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A novel macroreticular-type fluorous polystyrene resin and its application to the synthesis of a 3-amino-β-carboline derivative with *N*-methyl-*N*-nitrosourea conjugation via fluorous solid-phase reaction: a comparative study of fluorous solid-, solid-, and liquid-phase reactions

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ABSTRACT

A novel fluorous polystyrene (FPS) MR-resin was applied to a fluorous solid-phase (FSP) reaction. The MR-FPS resin actually was developed previously and possessed excellent chemical resistance to acids and alkalis, and a fluorous-tagged compound was homogeneously and loosely immobilized on the resin. The synthesis of an antitumor drug, an *N*-methyl-*N*-nirosourea conjugated 3-amino-β-carboline derivative, was accomplished with a high yield by using this new fluorous reaction system. Using only filtration, the fluorous 3-amino-β-carboline derivatives immobilized on the MR-FPS resin were easily recovered from the reaction mixtures. As an extention of this approach, a diversity synthesis of 3-amino-9-benzyl-β-carboline derivatives was applied to the FSP method giving high yields. Finally, the FSP synthesis was compared with the corresponding conventional solid- and liquid-phase methods of synthesis. The FSP reaction was superior in terms of the reactivity of the substrate and the ease of product separation.

1. Introduction

Fluorous chemistry has shown promise as a new field of green sustainable chemistry based on its capacity for reaction recyclability.[1] Generally speaking, fluorous chemistry utilizes the temperature dependency of the perfluoroalkanes in oleophobicity. These are typical properties of fluorous solvents, and they are ably utilized in fluorous biphasic systems (FBS). Although the fluorous-common organic biphase becomes homogeneous by mixing or heating, it returns to a biphasic state upon standing or cooling to room temperature following a reaction. As a result, a catalyst possessing a fluorous tag in a fluorous phase can be recovered without lixiviation from the fluorous phase to the organic phase, and the catalyst solution can be recycled in the next reaction as the fluorous phase. Since Horváth and Rábai introduced the concept of fluorous biphasic catalysis (FBC) in 1994,[2] it has attracted much attention with great effort devoted to developing fluorous chemistry.[3] A fluorous catalyst can be recycled, and the same conditions for reactions in usual non-fluorous solvents are applicable in the fluorous biphasic reactions, which is a methodology that has been widely applied to various reactions by many chemists.[4] Recently, the manufacture, the import/export, and the use of perfluorooctanesulfonic acid (PFOS) all were regulated by the Stockholm Convention on Persistent Organic Pollutants (POPs) because of its difficult degradability, its persistency, and its bioaccumulative toxicity. Sometimes, even the fluorous solvents used in fluorous chemistry present problems in these areas.[5] In order to accomplish a FBS reaction without a fluorous solvent and to improve its general applicability, perfluoroalkylated silica gels[6,7] and Teflon tape/shavings or Rastex fibers[8] have been used as solid-extraction materials and solid supports for fluorous catalysts. Originally, the silica gels have been used as packing material for reverse-phase HPLC columns[9] and as solid–liquid extraction cartridges to separate fluorinated compounds from organic compounds. However, silica gels have a tendency to dissolve in acidic or

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basic solutions, and it is particularly sensitive to bases. This property is a fatal flaw in green chemistry, and the development of a new type of fluorous support is desired.

Previously, we reported the development of a novel fluorous macroreticular polystyrene (MR-FPS) and its application to the acetylation of cyclohexanol, in which a fluorous Lewis acid immobilized on an MR-FPS resin was repeatedly used as a catalyst to give the ester in a high yield.[10] However, the yield of the cyclohexyl acetate decreased to only 48% in this esterification when the MR-FPS resin was not used. Although we believed that the porous MR-FPS resin may had acted as an effective reaction field through the homogeneous immobilization of the fluorous compound on the resin, we were not always able to examine the homogeneity of the immobilized fluorous compounds in detail in the previous report.[10] In this paper, we validated the homogeneity of the immobilized fluorous compound on the MR-FPS resin, and advocated a concept of the fluorous-solid phase (FSP) synthesis using MR-FPS resin, and then applied the FSP system to the synthesis of an *N*-methyl-*N*-nirosourea-conjugated 3-amino-β-carboline derivative, which we previously developed as a new antitumor drug.[11] We finally compared FSP synthesis of 3-amino-β-carboline derivative with the corresponding solid- and liquid-phase syntheses. A conceptual diagram for FSP system is briefly illustrated in Fig. 1.

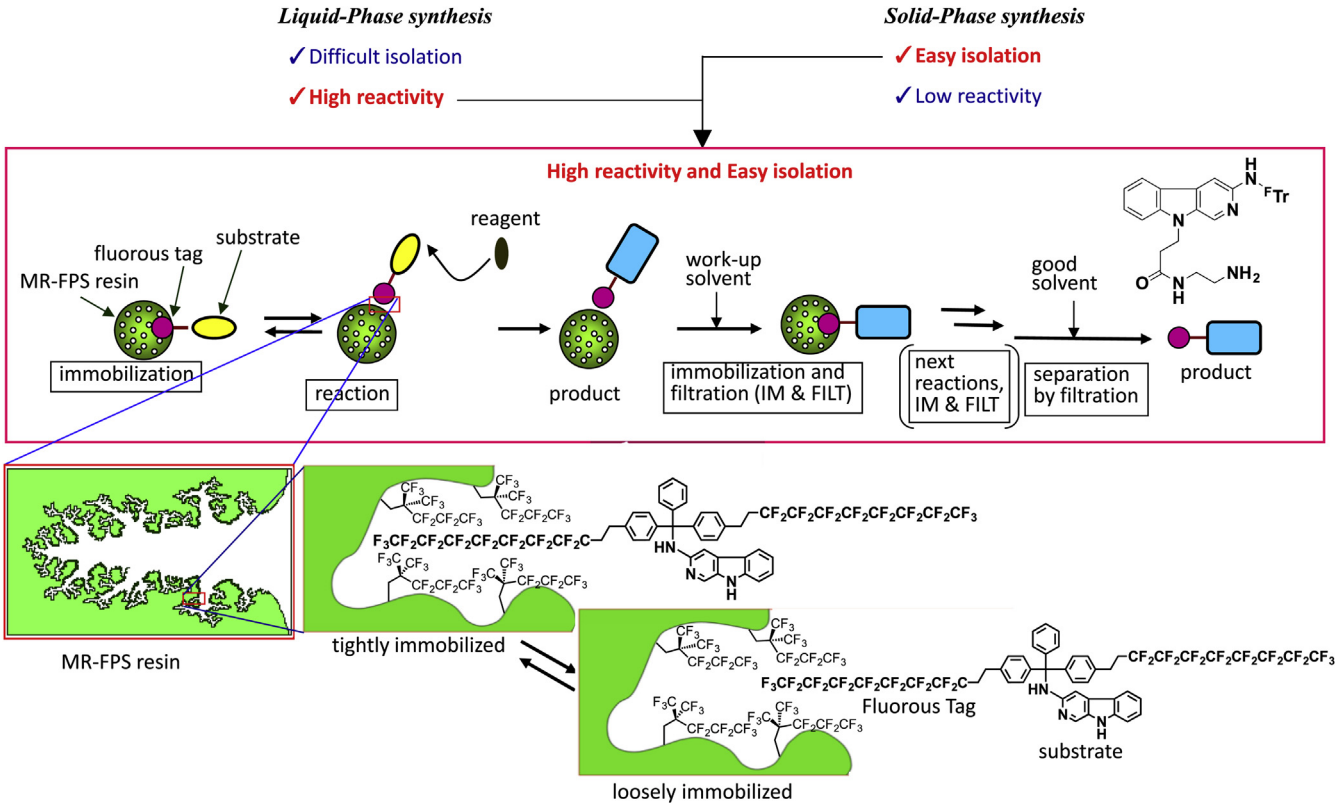
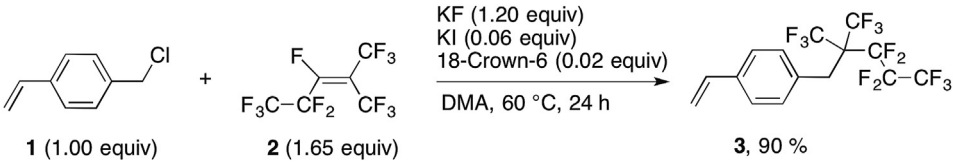


Fig. 1. Illustrated conceptual diagram for fluorous-solid phase (FSP) system.

2. Results and discussion

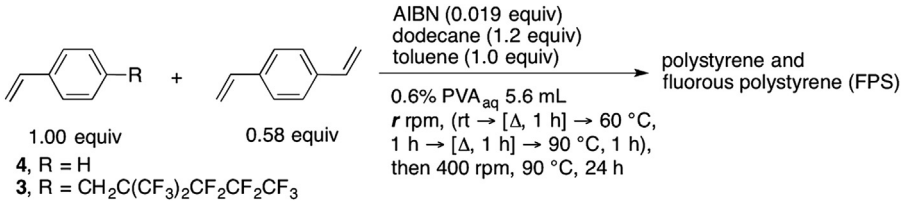
2.1. Preparation of a macroreticular-type fluorous polystyrene (MR-FPS) resin

First, 1-(3,3,4,4,5,5,5-heptafluoro-2,2-bis(trifluoromethyl)pentyl-4-vinylbenzene (**3**) was prepared from perfluoro(2-methyl-2-pentene) (**1**) and *p*-chloromethylstyrene (**2**) in a 90% yield via an analogous method, as reported previously (Scheme 1),[9a] and was then co-polymerized with divinylbenzene to obtain a fluorous polystyrene (FPS) resin.[10] Prior to the polymerization of **3**, styrene was copolymerized with divinylbenzene via suspension polymerization for use as a model reaction to obtain completely-spherical particles in the presence of AIBN (0.019 equiv) as an initiator, dodecane (1.2 equiv) as a poor dilution solvent, toluene (1.0 equiv) as a good dilution solvent, and 0.6% aqueous poly(vinyl acetate) (PVA) solution as a dispersing agent in a 10 mL round-bottomed flask (Table 1).[12] The obtained resin was passed through sieves (Table 1, entries 1–3). The stirring velocity (*r*) controlled the particle size so that when *r* was larger, the particle size became smaller. According to the results of the polystyrene, compound **3** was co-polymerized with divinylbenzene (0.58 equiv) under the same conditions with a stirring velocity of 1000 rpm (entry 4). However, the yield of particle size fractions >355 μm increased from 58 to 92%. This tendency toward a particle size increase was caused by values for the hydrophobicity and density for **3** that were larger than those for styrene. Therefore, the reaction vessel was changed from a 10 mL round-bottomed flask to an 18 mm test tube to decrease the particle size, because vessel shape affects the efficiency of stirring. The yield of smaller particles was increased to 28% (entry 5). Furthermore, the increased stirring velocity reduced the particle size. The yield of particles 355–250 μm in size was 70% at 1300 rpm and that of particles 250–180 μm in size was 67% at 1600 rpm. A resin particle with a larger surface area seemed better suited to solid-phase support. Although small particles result in a large surface area, particles smaller than 180 μm in diameter were difficult to handle because of static electrical charges. Therefore, entry 7, which produced 250–180 μm-sized particles as major products, was selected as the optimal reaction conditions.



Scheme 1. Synthesis of fluorous styrene **3**.

