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Convenient synthesis of chiral tryptophan derivatives using Negishi cross-coupling

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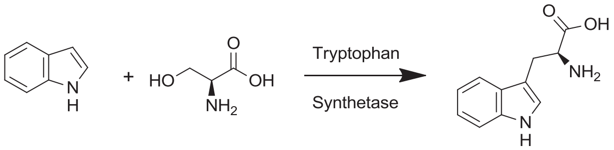
ABSTRACT

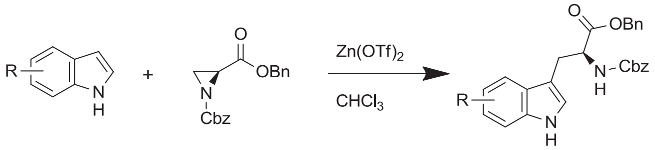
A facile synthetic procedure for chiral tryptophan derivatives using Negishi cross-coupling reaction of serine-derived iodoalanine with 3-haloindole is described. The best result was obtained when the reaction of *N*-tosyl-3-bromoindole with *N*-Cbz-iodoalanine methyl ester was carried out by the combination of $Pd_2(dba)_3$ and sterically hindered ferrocenyl ligand Q-PHOS. This reaction condition not only gave the desired tryptophan derivative as high as 76% yield, but also suppressed the formation of undesired products, the dehalogenated indole and the homodimer of indole, which were difficult to separate. This reaction was extended to the synthesis of various tryptophan derivatives having substituents on the benzene ring. The characteristic of this reaction is the practical biomimetic synthesis of chiral tryptophan derivatives in one-step.

1. Introduction

In biological systems, the syntheses of compounds essential for life are accomplished efficiently via enzymatic catalysis. One of the most attractive goals for a synthetic chemist is to develop a synthetic pathway similar to the biosynthetic one without the use of enzymes. Tryptophan, which is biosynthesized from indole and serine (Scheme 1), is not only important as a component of proteins but also as a source of bioactive compounds, such as serotonin. Although numerous synthetic methods for chiral tryptophan have been reported to date, there are few biomimetic syntheses that directly couple at the C3-position of indole with serine or its equivalents.[1–4] A typical example is the ring opening reaction of serine-derived aziridine with 3-*H*-indole;[3] however the yield is unsatisfactory, especially in substituted indole (Scheme 2).



Scheme 1. Biosynthesis of tryptophan.



Scheme 2. Ring opening reaction of aziridine with 3-*H*-indole.

In the course of our investigation into the total synthesis of ergot alkaloids,[5–9] we developed two biomimetic syntheses of tryptophan derivatives: (a) selective Pd-catalyzed vinylation of 4-bromoindole with dehydroalanine[5–7] and (b) one-step synthesis of *N*-acetyltryptophan from indole and serine in the presence of Ac_2O[8,9] (Scheme 3). However, these synthetic methods required asymmetric hydrogenation[5–7] or kinetic resolution using acylase.[8,9] Herein, we describe a new synthetic method for chiral tryptophan derivatives using the direct Negishi cross-coupling reaction of optically active serine-derived iodoalanine to 3-haloindole.

Since Jackson reported the asymmetric synthesis of substituted phenylalanine derivatives from aryl halides and readily available serine-derived iodoalanine using Negishi cross-coupling,[10] there have been several reports for Negishi cross-coupling reaction in order to synthesize various chiral aromatic amino acids,[11–14] but only limited reports for tryptophan synthesis utilizing this reaction. Recently, Rainier applied Negishi cross-coupling reaction of 3-iodoindole derivative to the synthesis of tryptophan unit in total synthesis of Kapakahine E for the first time.[15] However, it required equimolar amount of phosphine ligand and was limited to unsubstituted indole on the benzene ring. Therefore, we decided to establish the general synthetic method for chiral tryptophan

