 (s), 128.1 (s), 128.2 (s), 128.5 (s), 136.0 (s), 136.2 (s), 156.1 (s), 172.0 (s), 172.2 (s). MS (EI) *m*/*z* 466 ([M+H]$^+$), 465 ([M]$^+$). HRMS (EI) calcd for $C_{26}H_{31}N_3O_5$ ([M]$^+$): 465.2264, found 465.2263.

**(2*R*,3a*RS*,8a*SR*)-1-[(2*S*)-2-Benzyloxycarbonylamino-4-methylpentanoyl]-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (20a and 20b).**

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To a solution of **18** (931 mg, 2.00 mmol) in anhydrous THF (200 mL) was added **7** (868 mg, 3.00 mmol) at room temperature. After stirring at 60 °C for 7.5 h, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 3/1) to give an inseparable mixture of **20a** and **20b** (**20a**:**20b** = ca. 1:1, 814 mg, 84%) as a colourless viscous oil. Each of **20a** and **20b** was observed as a mixture of two rotamers (**20a**: ca. 1:1 ratio, **20b**: ca. 1:2 ratio) in $^1$H and $^{19}$F NMR. $\delta_H$ (400 MHz, $CDCl_3$) 0.77 (3/2H, d, *J* = 6.4Hz), 0.87 (5H, d, *J* = 6.4Hz), 0.93 (2H, d, *J* = 6.4Hz), 0.97 (1H, d, *J* = 6.4Hz), 1.00 (5/2H, d, *J* = 6.4Hz), 1.43–1.80 (6H, m), 2.55–3.11 (4H, m), 3.14 (3/2H, s), 3.28 (3/2H, s), 3.73 (1H, s), 3.83 (2H, s), 4.24 (1/2H, td, *J* = 9.6, 3.2 Hz), 4.31 (2/3H, td, *J* = 9.6, 3.7 Hz), 4.58 (1/2H, td, *J* = 9.6, 5.0 Hz), 4.64 (1/3H, dd, *J* = 8.7, 4.6 Hz), 4.88 (1/3H, td, *J* = 10.1, 5.5 Hz), 4.90–5.40 (29/3H, m), 5.62 (1H, dd, *J* = 17.4, 7.3 Hz), 5.83 (2/3H, dd, *J* = 25.2, 4.1 Hz), 5.90 (1/3H, dd, *J* = 22.0, 5.5 Hz), 6.64 (2/3H, d, *J* = 7.8 Hz), 6.65 (1/2H, d, *J* = 7.8 Hz), 6.78 (1/2H, t, *J* = 7.8 Hz), 6.821 (1/3H, d, *J* = 7.8 Hz), 6.824 (2/3H, t, *J* = 7.8 Hz), 6.96 (1/3H, t, *J* = 7.8 Hz), 7.20–7.37 (15H, m). $\delta_F$ (376 MHz, $CDCl_3$) –131.6 (1/3F, q, *J* = 20.2 Hz), –138.1 – –138.2 (1/2F, m), –141.8 (1/2F, br dd, *J* = 17.5, 11.3 Hz), –145.0 (2/3F, ddd, *J* = 32.8, 25.6, 17.5 Hz). MS (EI) *m*/*z* 483 ([M]$^+$), 463 ([M–HF]$^+$).

**(2*R*,3a*R*,8a*R*)-8-Acetyl-1-[(2*S*)-2-benzyloxycarbonylamino-4-methylpentanoyl]-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (8) and (2*R*,3a*S*,8a*S*)-8-acetyl-1-[(2*S*)-2-benzyloxycarbonylamino-4-methylpentanoyl]-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (21).**

Method A: To a solution of a mixture of **20a** and **20b** (**20a**:**20b** = ca. 1:1, 169 mg, 0.350 mmol) in acetic anhydride (1.40 mL) was added pyridine (0.085 mL, 1.05 mmol) at room temperature. After stirring at 60 °C for 42 h, the mixture was diluted with $CHCl_3$. The mixture was then washed sat. aq. $NaHCO_3$, water, 5% aq. citric acid, water and brine. The resulting organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 3/1) to give a mixture of **8** and **21** (**8**:**21** = ca. 2:1, 120 mg, 65%) and **20b** (containing small amounts of unidentified side products, 37 mg, <22%).

Method B: Acetylation of a mixture of **20a** and **20b** (**20a**:**20b** = ca. 1:1, 193 mg, 0.400 mmol) with acetic anhydride (1.60 mL) and pyridine (0.100 mL, 1.24 mmol) at 60 °C for 3 h gave a mixture of **8** and **21** (**8**:**21** = ca. 17:1, 95 mg, 45%) and **20b** (91 mg, 47%). Compound **20b** (86 mg, 0.178 mmol) was acetylated again with acetic anhydride (1.00 mL) and pyridine (0.0600 mL,

0.742 mmol) at 60 °C for 50 h to generate **21** (49 mg, 52%) and **20b** (35 mg, 41%).

