Scandium Perchlorate as a Superior Lewis Acid for Regioselective Ring Opening of Aziridine Carboxylate with Indoles

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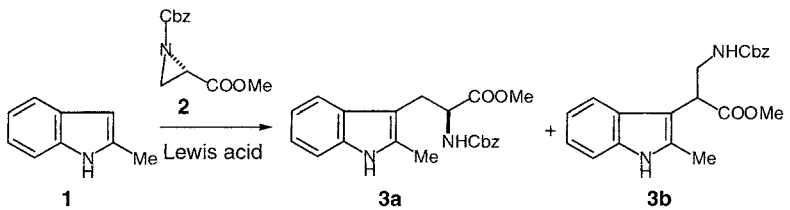
Abstract: In the synthesis of optically active tryptophan derivatives, Lewis acid-promoted coupling between indole and optically active serine-derived aziridine carboxylate is attractive because of the flexibility and convergence. Scandium perchlorate has been found to be a superior Lewis acid to the previously reported scandium triflate with respect to the yields as well as the regioselectivity of aziridine ring opening. The scope and limitation of this Lewis acid are also described.

Key words: tryptophan, indole, aziridine, scandium triflate, scandium perchlorate

In 1989, Kozikowski and Sato reported a novel tryptophan synthesis via a $Zn(OTf)_2$-mediated coupling of indole with optically active aziridine carboxylate ester.[1] Although the reaction scheme seems to be attractive with respect to high convergence and flexibility, little application has been reported so far,[2] probably because of the low yields in most of the cases. In 1998, Bennani and co-workers reported that scandium triflate [$Sc(OTf)_3$] was an alternative Lewis acid for this reaction to give the tryptophan derivatives in better yields.[3,4]

In the course of our synthetic studies on α-*C*-mannosyltryptophan,[5] a naturally occurring *C*-glycosylamino acid,[6] we planned to employ the above coupling between *C*-mannosylindole and the aziridine.[7] However, our preliminary experiments revealed that 2-methylindole (**1**) as a model substrate coupled with the aziridine **2**[8] in the presence of $Sc(OTf)_3$ as a Lewis acid to give a 3:2 mixture of tryptophan **3a** and the regioisomer **3b** (Scheme 1),[9,10] while a similar reaction between 2-methylindole (**1**) and the benzyl ester of **2** under the same conditions was reported to give exclusively the benzyl ester of **3a** in 66% yield.[3] This unexpected result prompted us to re-examine the conditions including the Lewis acid for this coupling reaction.[11] The extensive examination finally led us to find that $Sc(ClO_4)_3$ as an alternative superior Lewis acid, which was applicable to the synthesis of mannosyltryptophan.[7] This paper discloses the full details of our study.

Initially, we surveyed the effect of Lewis acids in the coupling between 2-methylindole (**1**) and the aziridine methyl ester **2**.[12] The typical results are summarized in Table 1. $BF_3{\cdot}OEt_2$, as a conventional Lewis acid for the opening of 3-substituted aziridine-carboxylates with indole,[13] effected a low yield with poor regioselectivity (entry 1). $Zn(OTf)_2$ exhibited high reactivity in this specific substrate[14] to give **3a** in good yield with high regioselectivity (entry 2), while the reactions with other indoles under the same reaction conditions were reported to afford the corresponding products in lower yields.[1] As mentioned above, $Sc(OTf)_3$ introduced by Bennani et al.[3] showed higher reactivity but with low selectivity (entry 3). In spite of the many attempts to reproduce the reported high regioselectivity in different experimental conditions, we could not significantly improve regioselectivity by means of $Sc(OTf)_3$. We were concerned about the quality and dryness of the reagent we used in accordance with Murai and co-workers' report, that *endo/exo* selectivity in $La(OTf)_3$-mediated cyclization of hydroxy epoxides strongly depended on the trace amount of water.[15] The reagent $Sc(OTf)_3$ purchased from different suppliers[16] and self-made $Sc(OTf)_3$ reagent according to the original procedure,[17] showed similar selectivity. Interestingly, when $Sc(OTf)_3$ azeotropically dried with benzene[18] was employed, the reaction was very sluggish, indicating the importance of trace amounts of water. Fortunately, further extensive efforts led us to find that $Sc(ClO_4)_3$[19] was a superior Lewis acid to give **3a** with high regioselectivity (entry 4) with reproducibility, although the difference between $Sc(OTf)_3$ and $Sc(ClO_4)_3$ has not been well docu-