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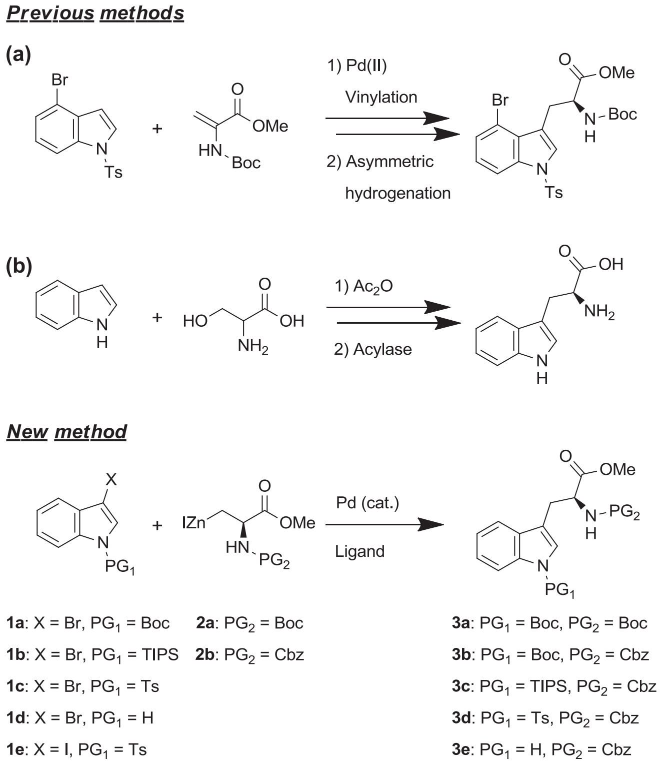


Scheme 3. Biomimetic syntheses of tryptophan.

derivatives having various substituents on the benzene ring using Negishi cross-coupling.

2. Results and discussion

Initially, we applied Jackson's condition[13] for the reaction of organozinc reagent **2a** with *N*-Boc-protected 3-bromoindole **1a**. Disappointingly, the isolated yield of **3a** was extremely low (11%), and the purification step was troublesome due to weak UV absorption and many minor side products (Table 1, entry 1). We then changed the protecting groups of **1** and **2**. At first, the protecting group of **2** was changed to Cbz from Boc for easy detection on TLC (entry 2) to give a complex mixture. The protecting group of indole affected the isolated yields of tryptophan **3**. In the cases of Boc and TIPS groups, the reaction systems were complicated and we were unable to isolate target compounds (entries 2 and 3). Although the Ts group gave desired product (**3d**) in low yield (22%), the reaction was clean without formation of side products, allowing recovery of starting material (**1c**) (entry 4). Therefore, further investigation was accomplished with this combination. With unprotected indole **1d**, the reaction did not proceed at all (entry 5).

Table 1
Effect of the protecting group (Scheme 3)[a]

Entry	3-Haloindole	Organozinc reagent	Product	Yield (%)[b]
1	**1a**	**2a**	**3a**	11
2	**1a**	**2b**	**3b**	—[c]
3	**1b**	**2b**	**3c**	—[c]
4	**1c**	**2b**	**3d**	22
5	**1d**	**2b**	**3e**	No reaction

[a] Conditions: **1** (0.65 mmol), **2** (0.5 mmol), $Pd_2(dba)_3$ (0.013 mmol), $P(o\text{-tol})_3$ (0.05 mmol), DMF (0.67 mL), 50 °C, 3 h.

[b] Yield is based on organozinc reagent **2**.

[c] Mixture of unidentified products.