**8**: colourless needles. Mp 166–167 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ –113.1 (*c* 0.5 in $CHCl_3$). $\nu_{max}$ (KBr)/$cm^{-1}$ 3374, 2959, 2871, 1717, 1687, 1673, 1509, 1477, 1468, 1456, 1419, 1386, 1339, 1321, 1285, 1255, 1226, 1212, 1171, 1142, 1128, 1096, 1058, 1038, 1021, 960, 919, 842, 805, 782, 762, 700. $\delta_H$ (400 MHz, $CDCl_3$) 0.76 (3H, d, *J* = 6.4 Hz), 0.88 (3H, d, *J* = 6.4 Hz), 1.43–1.51 (1H, m), 1.58–1.68 (2H, m), 2.61 (3H, s), 2.98 (1H, td, *J* = 12.8, 8.7 Hz), 3.16 (1H, d, *J* = 12.8 Hz), 3.21 (3H, s), 4.16–4.22 (1H, m), 5.07 (1H, d, *J* = 12.4 Hz), 5.12 (1H, d, *J* = 12.4 Hz), 5.28 (1H, br d, *J* = 8.7 Hz), 5.48 (1H, br d, *J* = 8.7 Hz), 6.31 (1H, br d, *J* = 12.4 Hz), 7.17 (1H, dd, *J* = 7.8, 7.3 Hz), 7.31–7.45 (7H, m), 8.06 (1H, br d, *J* = 8.2 Hz). $\delta_C$ (100 MHz, $CDCl_3$) 21.1 (s), 23.3 (s), 23.5 (s), 24.4 (s), 37.7 (d, *J* = 29.7 Hz), 40.9 (s), 50.3 (s), 52.5 (s), 59.9 (d, *J* = 5.8 Hz), 67.3 (s), 79.8 (d, *J* = 32.6 Hz), 102.0 (d, *J* = 204.2 Hz), 119.4 (s), 124.5 (d, *J* = 6.7 Hz), 124.6 (s), 126.3 (d, *J* = 22.0 Hz), 128.0 (s), 128.3 (s), 128.6 (s), 132.2 (d, *J* = 2.9 Hz), 135.8 (s), 145.0 (d, *J* = 3.8 Hz), 156.5 (s), 169.7 (s), 171.0 (s), 174.3 (s). $\delta_F$ (376 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:16 ratio) –142.4 (1/17F, br s), –143.9 (16/17F, br t, *J* = 12.2 Hz). MS (EI) *m/z* 526 ($[M+H]^+$), 525 ($[M]^+$). HRMS (EI) calcd for $C_{28}H_{32}FN_3O_6$ ($[M]^+$): 525.2275, found 525.2271.

**21**: colourless crystalline solid. Mp 157–158 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ +28.9 (*c* 0.25 in $CHCl_3$). $\nu_{max}$ (KBr)/$cm^{-1}$ 3242, 3033, 2994, 2953, 2868, 1749, 1703, 1685, 1672, 1607, 1539, 1479, 1469, 1415, 1389, 1317, 1294, 1260, 1219, 1179, 1051, 995, 941, 781, 758, 741, 700. $\delta_H$ (400 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:3 ratio) 0.71–0.97 (3H, br m), 0.89 (3H, d, *J* = 6.4 Hz), 1.21–1.44 (1H, br m), 1.49–1.80 (2H, br m), 2.19–2.79 (4H, br m), 2.80–3.29 (1H, br m), 3.60–4.10 (1H, br m), 3.70 (3/4H, br s), 3.83 (9/4H, br s), 4.58–5.33 (4H, br m), 6.08 (3/4H, br s), 6.83 (1/4H, br s), 7.15–7.59 (35/4H, br m), 7.97 (1/4H, br s). $\delta_F$ (376 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:3 ratio) –144.2 (3/4F, br s), –144.4 (1/4F, br s). MS (EI) *m/z* 526 ($[M+H]^+$), 525 ($[M]^+$). HRMS (EI) calcd for $C_{28}H_{32}FN_3O_6$ ($[M]^+$): 525.2275, found 525.2281.