Scheme 1

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mented.[20] Indium triflate $In(OTf)_3$[21] and ytterbium triflate $Yb(OTf)_3$[22] which have been employed as Lewis acids for opening simple aziridines with a variety of nucleophiles, were examined (entries 5 and 6). Although $Yb(OTf)_3$ showed the best regioselectivity in the reaction of this specific substrate, this reagent was not applicable to the synthesis of α-*C*-mannosyltryptophan.[23]

Table 1 The Coupling Between 2-Methylindole (**1**) and the Aziridine **2** in the Presence of a Variety of Lewis Acids

Entry	Conditions[a]				Product	
	Lewis acid	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	Selectivity **3a**:**3b**[c]
1	$BF_3{\cdot}Et_2O$	CH_2Cl_2	0	21	28	40:60
2	$Zn(OTf)_2$	$CHCl_3$	80	19	69	90:10
3	$Sc(OTf)_3$	CH_2Cl_2	0	20	68	60:40
4	$Sc(ClO_4)_3$	CH_2Cl_2	0	13	70	90:10
5	$Yb(OTf)_3$	CH_2Cl_2	r.t.	49	57	100:0
6	$In(OTf)_3$	CH_2Cl_2	0	20	34	40:60
7	$InCl_3$	CH_2Cl_2	0	5	68	55:45

[a] All reactions were carried out using 0.4–0.5 mmol of 2-methylindole (**1**) and the 0.5 equiv of the aziridine **2** and Lewis acid, see experimental.
[b] Yield based on the aziridine **2**.
[c] The ratios were determined by integration values of the ^1H NMR spectrum.

Next, solvent effects in the reaction with $Sc(ClO_4)_3$ were examined. The reaction in acetonitrile showed no regioselectivity (**3a**:**3b** = 1:1). When THF was used as a solvent, coupling products were not obtained while the aziridine **2** decomposed under the reaction conditions. Toluene was not a suitable solvent because of the low solubility of the Lewis acid. These experiments indicated that $Sc(ClO_4)_3$ in CH_2Cl_2 was the best combination with respect to the yield and regioselectivity.

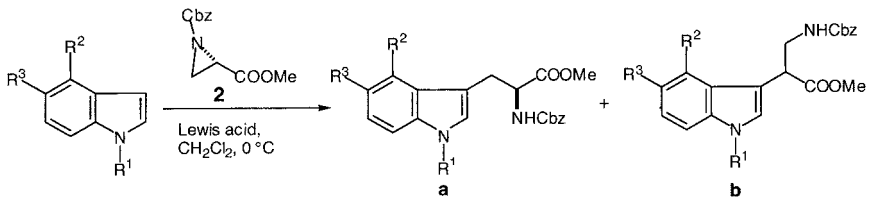
In order to ascertain the general usefulness of $Sc(ClO_4)_3$, the coupling of a variety of substituted indoles with aziridine **2** was examined in comparison with $Sc(OTf)_3$ (Scheme 2, Table 2). The reaction of indole (**4**) in the presence of $Sc(OTf)_3$ gave a mixture of **10a** and **10b** in low yield with no selectivity (entry 1). In sharp contrast, the same reaction with $Sc(ClO_4)_3$ as a Lewis acid gave the products in a moderate yield with higher regioselectivity (entry 2). Furthermore, the reactions of *N*-alkylindoles **5** and **6** gave much better yields (entries 3-6), indicating that *N*-benzylindole (**6**)[24] might be an alternative substrate for indole because the benzyl group of the indole nitrogen was removable. 4-Chlorotryptophan, a plausible biosynthetic precursor of 4-chloroindole-3-acetic acid as a potent naturally occurring auxin type of plant hormone,[25] was synthesized in moderate yield from 4-chloroindole (entries 7 and 8). In this substrate, the selectivity was significantly improved although the yield was not improved. The reaction of indoles substituted with strong electron-withdrawing or -donating groups such as nitro (**8**) and methoxy (**9**) were investigated. In the former case, extremely low yields of the product were obtained under both conditions utilizing of $Sc(OTf)_3$ and $Sc(ClO_4)_3$ (entries 9 and 10). In the latter case, coupled products were not obtained under both conditions, while 5-methoxyindole (**9**) decomposed under the reaction conditions (entries 11 and 12).