Next, we tried various combinations of palladium and phosphine ligands (Table 2). We initially used more reactive 3-iodoindole **1e** with a small excess of **2b**. Under standard conditions, no improvement was observed (entry 1). With $PdCl_2(PPh_3)_2$, which Jackson successfully used in the synthesis of pyridyl amino acids,[12] the reaction did not proceed (entry 2). Since Fu used $Pd[P(t\text{-}Bu)_3]_2$ for Negishi cross-coupling of aryl chlorides,[16] we used the same catalyst but the yield was still low (entry 3). Recently, Knochel reported the Negishi cross-coupling of aryl halides bearing acidic protons catalyzed by $Pd(OAc)_2$/*S*-PHOS in high yield.[17] Under this combination, significant improvement was observed (entry 4). In all cases, the major side products were the dehalogenated indole and the homodimer of indole, which were difficult to separate. Since Buchwald reported that the reactivity for the oxidative addition toward aryl bromides sometimes more reactive than aryl iodide,[18] we considered that acceleration of transmetalation would suppress undesirable side reaction. We changed **1e** to 3-bromoindole **1c**. In all cases, the formation of side products was suppressed. Surprisingly, remarkable improvement was achieved in the combination of $Pd(OAc)_2$ and *S*-PHOS to give the desired product in 60% yield (entry 7). However, the reaction was slow and **1c** was not consumed completely under heating (50 °C, 5 h). Recently, Jackson reported the improved synthesis of phenylalanine derivatives using $Pd_2(dba)_3$ and *S*-PHOS.[19] We applied that system to our tryptophan synthesis; however the yield of **3d** was not satisfactory (43% yield, entry 8). Since unreacted **1c** was remained under the heating conditions, catalyst deactivation might be a main reason for the low yields in above both cases.

The best result was obtained by the combination of $Pd_2(dba)_3$ and sterically hindered ferrocenyl ligand Q-PHOS.[20] Starting material **1c** was consumed within 3 h at room temperature to give the product in 66% yield (entry 9). The complex generated from Pd/Q-PHOS is highly active, long-lived catalyst.[21] Complete conversion at lower temperature and improvement of yield might be explained by those natures of Pd/Q-PHOS system. The use of ferrocenyl bidentate ligand $PdCl_2(dppf)$ did not give **3d** (entry 10).

The ee of **3d** was determined to be 97.2% by chiral HPLC analysis. Therefore, racemization did not occur in this reaction. It is noteworthy that the racemization also did not occur in every reported case.[10–13]

In order to investigate the scope and limitations, various kinds of substituted indoles were reacted under optimized conditions ($Pd_2(dba)_3$/Q-PHOS). The results are shown in Table 3. Negishi cross-coupling with chlorine-substituted indoles gave modest to high yield; the 4-chloroindole derivative especially gave the highest yield (76%, entry 1). Electron-rich and electron-deficient substituents at the C4-position of indole gave moderate yields (44 and 31%, entries 5 and 6). In the ring opening reaction of aziridine,[3] 4-NO_2 and 6-Cl derivatives gave poor results (3 and 12%). Sterically hindered 4-CO_2Me derivative gave low yields (entry 7). The reactions with *N*-Ts-2-methyl-3-bromoindole or *N*-Ts-3-chloroindole did not proceed (data not shown). The Rainier's condition[14] (equimolar amount of $P(o\text{-tol})_3$ and catalytic CuBr·DMS) did not work well (23% for **3f**, 11% for **3j**).

3. Conclusion

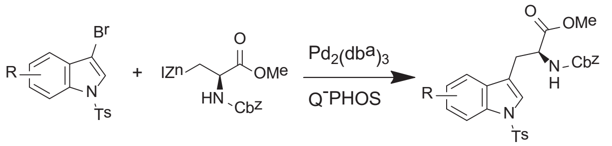
In summary, a one-step synthesis of tryptophan derivatives using Negishi cross-coupling from 3-haloindoles and iodoalanine derived from L-serine was developed. The reaction was found to proceed under mild conditions with yields as high as 76% without a loss of enantiomeric purity after optimization of reaction conditions. This method was also shown to be applicable to the synthesis of various optically active tryptophan derivatives having various substituents on the benzene ring.