**20b**: colourless crystalline solid. Mp 49–51 °C (dec.). $[\alpha]_D^{25}$ +150.4 (*c* 0.4 in $CHCl_3$). $\nu_{max}$ (KBr)/$cm^{-1}$ 3396, 3331, 2956, 2871, 1749, 1714, 1653, 1618, 1523, 1486, 1472, 1437, 1322, 1301, 1257, 1219, 1187, 1094, 1058, 922, 753, 698. $\delta_H$ (400 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2 ratio) 0.87 (2H, d, *J* = 6.4 Hz), 0.93 (2H, d, *J* = 6.4 Hz), 0.97 (1H, d, *J* = 6.4 Hz), 1.00 (1H, d, *J* = 6.4 Hz), 1.53–1.60 (1H, m), 1.65–1.78 (2H, m), 2.54–2.70 (1H, m), 2.79 (1/3H, ddd, *J* = 19.2, 14.2, 4.6 Hz), 2.97 (2/3H, dd, *J* = 17.4, 14.2 Hz), 3.72 (1H, s), 3.83 (2H, s), 4.32 (2/3H, td, *J* = 9.6, 3.7 Hz), 4.64 (1/3H, dd, *J* = 8.7, 4.6 Hz), 4.88 (1/3H, ddd, *J* = 10.1, 8.7, 5.5 Hz), 5.02 (2/3H, d, *J* = 12.4 Hz), 5.08 (2/3H, d, *J* = 12.4 Hz), 5.12 (1/3H, d, *J* = 11.9 Hz), 5.16 (1/3H, d, *J* = 11.9 Hz), 5.25–5.41 (8/3H, m), 5.82 (2/3H, dd, *J* = 25.7, 4.1 Hz), 5.90 (1/3H, dd, *J* = 22.4, 5.5 Hz), 6.63 (2/3H, d, *J* = 7.8 Hz), 6.820 (2/3H, t, *J* = 7.8 Hz), 6.823 (1/3H, d, *J* = 7.3 Hz), 6.96 (1/3H, t, *J* = 7.3 Hz), 7.21 (2/3H, t, *J* = 7.8 Hz), 7.26–7.36 (19/3H, m). $\delta_C$ (100 MHz, $CDCl_3$, major rotamer) 21.4 (s), 23.4 (s), 24.2 (s), 40.5 (s), 41.4 (d, *J* = 31.6 Hz), 50.3 (s), 53.0 (s), 60.1 (s), 67.1 (s), 84.1 (d, *J* = 27.8 Hz), 106.7 (d, *J* = 195.1 Hz), 110.5 (s), 119.4 (s), 123.4 (s), 126.5 (d, *J* = 24.0 Hz), 127.9 (s), 128.2 (s), 128.5 (s), 131.2 (s), 136.0 (s), 148.3 (d, *J* = 4.8 Hz), 156.2 (s), 171.7 (s), 173.5 (s). $\delta_F$ (376 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2 ratio) –131.6 (1/3F, q, *J* = 20.7 Hz), –145.0 (2/3F, ddd, *J* = 32.8, 25.2, 17.5 Hz). MS (EI) *m/z* 484 ($[M+H]^+$), 483 ($[M]^+$), 463 ($[M–HF]^+$). HRMS (EI) calcd for $C_{26}H_{30}FN_3O_5$ ($[M]^+$): 483.2169, found 483.2157.

**(3*S*,5a*R*,10b*R*,11a*R*)-6-Acetyl-10b-fluoro-6,10b,11,11a-tetrahydro-3-(2-methylpropyl)-2*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(3*H*,5a*H*)-dione (3).**

To a solution of **8** (109 mg, 0.207 mmol) in MeOH (0.4 mL) was added 10% palladium on carbon (22 mg) at room temperature. After stirring under 3–4 atm of hydrogen for 4 h, the mixture was filtered through a small pad of celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 2/3) to give **3** (37 mg, 50%) as a colourless crystalline solid. Mp 182–183 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ +27.3 (*c* 0.50 in $CHCl_3$). $\nu_{max}$ (KBr)/$cm^{-1}$ 3286, 2960, 2931, 2874, 1686, 1480, 1468, 1418, 1385, 1330, 1292, 1185, 1146, 1096, 1061, 1040, 937, 771, 759. $\delta_H$ (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* = 6.4 Hz), 0.97 (3H, d, *J* = 6.4 Hz), 1.63 (2H, dd, *J* = 7.8, 6.4 Hz), 1.71 (1H, septet, *J* = 6.4 Hz), 2.55 (3H, s), 2.92 (1H, ddd, *J* = 18.8, 14.2, 10.5 Hz), 3.37 (1H, dt, *J* = 14.2, 4.6 Hz), 3.77 (1H, td, *J* = 7.8, 4.6 Hz), 4.52 (1H, dd, *J* = 10.5, 4.6 Hz), 5.96 (1H, d, *J* = 12.4 Hz), 6.68 (1H, br d, *J* = 4.6 Hz), 7.17 (1H, dd, *J* = 7.8, 7.3 Hz), 7.39 (1H, tt, *J* = 7.8, 1.8 Hz), 7.47 (1H, dt, *J* = 7.3, 1.8 Hz), 8.00 (1H, br d, *J* = 7.8 Hz). $\delta_C$ (100 MHz, $CDCl_3$) 21.1 (s), 22.9 (s), 24.3 (s), 24.5 (s), 32.3 (d, *J* = 30.7 Hz), 41.3 (s), 55.8 (d, *J* = 4.8 Hz), 56.0 (s), 81.3 (d, *J* = 33.6 Hz), 100.9 (d, *J* = 201.3 Hz), 118.8 (s), 124.9 (s), 125.0 (d, *J* = 2.9 Hz), 127.6 (d, *J* = 22.0 Hz), 132.1 (d, *J* = 2.9 Hz), 142.8 (d, *J* = 3.8 Hz), 167.4 (s), 167.8 (s), 170.4 (s). $\delta_F$ (376 MHz, $CDCl_3$) –138.4 (1F, br t, *J* = 15.3 Hz). MS (EI) *m/z* 359 ($[M]^+$). HRMS (EI) calcd for $C_{19}H_{22}FN_3O_3$ ($[M]^+$): 359.1645, found 359.1637.

