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SYNTHESIS OF PHOTOPHORE AND FLUOROPHORE MODIFIED *O*-BENZYLSERINE DERIVATIVES

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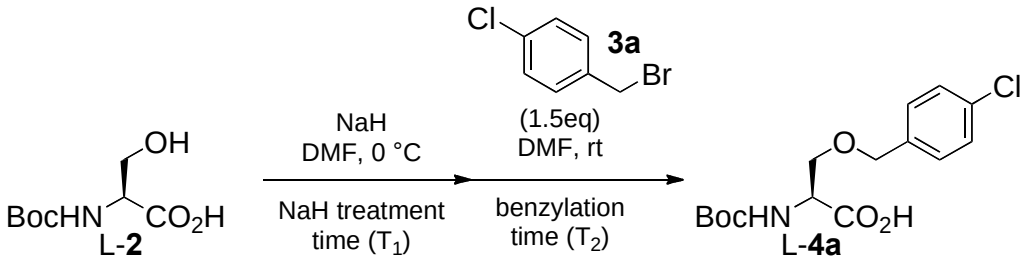
Abstract – *O*-Benzylation of serine is one of the important protection methods for solid phase peptide synthesis. The utilities of the protection group may be indicated that chemical modifications for *O*-benzylserine will be utilized to make functional peptides on solid phase synthesis. Detailed studies for effective synthesis of photoreactive and fluorophore containing *O*-benzylserine derivatives without racemization were reported.

INTRODUCTION

Primary hydroxyl group of serine plays important roles for biological activities.[1] The nucleophilic property of the hydroxyl group promoted that protection of the hydroxyl group will be essential for peptide synthesis. *O*-Benzylation will be well used for solid-phase peptide synthesis. The utilities of the protection group may be indicated that modifications on aromatic ring for *O*-benzylserine will be utilized to make functional peptides with solid phase synthesis.[2] Photoaffinity labeling is one of the methods used in the study of the interactions of low molecular bioactive compounds with biomolecules.[3] Various photophores, such as benzophenone, aryl azide and 3-(trifluoromethyl)phenyldiazirine, are used to elucidate the ligand-receptor or substrate-enzyme interactions. Fluorophore has been widely applying to localization of bioactive compounds in the cell.[4] But there has been few report of synthesis of photophore or fluorophore containing *O*-benzylserine derivatives.[5]

This paper is dedicated to Prof. Dr. Masakatsu Shibasaki on the occasion of his 70th birthday.

Several studies have been reported for synthesis *O*-benzylserine derivatives via from *N*-Boc-seine from 1950's.[6] Sodium hydride is one of the common reagents for this purpose without racemization. But the chemical yield of the benzylation with sodium hydride is not so high (up to 70%). It is necessary to improve chemical yields to apply precious photphore containing benzyl bromide derivatives. Special protecting group, 4-methoxybenzyloxycarbonyl, for *N*-terminal was utilized to dissolve the problem,[7] but cost of the reagents are not suitable for routine works. We here present the detailed synthesis of photophore and fluorophore containing *O*-benzylations of *N*-Boc-serine without racemization, followed by deprotection of Boc group to synthesize *O*-benzylserines effectively and *O*-benzylation with photophores and fluorophore derivatives to elucidate functional analysis.



Entry	NaH (eq)	NaH treatment time (T_1, min)	Benzylation time (T_2, min)	**L-4a** yield (%)
1	3.3	15	120	67
2	5.5	15	120	60
3	3.3	30	60	72
4	3.3	30	30	80
5	3.3	30	15	83
6	2.2	60	15	39
7	3.3	60	15	95
8	4.4	60	15	78
9	5.5	60	15	50

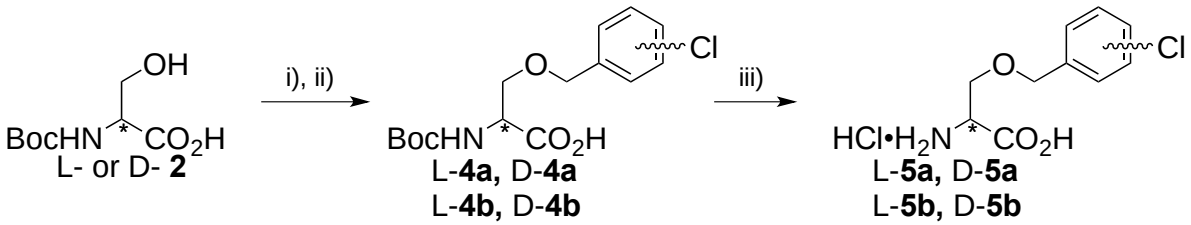
Scheme 1. *O*-Benzylation for Boc-L-Ser (L-**2**) with 4-chlorobenzyl bromide (**3a**)

RESULTS AND DISCUSSION

Boc-L-serine (L-**2**) was treated excess amount of sodium hydride (3.3 or 5.5 eq) at 0 °C in DMF for 15 min, then added 4-chlorobenzyl bromide (**3a**, 1.5 eq), the reaction mixture was stirred at rt for 120 min to afford Boc-L-Ser(4-chlorobenzyl) (L-**4a**) at 67 and 60% as isolation yields, respectively (Scheme 1, entries 1 and 2). Optimizations of times of treatment with NaH (T_1) and benzylation step (T_2) were revealed that long T_1 and short T_2 times were preferred for the *O*-benzylations (Scheme 1, entries 3-5).