Table 2 The Coupling Between a Variety of Indoles and the Aziridine **2** in the Presence of $Sc(OTf)_3$ and $Sc(ClO_4)_3$

Entry	Indole				Conditions[a]		Product		
	No.	R^1	R^2	R^3	Lewis acid	Time (h)		Yield (%)[b]	Selectivity (**a**:**b**)[c]
1	**4**	H	H	H	$Sc(OTf)_3$	23	**10**	29	50:50
2					$Sc(ClO_4)_3$	18.5		51	90:10
3	**5**	Me	H	H	$Sc(OTf)_3$	3.5	**11**	66	62:38
4					$Sc(ClO_4)_3$	3		75	95:5
5	**6**	Bn	H	H	$Sc(OTf)_3$	2	**12**	69	71:29
6					$Sc(ClO_4)_3$	8.5		61	92:8
7	**7**	H	Cl	H	$Sc(OTf)_3$	6	**13**	31	69:31
8					$Sc(ClO_4)_3$	8		36	88:12
9	**8**	H	H	NO_2	$Sc(OTf)_3$	19.5	**14**	10	100:0
10					$Sc(ClO_4)_3$	10.5		2	100:0
11	**9**	H	H	OMe	$Sc(OTf)_3$	25	**15**	0[d]	–
12					$Sc(ClO_4)_3$	6		0[d]	–

[a] All reactions were carried out using 0.4–0.5 mmol of indole **4**–**9** and 0.5 equiv of aziridine **2** and Lewis acid, see experimental.
[b] Yield based on the aziridine **2**.
[c] The ratio was determined by separation of the two regioisomers.
[d] The aziridine **2** was not consumed at the indicated time.

In summary, we have shown that $Sc(ClO_4)_3$ was a superior Lewis acid to $Sc(OTf)_3$ with respect to regioselectivity and reproducibility. Since this coupling strategy is straightforward,[26] this improved method by means of



Scheme 2

$Sc(ClO_4)_3$ has potential applicability to the syntheses of optically active tryptophan derivatives for components of peptidomimetics, chiral building block for the synthesis of indole-containing biologically active compounds.[27]

Scandium Perchlorate [$Sc(ClO_4)_3$][19]

To a stirred solution of $HClO_4$ (70%, 1.57 mL) in H_2O (1.57 mL) was added Sc_2O_3 as a powder (496 mg). The suspension was heated at 100 °C for 4 h, and then cooled to r.t. The resulting mixture was filtered through a pad of Super-Cel, and the precipitate was washed with H_2O. The combined filtrate was evaporated in vacuo. The residue (white solid) was dried with Kugelrohr distillation apparatus under vacuum (0.8 mmHg) at 50–130 °C over ca. 5 h and dried at 130 °C for an additional 33 h. The white solid was crushed and pulverized and further dried for 64 h at 130 °C to afford $Sc(ClO_4)_3$ (1.87 g, 89%).

CAUTION! We have never encountered any problem of explosion of $Sc(ClO_4)_3$, however, we suggest that $Sc(ClO_4)_3$ should be handled with special care, because metal perchlorates have potentially explosive property.[28] In particular, drying of the reagent with heating under vacuum should be conducted in a hood with a safety shield.