**(3*S*,5a*S*,10b*S*,11a*R*)-6-Acetyl-10b-fluoro-6,10b,11,11a-tetrahydro-3-(2-methylpropyl)-2*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(3*H*,5a*H*)-dione (22).**

To a solution of **21** (49 mg, 0.0930 mmol) in MeOH (0.4 mL) was added 10% palladium on carbon (10 mg) at room temperature. After stirring under 3–4 atm of hydrogen for 2 h, the mixture was filtered through a small pad of celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 2/3) to give **22** (26 mg, 78%) as colourless needles. Mp 214–216 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ +212.6 (*c* 0.20 in $CHCl_3$). $\nu_{max}$ (KBr)/$cm^{-1}$ 3233, 3161, 2968, 2932, 2871, 1685, 1669, 1645, 1483, 1466, 1437, 1392, 1330, 1294, 1200, 1146, 1090, 1060, 1037, 820, 793, 757. $\delta_H$ (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 6.4 Hz), 1.50–1.75 (3H, m), 2.62 (3H, s), 2.75 (1H, dt, *J* = 13.7, 12.4 Hz), 3.07 (1H, dd, *J* = 12.4,



 

5.5 Hz), 3.92–4.02 (2H, m), 6.37 (1H, d, *J* = 13.3 Hz), 7.04 (1H, br d, *J* = 2.8 Hz), 7.26 (1H, dd, *J* = 7.8, 7.3 Hz), 7.46–7.52 (2H, m), 8.17 (1H, br d, *J* = 7.8 Hz). $\delta_C$ (100 MHz, $CDCl_3$) 21.3 (s), 22.9 (s), 23.8 (s), 24.2 (s), 40.0 (d, *J* = 29.7 Hz), 43.9 (s), 55.7 (s), 58.2 (d, *J* = 5.8 Hz), 79.8 (d, *J* = 32.6 Hz), 102.0 (d, *J* = 204.2 Hz), 119.0 (s), 124.2 (s), 125.3 (d, *J* = 2.9 Hz), 126.0 (d, *J* = 22.0 Hz), 132.4 (d, *J* = 2.9 Hz), 144.5 (d, *J* = 3.8 Hz), 166.45 (s), 166.49 (s), 170.9 (s). $\delta_F$ (376 MHz, $CDCl_3$) –144.6 (1F, br t, *J* = 13.5 Hz). MS (EI) *m*/*z* 359 ($[M]^+$). HRMS (EI) calcd for $C_{19}H_{22}FN_3O_3$ ($[M]^+$): 359.1645, found 359.1652.

**(2*S*,3a*RS*,8a*SR*)-1-[(2*S*)-2-Benzyloxycarbonylamino-4-methylpentanoyl]-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (24a and 24b).**