2-((*tert*-Butoxycarbonyl)(4-chlorobenzyl)amino)acrylic acid[8] was found when the reaction was conducted over 15 min for T_2 reaction time. It is observed the optimized condition is reaction treated with 3.3 eq of sodium hydride in 60 min, followed by benzylation for 15 min to afford up to 95% yield (Scheme 1, entry 6). Based on the results, equivalence ratios of sodium hydride were conducted in the condition. Less amount of sodium hydride (2.2 eq), which has been reported in previous reported conditions,[6] afforded very low yields in the condition (Scheme 1, entry 6). On the other hand, larger amount of sodium hydride (> 4.4 eq) also promoted decrease the isolated yields (entries 8 and 9). Excess benzyl bromides did not utilize to benzyl ester formation and converted corresponding dibenzyl ether derivative on NMR analysis of the reaction mixture. Benzyl bromide was subjected to the optimized condition to afford Boc-L-Ser(Bn) with 92% and optical rotation of the product was measured. The results are in good agreement between our results (+20.0 c 1 EtOH) and the reference value (+20.4 c 2 EtOH) for L-form.[9]

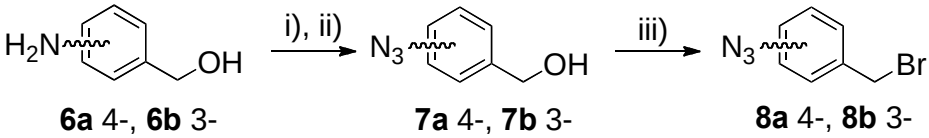
Boc- L- and D- Serine (L- and D- **2**) and 4- and 3- chlorobenzyl bromide (**3a** and **3b**) were subjected to established condition to afford *O*-benzylation products (**4a** and **4b**) over 90% yields. Boc group was deprotected with 4M HCl in dioxane at rt afforded the desired *O*-benzylserine derivatives with stereocontrolled manner (Scheme 2). TFA in CH_2Cl_2 treatment was also applicable for deprotection of Boc group. The synthetic strategies were improved isolation yields for optical pure *N*-Boc-Ser (L-**2** and D-**2**) compared with previous reports.



Scheme 2. Synthesis of *O*-benzylserine derivatives **5a** and **5b**
i) NaH (3.3 eq), DMF, 0 °C, 1 h, ii) 4-chlorobenzyl bromide (**3a**), 3-chlorobenzyl bromide (**3b**) (1.5 eq), 15 min, 97% (L-**4a**), 95% (D-**4a**), 92% (L-**4b**), 91% (D-**4b**), iii) 4 M HCl, 1,4-dioxane, rt, 1.5 h, 83% (L-**5a**), 81% (D-**5a**), 90% (L-**5b**), 88% (D-**5b**)

Based on these results, photophore and fluorophore containing benzyl bromide derivatives are conducted to *O*-benzylation of Boc-serine. For azide derivatives, 4- and 3-aminobenzyl alcohol (**6a**, **6b**) was diazotization followed by azidation to afford corresponding 4- and 3-azidobenzyl alcohol (**7a**[10] and **7b**[11]). 4-Azidobenzyl bromide[12] (**8a**) was prepared smoothly with 1.2 eq of phosphorus tribromide within an hour. 3-Azidobenzyl bromide (**8b**) has been reported by Mornet et al. from 3-azidotoluene with NBS less than 70% yield.[13] But it has not been reported that synthesis of **8b** from corresponding benzyl alcohol with bromination methods. 3-Azidobenzyl alcohol (**7b**), which was very slow reacted in the same condition for 4-Cl isomer **7a**, afforded 72% isolated yields of **8b** for 1 h. The reaction yields were

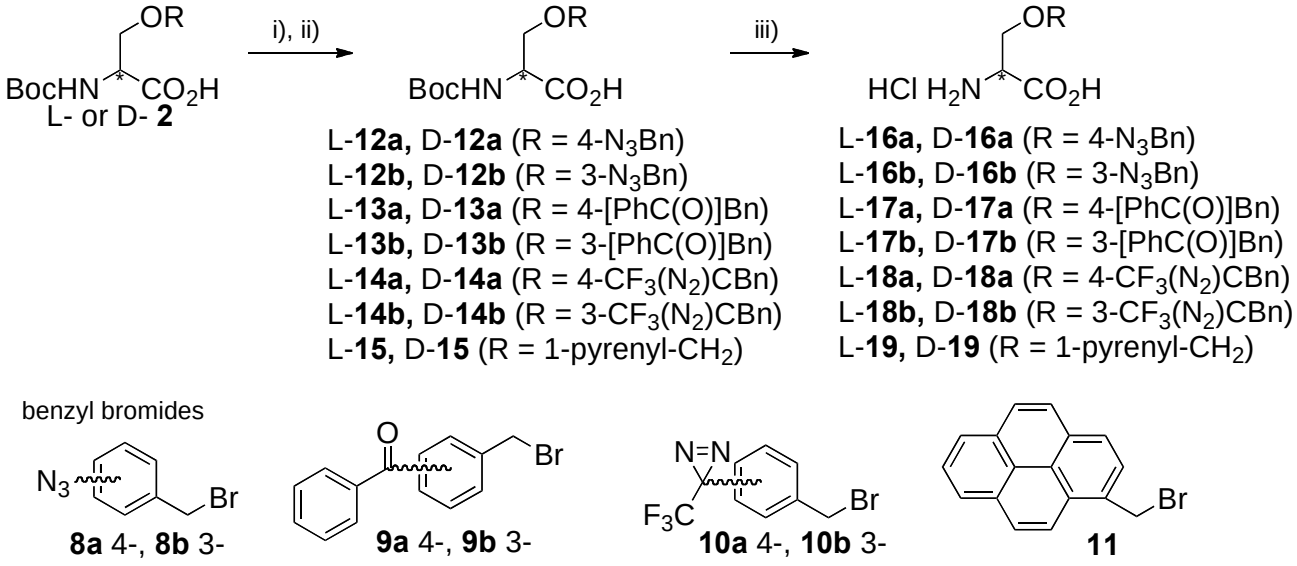
improved by elongation of reaction time (3 h, 95%). Furthermore, increasement of phosphorous tribromide (1.8 eq) can also improve the bromination reaction (1 h, 92%).