Table 1
Preparation of polystyrene resin and fluorous polystyrene (FPS) MR type resin



Entry	*r*/rpm[a]	Vessel	Monomer	Particle size/μm, wt %					
				>355	355–250	250–180	180–125	125–90	<90
1	700	Flask[b]	**4**	94	3	2	1	0	0
2	1000	Flask[b]	**4**	58	35	6	1	0	0
3	1300	Flask[b]	**4**	17	56	23	3	1	0
4	1000	Flask[b]	**3**	92	7	1	1	0	0
5	1000	Test tube[c]	**3**	67	28	4	1	0	0
6	1300	Test tube[c]	**3**	3	70	25	1	1	0
7	1600	Test tube[c]	**3**	1	21	67	10	1	0

[a] *r*: Stirring velocity.
[b] Flask: 10 mL round-bottomed flask.
[c] Test tube: 18 mm-diameter test tube.

Second, SEM was used to carefully monitor the thus-prepared FPS particles for micropores, and the particles were partially crashed in order to observe the fracture cross-sections (Fig. 2a). Many micropores with diameters that ranged from tens to hundreds of nm were evenly observed not only on the surfaces but also on the insides of the completely spherical FPS particles as evidence of the MR resin (Fig. 2b–e). These micropores were not observed in the gel-type FPS (G-FPS), which was obtained in the reaction using excess amounts of toluene (good solvent) or insufficient amounts of the diluent (Fig. 3a–c). The SEM images of the surface of the G-FPS resin were compared with those of the MR type FPS (MR-FPS) resin at almost the same magnification ratio (Fig. 3b vs Fig. 3d). The rough surface of the MR-FPS resin (Fig. 3d) was more characteristic than the smooth surface (Fig. 3b). A magnified image (×40,000) of the smooth surface is shown in Fig. 3c.

Next, the MR-FPS resin was treated with bases and acids to clarify its limits of tolerance, as we daringly selected very severe conditions in order to explore the possible use of the MR-FPS resin as a fluorous support in various kinds of reactions. When the MR-FPS resin was treated with water, 10 M sodium hydroxide, triethylamine, and 10 M sulfuric acid at 80 °C, there was no apparent change, which was verified spectroscopically after even one week in each sample of the MR-FPS resin, as shown in Fig. 4 by the absorption bands of the C–F bonds in the 1200–1300 cm^{-1} region in their micro-ATR-FTIR spectra. PFO-SiO_2, however, was easily decomposed when it was treated with 10 M sodium hydroxide for only 2 days—even at room temperature. This result shows that FPS indicates tolerance against bases and acids that is higher than that of PFO-SiO_2.

2.2. Preparation of fluorous Lewis acid supported on MR-FPS (5/MR-FPS) and SEM-EDX analysis

We selected a scandium(III) salt **5** of the fluorous sulfonamide[10,13] for use as a probe in the scanning electron microscope-enegy dispersive X-ray spectroscopy (SEM-EDX). In order to support the compound **5** on the MR-FPS resin, the MR-FPS particles were added to the solution of **5** in ethanol, and the solvent was rotary-evaporated under reduced pressure following stirring. The dried MR-FPS-supported **5** (**5**/MR-FPS) was not sticky and was easily handled unlike the fluorous Lewis acid **5** itself. The amount of **5** supported on the G-FPS resin was much smaller than that on the MR-FPS resin. The presence of the fluorous Lewis acid **5** on the MR-FPS particles was affirmed by SEM-EDX, which was operated under the conditions that are described in Fig. 2. A characteristic X-ray of scandium was observed at 4.1 (Kα) and 4.5 (Kβ) keV in EDX of the **5**/MR-FPS particles, which were coated with a vacuum-deposited platinum film and set on a copper stage (Fig. 5). The EDX mappings are shown for F, S and Sc in Fig. 6b–d, respectively, in a SEM image (Fig. 6a). The existence and homogeneous distribution of **5** on a MR-FPS particle was established by the EDX mapping of F, S, and Sc elements as shown in Fig. 6b–d.

2.3. Fluorous solid-phase (FSP) synthesis of 3-(3-amino-9*H*-pyrido[3,4-*b*]indol-9-yl)-*N*-(2-(3-methyl-3-nitrosoureido) ethyl)propanamide (13)

In the esterification of cyclohexanol reported previously,[10] the reaction gave very low yields in the absence of an MR-FPS support as well as in the absence of a fluorous catalyst. The former result suggests that the fluorous Lewis acid catalyst was loosely immobilized on the surface of the MR-FPS resin. This loosely-immobilized catalyst prevented the steric hindrance observed in solid-phase syntheses, and resulted in high reactivity, such as that seen in liquid-phase synthesis. This MR-FPS resin had micropores, strong hydrophobicity and oleophobicity; and enabled a reaction with the advantages of both solid-phase synthesis as well as those of liquid-phase synthesis, which resulted in a novel reaction field that was highly functional. On the basis of the above-mentioned attributes of the MR-FPS resin (microporocity, hydrophobicity,

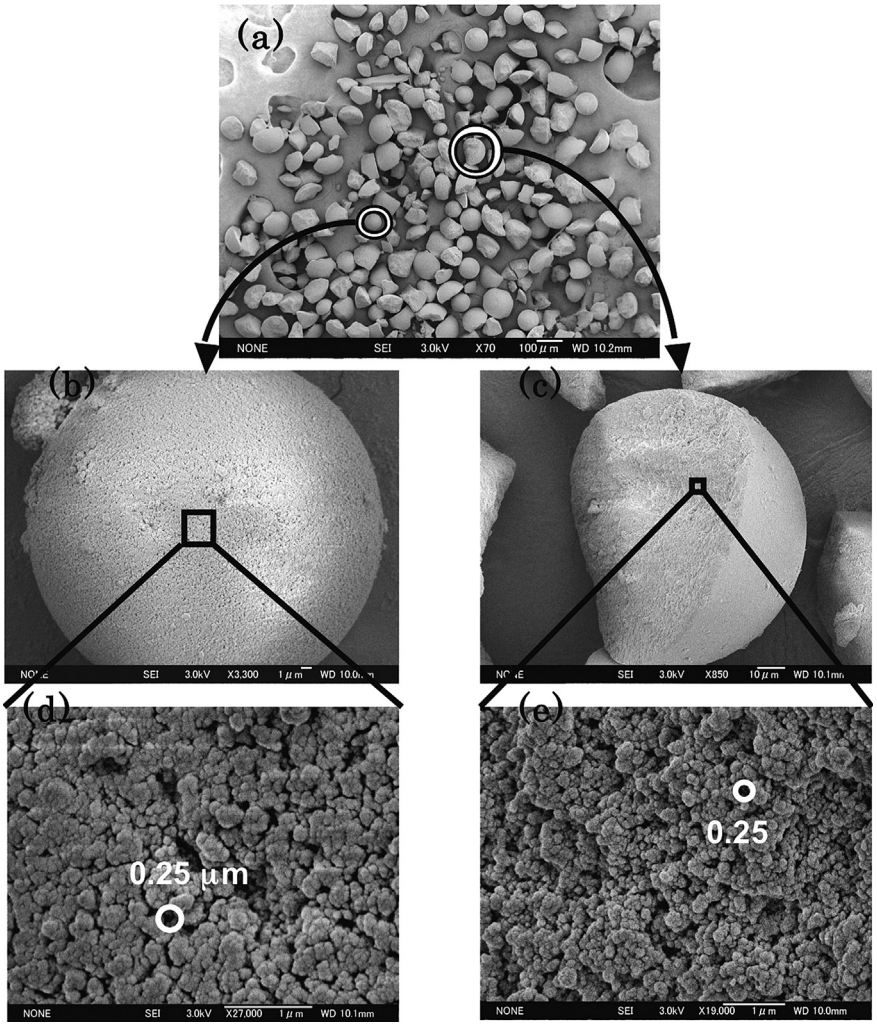
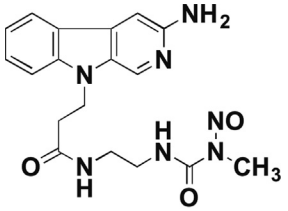


Fig. 2. SEM images of MR type fluorous polystyrene (MR-FPS) particles: (a) whole image (x70), (b) a completely-spherical shaped particle and its surface (x3,300), (c) macropores on the surface of FPS particle (x27,000), (d) view of the fracture cross-section (x850), (e) macropores on the surface of the fracture cross-section in FPS particle (x19,000). MR-FPS particles were coated with a vacuum-deposited platinum film (thickness: 26.5 nm) and set on a cupper stage. SEM was operated at 15.0 kV (electron accelerating voltage).

oleophobicity, high chemical tolerance, and homogeneous immobilization of fluorous compounds), we advocated a new concept of the fluorous-solid phase (FSP) synthesis using the MR-FPS resin. A conceptural diagram for FSP system is briefly illustrated in Fig. 1 to make it understandable. We attempted to employ the MR-FPS resin as a support for FSP synthesis using fluorous-tagged reagents or substances.[3b,14] In this application, we planned the synthesis of 3-(3-amino-9*H*-pyrido[3,4-*b*]indoL-9-yl)-*N*-(2-(3-methyl-3-nitrosoureido)ethyl)propanamide (**6**), which is a novel antitumor agent that we recently developed.[11c] Therefore, we designed a novel fluorous trityl chloride (^{F}Tr-Cl): 4,4′-(chloro(phenyl)methylene)bis((3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl) benzene) (**7**). This was a fluorous tag with a functional group that was analogous to the trityl chloride resin.[15] The synthetic strategy is shown in Scheme 2. First, the Heck reaction of *p*-bromobenzenediazonium tetrafluoroborate (**8**) with 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecene in the presence of Pd(II) acetate (0.5 mol %) gave the corresponding 1-(*p*-bromophenyl)-2-perfluorooctylethene (**9**) in a 93% yield, which was followed by hydrogenation with 1 MPa H_2 in the presence of a Rh/C catalyst at room temperature for 24 h to yield *p*-bromo(1*H*,1*H*,2*H*,2*H*)perfluorodecylbenzene (**10**) in a 95% yield. After lithiation with *n*-BuLi in THF at −40 °C, **10** was treated with methyl benzoate (0.32 equiv) to give 4,4′-bis((1*H*,1*H*,2*H*,2*H*)perfluorodecyl) trityl alcohol (**11**) in an 84% yield. When **11** was stirred in excess amounts of acetyl chloride at 65 °C for 3 h, the fluorous trityl chloride **7** was obtained in an 80% yield. Because the fluorine content in this molecule was 55 wt %, it could be a good fluorous tag in either an FBS reaction or in the FSP reaction.