Fluorocyclisation of *N*-Cbz-L-Leu-L-Trp-OMe (**23**)[17] (349 mg, 0.75 mmol) with **7** (325 mg, 1.13 mmol) in anhydrous THF (75 mL) at 60 °C for 7 h in a similar manner to that of **18** gave an inseparable mixture of **24a** and **24b** (**24a**:**24b** = ca. 1:1, 279 mg, 77%) as a colourless viscous oil. Each of **24a** and **24b** was observed as a mixture of two rotamers (**24a**: ca. 1:2 ratio, **24b**: ca. 1:4 ratio) in $^1H$ and $^{19}F$ NMR. $\delta_H$ (500 MHz, $CDCl_3$) 0.88 (3/5H, d, *J* = 6.3 Hz), 0.941 (2H, d, *J* = 6.3 Hz), 0.944 (3/5H, d, *J* = 6.3 Hz), 0.97 (2H, d, *J* = 6.3 Hz), 1.00 (12/5H, d, *J* = 6.9 Hz), 1.01 (12/5H, d, *J* = 6.9 Hz), 1.02 (1H, d, *J* = 6.3 Hz), 1.06 (1H, d, *J* = 6.3 Hz), 1.35–1.86 (6H, m), 2.63–3.13 (4H, m), 3.17 (2H, s), 3.31 (1H, s), 3.747 (3/5H, s), 3.754 (12/5H, s), 4.38–4.43 (13/15H, m), 4.47 (4/5H, t, *J* = 8.0 Hz), 4.55 (4/5H, td, *J* = 9.2, 5.7 Hz), 4.64 (2/3H, br d, *J* = 8.0 Hz), 4.65 (1/5H, br d, *J* = 9.2 Hz), 4.70 (1/3H, td, *J* = 9.7, 4.6 Hz), 4.77 (1/3H, br d, *J* = 4.0 Hz), 4.996 (1/3H, br d, *J* = 9.2 Hz), 5.001 (1/3H, br d, *J* = 9.2 Hz), 5.02 (2/3H, d, *J* = 12.6 Hz), 5.06 (2/3H, d, *J* = 12.6 Hz), 5.10 (1/3H, d, *J* = 12.0 Hz), 5.11 (2/5H, s), 5.12 (4/5H, d, *J* = 12.0 Hz), 5.13 (1/3H, d, *J* = 12.0 Hz), 5.15 (4/5H, d, *J* = 12.0 Hz), 5.26 (1/5H, br d, *J* = 9.2 Hz), 5.31 (2/3H, br s), 5.33 (4/5H, br d, *J* = 9.2 Hz), 5.41 (1/5H, br d, *J* = 9.2 Hz), 5.43 (2/3H, br d, *J* = 9.2 Hz), 5.59 (2/3H, d, *J* = 17.8 Hz), 5.81 (4/5H, dd, *J* = 18.9, 2.3 Hz), 5.87 (1/5H, dd, *J* = 25.8, 4.0 Hz), 5.97 (1/3H, dd, *J* = 17.8, 4.0 Hz), 6.49 (4/5H, br d, *J* = 2.3 Hz), 6.61 (4/5H, d, *J* = 8.0 Hz), 6.63 (2/3H, d, *J* = 8.0 Hz), 6.66 (1/5H, d, *J* = 8.0 Hz), 6.77 (2/3H, t, *J* = 8.0 Hz), 6.81 (1/3H, d, *J* = 8.0 Hz), 6.83 (4/5H, t, *J* = 8.0 Hz), 6.84 (1/5H, t, *J* = 8.0 Hz), 6.93 (1/3H, t, *J* = 8.0 Hz), 7.18–7.39 (14H, m). $\delta_F$ (470 MHz, $CDCl_3$) –133.3 – –133.4 (1/3F, m), –140.8 – –141.0 (5/3F, m). MS (EI) *m*/*z* 483 ($[M]^+$), 463 ($[M–HF]^+$).

**(2*S*,3a*S*,8a*S*)-8-Acetyl-1-[(2*S*)-2-benzyloxycarbonylamino-4-methylpentanoyl]-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (25a) and (2*S*,3a*R*,8a*R*)-8-acetyl-1-[(2*S*)-2-benzyloxycarbonylamino-4-methylpentanoyl]-3a-fluoro-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylic acid methyl ester (25b).**

Acetylation of a mixture of **24a** and **24b** (**24a**:**24b** = ca. 1:1, 224 mg, 0.463 mmol) with acetic anhydride (1.85 mL) and pyridine (0.110 mL, 1.39 mmol) at 60 °C for 4 h in a similar manner to that of **20a** and **20b** gave a mixture of **25a** and **25b** (**25a**:**25b** = ca. 30:1, 120 mg, 49%) and **24b** (97 mg, 43%). Compound **24b** (76 mg, 0.157 mmol) was acetylated again with acetic anhydride (0.63 mL) and pyridine (0.0380 mL, 0.472 mmol) at 60 °C for 50 h to generate **25b** (43 mg, 52%) and **24b** (17 mg, 22%). The data of pure **25a** was obtained after recrystallization of the mixture of **25a** and **25b** from hexane and dichloromethane.