***N*$^{\alpha}$-(Benzyloxycarbonyl)-2-methyl-L-tryptophan Methyl Ester (3a) and α-[(Benzyloxycarbonylamino)methyl]-2-methylindol-3-acetic Acid Methyl Ester (3b); Typical Procedure (Tables 1 and 2)**

2-Methylindole (**1**; 52.4 mg, 0.400 mmol) and aziridine carboxylate **2** (47.0 mg, 0.200 mmol), dried azeotropically with benzene before use were dissolved in anhyd CH_2Cl_2 (1.6 mL) and the solution was cooled to 0 °C. To this solution was added $Sc(ClO_4)_3$ (68.6 mg, 0.200 mmol). After stirring at the same temperature for 13 h, the reaction was quenched with aq sat. $NaHCO_3$ solution (1.5 mL). The mixture was diluted with CH_2Cl_2 (1.5 mL) and extracted with CH_2Cl_2 (3 × 1.5 mL). The combined organic extracts were passed through a column packed with anhyd Na_2SO_4 and a thin layer of Na_2CO_3, and concentrated. The residue was purified by column chromatography (silica gel, 10 g, EtOAc–hexane, 1:5 to 1:2) to give a mixture of **3a** and **3b** (51.2 mg, 70%, **3a**:**3b** = 10:1 by ^{1}H NMR). A part of these two products were separated by repeated TLC (CH_2Cl_2, 5 times).

3a

$[\alpha]_D^{24}$ +57.2 (*c* = 1.14, $CHCl_3$) {Lit.[2] D-tryptophan analog $[\alpha]_D^{20}$–59.2 (*c* = 1.0, $CHCl_3$)}.

IR (KBr): 3393, 2952, 1717, 1507, 1215, 1064 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (3 H, s, ArCH_3), 3.25 (2 H, d, *J* = 5.5 Hz, ArCH_2CH), 3.65 (3 H, s, CO_2CH_3), 4.63–4.72 (1 H, m, C*H*CO_2Me), 5.07 (1 H, d, *J* = 12 Hz, CH_AH$_B$Ph), 5.13 (1 H, d, *J* = 12 Hz, CH$_A$$H_B$Ph), 5.31 (1 H, br d, *J* = 8 Hz, N*H*Cbz), 7.04 (1 H$_{arom}$, t, *J* = 8 Hz), 7.10 (1 H$_{arom}$, t, *J* = 8 Hz), 7.24 (1 H$_{arom}$, d, *J* = 8.5 Hz), 7.41 (1 H$_{arom}$, d, *J* = 8 Hz), 7.86 (1 H, br s, NH of indole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 27.1, 52.3, 54.5, 66.8, 105.5, 110.3, 117.8, 119.5, 121.2, 128.0, 128.1, 128.5, 128.8, 132.9, 135.2, 136.3, 155.7, 172.6.

MS (EI): *m*/*z* = 366 (M$^+$).

HRMS (FAB): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ (M + H), 367.1658, found 367.1689.

3b

$[\alpha]_D^{24}$ +84.0 (*c* = 0.91, $CHCl_3$).

IR (KBr): 3398, 2951, 1716, 1508, 1458, 1248 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37(3 H br s, ArCH_3), 3.59 (1 H, dt, *J* = 14, 6.5 Hz, CH_AH$_B$NH), 3.66 (3 H, s, OCH_3), 3.88 (1 H, ddd, *J* = 14, 8.5, 6.5 Hz, CH$_A$$H_B$NH), 4.13 (1 H, dd, *J* = 8.5, 7 Hz, C*H*CO_2Me), 5.05 (1 H, d, *J* = 12 Hz, OCH_AH$_B$Ph), 5.13 (1 H, d, *J* = 12 Hz, OCH$_A$$H_B$Ph), 5.18 (1 H, br t, *J* = 6.5 Hz, N*H*Cbz), 7.06 (1 H$_{arom}$, br t, *J* = 7 Hz), 7.12 (1 H$_{arom}$, td, *J* = 7, 1 Hz), 7.26 (1 H$_{arom}$, br d, *J* = 8 Hz), 7.30–7.40(5 H$_{arom}$, m), 7.52 (1 H$_{arom}$, d, *J* = 7.5 Hz), 7.97 (1 H, br s, NH of indole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 42.0, 42.4, 52.0, 66.6, 106.3, 110.5, 118.4, 119.8, 121.4, 127.0, 128.1, 128.6, 133.1, 135.2, 156.5, 174.0.