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Next, 3-amino-β-carboline (**12**) was treated with ^{F}Tr-Cl **7** in the presence of *N*,*N*-diisopropylethylamine (DIPEA) in DMF. The reaction, however, would not proceed, because **7** was only minutely soluble in DMF. When THF was used as a solvent instead of DMF, 3-(^{F}Tr-amino)-β-carboline (**13a**) was obtained in a quantitative yield (Table 2, entries 1 and 2, 98%). The yield was comparable to that of the reaction of *o*-chlorotrityl chloride resin in a solid phase (entries 3 and 4, **13b**:99%). However, the corresponding *o*-chlorotrityl-

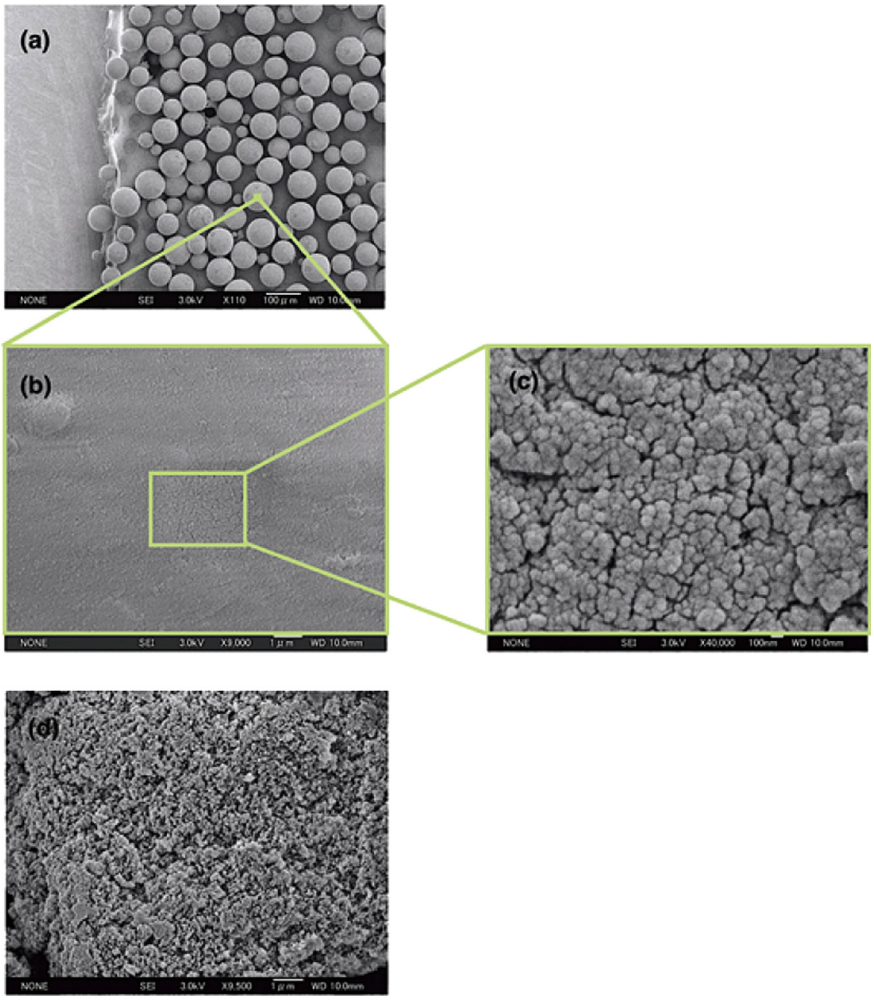


Fig. 3. SEM images of the gel type fluorous polystyrene (G-FPS) particles and MR-FPS particles: (a) Whole image, completely-spherical shaped particles (x110), (b) the surface of gel type FPS resin particle (x9,000), (c) the surface of gel type FPS resin particle (x40,000), (d) the surface of the MR type FPS resin particle in the almost same magnification ratio (x9,500) as Fig. 2b. The gel type FPS particles were coated with a vacuum-deposited platinum film (thickness: 26.5 nm) and set on a cupper stage. SEM was operated at 15.0 kV (electron accelerating voltage).

protected compound **13c** was produced by an analogous reaction in a yield of 82% (entry 5). The obtained **13a** was immobilized on the MR-FPS resin by rotary-evaporation of the solvent from the mixture of the resin and **13a**, which was dissolved in a minimum amount of methanol. In order to synthesize 3-(3-amino-9*H*-pyrido[3,4-*b*]indol-9-yl)-*N*-(2-(3-methyl-3-nitrosoureido)ethyl)propanamide (**6**), a Michael addition of **13a** to methyl acrylate was performed, and led to the formation of **14a** via FSP synthesis. The fluorous-tagged 3-amino-β-carboline **13a** was immmobilized on the MR-FPS resin, and treated with 1 equiv of sodium ethoxide in 2 mL of THF for 1 h at room temperature, and then, it was reacted with an excess amount of methyl acrylate for 1 h. After completion of the reaction, the reaction mixture was diluted with a work-up solvent to re-immobilize the fluorous-tagged product on the surface of the MR-FPS resin, because compound **13a** was loosely bound on the surface of the MR-FPS resin (or partially released from its surface) during the reaction described above. As a work-up solvent, we selected three solvent systems that are generally used in FBS.[16] When 5 mL of 20% H_2O-DMF was used, the recovery of the product was only 31%, and 61% of product **14a** was lost in the filtrate (Table 3, entry 1). Although we increased both the volume of the 20% H_2O-DMF work-up solvent and the water content in DMF, the recovery of **14a** did not improve (Table 3, entries 2, 3, and 4). When aqueous acetonitrile was added, the product would not immobilize on the resin (entries 6, 7, and 8). Toluene (5 mL) as a nonpolar work-up solvent, however, led to a complete immobilization of **14a** on the MR-FPS resin (93%). The recovery of **14a** was unaffected by the use of increased amounts of toluene (entries 10 and 11). As a consequence of many trials, we decided that 5 mL of toluene was optimal as the work-up solvent (see Table 2, entry 2). After filtration of the reaction mixture, the fluorous-tagged product **14a** was recovered from the resin by washing with methanol. However, the yield of **14a** also was 93% when the reaction was performed without MR-FPS resin (Table 2, entry 1). The reactions of **13b** and **13c** gave **14b** and **14c** in 90, 90 and 78% yields, respectively (Table 2, entries 3–5).

Furthermore, treating compound **14a**, immobilized on MR-FPS resin, with excess amounts of ethylenediamine (EDA) under reflux for 3 days ensured the complete formation of amide **15a** in a high yield (84%; Table 2, entry 2). Although the excess amounts of EDA frequently disturbed the isolation of the product, **15a** was easily isolated from the reaction mixture in the FSP system. However, compound **14b** scarcely reacted with EDA—even in DMF and THF, which greatly swelled the resin (entry 3). Therefore, an excess amount of pyridine was added. As a result, the yield of **15b** was drastically improved (77% yield, entry 4), and the purity of compound **16**, obtained by the cleavage of the resin **15b**, was about 80%

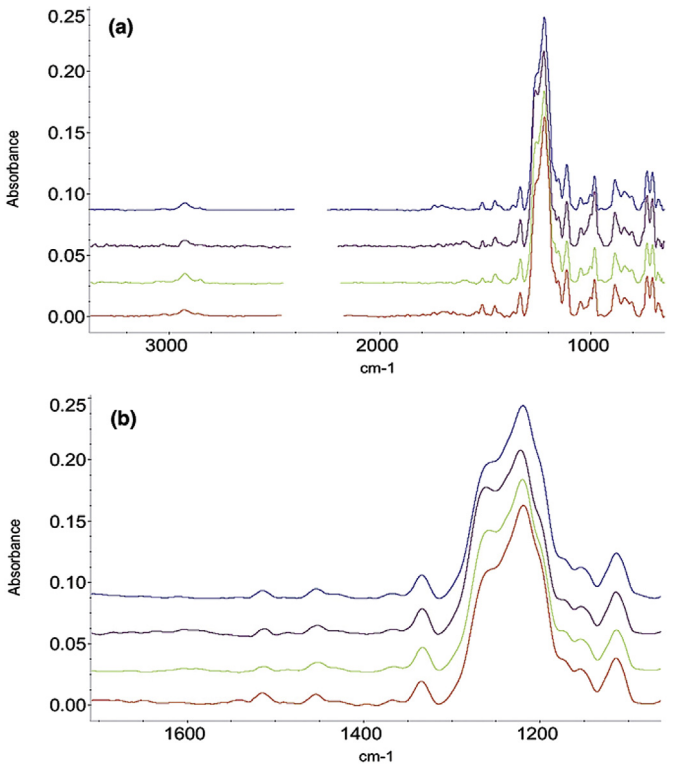


Fig. 4. Tolerance of FPS against bases and acid; micro-ATR-FTIR spectra of the FPS particles after treatment with bases or acid: FPS particles were treated with H_2O (blue line), 10 M NaOH (brown line), Et_3N (green line), 10 M H_2SO_4 (red line) at 80 °C for 1 week with shaking under atmosphere. No changes in absorbance were observed. (a) Whole range of micro ATR-FTIR spectra of the samples and (b) offset spectra of the 1100–1700 cm^{-1} range.

(see Suporting Information). Pyridine may act as a catalyst that activates the carbonyl carbon atom or a solvent and causes the resin to swell.

The formations of **13b**, **14b**, and **15b** were monitored by both increasing and decreasing the absorption bands for N–H stretching (3407 cm^{-1}), the >C=O stretching of the ester group (1737 cm^{-1}), and the >C=O stretching of the amide group (1660 cm^{-1}) in the microscopic ATR spectrum of the corresponding loaded resins (see Supplementary data).

Generally, a trityl group is cleaved using trifluoroacetic acid (TFA) in dichloromethane. If the fluorous trityl group is cleaved at the final stage in the FSP synthesis of 3-(3-amino-9*H*-pyrido[3,4-*b*]indol-9-yl)-*N*-(2-(3-methyl-3-nitrosoureido)ethyl)propanamide (**6**), the *N*-methyl-*N*-nitrosourea group must decompose.[17] For this reason, we decided to synthesize **6** from the free amine derivative **16** via a liquid-phase reaction rather than a FSP reaction. Based on this decision, compounds **13a**–**c** were treated with 10% (or 50%) trifluoroacetic acid to obtain **16** in 84, 84, 77, and 54% yields, respectively (Table 2, entries 1–4). Fluorous trityl alcohol **11** was recovered by immobilization on the MR-FPS resin, and it was available for re-use after chlorination with acetyl chloride. When compound **16** was treated with *p*-nitrophenyl *N*-methyl-*N*-nitrosocarbamate (**17**) in the presence of DIPEA in methanol at room temperature for 2 h, we succeeded in synthesizing the objective compound **6** in a 79% yield, as shown in Scheme 3.

2.4. Application of the fluorous solid-phase (FSP) system to synthesize 3-amino-9-benzyl-β-carboline derivatives (19)

In order to demonstrate the generality of the FSP synthesis, we applied it to the synthesis of 5 kinds of 3-amino-9-benzyl-β-carboline derivatives **19a**–**e** (Table 4). First, the reaction of 3-(^{F}Tr-amino)-β-carboline (**15a**) immobilized on the MR-FPS resin with benzyl bromide (**18a**) was performed in the presence of sodium ethoxide in THF at room temperature for 3 days. After completion of the reaction, a work-up solvent (toluene) was added to the reaction mixture to re-immobilize the fluorous-tagged product on the resin, and then the resin was separated by filtration followed by rinsing with methanol to obtaine **19a** in a 75% yield. The electron-withdrawing groups (F and CF_3) at the *para* position of benzyl bromide enhanced the yields of the corresponding products **19b** and **19c** (93 and 90%, respectively), while the electron-donating groups (CH_3 and OCH_3) had no affect on the yields of the products **19d** and **19e** (72 and 74%, respectively). The protecting group ^{F}Tr could be removed by treatment with trifluoroacetic acid, as described above.

2.5. Characteristcs of FSP and comparisons with solid and liquid phases

Finally, we compared FSP (or the MR-FPS resin) with solid-phase, liquid-phase, and fluorous-silica gels in order to highlight the usefulness of the FSP reaction field. The characteristics of each reaction field (or materials) are shown in Table 5. FSP (or the MR-FPS resin) exhibited excellent characteristics such as high reactivity, easy monitoring of the reaction, easy separation of the intermediates and products, excellent recyclability of the fluorous catalyst, easy application to the sequential reactions, and high tolerance to strong bases and acids. Specifically, the reactivity of the substrate (or the reactant) in FSP was very high unlike that in the solid phase, and the FSP reaction was similar in reactivity to that of the liquid-phase reaction. In the solid-phase reaction, the solvent was limited to polar aprotic solvents such as pyridine, THF and DMF in order to swell the resin, whereas various kinds of solvents were applicable in the FSP reaction when using a nonpolar solvent as a work-up solvent. In the FSP reaction, the fluorous-tagged catalyst and substrate were loosely bound on the surface of an MR-type resin, or were partially released from it, whereas they were covalently bonded onto the surface of a resin in the solid-phase reaction. This is why the reaction of the former was faster than that of the latter. In addition, the progress of the reaction could be monitored by conventional methods such as TLC, NMR, and UV in the FSP reactions similar to the liquid-phase reaction. This was different from the solid-phase reaction, in which the product was cleaved from the resin at the corresponding step for quantitative analysis. In the FSP reaction, the products including the intermediates were easily separated from the reaction mixture by only the addition of the work-up solvent followed by filtration, as with the solid-phase reaction. The MR-FPS resin exhibited high chemical tolerance against strong bases and acids such as sodium hydroxide, sodium ethoxide, triethylamine, trifluoroacetic acid, and sulfuric acid. However, the fluorous silica gel was easily decomposed with strong bases. This is why the fluorous catalyst that was immobilized on the surface of the MR-FPS resin could be used repetedly in the same reaction, and it is also why the MR-FPS resin was able to be used like a resin in sequential solid-phase reactions.