**25a**: colourless needles. Mp 131–132 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{23}$ +27.5 (*c* 0.5 in $CHCl_3$). $\nu_{max}$ (KBr)/$cm^{-1}$ 3414, 2952, 1726, 1677, 1670, 1513, 1480, 1468, 1419, 1385, 1343, 1321, 1287, 1224, 1172, 1142, 1097, 1062, 1040, 1028, 775, 751, 698. $\delta_H$ (500 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2 ratio) 0.93–0.96 (6H, br m), 1.34–1.38 (2/3H, br m), 1.52–1.80 (7/3H, br m), 2.44 (1H, br s), 2.63 (2H, br s), 2.75–3.20 (2H, br m), 3.06 (2H, br s), 3.18 (1H, br s), 4.38 (2/3H, br t, *J* = 8.6 Hz), 4.61 (2/3H, br d, *J* = 8.6 Hz), 4.99–5.37 (4H, br m), 6.19 (2/3H, br d, *J* = 12.0 Hz), 7.03 (1/3H, br d, *J* = 8.0 Hz), 7.14–7.47 (8H, br m), 8.03 (2/3H, br d, *J* = 6.3 Hz). $\delta_C$ (126 MHz, $CDCl_3$) 21.6 (s), 23.4 (s), 23.7 (s), 24.4 (s), 37.6 (d, *J* = 31.2 Hz), 43.0 (s), 50.4 (s), 52.8 (s), 59.3 (d, *J* = 4.8 Hz), 66.9 (s), 80.4 (d, *J* = 32.4 Hz), 101.5 (d, *J* = 203.9 Hz), 119.3 (s), 124.6 (d, *J* = 12.0 Hz), 125.6 (s), 128.0 (s x 2), 128.1 (s), 128.4 (s), 132.3 (s), 136.1 (s), 145.1 (s), 155.5 (s), 169.0 (s), 171.2 (s), 172.8 (s). $\delta_F$ (470 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:2 ratio) –143.7 (2/3F, br s), –143.8 (1/3F, br s). MS (EI) *m*/*z* 526 ($[M+H]^+$), 525 ($[M]^+$). HRMS (EI) calcd for $C_{28}H_{32}FN_3O_6$ ($[M]^+$): 525.2275, found 525.2275.

**25b**: colourless crystalline solid. Mp 56–59 °C (from hexane/$CHCl_3$). $[\alpha]_D^{23}$ –67.2 (*c* 0.75 in $CHCl_3$). $\nu_{max}$ (KBr)/$cm^{-1}$ 3385, 2956, 2871, 1752, 1721, 1683, 1608, 1520, 1481, 1468, 1416, 1370, 1326, 1288, 1281, 1257, 1246, 1214, 1174, 1043, 778, 760, 740, 699. $\delta_H$ (500 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:3 ratio) 0.60 (3/4H, d, *J* = 6.3 Hz), 0.71 (3/4H, d, *J* = 6.3 Hz), 0.83–0.90 (1/4H, m), 1.02 (9/4H, d, *J* = 6.9 Hz), 1.08 (9/4H, d, *J* = 6.9 Hz), 1.19–1.35 (1/2H, m), 1.45–1.51 (3/4H, m), 1.65–1.70 (3/4H, m), 1.83 (3/4H, septet, *J* = 6.9 Hz), 2.43 (9/4H, s), 2.62 (3/4H, td, *J* = 12.6, 11.5 Hz), 2.63 (3/4H, s), 2.77 (1/4H, td, *J* = 13.2, 9.7 Hz), 2.95 (3/4H, dd, *J* = 12.6, 6.9 Hz), 3.19 (1/4H, dd, *J* = 13.2, 8.6 Hz), 3.72 (9/4H, s), 3.77 (3/4H, s), 4.01 (3/4H, dd, *J* = 11.5, 6.9 Hz), 4.08 (1/4H, td, *J* = 8.6, 5.2 Hz), 4.17 (1/4H, br t, *J* = 8.6 Hz), 5.00–5.07 (7/2H, m), 5.35 (1/4H, br d, *J* = 9.2 Hz), 6.13 (1/4H, d, *J* = 9.2 Hz), 6.64 (3/4H, d, *J* = 8.0 Hz), 7.09 (3/4H, d, *J* = 8.0 Hz), 7.22–7.49 (8H, m), 8.02 (1/4H, br d, *J* = 8.0 Hz). $\delta_C$ (126 MHz, $CDCl_3$, major rotamer) 22.1 (s), 23.0 (s), 23.4 (s), 24.9 (s), 33.7 (d, *J* = 26.4 Hz), 42.4 (s), 50.2 (s), 52.4 (s), 59.0 (d, *J* = 3.6 Hz), 66.6 (s), 77.7 (d, *J* = 33.6 Hz), 100.2 (d, *J* = 205.1 Hz), 119.5 (s), 124.7 (s), 125.7 (s), 127.9 (s), 128.0 (s), 128.4 (s), 129.1 (d, *J* = 21.6 Hz), 132.1 (d, *J* = 2.4 Hz), 136.7 (s), 143.4 (d, *J* = 3.6 Hz), 155.4 (s), 170.5 (s), 171.8 (s), 174.9 (s). $\delta_F$ (470 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:3 ratio) –144.3 (3/4F, br t, *J* = 10.3 Hz), –144.8 (1/4F, br t, *J* = 11.4 Hz). MS (EI) *m*/*z* 526 ($[M+H]^+$), 525 ($[M]^+$). HRMS (EI) calcd for $C_{28}H_{32}FN_3O_6$ ($[M]+$): 525.2275, found 525.2261.