6a 4-, **6b** 3- **7a** 4-, **7b** 3- **8a** 4-, **8b** 3-

Scheme 3. Synthesis of 4- and 3-azidebenzyl bromides **8a** and **8b**
i) $NaNO_2$, 6 M HCl, 0 °C, 0.5 h, ii) NaN_3, 6 M HCl, 0 °C, 0.5 h, 90% (**7a**), 92% (**7b**), iii) PBr_3, $CHCl_3$, rt, 1 h, 96% (**8a**) or 3 h, 95% (**8b**)

Other photophore and fluorophore contained benzyl bromides, phenyl azides (**8a** and **8b**), benzophenones (**9a** and **9b**), diazirines (**10a**[14] and **10b**[15]), and pyrene fluorophore (**11**), were subjected to the established conditions to afford *O*-benzylated products (**12**–**15**) with over 80% yields (scheme 4). Boc group was deprotected in 4 M HCl – dioxane to afford photophore and fluorophore containing *O*-benzylserine derivatives (**17**–**20**) with stereocontrolled manner (Scheme 4). Deprotection with TFA in CH_2Cl_2 cannot apply for phenylazide derivatives (**12a** and **12b**) because azide moiety was decomposed. It is consistent with our previous results.[16]



8a 4-, **8b** 3- **9a** 4-, **9b** 3- **10a** 4-, **10b** 3- **11**

Scheme 4. Synthesis of photophore and fluorophore containing *O*-benzylserine derivatives
i) NaH (3.3 eq), DMF, 0 °C, 1 h, ii) benzyl bromides (1.5 eq), 15 min, 84% (L-**12a**), 86% (D-**12a**), 85% (L-**12b**), 81% (D-**12b**), 80% (L-**13a**), 80% (D-**13a**), 89% (L-**13b**), 91% (D-**13b**), 95% (L-**14a**), 95% (D-**14a**), 93% (L-**14b**), 95% (D-**14b**), 85% (L-**15**), 83% (D-**15**), iii) 4 M HCl, 1,4-dioxane, rt, 1.5 h, 82% (L-**16a**), 80% (D-**16a**), 84% (L-**16b**), 86% (D-**16b**), 92% (L-**17a**), 95% (D-**17a**), 95% (L-**17b**), 96% (D-**17b**), 83% (L-**18a**), 85% (D-**18a**), 85% (L-**18b**), 85% (D-**18b**), 86% (L-**19**), 85% (D-**19**)

The reinvestigation for *O*-benzylation of Boc-Ser improved the chemical yields and the improvements promoted us to synthesize photophore and fluorophore containing *O*-benzylserine derivatives. It has been

reported that optically pure D-Ser(Bn) was utilized as drug for eating disorder.[17] Our reinvestigated for the comprehensive synthesis of photophore and fluorophore containing *O*-benzylserine derivatives may be useful for functional analysis of eating disorder with chiral recognition.[18]

EXPERIMENTALS

General methods. NMR spectra were measured by JEOL EX-270 spectrometers. ESI-TOF-MS data were obtained with a Waters UPLC ESI-TOF mass spectrometer. Optical rotation data were obtained with a JASCO DIP-370 polarimeter at 23 °C. 4-Aminobenzyl alcohol **6a** and 1-(bromomethyl)pyrene **12** were obtained from Sigma-Aldrich. 4-Chlorobenzyl bromide **3a**, 3-chlorobenzyl bromide **3b**, 3-aminobenzyl alcohol **6b** and 4-(bromomethyl)benzophenone **10a** were purchased from TCI. 3-(Bromomethyl)benzophenone **10b** was obtained from Combi-Blocks.