3. Conclusions

In conclusion, we succeeded in developing a new type of fluorous polystyrene (FPS) for use as a fluorous reaction field, via the suspension co-polymerization of 1-(3,3,4,4,5,5,5-heptafluoro-2,2-bis(trifluoromethyl)-pentyl)-4-vinylbenzene (**3**) with divinylbenzene as a cross-linking agent. SEM analysis revealed the FPS resin to be that of a macroreticular type. As far as we could ascertain, there is no report on the support of fluorous catalysts, with the exception of PFO-SiO_2[6] and Teflon tape.[9] The MR-FPS resin reported in this

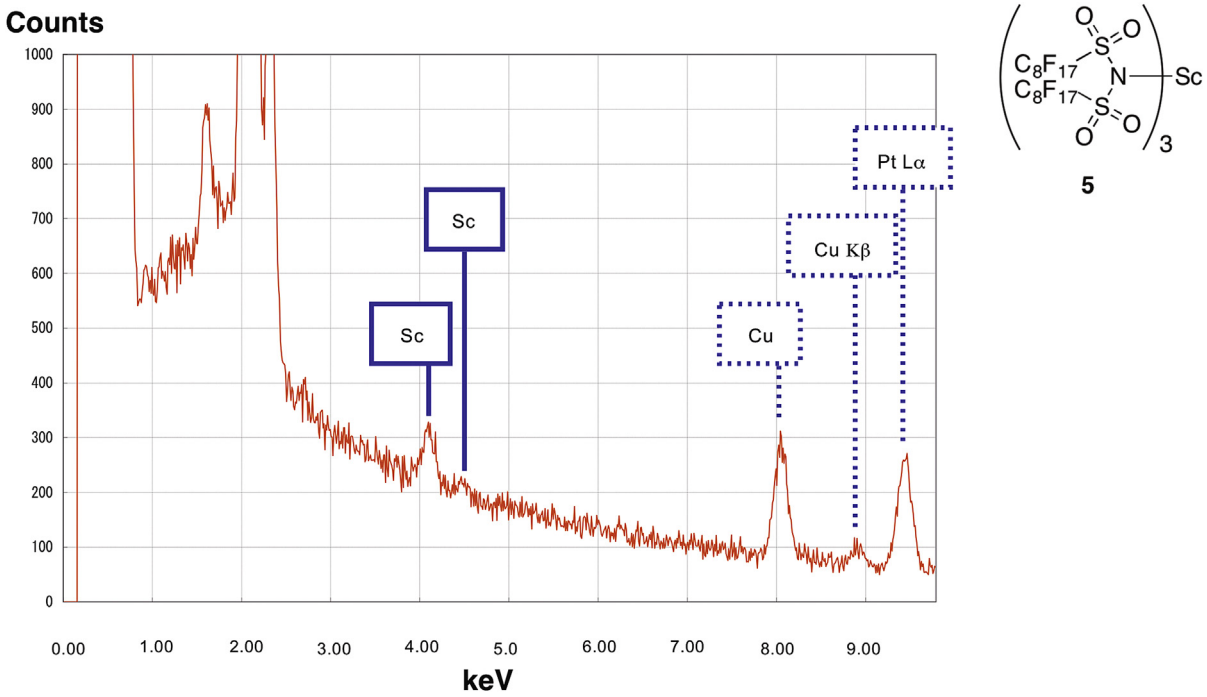


Fig. 5. SEM-EDX of the **5**/MR-FPS particles: FPS particles were coated with a vacuum-deposited platinum film and set on a cupper stage. SEM was operated at the following conditions; electron accelerating voltage: 15.0 kV, multiplying factor: ×350, sweeps: 101 times.

paper is the first example of using a fluorous resin as a support for fluorous catalysts in FBS and in the FSP synthesis, which was newly advocated in this paper. This resin showed excellent chemical resistance to acids and bases. Furthermore, EDX mapping showed that the fluorous Lewis acid supported on MR-FPS was homogeneously dispersed. This new fluorous reaction field using MR-FPS was applied to the synthesis of β-carboline derivatives using a fluorous tag. The products immobilized on the MR-FPS resin were easily recovered from the reaction mixture by filtration after completion of the reaction. Because the MR-FPS resin showed strong chemical tolerance against bases and acids such as sodium hydroxide, sodium ethoxide, trifluoroacetic acid and sulfuric acid, it was applicable to sequential reactions **13** to **16** without isolation of the intermediates. Furthermore, the MR-FPS resin allowed for an effective novel reaction field, which had the advantages of liquid- (high reactivity) and solid-phase reactions (easy separation), which was due to both the loose binding nature of a fluorous tag on the surface of the FPS resin as well as to its porosity and a high chemical tolerance to bases and acids.

4. Experimental section

4.1. Materials and methods

All organic solvents purchased from TCI were dried and distilled prior to use. All reagents were commercially available (TCI) and used without further purification unless otherwise noted. Reaction progress and compound purity were monitored using thin-layer chromatography (TLC) with hexane–ethyl acetate as the irrigating system and UV light at shorter wavelengths as the visualizer. Column chromatography was performed using Silica gel 60 (Merck), NH Silica (Fujigel) and ODS (YMC). 2-Chlorotrityl chloride resin (100–200 mesh, 1% divinylbenzene, 1.3 mmol/g) was purchased from Merck. Scandium(III) salt **5** of bis(perfluorooctanesulfonyl)imide,[10,13] 3-amino-β-carboline derivertive **12**[11b–d] and *p*-nitrophenyl *N*-methylcarbamate (**17**)[18] were prepared according to previously reported procedures. All reactions were carried out under N_2 atmosphere, unless otherwise noted. Solid-phase synthesis was performed with EYELA Solid Organic Synthesizer CCA-150M equipped with a polypropylene reaction vessel and CCS-150M equipped with a glass reaction vessel. Melting points were determined using a Yanaco micro-melting-point apparatus and uncorrected values were reported. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using a JEOL JNM ECP-500 (500, 125 and 470 MHz for ^{1}H, ^{13}C, and ^{19}F, respectively) and a JEOL JNM ECP 300 (300 and 75 MHz for ^{1}H and ^{13}C, respectively). The ^{1}H, ^{13}C chemical shifts were referenced to TMS or dimethyl silapentanesulfonate (δ=0.00) using the solvent residual peak as a reference and *J* values are reported in Hertz. The ^{19}F chemical shift was referenced to $CFCl_3$. Mass spectra (LRMS and HRMS) were recorded on a JEOL JMS-MS 700 mass spectrometer using NBA (3-nitrobenzyl alcohol), glycerol, and diethanolamine as a matrix and xenon (6 kV, 10 mA) as the fast atom bombardment (FAB) gas, or a JEOL JMS-T100CS mass spectrometer at ESI mode. Attenuated total reflection (ATR) FTIR was measured on Thermo Nicolet Continum Microscope IR. HPLC was performed on CTO-10AVP (Shimadzu) using a Develosil ODS-5 column (Nomura) eluting with a 20% MeOH in water containing 20 mM CH_3COONH_4 as buffer over 20 min at 0.5 mL/min. SEM and SEM-EDX were determined on a JEOL JSM-6500F and were operated at the following conditions for the sample coated with a vacuum-deposited platinum film (thickness: 26.5 nm) and set on a cupper stage; electron accelerating voltage: 15.0 kV, multiplying factor: ×350, sweeps: 101 times.

4.2. Synthesis

*4.2.1. Synthesis of 1-(3,3,4,4,5,5,5-heptafluoro-2,2-bis(trifluoromethyl)pentyl)-4-vinylbenzene (**3**).* Perfluoro(2-methyl-2-pentene) (**2**) (16.8 g), potassium fluoride (spray dried) (2.40 g), potassium iodide (0.36 g), 18-crown-6 (0.15 g), *p*-Chloromethylstyrene (5.17 g), and DMA (13 mL) were placed in a 50 mL reaction flask under argon, and heated at 60 °C for 24 h with stirring. The reaction mixture was poured into ether, and washed with portions of water. After the organic phase was separated, dried over