Table 2
Combination of palladium and phosphine ligands (Scheme 3)[a]

Entry	3-Haloindole	Organozinc reagent	Palladium	Ligand	Temp/°C	Time/h	Product	Yield (%)[b]
1	**1e**	**2b**	$Pd_2(dba)_3$	P(*o*-tol)$_3$	50	3	**3d**	20
2	**1e**	**2b**	$PdCl_2(PPh_3)_2$	—	50	3	**3d**	No reaction
3	**1e**	**2b**	Pd[P(*t*-Bu$_3$)]$_2$	—	50	3	**3d**	18
4	**1e**	**2b**	$Pd(OAc)_2$	*S*-PHOS	35	3	**3d**	40
5	**1c**	**2b**	$Pd_2(dba)_3$	P(*o*-tol)$_3$	50	5	**3d**	22
6	**1c**	**2b**	Pd[P(*t*-Bu$_3$)]$_2$	—	50	5	**3d**	17
7	**1c**	**2b**	$Pd(OAc)_2$	*S*-PHOS	50	5	**3d**	60
8	**1c**	**2b**	$Pd_2(dba)_3$	*S*-PHOS	50	5	**3d**	43
9	**1c**	**2b**	$Pd_2(dba)_3$	Q-PHOS[c]	35	3	**3d**	66
10	**1c**	**2b**	$PdCl_2(dppf)$	—	80	5	**3d**	No reaction

[a] Conditions: **1** (0.5 mmol), **2** (0.65 mmol), Palladium (0.025 mmol), Ligand (0.05 mmol), DMF (0.67 mL).
[b] Yield is based on 3-haloindole **1**.
[c] Q-PHOS (0.025 mmol) was used.

Table 3
Negishi cross-coupling of **2b** with substituted indoles[a]



1f~1l **2b** **3f~3l**

Entry	R	Product	Yield (%)
1	4-Cl	**3f**	76
2	5-Cl	**3g**	50
3	6-Cl	**3h**	47
4	7-Cl	**3i**	45
5	4-OMe	**3j**	44
6	4-NO_2	**3k**	31
7	4-CO_2Me	**3l**	18

[a] Conditions: **1** (0.5 mmol), **2** (0.65 mmol), $Pd_2(dba)_3$ (0.013 mmol), Q-PHOS (0.025 mmol), DMF (0.67 mL), 35 °C, 3 h.

4. Experimental

4.1. General experimental

Silica gel column chromatography was performed using Fuji Silysia PSQ100B. ^1H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer. Chemical shifts are expressed in parts per million relative to TMS as an internal standard. Mass spectra were measured in a combination with a Waters Acquity UPLC system (0.05% TFA in acetonitrile/0.05% TFA in water) and a Micromass ZQ (ESI) spectrometer. High-resolution (HR) mass spectra were performed on a JEOL GC mate spectrometer. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum One spectrometer. Optical rotations were measured with the JASCO DIP-1000. High performance liquid chromatography (HPLC) was performed on a Waters 2695 Series chromatographs using Chiralpak IC column (15 cm) in mixture of hexane/ethanol/Diethylamine (70:30:0.1).

4.2. General procedure for the synthesis of substituted 3-bromoindole derivatives

Sodium hydride (132 mg, 3.3 mmol) was added to a stirred solution of the indole (3 mmol) in DMF (6.0 mL) at 0 °C, then stirred for 30 min. To the reaction mixture, tosyl chloride (629 mg, 3.3 mmol) was added and stirred at room temperature for 2 h. After pouring into water, the mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (2×50 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was solved in dichloromethane (30 mL) and cooled on iced bath. To the reaction mixture, bromine (170 μL, 3.3 mmol) was added and stirred at 0 °C for 15 min. The reaction mixture was concentrated in vacuo, the residue was purified by silica gel column chromatography (hexane–ethyl acetate) to give the product.