**24b**: colourless crystalline solid. Mp 45–47 °C (dec.) (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ –178.5 (*c* 0.5 in $CHCl_3$). $\nu_{max}$

(KBr)/cm$^{-1}$ 3317, 2956, 2871, 1752, 1717, 1698, 1654, 1618, 1541, 1523, 1474, 1437, 1320, 1259, 1216, 1190, 1177, 1121, 1095, 1057, 749, 698. $\delta_H$ (500 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:4 ratio) 0.86 (3/5H, d, $J$ = 6.3 Hz), 0.93 (3/5H, d, $J$ = 6.3 Hz), 0.99 (12/5H, d, $J$ = 6.9 Hz), 1.00 (12/5H, d, $J$ = 6.9 Hz), 1.35 (1/5H, ddd, $J$ = 14.3, 9.7, 4.0 Hz), 1.52 (1/5H, ddd, $J$ = 14.3, 9.7, 4.6 Hz), 1.61–1.71 (8/5H, m), 1.77–1.85 (1H, m), 2.60–2.79 (9/5H, m), 2.98–3.05 (1/5H, m), 3.73 (12/5H, s), 3.74 (3/5H, s), 4.41 (1/5H, td, $J$ = 9.7, 4.0 Hz), 4.45 (4/5H, t, $J$ = 8.0 Hz), 4.56 (4/5H, td, $J$ = 9.2, 5.7 Hz), 4.63 (1/5H, br d, $J$ = 8.0 Hz), 5.08 (2/5H, s), 5.11 (4/5H, d, $J$ = 12.6 Hz), 5.13 (4/5H, d, $J$ = 12.6 Hz), 5.37 (1/5H, br d, $J$ = 4.0 Hz), 5.55 (1/5H, d, $J$ = 9.2 Hz), 5.63 (4/5H, d, $J$ = 9.7 Hz), 5.81 (4/5H, dd, $J$ = 18.9, 2.3 Hz), 5.85 (1/5H, dd, $J$ = 25.5, 4.0 Hz), 6.54 (4/5H, br d, $J$ = 2.3 Hz), 6.59 (4/5H, d, $J$ = 8.0 Hz), 6.64 (1/5H, d, $J$ = 8.0 Hz), 6.82 (1H, br t, $J$ = 8.0 Hz), 7.19–7.22 (1H, m), 7.28–7.34 (6H, m). $\delta_C$ (126 MHz, $CDCl_3$, major rotamer) 22.1 (s), 23.1 (s), 24.3 (s), 38.6 (d, $J$ = 31.2 Hz), 42.0 (s), 50.9 (s), 52.5 (s), 59.5 (s), 67.4 (s), 80.9 (d, $J$ = 30.0 Hz), 107.5 (d, $J$ = 199.1 Hz), 110.6 (s), 119.5 (d, $J$ = 2.4 Hz), 123.81 (s), 123.85 (d, $J$ = 22.8 Hz), 128.0 (s), 128.3 (s), 128.6 (s), 131.9 (d, $J$ = 2.4 Hz), 135.9 (s), 149.4 (d, $J$ = 4.8 Hz), 156.8 (s), 170.6 (s), 172.8 (s). $\delta_F$ (470 MHz, $CDCl_3$, a mixture of two rotamers in ca. 1:4 ratio) –140.8 – –140.9 (4/5F, m), –140.8 – –141.0 (1/5F, m). MS (EI) $m/z$ 484 ([M+H]$^+$), 483 ([M]$^+$). HRMS (EI) calcd for $C_{26}H_{30}FN_3O_5$ ([M]$^+$): 483.2169, found 483.2151.

**(3*S*,5a*R*,10b*R*,11a*S*)-6-Acetyl-10b-fluoro-6,10b,11,11a-tetrahydro-3-(2-methylpropyl)-2*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(3*H*,5a*H*)-dione (4).**

Deprotection and subsequent DKP formation of **25b** (42 mg, 0.080 mmol) using 10% palladium on carbon (8 mg) in MeOH (1.0 mL) at room temperature for 1.5 h in a similar manner to those of **8** gave **4** (25 mg, 87%) as a colourless crystalline solid. Mp 93–96 °C (from hexane/$CHCl_3$). $[\alpha]_D^{22}$ –244.6 (*c* 0.40 in $CHCl_3$). $\nu_{max}$ (KBr)/cm$^{-1}$ 3246, 2959, 2930, 2871, 1685, 1480, 1467, 1408, 1384, 1351, 1332, 1295, 1284, 1179, 1158, 1143, 1104, 1092, 1061, 1045, 925, 767, 755. $\delta_H$ (500 MHz, $CDCl_3$) 0.92 (3H, d, $J$ = 6.3 Hz), 1.00 (3H, d, $J$ = 6.3 Hz), 1.58 (1H, ddd, $J$ = 14.4, 9.8, 5.2 Hz), 1.72–1.80 (1H, m), 2.01 (1H, ddd, $J$ = 14.4, 9.8, 3.5 Hz), 2.65 (3H, s), 2.79 (1H, td, $J$ = 12.6, 12.1 Hz), 3.07 (1H, dd, $J$ = 12.6, 6.3 Hz), 3.97–4.01 (2H, m), 6.24 (1H, d, $J$ = 12.1 Hz), 6.58 (1H, s), 7.24 (1H, t, $J$ = 7.5 Hz), 7.46–7.52 (2H, m), 8.13 (1H, br d, $J$ = 8.0 Hz). $\delta_C$ (126 MHz, $CDCl_3$) 21.1 (s), 23.3 (s), 23.8 (s), 24.3 (s), 37.8 (d, $J$ = 30.0 Hz), 39.0 (s), 53.1 (s), 58.8 (d, $J$ = 6.0 Hz), 79.8 (d, $J$ = 32.4 Hz), 101.7 (d, $J$ = 205.1 Hz), 119.3 (s), 124.1 (s), 125.2 (d, $J$ = 2.4 Hz), 126.2 (d, $J$ = 22.8 Hz), 132.4 (d, $J$ = 3.6 Hz), 144.5 (d, $J$ = 3.6 Hz), 166.5 (s), 167.5 (s), 170.9 (s). $\delta_F$ (470 MHz, $CDCl_3$) –144.9 (1F, br t, $J$ = 11.9 Hz). MS (EI) $m/z$ 359 ([M]$^+$). HRMS (EI) calcd for $C_{19}H_{22}FN_3O_3$ ([M]$^+$): 359.1645, found 359.1653.