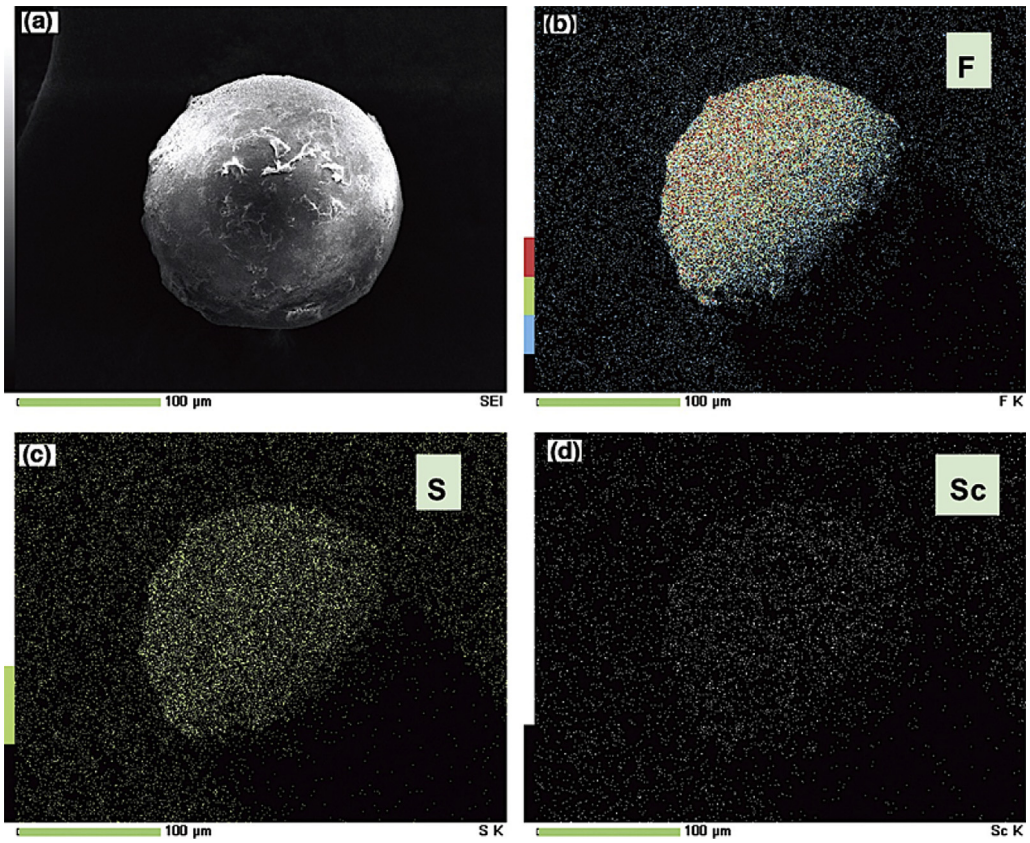
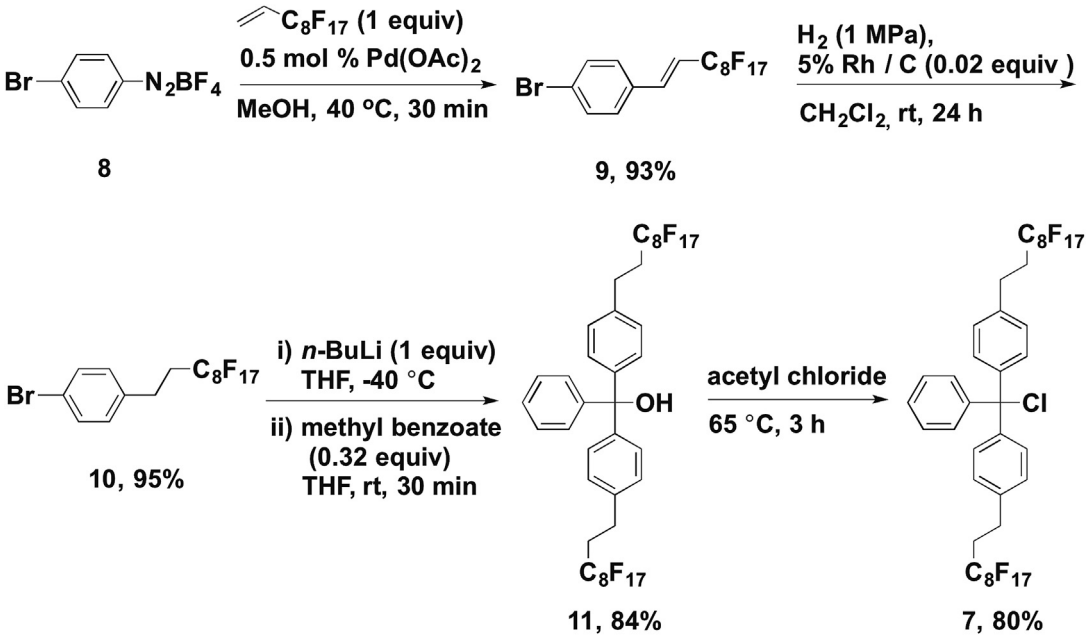
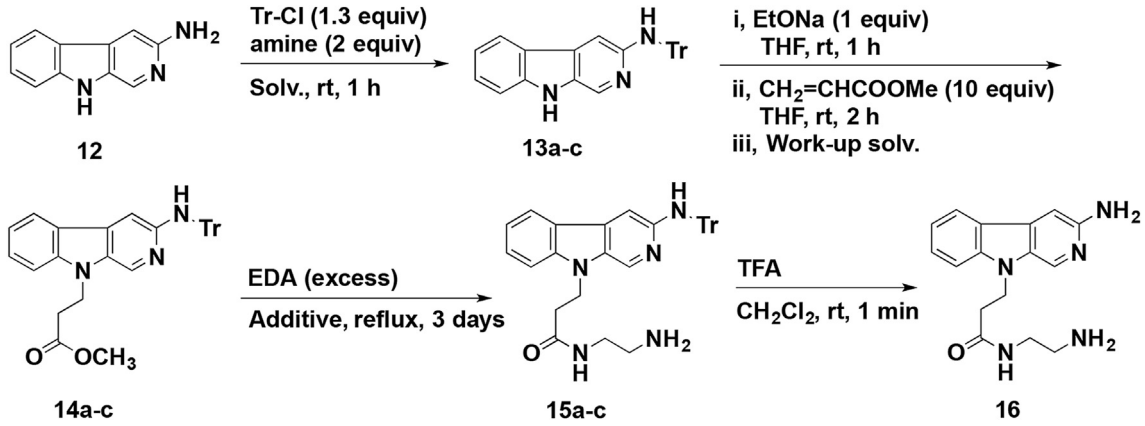


Fig. 6. SEM images and SEM-EDX mappings of the **5**/MR-FPS particle: MR-FPS particle was coated with a vacuum-deposited platinum film and set on a cupper stage. (a) SEM image of **5**/MR-FPS particle, (b) SEM-EDX map of the **5**/MR-FPS particle by the F element, (c) SEM-EDX map of the **5**/MR-FPS particle by the S element, (d) SEM-EDX map of the **5**/MR-FPS particle by the Sc element. SEM was operated at the following conditions; electron accelerating voltage: 15.0 kV, multiplying factor: ×350, sweeps: 101 times.



Scheme 2. Synthesis of fluorous trityl chloride **7**.

Table 2
Synthesis of 3-(3-amino-9*H*-pyrido[3,4-*b*]indol-9-yl)-*N*-(2-aminoethyl)propanamide (**16**)



Entry	Method[a]	Reaction from **12** to **13a–c**				**13a–c** to **14a–c**		**14a–c** to **15a–c**		**15a–c** to **16**	
		Amine	Solv.	Tr[b]	Yield/%	Work-up solv.	Yield/%	Additive	Yield/%	TFA	Yield/%
1	LP	DIPEA	THF	^{F}Tr	**13a**:98	None	**14a**:93	None	**15a**:90	10%	84
2	FSP	DIPEA	THF	^{F}Tr	**13a**:98[c]	Toluene[d]	**14a**:93[e]	None	**15a**:84[e]	10%	84
3	SP	None	DMF	Tr(Cl)-resin	**13b**:99[f,g]	None	**14b**:90[f,h,i]	None	**15b**:0	—	—
4	SP	None	DMF	Tr(Cl)-resin	**13b**:99[f,g]	None	**14b**:90[f,h,i]	Py[j]	**15b**:77[f,k,l]	50%	77[m]
5	LP	None	DMF	Tr(Cl)	**13c**:82	None	**14c**:78[n]	None	**15c**:85	10%	54

[a] LP: Liquid Phase reaction, FSP: Fluorous-Solid Phase reaction using MR-FPS (macroreticular-type fluorous polystyrene), SP: Solid Phase reaction.
[b] ^{F}Tr: Fluorous trityl group generated from **7**, Tr(Cl)-resin: *o*-Chlorotrityl group on the resin, Tr(Cl): *o*-Chlorotrityl group.
[c] The reaction without MR-FPS resin.
[d] The optimization of the work-up solvent is shown in Table 3.
[e] The MR-FPS resin immobilized with the product was rinsed with MeOH to recover the product.
[f] The yield was determined by cleavage of the loaded resin.
[g] An absorption band of the N–H stretching appeared at 3407 cm^{-1} in the microscope ATR spectrum of the loaded resin **13b**.
[h] Excess amounts of EtONa (5 equiv) were used.
[i] An absorption band for the >C=O stretching of the ester group appeared at 1737 cm^{-1} in the microscope ATR spectrum of the loaded resin **14b**.
[j] Thirty-six equivalent of pyridine was added.
[k] Reaction time: 4 days.
[l] An absorption band for the >C=O stretching of the amide group appeared at 1660 cm^{-1} in stead of the ester absorption band at 1737 cm^{-1} in the microscope ATR spectrum of the loaded resin **15b**.
[m] Reaction time: 1 h.
[n] The mixture of **13c** and EtONa was stirred for 20 min in THF at rt.

magnesium sulfate, and the solvent evaporated, the desired crude product was purified by silica gel column chromatography (hexane) to afford the monomer **3** (13.3 g, 90% yield) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 2H), 5.27 (dd, J=11.0 Hz, J=1.0 Hz, 1H), 5.75 (dd, J=17.0 Hz, J=1.0 Hz, 1H), 6.68 (dd, J=17.0 Hz, J=11.0 Hz, 1H), 7.24 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.4, 114.6, 116.0, 118.7, 120.9, 123.2, 126.0, 130.3, 131.7, 136.1, 137.4; ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −62.2, −80.0, −105.9, −122.8; MS (FAB^+) *m*/*z* 436 (M^+).

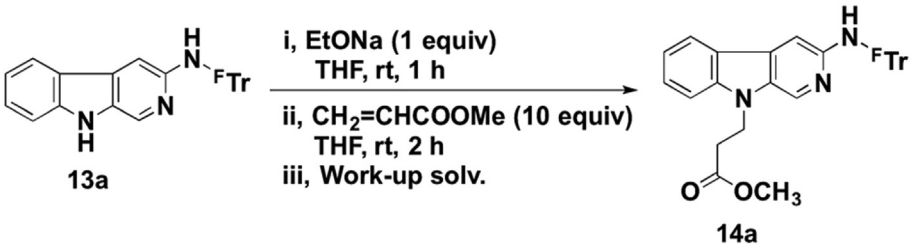
4.2.2. Suspension copolymerization of styrene. To a reaction vessel containing AIBN were added diluents, divinylbenzene and styrene, and then the mixture was stirred with a stirring rod at 1000 rpm until AIBN was dissolved at rt. An aq solution of 0.6% PVA was added to the vessel and stirred. The suspension was heated slowly to 90 °C for 4 h (to 60 °C during 1 h, held for 1 h at 60 °C, to 90 °C during 1 h, and then held 1 h at 90 °C), and finally held at 90 °C for 24 h with slowly stirring at 400 rpm. The obtained resin was filtered, successively washed with boiling water (10×5 mL), water (2×5 mL), acetone (5×5 mL), benzene (2×5 mL), and dried in vacuum. The results were summarized in Table 1 (entries 1–3) with reaction conditions.

*4.2.3. Suspension copolymerization of 1-(3,3,4,4,5,5,5-heptafluoro-2,2-bis(trifluoromethyl)pentyl)-4-vinylbenzene (**3**).* To a test tube (Φ=18 mm) containing AIBN were added diluents, divinylbenzene and fluorous styrene **3**, and then the mixture was stirred with the stirring rod at 1600 rpm until AIBN was dissolved at rt. An aq solution of 0.6% PVA was added to the test tube and stirred. The suspension was heated slowly to 90 °C for 4 h (to 60 °C during 1 h, held for 1 h at 60 °C, to 90 °C during 1 h, and then held 1 h at 90 °C), and finally held at 90 °C for 24 h with slowly stirring at 400 rpm. The obtained resin (MR-FPS) was filtered, successively washed with boiling water (10×5 mL), water (2×5 mL), acetone (5×5 mL), benzene (2×5 mL), and dried in vacuum. The results were summarized in Table 1 (entries 4–7) with reaction conditions.

*4.2.4. Procedure for the synthesis of FPS-supported Lewis acid **5**/MR-FPF.* To a solution of fluorous Lewis acid **5** (200 mg) in ethanol (10 mL), the MR-FPS resin (d=250–180 μm, 630 mg) was added and the resulting mixture was stirred for 1 h at rt. After removal of the solvent under reduced pressure, residual **5**/MR-FPS resin was dried in vaccuo at 80 °C for 6 h.