MS (EI): *m*/*z* = 366 (M$^+$).

HRMS (FAB): *m*/*z* calcd for $C_{21}H_{23}O_4N_2$ (M + H), 367.1658, found 367.1609.

***N*$^{\alpha}$-(Benzyloxycarbonyl)-L-tryptophan Methyl Ester (10a)**

$[\alpha]_D^{20}$ +42.0 (*c* = 1.85, $CHCl_3$); $[\alpha]_D^{20}$ –7.2 (*c* = 1.42, MeOH), {Lit.[29] $[\alpha]_D^{20}$ –11.4 (*c* = 1.1, MeOH)}.[30]

IR (KBr): 3408, 2952, 1706, 1510, 1341, 1215, 1059 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.30 (2 H, d, *J* = 5 Hz, ArCH_2), 3.66 (3 H, s, CO_2CH_3), 4.71 (1 H, dt, *J* = 8, 5 Hz, CH_2C*H*), 5.06 (1 H, d, *J* = 11 Hz, CH_AH$_B$Ph), 5.12 (1 H, d, *J* = 11 Hz, CH$_A$$H_B$Ph), 5.34 (1 H, d, *J* = 8 Hz, CHN*H*Cbz), 6.91 (1 H, d, *J* = 2 Hz, H-2 of indole), 7.08 (1 H$_{arom}$, td, *J* = 8, 1 Hz), 7.17 (1 H$_{arom}$, td, *J* = 8, 1 Hz), 7.22–7.40 (6 H$_{arom}$, m), 7.51 (1 H$_{arom}$, d, *J* = 8 Hz), 8.16 (1 H, br s, NH of indole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 52.3, 54.4, 66.9, 109.8, 111.3, 118.6, 119.7, 122.2, 122.9, 127.5, 128.1, 128.2, 128.5, 136.2, 136.3, 155.9, 172.5.

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.16; H, 5.93; N, 7.89.

α-[(Benzyloxycarbonylamino)methyl]indole-3-acetic Acid Methyl Ester (10b)

$[\alpha]_D^{26}$ +46.0 (*c* = 0.39, $CHCl_3$).

IR (KBr): 3358, 2954, 1717, 1522, 1437, 1249 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.68 (3 H, s, CO_2CH_3), 3.62–3.82 (2 H, m, CHCH_2NH), 4.21 (1 H, dd, *J* = 8, 6.5 Hz, C*H*CH_2), 5.08 (1 H, d, *J* = 12 Hz, CH_AH$_B$Ph), 5.12 (1 H, d, *J* = 12 Hz, CH$_A$$H_B$Ph), 5.16 (1 H, m, CH_2N*H*), 7.10–7.18 (2 H$_{arom}$, m), 7.21 (1 H$_{arom}$, td, *J* = 7, 1 Hz), 7.29–7.40 (6 H$_{arom}$, m), 7.69 (1 H$_{arom}$, d, *J* = 8 Hz), 8.14 (1 H, br s, NH of indole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.1, 43.2, 52.1, 66.8, 111.0, 111.3, 119.1, 120.1, 122.4, 122.5, 126.3, 128.1, 128.5, 136.2, 136.5, 156.3, 173.7.

HRMS (FAB): *m*/*z* calcd for $C_{20}H_{21}N_2O_4$ (M + H) 352.1423, found 352.1500.