Typical procedure for *O*-benzylation of optically pure Boc-Ser (L-2 and D-2). *N*-Boc serine (0.090 g, 0.44 mmol) in DMF (4.5 mL) was treated with NaH (60%, 0.058 g, 1.45 mmol) at 0 °C for 1 h. Solution of benzyl bromides (0.66 mmol, 1.5 eq) in DMF (1.5 mL) was added at 0 °C. The reaction mixture was stirred at rt for 15 min and quenched with ice water (20 mL). The water layer was washed with Et_2O and made acidified with citric acid to pH 2~3. After extraction with AcOEt, the organic layer was washed with saturated aq. NaCl, dried over $MgSO_4$, filtrated and concentrated. The residue was subjected to silica gel column chromatography (MeOH : $CHCl_3$ = 1 : 20) to afford Boc-Ser(Bn) derivatives.

Typical procedure for deprotection of optically pure Boc-Ser(Bn) derivatives. *N*-Boc-Ser(Bn) (0.30 mmol) derivatives were dissolved in 4 M HCl-dioxane (10 mL). The reaction mixture was stirred at rt for 1.5 h and concentrated. The residue was subjected to silica gel (prewashed with MeOH) column chromatography (AcOEt : MeOH : $CHCl_3$ = 4 : 1 : 0.5) to afford Ser(Bn) HCl salt.

Boc-L-Ser(4-ClBn) (L-4a). $[\alpha]_D$ +23.0 (c 2.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 7.31 (2H, d, J = 8.2 Hz), 7.22 (2H, d, J = 8.2 Hz), 5.38 (1H, d, J = 7.6 Hz), 4.51-4.46 (1H, m), 4.51 (2H, s), 3.92 (1H, dd, J = 9.6, 2.8 Hz), 3.70 (1H, dd, J = 9.6, 3.6 Hz), 1.45 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 175.3, 155.7, 135.8, 133.6, 128.9, 128.6, 80.5, 72.6, 69.8, 53.8, 28.3. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}ClNO_5Na$ 352.0922, found 352.0918.

Boc-D-Ser(4-ClBn) (D-4a). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**4a**. $[\alpha]_D$ –22.5 (c 2.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}ClNO_5Na$ 352.0922, found 352.0924.

Boc-D-Ser(3-ClBn) (L-4b). $[\alpha]_D$ +18.0 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 7.20 (1H, d, J = 8.2 Hz), 7.19 (1H, s), 7.19 (1H, d, J = 8.2 Hz), 7.09 (1H, t, J = 8.2 Hz), 5.34 (1H, d, J = 6.6 Hz), 4.46-4.42 (1H, m),

4.44 (2H, s), 3.86 (1H, dd, *J* = 9.4, 2.8 Hz), 3.65 (1H, dd, *J* = 9.4, 3.5 Hz), 1.38 (9H, s). ^{13}C-NMR ($CDCl_3$) *δ*: 174.6, 155.7, 139.4, 134.4, 129.8, 128.0, 127.6, 125.6, 80.5, 72.6, 69.9, 53.7, 28.3. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}ClNO_5Na$ 352.0922, found 352.0921.

Boc-D-Ser(3-ClBn) (D-4b). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**4b**. $[\alpha]_D$ –18.0 (c 1.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}ClNO_5Na$ 352.0922, found 352.0927.

L-Ser(4-ClBn) HCl (L-5a). $[\alpha]_D$ +20.0 (c 1.0, AcOH : H_2O = 4 : 1). ^{1}H-NMR (D_2O) *δ*: 7.27 (2H, d, *J* = 8.6 Hz), 7.20 (2H, d, *J* = 8.6 Hz), 4.49 (1H, d, J = 12.2 Hz), 4.40 (1H, d, *J* = 12.2 Hz), 4.19 (1H, t, *J* = 3.6 Hz), 3.85 (1H, dd, *J* = 11.0, 4.1 Hz), 3.77 (1H, dd, *J* = 11.0, 3.1 Hz). ^{13}C-NMR (D_2O) *δ*: 170.3, 136.1, 134.0, 130.4, 129.2, 73.0, 67.2, 53.7. ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}ClNO_3$ 230.0578, found 230.0580.

D-Ser(4-ClBn) HCl (D-5a). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**5a**. $[\alpha]_D$ –20.0 (c 1.0, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}ClNO_3$ 230.0578, found 230.0574.

L-Ser(3-ClBn) HCl (L-5b). $[\alpha]_D$ +20.0 (c 1.0, AcOH : H_2O = 4 : 1). ^{1}H-NMR (D_2O) *δ*: 6.99 (1H, d, *J* = 7.6 Hz), 6.96 (2H, s), 6.89 (2H, t, *J* = 7.6 Hz), 4.24 (1H, d, *J* = 12.5 Hz), 4.14 (1H, d, *J* = 12.5 Hz), 3.92 (1H, t, *J* = 3.6 Hz), 3.60 (1H, dd, *J* = 11.0, 4.2 Hz), 3.50 (1H, dd, *J* = 11.0, 3.2 Hz). ^{13}C-NMR (D_2O) *δ*: 170.3, 139.7, 134.4, 130.9, 128.8, 128.5, 127.1, 73.0, 67.3, 53.8. ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}ClNO_3$ 230.0578, found 230.0580.

D-Ser(3-ClBn) HCl (D-5b). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**5b**. $[\alpha]_D$ –19.0 (c 1.0, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}ClNO_3$ 230.0578, found 230.0578.