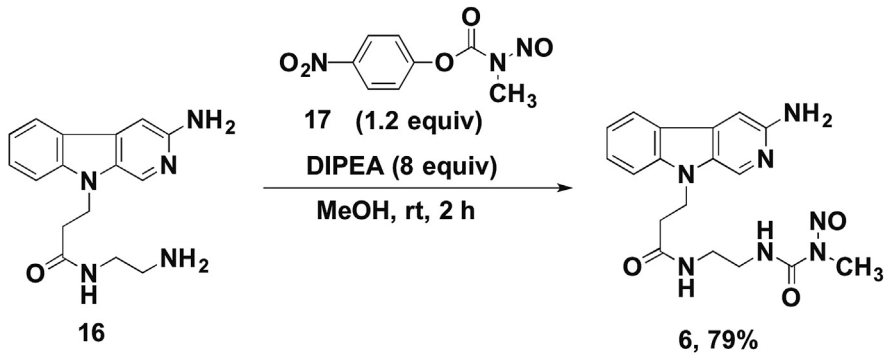
*4.2.5. Procedure for the synthesis of 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecen-1-yl)benzene (**9**).* To a stirred suspension of 4-bromobenzenediazonium tetrafluoroborate (**8**) (5.0 g, 18.4 mmol) and $Pd(OAc)_2$ (20.7 mg, 0.0923 mmol) in MeOH (18.5 mL) was added 1*H*,1*H*,2*H*-perfluorodecene (8.23 g, 18.5 mmol) under argon. The mixture was

Table 3
Optimization of work-up solvents in the fluorous-solid phase (FSP) synthesis of **14a** using the fluorous MR-type polystyrene resin (MR-FPS)[a]



Entry	Work-up solv.	Added volume/mL	**14a** in the filtrate/%	**14a** on MR-FPS/%
1	20% H_2O-DMF	5	61	31
2	20% H_2O-DMF	10	46	45
3	20% H_2O-DMF	15	45	46
4	30% H_2O-DMF	5	45	46
5	20% H_2O–MeCN	5	93	0
6	20% H_2O–MeCN	10	92	0
7	20% H_2O–MeCN	15	93	0
8	30% H_2O–MeCN	5	93	0
9	Toluene	5	Trace	93
10	Toluene	10	Trace	91
11	Toluene	15	Trace	92

[a] The mixture of **13a** (0.020 mmol) immobilized on the MR-FPS (500 mg) and sodium ethoxide (10 mg, 0.14 mmol) was shaken in THF (2 mL) for 1 h at rt, and then methyl acrylate (0.13 mL; 1.4 mmol) was added drop by drop. After the completion of the reaction, the work-up solvent was added to the reaction mixture and shaken for 30 min at rt to immobilize the fluorous-tagged product **14a** on the MR-FPS resin.



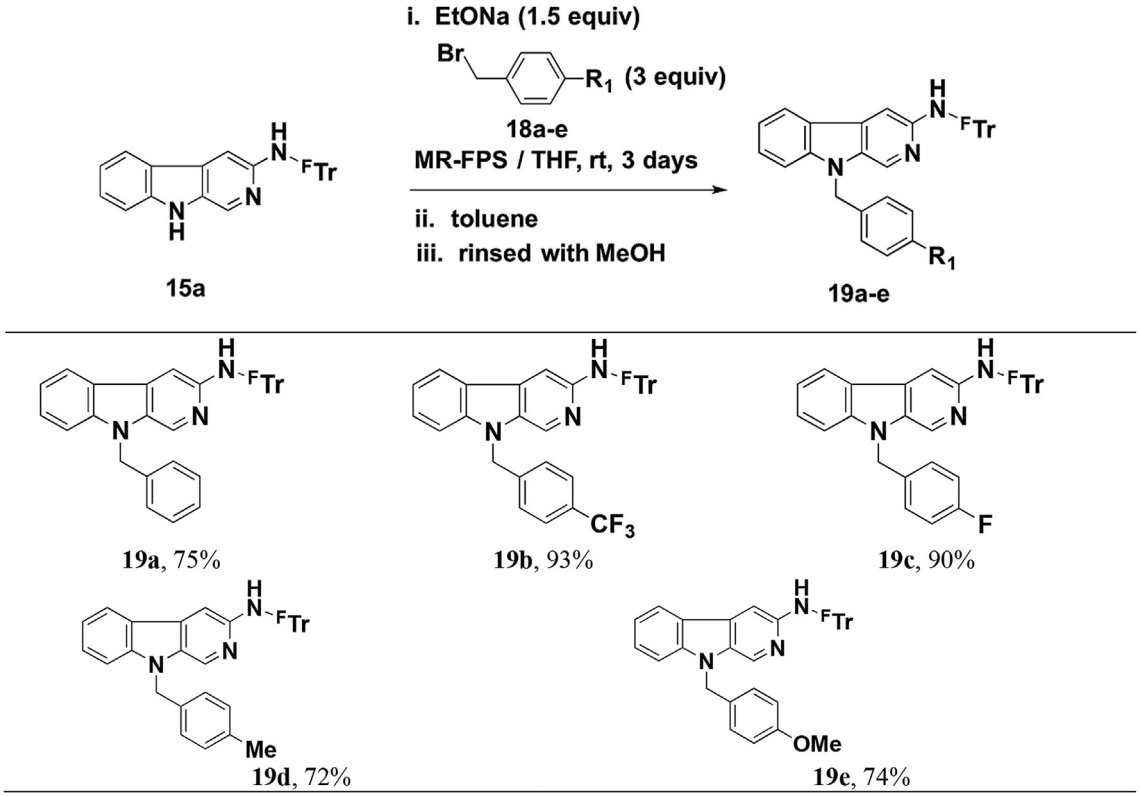
Scheme 3. Synthesis of 3-(3-amino-9*H*-pyrido[3,4-*b*]indol-9-yl)-*N*-(2-(3-methyl-3-nitrosoureido)ethyl)propanamide (**6**).

heated at 40 °C until gas evolution ceased. The resulting mixture was stirred for additional 10 min and MeOH was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluted with hexane) afforded **9** (10 g, 93% yield) as a white solid: mp 42.6–43.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (m, 1H), 2.87 (m, 1H), 7.09 (m, 2H), 7.43 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 26.0, 32.6, 115.0, 115.1, 115.3, 120.6, 124.5, 129.1, 130.0, 132.0, 132.2, 132.5, 138.1, 138.5, 138.56, 138.64; ^{9}F NMR ($CDCl_3$, 470 MHz) δ −126.7 (s, 2 F), −123.5 (s, 2 F), −122.7 (s, 2 F), −121.9 (s, 4 F), −121.7 (s, 2 F), −114.7 (s, 2 F), −80.8 (s, 3 F); MS (FAB) *m*/*z* 601 $[M+H]^+$; HRMS (FAB) found 600.9490 $[M+H]^+$ calcd for $C_{16}H_7^{79}BrF_{17}^+$ 600.9454.

*4.2.6. Procedure for the synthesis of 1-bromo-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)benzene (**10**).* A suspension of **9** (9.1 g, 15.1 mmol) and 5% Rh/C (626 mg, 0.34 mol) in a degassed dichloromethane (61 mL) was placed under 1.0 MPa of H_2 and stirred at room temperature for 24 h. At the end of the reaction, the mixture was filtered and evaporated. The residue was purified by silica gel column chromatography (hexane) and the solvent was removed under reduced pressure to afford **10** (8.7 g, 95% yield) as a white solid; mp 49.6–50.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (m, 2H), 2.87 (m, 2H), 7.08 (m, 2H), 7.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 32.6, 32.8, 32.9, 120.6, 130.0, 131.9, 138.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −126.1 (s, 2 F), −123.5 (s, 2 F), −122.7 (s, 2 F), −121.9 (s, 4 F), −121.6 (s, 2 F), −114.6 (s, 2 F), −80.8 (s, 3 F); MS (FAB) *m*/*z* 602 $[M]^+$; HRMS (FAB) found 601.9532 $[M]^+$ calcd for $C_{16}H_8^{79}BrF_{17}^+$ 601.9538.

*4.2.7. Procedure for the synthesis of 4,4′-bis((1H,1H,2H,2H)-perfluorodecyl)trityl alcohol (**11**).* To a cooled (−40 °C) mixture of compound **10** (1.0 g, 1.66 mmol) in anhydrous THF (10 mL) was added dropwise *n*-BuLi (1.2 mL, 1.59 M in hexane, 1.99 mmol) keeping the internal temperature below −40 °C. The solution, turned a yellow-green color, was stirred for 5 min. Methyl benzoate (66 μL, 0.53 mmol) was added dropwise at −40 °C and the mixture was stirred at room temperature for 30 min. The mixture was quenched with water (excess), and then stirred for 1 h. The organic layer was collected and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane–ether=100:1) to afford **11** (1.6 g, 84% yield) as a white liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (m, 4H), 2.76 (s, 1H), 2.89 (m, 4H), 7.30 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 32.9, 81.7, 127.4, 127.8, 127.9, 128.0, 128.3, 138.2, 145.4, 146.8; ^{19}F NMR ($CDCl_3$,

Table 4
Synthesis of 3-amino-9-benzyl-β-carboline derivatives **19a**–**e**[a]



[a] FTr is a fluorous trityl group generated from **7**.

Table 5
Comparison of FSP (or the MR-FPS resin) with solid-phase, liquid-phase, and fluorous silica gels

No	Function	Fluorous-solid phase (FSP) or MR-FPS resin	Solid-phase	Liquid-phase	Fluorous SiO_2
1	Reactivity	High (rapid reaction)	Low (needs long time)	High (rapid reaction)	
2	Solvent	Not limited	Limited	Not limited	
3	Association state	Loosely bound on or partially released from the resin surface	Covalently bonded	Dissolved	
3	Reaction Monitoring	Easy: direct analysis with TLC, NMR etc.	Not easy	Easy: direct analysis with TLC, NMR etc.	
4	Separation of the product	Easy: addition of work-up solvent followed by filtration	Easy: filtration	Not easy: requires time and effort (Distillation, recrystallization, chromatography)	
5	Application	Repetitive use of fluorous catalyst, sequential reactions, solid extraction	Sequential reactions	Widely used	Solid extraction
6	Chemical tolerance	High tolerance against NaOH, NaOEt, $N(Et)_3$, TFA, H_2SO_4			Decomposed by NaOH
7	Recyclability	High			Difficult

470 MHz) δ −126.1 (s, 4 F), −123.4 (s, 4 F), −122.7 (s, 4 F), −121.9 (s, 8 F), −121.6 (s, 4 F), −114.6 (s, 4 F), −80.8 (s, 6 F); MS (FAB) *m*/*z* 1135 $[M-OH]^+$; HRMS (ESI^+) found 1175.10046 $[M+Na]^+$ calcd for $C_{39}H_{22}F_{34}NaO^+$1175.10254.

*4.2.8. Procedure for the synthesis of 4,4′-bis((1H,1H,2H,2H)-perfluorodecyl)trityl chloride (**7**).* A solution of **11** (200 mg, 0.17 mmol) in acetyl chloride (0.67 mL) was stirred at 65 °C for 3 h. After the reaction, the solution was evaporated under reduced pressure. The crude product was purified by recrystallization from acetyl chloride/MeCN afforded **7** (159 mg, 80% yield) as a white solid; mp 134.0–135.7 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 2.32 (m, 4H), 2.86 (m, 4H), 7.1–7.2 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 32.8, 112.3, 127.7, 127.8, 127.9, 128.3, 129.6, 130.1, 138.8, 143.8; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −126.6 (s, 4 F), −124.0 (s, 4 F), −123.2 (s, 4 F), −122.4 (s, 8 F), −122.2 (s, 4 F), −115.1 (s, 4 F), −81.3 (s, 6 F); MS (FAB) *m*/*z* 1135 $[M-Cl]^+$.

*4.2.9. Fluorous liquid-phase synthesis of β-carboline derivatives **13**–**16***

*4.2.9.1. Procedure for the synthesis of 3-(4,4′-(4-(1H,1H,2H,2H)-perfluorodecyl)trity)amino-β-carboline (**13a**).* Compound **7** (410 mg, 0.35 mmol) was added to a solution of **12** (50 mg, 0.27 mmol) in THF (15 mL). The mixture was stirred for 1 h at room temperature

and MeOH was added to quench the reaction. The mixture was extracted with ether and dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt=4/1) afforded **13a** (349 mg, 98% yield) as a yellow solid; mp 92.6–93.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (m, 4H), 2.84 (m, 4H), 6.00 (s, 1H), 6.41 (s, 1H) 7.37 (m, 16H), 7.62 (s, 1H), 7.931 (s, 1H), 8.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 32.6, 70.7, 99.2, 111.2, 119.1, 121.5, 126.9, 127.8, 128.3, 129.1, 130.4, 131.4, 137.6, 141.6, 143.9, 145.2, 151.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ-126.7 (s, 4 F), −123.9 (s, 4 F), −123.2 (s, 4 F), −122.4 (s, 8 F), −122.2 (s, 4 F), −115.1 (s, 4 F), −81.4 (s, 6 F); MS (FAB) *m*/*z* 1318 $[M+H]^+$; HRMS (ESI^+) found 1318.18723 $[M+H]^+$ calcd for $C_{50}H_{30}F_{34}N_3^+$1318.18913.