**(3*S*,5a*S*,10b*S*,11a*S*)-6-Acetyl-10b-fluoro-6,10b,11,11a-tetrahydro-3-(2-methylpropyl)-2*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4(3*H*,5a*H*)-dione (26).**



Deprotection and subsequent DKP formation of **25a** (59 mg, 0.100 mmol) using 10% palladium on carbon (11 mg) in MeOH (1.0 mL) at room temperature for 5 h in a similar manner to those of **8** gave **26** (31 mg, 86%) as a colourless crystalline solid. Mp 105–106 °C (from hexane/$CH_2Cl_2$). $[\alpha]_D^{25}$ –15.5 (*c* 0.40 in $CHCl_3$). $\nu_{max}$ (KBr)/cm$^{-1}$ 3227, 3120, 2959, 2937, 2871, 1689, 1680, 1673, 1480, 1468, 1406, 1385, 1334, 1293, 1184, 1042, 938, 769, 755. $\delta_H$ (500 MHz, $CDCl_3$) 0.89 (3H, d, $J$ = 6.3 Hz), 0.90 (3H, d, $J$ = 6.3 Hz), 1.42 (1H, ddd, $J$ = 14.3, 9.7, 5.2 Hz), 1.56–1.65 (1H, m), 1.91 (1H, ddd, $J$ = 14.3, 9.7, 4.0 Hz), 2.58 (3H, s), 2.91 (1H, ddd, $J$ = 17.8, 14.3, 10.9 Hz), 3.51 (1H, ddd, $J$ = 14.3, 3.4, 1.7 Hz), 3.90 (1H, dd, $J$ = 9.7, 4.0 Hz), 4.50 (1H, dd, $J$ = 10.9, 3.4 Hz), 5.62 (1H, s), 5.98 (1H, d, $J$ = 11.5 Hz), 7.19 (1H, t, $J$ = 7.5 Hz), 7.42 (1H, dddd, $J$ = 8.6, 7.5, 2.3, 1.2 Hz), 7.52 (1H, br d, $J$ = 7.5 Hz), 7.99 (1H, br d, $J$ = 8.6 Hz). $\delta_C$ (126 MHz, $CDCl_3$) 21.1 (s), 23.0 (s), 24.2 (s), 24.5 (s), 30.9 (d, $J$ = 30.0 Hz), 37.7 (s), 53.5 (s), 57.5 (d, $J$ = 6.0 Hz), 80.8 (d, $J$ = 33.6 Hz), 101.2 (d, $J$ = 201.5 Hz), 118.9 (s), 125.0 (d, $J$ = 2.4 Hz), 125.1 (s), 127.3 (d, $J$ = 21.6 Hz), 132.2 (d, $J$ = 3.6 Hz), 142.9 (d, $J$ = 4.8 Hz), 167.9 (s), 168.1 (s), 170.2 (s). $\delta_F$ (470 MHz, $CDCl_3$) –138.5 (1F, br t, $J$ = 14.1 Hz). MS (EI) $m/z$ 359 ([M]$^+$), 339 ([M–HF]$^+$). HRMS (EI) calcd for $C_{19}H_{22}FN_3O_3$ ([M]+): 359.1645, found 359.1638.

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*Graphical abstract*

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# Synthesis of 10b-fluorinated analogues of protubonine A and its 11a-epimer *via* fluorocyclisation of tryptophan-containing dipeptides

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The 10b-fluorinated analogues of protubonine A and its 11a-epimer were synthesised *via* fluorocyclisation of tryptophan-containing dipeptides with *N*-fluoro-2,4,6-trimethylpyridinium triflate.