(4-Azidophenyl)methanol (7a). (4-Aminophenyl)methannol **6a** (2.00 g, 16 mmol) was dissolved in 6M HCl (16 mL). Sodium nitrate (1.67 g, 24 mmol) was added slowly at 0 °C. After stirring at same temperature for 30 min, sodium azide (4.23 g, 65 mmol) was added slowly at 0 °C. The reaction mixture was stirred at same temperature for 30 min then extracted with Et_2O twice. The organic layer was washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over $MgSO_4$, filtrated and concentrated. The residue was subjected to silica column chromatography (AcOEt : hexane = 1 : 1) to afford yellow oil (2.17 g, 90%). IR (neat, cm^{-1}) 2154. ^{1}H-NMR ($CDCl_3$) *δ*: 7.24 (2H, d, *J* = 8.6 Hz), 6.94 (2H, d, *J* = 8.6 Hz), 4.52 (2H, s), 3.27 (1H, s). ^{13}C-NMR ($CDCl_3$) *δ*: 139.0, 137.4, 128.3, 118.8, 64.1. ESI-TOF-MS: $[M+H]^+$ calculated for $C_7H_7N_3O$ 150.0667, found 150.0663.

(3-Azidophenyl)methanol (7b). (3-Aminophenyl)methannol **6b** (2.00 g, 16 mmol) was treated with identical manner described above to afford yellow oil (2.22 g, 92%). IR (neat, cm^{-1}) 2130. ^{1}H-NMR ($CDCl_3$) δ: 7.33 (1H, t, J = 7.9 Hz), 7.11 (1H, d, J = 7.9 Hz), 7.04 (1H, s), 6.94 (1H, d, J = 7.9 Hz), 4.67 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 142.9, 140.3, 129.9, 123.2, 118.2, 117.3, 64.7. ESI-TOF-MS: $[M+H]^+$ calculated for $C_7H_7N_3O$ 150.0667, found 150.0657.

1-Azido-4-(bromomethyl)benzene (8a). (4-Azidophenyl)methannol (1.77 g, 12 mmol) was dissolved in $CHCl_3$ (35 mL). Phosphorous tribromide (3.82 g, 14 mmol) was added slowly at 0 °C. The reaction mixture was stirred at same temperature for an hour then added water. The organic layer was washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over $MgSO_4$, filtrated and concentrated. The residue was subjected to silica column chromatography (AcOEt : hexane = 2 : 3) to afford yellow oil (2.08 g, 96%). IR (neat, cm^{-1}) 2139. ^{1}H-NMR ($CDCl_3$) δ: 7.35 (2H, d, J = 8.2 Hz), 6.96 (2H, d, J = 8.2 Hz), 4.45 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 140.1, 134.4, 130.5, 119.3, 32.8. ESI-TOF-MS: $[M+H]^+$ calculated for $C_7H_7BrN_3$ 211.9823, found 211.9833.

1-Azido-3-(bromomethyl)benzene (8b). (3-Azidophenyl)methanol **7b** (1.13 g, 7.6 mmol) was treated with identical manner described above expected rection time (3 h) to afford yellow oil (1.52 g, 95%). IR (neat, cm^{-1}) 2110. ^{1}H-NMR ($CDCl_3$) δ: 7.33 (1H, t, J = 7.9 Hz), 7.16 (1H, d, J = 7.9 Hz), 7.05 (1H, s), 6.96 (1H, d, J = 7.9 Hz), 4.45 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 140.6, 139.7, 130.2, 125.5, 119.5, 119.0, 32.4. $[M+H]^+$ calculated for $C_7H_7BrN_3$ 211.9823, found 211.9816.

Boc-L-Ser(4-N_3Bn) (L-12a). $[\alpha]_D$ +22.0 (c 2.0, $CHCl_3$). IR (neat, cm^{-1}) 2113. ^{1}H-NMR ($CDCl_3$) δ: 7.27 (2H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.6 Hz), 5.42 (1H, d, J = 7.3 Hz), 4.51-4.48 (1H, m), 4.50 (2H, s), 3.91 (1H, dd, J = 9.4, 2.1 Hz), 3.69 (1H, dd, J = 9.4, 3.5 Hz), 1.44 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 175.2, 155.7, 139.6, 134.1, 129.2, 119.0, 80.4, 72.8, 69.7, 53.8, 28.3. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}N_4O_5Na$ 359.1326, found 359.1325.

Boc-D-Ser(4-N_3Bn) (D-12a). The ^{1}H-, ^{13}C-NMR and IR data for the sample were identical to those record for L-**12a**. $[\alpha]_D$ –22.5 (c 2.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}N_4O_5Na$ 359.1326, found 359.1320.

Boc-L-Ser(3-N_3Bn) (L-12b). $[\alpha]_D$ +17.0 (c 2.0, $CHCl_3$). IR (neat, cm^{-1}) 2120. ^{1}H-NMR ($CDCl_3$) δ: 7.30 (1H, t, J = 7.6 Hz), 7.05 (1H, d, J = 7.6 Hz), 6.95 (1H, s), 6.94 (1H, d, J = 7.6 Hz), 5.44 (1H, d, J = 6.6 Hz), 4.53-4.50 (1H, m), 4.51 (2H, s), 3.91 (1H, dd, J = 9.1, 1.8 Hz), 3.72 (1H, dd, J = 9.1, 3.1 Hz), 1.44 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 175.0, 155.7, 140.2, 139.5, 129.8, 124.0, 118.4, 118.0, 80.4, 72.8, 69.9, 53.9, 28.3. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}N_4O_5Na$ 359.1326, found 359.1326.