*4.2.1. 3-Bromo-4-methoxy-1-(toluene-4-sulfonyl)-1H-indole (**1j**).* Yield 48%. Colorless solid; ^1H NMR (400 MHz, $CDCl_3$): δ=7.75 (d, J=8.0 Hz, 2H), 7.60 (d, J=8.0 Hz, 1H), 7.50 (s, 1H), 7.22–7.27 (m, 3H), 6.66 (d, J=8.0 Hz, 1H), 3.88 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.8, 145.3, 135.9, 134.7, 130.0, 127.0, 126.6, 124.2, 118.4, 110.3, 106.4, 105.9, 104.6, 96.2, 55.6, 21.6; MS (ESI): m/z=380 [M+H], 382 [M+2+H]; HRMS (EI): $C_{16}H_{14}BrNO_3S$ requires m/z 378.9878, found m/z 378.9873; IR (ATR): 1367, 1166, 1099 cm^{-1}.

*4.2.2. 3-Bromo-4-nitro-1-(toluene-4-sulfonyl)-1H-indole (**1k**).* Yield 39%. Pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ=8.28 (d, J=8.0 Hz, 1H), 7.84 (s, 1H), 7.79 (d, J=8.0 Hz, 2H), 7.75 (d, J=8.0 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 7.30 (d, J=8.0 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=146.4, 143.2, 135.8, 134.1, 130.4, 129.5, 127.1, 124.8, 120.6, 120.0, 117.9, 94.9, 21.7; MS (ESI): m/z=395 [M+H], 397 [M+2+H]; HRMS (EI): $C_{15}H_{11}BrN_2O_4S$ requires m/z 393.9623, found m/z 393.9620; IR (ATR): 1517, 1360, 1346, 1167 cm^{-1}.

*4.2.3. 3-Bromo-1-(toluene-4-sulfonyl)-1H-indole-4-carboxylic acid methyl ester (**1l**).* Yield 35%. Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$): δ=8.16 (d, J=8.0 Hz, 1H), 7.75–7.77 (m, 3H), 7.54 (d, J=8.0 Hz, 1H), 7.39 (t, J=8.0 Hz, 1H), 7.25 (d, J=8.0 Hz, 2H), 3.96 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.5, 145.8, 134.9, 134.4, 130.2, 127.7, 127.0, 125.9, 124.9, 124.7, 116.3, 97.1, 52.3, 21.6; MS (ESI): m/z=408 [M+H], 410 [M+2+H]; HRMS (EI): $C_{17}H_{14}BrNO_4S$ requires m/z 406.9827, found m/z 406.9819; IR (ATR): 1724, 1374, 1151 cm^{-1}.

4.3. Synthesis of racemic-2-benzyloxycarbonylamino-3-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]propionic acid methyl ester (racemic-3d)

Benzyl chloroformate (157 μL, 1.1 mmol) was added to a stirred solution of 2-amino-3-(1*H*-indol-3-yl)propionic acid methyl ester hydrochloride (255 mg, 1.0 mmol) in dichloromethane (4.0 mL) and saturated aqueous solution of sodium hydrogen carbonate (4.0 mL), and the mixture was stirred for 2 h. The reaction mixture was extracted with dichloromethane (2×50 mL). The combined organic layers were washed with brine (2×50 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was dissolved in dichloromethane (6.3 mL), sodium hydroxide (120 mg, 3 mmol), tetrabutylammonium hydrogen sulfide (17 mg, 0.050 mmol), and *p*-toluenesulfonyl chloride (229 mg, 1.2 mmol) were added, and the mixture was stirred for 4 h. After pouring into water, the mixture was extracted with dichloromethane (2×50 mL). The combined organic layers were washed with brine (2×50 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate) to give the title compound (456 mg, 90%) as colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.95 (d, J=8.0 Hz, 1H), 7.69 (d, J=8.0 Hz, 2H), 7.26–7.42 (m, 9H), 7.16–7.20 (m, 3H), 5.29 (d, J=8.0 Hz, 1H), 5.12 (dd, J=24.0, 12.0 Hz, 2H), 4.68–4.73 (m, 1H), 3.64 (s, 3H), 3.17–3.28 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=171.6, 155.6, 144.9, 136.1, 135.1, 130.8, 130.0, 128.6, 128.3, 128.2, 126.7, 124.9, 124.5, 123.3, 119.3, 116.9, 113.7, 67.1, 53.9, 52.5, 27.8, 21.5; MS (ESI): m/z=529 [M+Na]; HRMS (EI): $C_{27}H_{26}N_2O_6S$ requires m/z 506.1512, found m/z 506.1515.