*4.2.9.2. Procedure for the synthesis of methyl 3-(3-(4,4′-(4-(1H,1H,2H,2H)-perfluorodecyl)trityl)amino-9H-pyrido[3,4-b]indol-9-yl)propanoate (**14a**).* Sodium ethoxide (18 mg, 0.26 mmol) was added to a solution of **13a** (340 mg, 0.26 mmol) in THF (10 mL). The mixture was stirred for 20 min at rt and methyl acrylate (0.24 mL, 2.6 mmol) was added dropwise. The mixture was stirred for 2 h at room temperature. After the reaction, the solution was evaporated under reduced pressure. The residue was extracted with ethyl acetate and dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt=3/2) afforded **14a** (339 mg, 93% yield) as a yellow solid; mp 102.9–103.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2–2.4 (m, 4H), 2.7–2.9 (m, 4H), 3.42 (t, *J*=6.6 Hz, 2H), 3.57 (s, 3H), 4.42 (m, 2H), 6.47 (s, 1H), 7.10 (m, 5H), 7.15–7.38 (m, 10H), 7.50 (d, *J*=7.5 Hz, 1H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 33.4, 51.7, 51.9, 70.0, 99.1, 110.3, 118.4, 121.3, 121.7, 125.2, 126.2, 127.8, 127.9, 128.4, 129.1, 137.6, 141.7, 143.8, 145.2, 151.0, 171.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −126.7 (s, 4 F), −123.9 (s, 4 F), −123.2 (s, 4 F), −122.4 (s, 8 F), −122.2 (s, 4 F), −115.1 (s, 4 F), −81.4 (s, 6 F); MS (FAB) *m*/*z* 1404 $[M+H]^+$.

*4.2.9.3. Procedure for the synthesis of 3-(3-(4,4′-(4-(1H,1H,2H,2H)-perfluorodecyl)trityl)amino-9H-pyrido[3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide (**15a**).* A solution of **14a** (330 mg, 0.24 mmol) in ethylenediamine (11 mL, excess) was stirred under reflux for 3 days. After the reaction, the solution was evaporated under reduced pressure. The crude product was purified by column chromatography on NH silica gel (AcOEt/MeOH=9/1) afforded **15a** (309 mg, 90% yield) as a yellow solid; mp 89.4–90.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (m, 4H), 2.59 (t, *J*=7.5 Hz, 2H), 2.83 (m, 4H), 2.88 (t, *J*=6.6 Hz, 2H), 3.16 (t, *J*=7.5 Hz, 2H), 4.50 (t, *J*=6.6 Hz, 2H), 7.36 (m, 16H), 7.62 (s, 1H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 32.5, 36.4, 41.0, 50.6, 51.0, 69.8, 99.0, 110.1, 117.9, 120.7, 121.2, 124.9, 126.0, 127.2, 127.6, 128.0, 128.9, 137.1, 141.2, 143.2, 144.9, 150.5, 170.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.0 (4F), −123.4 (4F), −122.7 (4F), −121.8 (12F), −114.6 (4F), −80.7 (6F); MS (FAB) *m*/*z* 1432 $[M+H]^+$.

*4.2.9.4. Procedure for the synthesis of 3-(3-amino-9H-pyrido[3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide (**16**).* A solution of compound **15a** (300 mg, 0.21 mmol) in a mixture of dichloromethane and trifluoroacetic acid (5 mL of a 9:1 mixture) was stirred at room temperature for 1 min and then made alkaline with aqueous Na_2CO_3. The solution was extracted with $CHCl_3$ and the combined organic layer was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on ODS (water/MeOH=9/1) and NH silica gel (AcOEt/MeOH=3/2), to afford pure **16** (52 mg, 84% yield) as a yellow solid; mp 178.0–178.5 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 2.59 (t, *J*=6.5 Hz, 2H), 2.70 (t, *J*=6.5 Hz, 2H), 3.15 (t, *J*=6.5 Hz, 2H), 4.62 (t, *J*=6.5 Hz, 2H), 7.16 (t, *J*=7.5 Hz, 1H), 7.27 (s, 1H), 7.51 (m, 2H), 8.02 (d, *J*=7.5 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 36.4, 40.5, 40.7, 41.0, 99.6, 110.6, 120.1, 122.0, 123.0, 129.2, 130.0, 133.0, 134.3, 143.9, 153.6, 174.3; MS (FAB) *m*/*z* 298 $[M+H]^+$; HRMS (FAB) found 298.1671 $[M+H]^+$ calcd for $C_{16}H_{20}ON_5^+$298.1668.

*4.2.10. Fluorous solid-phase (FSP) synthesis of β-carboline derivatives **14a**, **15a**, and **16***

*4.2.10.1. Procedure for the synthesis of methyl 3-(3-(4,4′-(4-(1H,1H,2H,2H)-perfluorodecyl)trityl)amino-9H-pyrido[3,4-b]indol-9-yl)propanoate (**14a**).* To a suspension of MR-FPS-supported **13a** (500 mg, 0.020 mmol) in THF (2 mL), sodium ethoxide (10 mg, 0.14 mmol) was added. Then, the reaction mixture was shaken for 1 h at room temperature, and methyl acrylate (0.13 mL, 1.4 mmol) was added dropwise. After the reaction completed, toluene (5 mL) was added, and the mixture was shaken for 30 min at room temperature. The resin was filtrated and dried in vacuo. Methanol was added to the dry resin to extract the crude product. The filtrate was evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography on silica gel (hexane/AcOEt=3/2) to afford **14a** (26 mg, 93% yield).

*4.2.10.2. Procedure for the synthesis of 3-(3-(4,4′-(4-(1H,1H,2H,2H)-perfluorodecyl)trityl)amino-9H-pyrido[3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide (**15a**).* The MR-FPS-supported **14a** (500 mg, 0.019 mmol) was added to ethylenediamine (1.5 mL, excess), and the mixture was refluxed for 3 days. After the reaction completed, toluene (5 mL) was added to the mixture and shaken for 30 min at room temperature. The resin was filtrated and dried in vacuo. Methanol was added to the dry resin to extract the crude product. The filtrate was evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography on NH silica gel (AcOEt/MeOH=9/1) to afford **15a** (23 mg, 84% yield).

*4.2.10.3. Procedure for the synthesis of 3-(3-amino-9H-pyrido[3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide (**16**).* A solution of compound **15a** (20 mg, 0.014 mmol) in a mixture of CH_2Cl_2 and trifluoroacetic acid (5 mL of a 9:1 mixture) was stirred at room temperature for 1 min and then neutralized with aqueous Na_2CO_3. The solution was washed with $CHCl_3$ and the water layer was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on ODS silica gel (water/MeOH=10/1) and NH silica gel (AcOEt/MeOH=3/2), to afford pure **16** (4 mg, 84% yield).

*4.2.11. Solid-phase synthesis of β-carboline derivatives **13b**–**15b** and **16***

*4.2.11.1. Procedure for the synthesis of 3-amino-β-carboline loaded on 2-chlorotrityl resin at the 3-amino nitrogen atom **13b**.* 2-Chlorotrityl chloride resin (140 mg, 0.17 mmol; loading 1.3 mmol/g) was swollen in DMF (1.0 mL). Compound **12** (100 mg, 0.55 mmol) was added to the supension of the resin. After the reaction mixture was shaken for 1 h at room temperature, the resin was filtrated and successively washed with DMF (3×2 mL), THF (3×2 mL), $CHCl_3$ (3×2 mL) and MeOH (3×2 mL). And then, the resin was dried in vacuo. The corresponding loaded resin **13b** exhibited the IR absorption band at 3407 cm^{-1} for the NH streching.

*4.2.11.2. Procedure for the synthesis of methyl 3-(3-amino-9H-pyrido[3,4-b]indol-9-yl)propanoate loaded on 2-chlorotrityl resin at the 3-amino nitrogen atom **14b**.* Resin **13b**(140 mg, 0.17 mmol; loading 1.3 mmol/g) was swollen in THF (1.0 mL). Sodium ethoxide (58 mg, 0.85 mmol) was added to the suspension of the resin. After the reaction mixture was shaken for 1 h at room temperature, methyl acrylate (0.77 mL, 8.5 mmol) was added dropwise. When the reaction was completed, the resin was filtrated and successively

washed with DMF (3×2 mL), THF (3×2 mL), $CHCl_3$ (3×2 mL) and MeOH (3×2 mL). And then, the resin was dried in vacuo. The corresponding loaded resin **14b** exhibited the IR absorption band at 1737 cm^{-1} for the >C=O streching of the ester group.

*4.2.11.3. Procedure for the synthesis of 3-(3-amino-9H-pyrido [3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide loaded on 2-chlorotrityl resin at the 3-amino nitrogen atom **15b**.* To a solution of pyridine and ethylenediamine (2.5 mL of a 1:4 mixture) was added the resin **14b** (140 mg, 0.17 mmol; loading 1.3 mmol/g). The reaction mixture was reflux for 4 days. After the reaction completed, the resin was filtrated and successively washed with DMF (3×2 mL), THF (3×2 mL), $CHCl_3$ (3×2 mL) and MeOH (3×2 mL), and dried under reduced pressure. An absorption band for the >C=O stretching of the amide group appeared at 1660 cm^{-1} in stead of the ester absorption band at 1737 cm^{-1} in the microscope ATR spectrum of the corresponding loaded resin **15b**.

*4.2.11.4. Procedure for the synthesis of 3-(3-amino-9H-pyrido [3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide (**16**); cleavage of the resin **15b**.* The resin **15b** (140 mg, 0.17 mmol; loading 1.3 mmol/g) was swollen in CH_2Cl_2 (1 mL), and then trifluoroacetic acid (1 mL) was added to the suspension of the resin. After the reaction mixture was shaken for 1 h at room temperature, the resin was filtrated and successively washed with CH_2Cl_2 and MeOH. The filtrate was made alkaline with aqueous Na_2CO_3. The aqueous layer was extracted with $CHCl_3$, and the combined organic layer was evaporated under reduced pressure. The obtained crude product was purified by ODS (MeOH/H_2O=1/10) and NH silica gel column chromatography (AcOEt/MeOH=10/1) to afford pure **16** (39 mg, 77% yield).

*4.2.12. Liquid-phase synthesis of β-carboline derivatives **13c**–**15c** and **16***

*4.2.12.1. Procedure for the synthesis of 3-(2-chlorotrityl)amino-β-carboline (**13c**).* 2-Chlorotrityl chloride (50 mg, 0.21 mmol) was added to a solution of **12** in DMF (2.0 mL). The mixture was stirred for 1 h at room temperature and MeOH was added to quench the reaction. The mixture was extracted with $CHCl_3$ and dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt=4/1) to afforded **13c** (79 mg, 82% yield) as a yellow solid; mp 141.0–141.2 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (1H, s), 6.50 (s, 1H), 7.04 (t, *J*=7.0 Hz, 1H), 7.10–7.13 (m, 1H), 7.24 (m, 10H), 7.37 (t, *J*=7.0 Hz, 4H), 7.45 (d, *J*=7.5 Hz, 1H), 7.63 (d, *J*=8.0 Hz, 1H), 7.74 (d, *J*=8.0 Hz, 1H), 8.01 (s, 1H), 8.33 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 71.6, 98.7, 111.2, 118.9, 121.4, 121.5, 125.5, 126.7, 128.0, 128.4, 128.8, 130.6, 130.8, 131.0, 132.7, 133.0, 134.6, 140.0, 141.5, 144.7, 150.8; MS (FAB) *m/z* 459 $[M]^+$; HRMS (ESI^+) found 460.15548 $[M+H]^+$ calcd for $C_{30}H_{23}ClN_3^+$460.15805.