Boc-D-Ser(3-N_3Bn) (D-12b). The ^{1}H-, ^{13}C-NMR and IR data for the sample were identical to those record for L-**12b**. $[\alpha]_D$ –17.0 (c 2.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{15}H_{20}N_4O_5Na$ 359.1326, found 359.1328.

L-Ser(4-BzBn) (L-13a). $[\alpha]_D$ +19.0 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 7.79 (2H, d, J = 7.4 Hz), 7.78 (2H, d, J = 7.6 Hz), 7.59 (1H, t, J = 7.6 Hz), 7.48 (2H, t, J = 7.4 Hz), 7.40 (2H, d, J = 7.4 Hz), 5.43 (1H, d, J = 6.9 Hz), 4.64 (2H, s), 4.52 (1H, m), 3.99 (1H, dd, J = 9.9, 4.0 Hz), 3.78 (1H, dd, J = 9.9, 3.6 Hz), 1.46 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 196.4, 175.1, 155.8, 142.2, 137.5, 136.9, 132.4, 130.3, 130.0, 128.3, 127.1, 80.4, 72.7, 70.2, 53.9, 28.3. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{22}H_{25}NO_6Na$ 422.1574, found 422.1571.

D-Ser(4-BzBn) (D-13a). The ^{1}H- and ^{13}C-NMR for the sample were identical to those record for L-**13a**. $[\alpha]_D$ –19.0 (c 1.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{22}H_{25}NO_6Na$ 422.1574, found 422.1571.

L-Ser(3-BzBn) (L-13b). $[\alpha]_D$ +20.5 (c 2.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 7.72 (2H, d, J = 7.3 Hz), 7.67 (1H, s), 7.60 (1H, d, J = 7.6 Hz), 7.53 (1H, t, J = 7.3 Hz), 7.44 (2H, t, J = 7.6 Hz), 7.40 (1H, d, J = 7.6 Hz), 7.37 (1H, t, J = 7.6 Hz), 5.36 (1H, d, J = 8.2 Hz), 4.57 (1H, d, J = 12.5 Hz), 4.49 (1H, d, J = 12.5 Hz), 4.44-4.41 (1H, m), 3.87 (1H, dd, J = 9.4, 3.1 Hz), 3.68 (1H, dd, J = 9.4, 3.5 Hz), 1.37 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 196.8, 174.4, 155.7, 138.0, 137.7, 137.4, 132.6, 131.6, 130.1, 129.7, 129.0, 128.4, 128.3, 80.4, 72.8, 70.0, 53.9, 28.3. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{22}H_{25}NO_6Na$ 422.1574, found 422.1576.

D-Ser(3-BzBn) (D-13b). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**13b**. $[\alpha]_D$ –20.5 (c 2.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{22}H_{25}NO_6Na$ 422.1574, found 422.1579.

Boc-L-Ser(4-[$CF_3(N_2)C$]Bn) (L-14a). $[\alpha]_D$ +17.0 (c 2.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 7.30 (2H, d, J = 7.9 Hz), 7.14 (2H, d, J = 7.9 Hz), 5.47 (1H, s), 4.52 (2H, s), 4.52-4.47 (1H, m), 3.90 (1H, d, J = 6.6 Hz), 3.70 (1H, d, J = 6.6 Hz), 1.43 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 175.3, 155.9, 139.3, 128.6, 127.8, 126.6, 122.1 (q, $^1J_{CF}$ = 275.1 Hz), 80.5, 72.5, 70.1, 54.1, 28.3, 28.2 (q, $^2J_{CF}$ = 40.2 Hz). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{17}H_{20}F_3N_3O_5Na$ 426.1247, found 426.1245.

Boc-D-Ser(4-[$CF_3(N_2)C$]Bn) (D-14a). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**14a**. $[\alpha]_D$ –17.5 (c 2.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{17}H_{20}F_3N_3O_5Na$ 426.1247, found 426.1248.

Boc-L-Ser(3-[$CF_3(N_2)C$]Bn) (L-14b). $[\alpha]_D$ +14.0 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 7.36 (1H, t, J = 7.2 Hz), 7.35 (1H, d, J = 7.2 Hz), 7.12 (1H, d, J = 7.2 Hz), 7.07 (1H, s), 5.37 (1H, d, J = 7.3 Hz), 4.52 (2H, s), 4.47 (1H, m), 3.91 (1H, dd, J = 9.6, 3.6 Hz), 3.69 (1H, dd, J = 9.6, 3.5 Hz), 1.44 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 175.2, 155.7, 138.5, 129.3, 129.0, 128.7, 125.9, 125.3, 122.1 (q, $^1J_{CF}$ = 274.7 Hz), 80.5, 72.6, 70.1, 53.8, 28.4 (q, $^2J_{CF}$ = 40.2 Hz), 28.2. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{17}H_{20}F_3N_3O_5Na$ 426.1247, found 426.1251.