4.4. General procedure for the synthesis of tryptophan derivatives using Negishi cross-coupling reaction

1,2-Dibromoethane (17 μL, 0.20 mmol) was added to a stirred suspension of zinc dust (255 mg, 3.9 mmol) in DMF (0.33 mL), and the mixture was stirred at 50 °C for 30 min. The reaction mixture was allowed to cool to room temperature. Chlorotrimethylsilane (5 μL, 0.039 mmol) was added to the mixture, and the mixture was stirred for a further 30 min vigorously. *N*-Cbz-3-iodoalanine methyl ester (236 mg, 0.65 mmol) in DMF (0.33 mL) was added to the reaction mixture, which was then stirred at room temperature for 2 h. The reaction mixture was then standing for another 30 min, the supernatant liquid was transferred to the 3-bromo-1-(toluene-4-sulfonyl)-1*H*-indole (175 mg, 0.50 mmol), Pd$_2$(dba)$_3$ (11 mg, 0.013 mmol), and Q-PHOS (18 mg, 0.025 mmol) via syringe. The reaction mixture was stirred at 35 °C for 4 h. After pouring into water, the mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with brine (2×50 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate) to give the product.

*4.4.1. (S)-2-Benzyloxycarbonylamino-3-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]propionic acid methyl ester (**3d**).* Yield 66%, 97.2% ee. Colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.95 (d, J=8.0 Hz, 1H), 7.69 (d, J=8.0 Hz, 2H), 7.26–7.42 (m, 9H), 7.16–7.20 (m, 3H), 5.29 (d, J=8.0 Hz, 1H), 5.12 (dd, J=24.0, 12.0 Hz, 2H), 4.68–4.73 (m, 1H), 3.64 (s, 3H), 3.17–3.28 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=171.6, 155.6, 144.9, 136.1, 135.1, 130.8, 130.0, 128.6, 128.3, 128.2, 126.7, 124.9, 124.5, 123.3, 119.3, 116.9, 113.7, 67.1, 53.9, 52.5, 27.8, 21.5; MS (ESI): m/z=529 [M+Na]; HRMS (EI): $C_{27}H_{26}N_2O_6S$ requires m/z 506.1512, found m/z 506.1511.

*4.4.2. (S)-2-Benzyloxycarbonylamino-3-[4-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]propionic acid methyl ester (**3f**).* Yield 76%, Colorless solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.88 (d, J=8.0 Hz, 1H), 7.70 (d, J=8.0 Hz, 2H), 7.43 (s, 1H), 7.30–7.37 (m, 4H), 7.16–7.20 (m, 5H), 5.28 (d, J=8.0 Hz, 1H), 5.06 (s, 2H), 4.72–4.78 (m, 1H), 3.70 (s, 3H), 3.58 (dd, J=16.0, 4.0 Hz, 1H), 3.30 (dd, J=16.0, 8.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=172.1, 155.7, 145.3, 136.4, 136.1, 134.7, 130.0, 128.6, 128.2, 128.1, 127.2, 126.8, 126.6, 125.9, 125.4, 124.6, 117.0, 112.4, 67.0, 54.5, 52.5, 29.1, 21.6; MS (ESI): m/z=563 [M+Na], 565 [M+2+Na]; HRMS (EI): $C_{27}H_{25}ClN_2O_6S$ requires m/z 540.1122, found m/z 540.1111; IR (ATR): 3358, 1716, 1371, 1171 cm^{-1}; $[\alpha]_D^{15}$ −41.4 (*c* 0.50, MeOH).