*4.2.12.2. Procedure for the synthesis of methyl 3-(3-(2-chlorotrityl)amino-9H-pyrido[3,4-b]indol-9-yl)propanoate (**14c**).* Sodium ethoxide (15 mg, 0.22 mmol) was added to a solution of **13c** (100 mg, 0.22 mmol) in THF (5 mL). The mixture was stirred for 20 min at room temperature and methyl acrylate (0.20 mL, 2.20 mmol) was added dropwise. The mixture was stirred for 2 h at room temperature. After the reaction completed, the solution was evaporated under reduced pressure. The residure was extracted with ethyl acetate and dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt=9/1) afforded **14c** (94 mg, 78% yield) as a yellow solid; mp 106.3–107.0 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 2.78 (t, *J*=7.0 Hz, 2H), 3.59 (s, 3H), 4.48 (t, *J*=7.0 Hz, 2H), 6.31 (s, 1H), 6.51 (s, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 7.11 (t, *J*=7.5 Hz, 1H), 7.22–7.18 (m, 10H), 7.45 (t, *J*=7.5 Hz, 5H), 7.62 (d, *J*=7.0 Hz, 1H), 7.74 (d, *J*=7.0 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.3, 38.8, 51.8, 71.5, 98.7, 108.9, 118.6, 121.2, 121.6, 125.5, 126.7, 127.97, 128.0, 128.4, 128.7, 128.80, 128.84, 130.6, 131.1, 132.0, 132.1, 132.96, 133.03, 134.5, 134.6, 140.0, 141.5, 144.6, 150.8, 171.5; MS (FAB) *m/z* 546 $[M+H]^+$; MS (ESI^+) found 546.19455 $[M+H]^+$ calcd for $C_{34}H_{29}ClN_3O_2^+$546.19483.

*4.2.12.3. Procedure for the synthesis of 3-(3-(2-chlorotrityl) amino-9H-pyrido[3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide (**15c**).* A solution of **14c** (60 mg, 0.11 mmol) in ethylenediamine (5.0 mL, excess) was stirred under reflux for 3 days. After the reaction completed, the solution was evaporated under reduced pressure. The crude product was purified by column chromatography on NH silica gel (AcOEt/MeOH=10/1) to afford **15c** (54 mg, 85% yield) as a yellow solid; mp 178.2–178.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 (t, 2H, *J*=7.0 Hz), 2.63 (t, 2H, *J*=7.5 Hz), 3.46 (t, 2H, *J*=7.0 Hz), 4.57 (t, 2H, *J*=7.5 Hz), 6.30 (s, 1H), 6.49 (s, 1H), 7.03 (t, 1H, *J*=6.5 Hz), 7.15 (t, 2H, *J*=6.5 Hz), 7.26 (m, 10H) 7.45 (m, 4H), 7.62 (d, 1H, *J*=6.5 Hz) 7.75 (d, 1H, *J*=6.5 Hz), 8.20 (s, 1H), 8.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.0, 39.7, 40.7, 41.9, 71.5, 98.6, 101.8, 109.7, 118.6, 121.0, 121.5, 125.6, 126.4, 128.0, 128.2, 128.4, 128.8, 129.1, 131.2, 132.1, 140.0, 141.7, 144.6, 150.9, 170.5; MS (FAB) *m/z* 573 $[M]^+$; HRMS (FAB) found 573.1804 $[M]^+$ calcd for $C_{35}H_{32}ClN_5O^+$573.1810.

*4.2.12.4. Procedure for the synthesis of 3-(3-amino-9H-pyrido [3,4-b]indol-9-yl)-N-(2-aminoethyl)propanamide (**16**).* A solution of compound **15c** (80 mg, 0.14 mmol) in a mixture of dichloromethane and trifluoroacetic acid (5 mL of a 9:1 mixture) was stirred at room temperature for 1 min and then made alkaline with aqueous Na_2CO_3. The solution was extracted with $CHCl_3$ and the organic layer was evaporated under reduced pressure. The crude product was purified by column chromatography on ODS (water/MeOH=10/1) and NH silica gel (AcOEt/MeOH=10/1) to afford **16** (22 mg, 54% yield) as a yellow solid.

*4.2.13. Procedure for the synthesis of 3-(3-amino-9H-pyrido[3,4-b] indol-9-yl)-N-(2-(3-methyl-3-nitrosoureido)ethyl)propanamide (**6**).* A solution of compound **16** (50.3 mg, 0.17 mmol), *p*-nitrophenyl-*N*-methyl-*N*-nitrosocarbamate (**17**) (47 mg, 0.21 mmol) and *N*,*N*-diidopropylethylamine (0.25 mL, 1.30 mmol) in MeOH was stirred at rt for 2 h, and then evaporated under reduced pressure. The residue was solved in MeOH (18.0 mL) and poured on Amberlist A-21. After agitating for 5 min, the mixture was filtered. Then the filtrate was evaporated under reduced pressure to give the crude product, which was purified by column chromatography on NH silica (AcOEt/MeOH=1/1) to afford **6** (63 mg, 79% yield) as a yellow solid; mp 271.1–272.4 °C. ^1H NMR (D_2O, 500 MHz) δ 2.64 (t, *J*=6.5 Hz, 2H), 2.97 (s, 3H), 3.19 (m, 4H), 4.54 (t, *J*=6.5 Hz, 2H), 7.20 (t, *J*=8.0 Hz, 1H), 7.47 (s, 1H), 7.50 (d, *J*=8.0 Hz 1H), 7.64 (t, *J*=8.0 Hz, 1H), 8.07 (d, *J*=8.0 Hz, 1H), 8.26 (s, 1H); MS (FAB) *m/z* 384 $[M+H]^+$; HRMS (FAB) found 384.1777 $[M+H]^+$ calcd for $C_{18}H_{22}O_3N_7^+$384.1772.

*4.2.14. General procedure for the synthesis of 3-amino-9-benzyl-β-carboline derivatives (**19a**–**e**).* To a mixture of MR-FPS-supported **15a** (500 mg, 0.020 mmol) in THF (2 mL) was added sodium ethoxide (10 mg, 0.14 mmol). After the reaction mixture was shaken for 1 h at room temperature, 4-substituted benzyl bromide **18** (0.020 mmol) was added dropwise, and then stirred at room temperature for 3 days. After the reaction completed, toluene was added to the mixture and was shaken for 30 min at room temperature. The resin was filtrated, and then dried in vacuo. Methanol was added to the dry resin to extract the crude product. The mixture was filtrated, and the methanolic filtrate was evaporated under reduced pressure to dryness. The thus-obtained crude product was

purified by column chromatography on silica gel (chloroform) to afford **19a**–**e**.

*4.2.14.1. 3-Amino-9-benzyl-β-carboline (**19a**).* Yellow solid (yield 75%); mp 201.5–201.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (m, 4H), 2.59 (t, 2H), 2.83 (m, 4H), 5.36 (s, 2H), 6.52 (s, 2H), 7.03 (t, *J*=7.5 Hz, 1H), 7.22 (m, 18H), 7.40 (m, 5H), 7.65 (d, *J*=7.5 Hz, 1H), 7.75 (d, *J*=7.5 Hz, 1H), 8.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 33.5, 46.8, 99.5, 109.5, 118.9, 121.7125.8, 126.1, 126.4, 127.9, 128.0, 128.6, 128.9, 132.6, 133.8, 134.8; ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −126.0 (4F), −123.4 (4F), −122.7 (4F), −121.8 (12F), −114.6 (4F), −80.7 (6F); MS (FAB) *m*/*z* 1408 $[M+H]^+$.

*4.2.14.2. 3-Amino-9-(p-trifluoromethylbenzyl)-β-carboline (**19b**).* Yellow solid (yield 93%); mp 184.6–185.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (m, 4H), 2.83 (m, 4H), 4.43 (s, 2H), 6.69 (s, 1H), 7.12 (d, *J*=7.5 Hz, 1H), 7.30 (m, 21H), 7.45 (d, *J*=7.5 Hz, 2H), 7.50 (d, *J*=7.5 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 33.7, 41.0, 82.6, 110.1, 117.7, 126.4, 127.2, 127.7, 127.8, 128.0, 128.6, 129.0, 129.1, 129.5, 130.1, 131.1, 133.3, 143.8, 145.6; ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −126.0 (4F), −123.4 (4F), −122.7 (4F), −121.8 (12F), −114.6 (4F), −80.7 (6F); MS (FAB) *m*/*z* 1476 $[M+H]^+$.

*4.2.14.3. 3-Amino-9-(p-fluorobenzyl)-β-carboline (**19c**).* Yellow solid (yield 90%); mp 164.2–164.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (m, 4H), 2.83 (m, 4H), 4.45 (s, 2H), 7.10 (s, 1H), 7.12 (d, *J*=7.5 Hz, 1H), 7.35 (m, 21H), 7.47 (d, *J*=7.5 Hz, 2H), 7.61 (d, *J*=7.5 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 33.9, 41.5, 82.4, 109.3, 117.5, 126.0, 127.3, 127.7, 127.9, 128.0, 128.9, 129.2, 129.5, 129.8, 130.0, 131.4, 133.7, 144.7, 145.9, 171.2; ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −126.0 (4F), −123.4 (4F), −122.7 (4F), −121.8 (12F), −114.6 (4F), −80.7 (6F); MS (FAB) *m*/*z* 1426 $[M+H]^+$.

*4.2.14.4. 3-Amino-9-(p-methylbenzyl)-β-carboline (**19d**).* Yellow solid (yield 72%); mp 147.9–148.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (m, 4H), 2.85 (m, 4H), 3.32 (s, 3H), 4.46 (s, 2H), 7.01 (s, 1H), 7.16 (d, *J*=7.5 Hz, 1H), 7.35 (m, 21H), 7.48 (d, *J*=7.5 Hz, 2H), 7.62 (d, *J*=7.5 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 24.2, 33.3, 44.2, 82.8, 109.3, 115.0, 126.0, 127.4, 127.6, 127.8, 128.2, 128.7, 129.0, 129.3, 129.8, 130.8, 131.5, 133.4, 142.6, 145.9; ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −126.0 (4F), −123.4 (4F), −122.7 (4F), −121.8 (12F), −114.6 (4F), −80.7 (6F); MS (FAB) *m*/*z* 1422 $[M+H]^+$.

*4.2.14.5. 3-Amino-9-(p-methoxylbenzyl)-β-carboline (**19e**).* Yellow solid (yield 74%); mp 155.9–156.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (m, 4H), 2.86 (m, 4H), 3.30 (s, 3H), 4.43 (s, 2H), 7.00 (s, 1H), 7.12 (d, *J*=7.5 Hz, 1H), 7.36 (m, 21H), 7.50 (d, *J*=7.5 Hz, 2H), 7.64 (d, *J*=7.5 Hz, 1H), 8.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0, 33.7, 44.4, 55.3, 82.9, 109.6, 115.7, 126.4, 127.2, 127.6, 127.9, 128.3, 128.9, 129.1, 129.6, 129.9, 130.7, 131.8, 133.9, 142.3, 145.5, 159,9; ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −126.0 (4F), −123.4 (4F), −122.7 (4F), −121.8 (12F), −114.6 (4F), −80.7 (6F); MS (FAB) *m*/*z* 1438 $[M+H]^+$.

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Supplementary data

Supplementary data (Copies of the ^{1}H NMR, ^{13}C NMR, MS, and IR spectra for key intermediates and final products.) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.05.072.

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