Boc-D-Ser(3-[$CF_3(N_2)C$]Bn) (D-14b). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**14b**. $[\alpha]_D$ –15.0 (c 1.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{17}H_{20}F_3N_3O_5Na$ 426.1247, found 426.1253.

Boc-L-Ser(1-pyrenylmethyl) (L-15). $[\alpha]_D$ +22.0 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 8.21 (1H, d, J = 8.2 Hz), 8.13 (2H, d, J = 7.6 Hz), 8.04 (2H, d, J = 8.2 Hz), 7.98-7.95 (3H, m), 7.90 (1H, t, J = 7.6 Hz), 5.39 (1H, d, J = 5.9 Hz), 5.20 (1H, d, J = 11.9 Hz), 5.14 (1H, d, J = 11.9 Hz), 4.46-4.45 (1H, m), 4.01 (1H, dd, J = 8.7, 2.1 Hz), 3.78 (1H, dd, J = 8.7, 2.8 Hz), 1.34 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 174.9, 155.7, 131.4, 131.1, 130.7, 130.2, 129.3, 127.8, 127.5, 127.3, 127.1, 125.9, 125.3, 125.2, 124.8, 124.6, 124.3, 123.1, 80.2, 72.0, 69.5, 53.9, 28.2. ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{25}H_{25}NO_5Na$ 442.1625, found 442.1625.

Boc-D-Ser(1-pyrenylmethyl) (D-15). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**15**. $[\alpha]_D$ –23.0 (c 1.0, $CHCl_3$). ESI-TOF-MS: $[M+Na]^+$ calculated for $C_{25}H_{25}NO_5Na$ 442.1625, found 442.1623.

L-Ser(4-N_3Bn) HCl (L-16a). $[\alpha]_D$ +22.0 (c 1.0, AcOH : H_2O = 4 : 1). IR (neat, cm^{-1}) 2125. ^{1}H-NMR (D_2O) δ: 6.99 (2H, d, J = 8.2 Hz), 6.69 (2H, d, J = 8.2 Hz), 4.22 (1H, d, J = 12.2 Hz), 4.13 (1H, d, J = 12.2 Hz), 3.91 (1H, t, J = 3.8 Hz), 3.58 (1H, dd, J = 11.0, 4.1 Hz), 3.49 (1H, dd, J = 11.0, 3.5 Hz). ^{13}C-NMR (D_2O) δ: 170.9, 140.5, 134.2, 130.7, 119.8, 73.2, 67.4, 54.1. ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}N_4O_3$ 237.0982, found 237.0982.

D-Ser(4-N_3Bn) HCl (D-16a). The ^{1}H-, ^{13}C-NMR and IR data for the sample were identical to those record for L-**16a**. $[\alpha]_D$ –21.0 (c 1.0, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}N_4O_3$ 237.0982, found 237.0979.

L-Ser(3-N_3Bn) HCl (L-16b). $[\alpha]_D$ +19.0 (c 1.0, AcOH : H_2O = 4 : 1). IR (neat, cm^{-1}) 2113. ^{1}H-NMR (D_2O) δ: 7.02 (1H, t, J = 8.2 Hz), 6.78 (1H, d, J = 8.2 Hz), 6.70 (1H, s), 6.67 (1H, d, J = 8.2 Hz), 4.18 (2H, s), 3.54-3.46 (3H, m). ^{13}C-NMR (D_2O) δ: 170.3, 140.7, 139.5, 130.8, 125.2, 119.3, 119.0, 73.1, 67.2, 53.7. ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}N_4O_3$ 237.0982, found 237.0981.

D-Ser(3-N_3Bn) HCl (D-16b). The ^{1}H-, ^{13}C-NMR and IR data for the sample were identical to those record for L-**16b**. $[\alpha]_D$ –20.0 (c 1.0, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{10}H_{13}N_4O_3$ 237.0982, found 237.0980.

L-Ser(4-BzBn) HCl (L-17a). $[\alpha]_D$ +24.0 (c 0.5, AcOH : H_2O = 4 : 1). ^{1}H-NMR (D_2O) δ: 7.31-7.24 (5H, m), 7.12 (2H, d, J = 7.9 Hz), 7.07 (2H, d, J = 7.9 Hz), 4.37 (1H, d, J = 12.9 Hz), 4.26 (1H, d, J = 12.9 Hz), 4.02 (1H, t, J = 3.6 Hz), 3.67 (1H, dd, J = 11.0, 4.3 Hz), 3.59 (1H, dd, J = 11.0, 3.1 Hz). ^{13}C-NMR (D_2O) δ: 201.0, 170.4, 143.2, 137.4, 137.1, 134.2, 131.3, 130.9, 129.3, 128.4, 73.1, 67.6, 53.8. ESI-TOF-MS: $[M+H]^+$ calculated for $C_{17}H_{18}NO_4$ 300.1230, found 300.1234.

D-Ser(4-BzBn) HCl (D-17a). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**17a**. $[\alpha]_D$ –22.0 (c 0.5, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{17}H_{18}NO_4$ 300.1230, found 300.1223.