*4.4.3. (S)-2-Benzyloxycarbonylamino-3-[5-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]propionic acid methyl ester (**3g**).* Yield 50%. Colorless solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.87 (d, J=8.0 Hz, 1H), 7.67 (d, J=8.0 Hz, 2H), 7.40 (s, 1H), 7.33–7.36 (m, 6H), 7.25 (d, J=4.0 Hz, 1H), 7.18 (d, J=4.0 Hz, 2H), 5.29 (d, J=8.0 Hz, 1H), 5.13 (s, 2H), 4.68–4.71 (m, 1H), 3.68 (s, 3H), 3.13–3.27 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=171.4, 155.5, 145.3, 136.0, 134.8, 133.4, 132.1, 130.0, 129.3, 128.6, 128.3, 128.2, 126.7, 125.9, 125.2, 119.1, 116.4, 114.8, 67.3, 53.8, 52.6, 27.6, 21.6; MS (ESI): m/z=563 [M+Na], 565 [M+2+Na]; HRMS (EI): $C_{27}H_{25}ClN_2O_6S$ requires m/z 540.1122, found m/z 540.1115; IR (ATR): 3301, 1738, 1690, 1374, 1168 cm^{-1}; $[\alpha]_D^{15}$ −22.5 (*c* 0.20, MeOH).

*4.4.4. (S)-2-Benzyloxycarbonylamino-3-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]propionic acid methyl ester (**3h**).* Yield 47%, Brown solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.87 (d, J=8.0 Hz, 1H), 7.67 (d, J=8.0 Hz, 2H), 7.40 (s, 1H), 7.33–7.36 (m, 6H), 7.25 (d, J=4.0 Hz, 1H), 7.18 (d, J=4.0 Hz, 2H), 5.28 (d, J=8.0 Hz, 1H), 5.13 (s, 2H), 4.66–4.71 (m, 1H), 3.68 (s, 3H), 3.13–3.27 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=171.4, 155.5, 145.3, 136.0, 134.8, 133.4, 132.1, 130.0, 129.3, 128.6, 128.3, 128.2, 126.7, 125.9, 125.2, 119.1, 116.4, 114.8, 67.3, 53.8, 52.6, 27.6, 21.6; MS (ESI): m/z=563 [M+Na], 565 [M+2+Na]; HRMS (EI): $C_{27}H_{25}ClN_2O_6S$ requires m/z 540.1122, found m/z 540.1122; IR (ATR): 3357, 1716, 1367, 1171 cm^{-1}; $[\alpha]_D^{15}$ −17.6 (*c* 0.50, MeOH).

*4.4.5. (S)-2-Benzyloxycarbonylamino-3-[7-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]propionic acid methyl ester (**3i**).* Yield 45%. Brown solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.69 (s, 1H), 7.64 (d, J=4.0 Hz, 2H), 7.32–7.39 (m, 6H), 7.19–7.24 (m, 3H), 7.07 (t, J=8.0 Hz, 1H), 5.39 (d, J=8.0 Hz, 1H), 5.08–5.17 (m, 2H), 4.72–4.76 (m, 1H), 3.73 (s, 3H), 3.19–3.34 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=171.6, 155.6, 144.7, 136.9, 136.1, 134.6, 131.9, 129.7, 128.6, 128.3, 128.2, 127.2, 127.1, 124.1, 119.2, 117.9, 115.0, 67.1, 54.1, 52.6, 27.8, 21.6; MS (ESI): m/z=563 [M+Na], 565 [M+2+Na]; HRMS (EI): $C_{27}H_{25}ClN_2O_6S$ requires m/z 540.1122, found m/z 540.1126; IR (ATR): 3358, 1716, 1358, 1171 cm^{-1}; $[\alpha]_D^{15}$ +16.3 (*c* 0.10, MeOH).