L-Ser(3-BzBn) HCl (L-17b). $[\alpha]_D$ +17.0 (c 1.0, AcOH : H_2O = 4 : 1). ^{1}H-NMR (D_2O) δ: 7.28-7.24 (6H, m), 7.13-7.10 (3H, m), 4.28 (1H, d, J = 12.2 Hz), 4.18 (1H, d, J = 12.2 Hz), 3.92 (1H, t, J = 3.5 Hz), 3.59 (1H, dd, J = 10.7, 4.0 Hz), 3.50 (1H, dd, J = 10.7, 3.1 Hz). ^{13}C-NMR (D_2O) δ: 201.1, 170.3, 137.9, 137.7, 137.2, 134.2, 133.6, 130.9, 130.7, 130.1, 129.5, 129.2, 73.1, 67.3, 53.7. ESI-TOF-MS: $[M+H]^+$ calculated for $C_{17}H_{18}NO_4$ 300.1230, found 300.1231.

D-Ser(3-BzBn) HCl (D-17b). The ^{1}H-, ^{13}C-NMR and ESI-TOF-MS data for the sample were identical to those record for L-**17b**. $[\alpha]_D$ –17.0 (c 1.0, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{17}H_{18}NO_4$ 300.1230, found 300.1233.

L-Ser(4-[CF_3(N_2)C]Bn) HCl (L-18a). $[\alpha]_D$ +19.0 (c 1.0, AcOH : H_2O = 4 : 1). ^{1}H-NMR (D_2O) δ: 6.51 (2H, d, J = 8.2 Hz), 6.34 (2H, d, J = 8.2 Hz), 3.77 (1H, d, J = 12.5 Hz), 3.67 (1H, d, J = 12.5 Hz), 3.47 (1H, t, J = 3.8 Hz), 3.10 (1H, dd, J = 11.0, 4.5 Hz), 3.02 (1H, dd, J = 11.0, 3.3 Hz). ^{13}C-NMR (D_2O) δ: 170.3, 139.4, 129.0, 127.9, 127.3, 126.6 (q, $^1J_{CF}$ = 275.4 Hz), 73.0, 67.4, 53.7, 29.0 (d, $^2J_{CF}$ = 35.2 Hz). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{12}H_{13}F_3N_3O_3$ 304.0904, found 304.0903.

D-Ser(4-[CF_3(N_2)C]Bn) HCl (D-18a). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**18a**. $[\alpha]_D$ –19.0 (c 1.0, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{12}H_{13}F_3N_3O_3$ 304.0904, found 304.0905.

L-Ser(3-[CF_3(N_2)C]Bn) HCl (L-18b). $[\alpha]_D$ +17.0 (c 1.0, AcOH : H_2O = 4 : 1). ^{1}H-NMR (D_2O) δ: 7.35 (1H, t, J = 8.2 Hz), 7.35 (1H, d, J = 8.2 Hz), 7.16 (1H, d, J = 8.2 Hz), 7.12 (1H, s), 4.54 (1H, d, J = 12.5 Hz), 4.43 (1H, d, J = 12.5 Hz), 4.19 (1H, t, J = 3.6 Hz), 3.85 (1H, dd, J = 11.0, 4.3 Hz), 3.75 (1H, dd, J = 11.0, 3.1 Hz). ^{13}C-NMR (D_2O) δ: 170.2, 138.5, 129.9, 129.8, 129.5, 126.8, 126.1, 122.5 (d, $^1J_{CF}$ = 276.0

Hz), 73.0, 67.3, 53.7, 28.9 (d, $^{2}J_{CF}$ = 40.8 Hz). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{12}H_{13}F_3N_3O_3$ 304.0904, found 304.0900.

D-Ser(3-[CF$_3$(N$_2$)C]Bn) HCl (D-18b). The ^{1}H- and ^{13}C-NMR ata for the sample were identical to those record for L-**18b**. $[\alpha]_D$ –16.0 (c 1.0, AcOH : H_2O = 4 : 1). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{12}H_{13}F_3N_3O_3$ 304.0904, found 304.0900.

L-Ser(1-pyrenylmethyl) HCl (L-19). $[\alpha]_D$ +22.0 (c 0.5, DMSO). ^{1}H-NMR (DMSO-d_6) δ: 8.40 (1H, d, J = 8.2 Hz), 8.32-8.26 (4H, m), 8.18 (3H, s), 8.18 (3H, d, J = 8.2 Hz), 8.09 (1H, t, J = 8.2 Hz), 5.25 (2H, s), 3.99 (1H, dd, J = 10.4, 3.1 Hz), 3.84 (1H, dd, J = 10.4, 8.1 Hz), 3.53 (1H, dd, J = 8.1, 3.1 Hz). ^{13}C-NMR (DMSO-d_6) δ: 167.2, 131.6, 130.8, 130.7, 130.4, 128.6, 127.7, 127.5, 127.4, 127.2, 126.4, 125.4, 125.3, 124.6, 124.0, 123.9, 123.7, 70.5, 69.7, 54.2. ESI-TOF-MS: $[M+H]^+$ calculated for $C_{20}H_{18}NO_3$ 320.1281, found 320.1276.

D-Ser(1-pyrenylmethyl) HCl (D-19). The ^{1}H- and ^{13}C-NMR data for the sample were identical to those record for L-**19**. $[\alpha]_D$ –22.0 (c 0.5, DMSO). ESI-TOF-MS: $[M+H]^+$ calculated for $C_{20}H_{18}NO_3$ 320.1281, found 320.1277.

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