*4.4.6. (S)-2-Benzyloxycarbonylamino-3-[4-methoxy-1-(toluene-4-sulfonyl)-1H-indol-3-yl]propionic acid methyl ester (**3j**).* Yield 44%. Brown oil; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.69 (d, J=8.0 Hz, 2H), 7.56 (s, J=4.0 Hz, 1H), 7.29–7.38 (m, 5H), 7.15–7.23 (m, 3H), 6.62 (d, J=8.0 Hz, 1H), 5.59 (d, J=4.0 Hz, 1H), 5.11 (s, 1H), 5.03 (s, 2H), 4.63–4.68 (m, 1H), 3.86 (s, 3H), 3.67 (s, 3H), 3.36 (dd, J=16.0, 4.0 Hz), 3.19 (dd, J=12.0, 8.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=172.4, 155.7, 153.9, 144.9, 136.6, 136.3, 135.1, 129.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 126.8, 125.8, 123.5, 120.0, 117.2, 106.8, 103.8, 67.0, 66.8, 55.2, 55.0, 29.3, 21.5; MS (ESI): m/z=559 [M+Na]; HRMS (EI): $C_{28}H_{28}N_2O_7S$ requires m/z 536.1617, found m/z 536.1612; IR (ATR): 3364, 1717, 1363, 1176 cm^{-1}; $[\alpha]_D^{15}$ −23.7 (*c* 0.50, MeOH).

*4.4.7. (S)-2-Benzyloxycarbonylamino-3-[4-nitro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]propionic acid methyl ester (**3k**).* Yield 31%, Brown solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.28 (d, J=8.0 Hz, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.68–7.72 (m, 3H), 7.32–7.39 (m, 6H), 7.19 (d, J=8.0 Hz, 2H), 5.23 (d, J=8.0 Hz, 1H), 5.06 (s, 2H), 4.62–4.67 (m, 1H), 3.696 (s, 3H), 3.45 (dd, J=16.0, 4.0 Hz, 1H), 3.19 (dd, J=16.0, 8.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=172.0, 155.7, 145.9, 143.4, 136.9, 136.0, 134.4, 130.2, 129.3, 128.6, 128.2, 128.1, 126.9, 123.9, 122.8, 120.5, 118.9, 115.7, 67.1, 54.2, 52.6, 30.1, 21.6; MS (ESI): m/z=574 [M+Na]; HRMS (EI): $C_{27}H_{25}N_3O_8S$ requires m/z 551.1362, found m/z 551.1359; IR (ATR): 3344, 1740, 1682, 1520, 1379, 1361, 1169 cm^{-1}; $[\alpha]_D^{15}$ −47.4 (*c* 0.20, MeOH).

*4.4.8. (S)-3-(2-Benzyloxycarbonylamino-2-methoxycarbonyl-ethyl)-1-(toluene-4-sulfonyl)-1H-indole-4-carboxylic acid methyl ester (**3l**).* Yield 18%. Brown solid; ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.18 (d, J=8.0 Hz, 1H), 7.69–7.73 (m, 3H), 7.58 (s, 1H), 7.28–7.38 (m, 6H), 7.16–7.17 (m, 2H), 5.51 (d, J=8.0 Hz, 1H), 5.02 (s, 2H), 4.55–4.60 (m, 1H), 3.92 (s, 3H), 3.65 (s, 3H), 3.45 (dd, J=16.0, 8.0 Hz, 1H), 3.31 (dd, J=16.0, 8.0 Hz), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=172.3, 168.0, 155.8, 145.3, 136.1, 134.8, 130.0, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.6, 126.8, 126.1, 124.9, 123.9, 117.5, 66.9, 54.8, 52.6, 52.4, 29.4, 21.6; MS (ESI): m/z=587 [M+Na]; HRMS (EI): $C_{29}H_{28}N_2O_8S$ requires m/z 564.1566, found m/z 564.1563; IR (ATR): 3361, 1739, 1694, 1376, 1167 cm^{-1}; $[\alpha]_D^{15}$ −23.0 (c 0.10, MeOH).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.053.

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