***N*$^{\alpha}$-(Benzyloxycarbonyl)-*N*-methyl-L-tryptophan Methyl Ester (11a)**

$[\alpha]_D^{24}$ +50.0 (*c* = 0.97, $CHCl_3$).

IR (KBr): 3344, 2952, 1718, 1508, 1327, 1213, 1058 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.30 (2 H, d, *J* = 5 Hz, ArCH_2CH), 3.68 (3 H, br s, CH_3), 3.72 (3 H, s, CH_3), 4.70 (1 H, td, *J* = 8, 5 Hz, CH_2C*H*), 5.07 (1 H, d, *J* = 12 Hz, CH_AH$_B$Ph), 5.13 (1 H, d, *J* = 12 Hz, CH$_A$$H_B$Ph), 5.31 (1 H, br d, *J* = 8 Hz, CHN*H*Cbz), 6.81 (1 H, s, H-2 of indole), 7.08 (1 H$_{arom}$, td, *J* = 7, 1 Hz), 7.21 (1 H$_{arom}$, td, *J* = 7, 1 Hz), 7.14–7.40 (7 H$_{arom}$, m), 7.49 (1 H$_{arom}$, br d, *J* = 8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7, 32.6, 52.3, 54.4, 66.8, 108.1, 109.3, 118.7, 119.2, 121.8, 127.5, 128.2, 128.5, 136.4, 136.9, 155.8, 172.5.

Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.93; H, 6.32; N, 7.50.

α-[(Benzyloxycarbonylamino)methyl]-1-methylindole-3-acetic Acid Methyl Ester (11b)

$[\alpha]_D^{25}$ +78.0 (*c* = 0.90, $CHCl_3$).

IR (KBr): 3357, 2950, 1717, 1522, 1332, 1254, 1045 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.68 (3 H, s, CH_3), 3.74 (3 H, s, CH_3), 3.64–3.83 (2 H, m, C*H*$_2$NH), 4.18 (1 H, t, *J* = 7 Hz, C*H*CH_2), 5.07 (1 H, d, *J* = 12 Hz, C*H*$_A$H$_B$Ph), 5.12 (1 H, d, *J* = 12 Hz, C*H*$_A$H$_B$Ph), 5.15 (1 H, m, CH_2N*H*), 6.99 (1 H, s, H-2 of indole), 7.12 (1 H_{arom}, t, *J* = 7 Hz), 7.20–7.40 (7 H_{arom}, s), 7.67 (1 H_{arom}, br d, *J* = 8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.7, 43.0, 43.1, 52.1, 66.7, 109.2, 109.4, 119.2, 119.6, 122.1, 126.8, 127.1, 128.1, 128.6, 136.5, 137.0, 156.4, 173.9.

HRMS (FAB): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ (M + H) 366.1580, found 366.1643.

***N*$^{\alpha}$-(Benzyloxycarbonyl)-*N*-benzyl-L-tryptophan Methyl Ester (12a)**

$[\alpha]_D^{25}$ +47.0 (*c* = 1.76, $CHCl_3$).

IR (KBr): 3338, 2951, 1718, 1508, 1340, 1213, 1060 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.31 (2 H, d, *J* = 5 Hz, ArC*H*$_2$CH), 3.62 (3 H, s, CO_2CH_3), 4.71 (1 H, td, *J* = 8, 5.5 Hz, CH_2C*H*), 5.07 (1 H, d, *J* = 12 Hz, OC*H*$_A$H$_B$Ph), 5.13 (1 H, d, *J* = 12 Hz, OCH$_A$*H*$_B$Ph), 5.25 (2 H, s, NC*H*$_2$Ph of indole), 5.32 (1 H, br d, *J* = 8 Hz, CHN*H*Cbz), 6.88 (1 H, s, H-2 of indole), 7.02–7.40 (13 H_{arom}, m), 7.52 (1 H_{arom}, d, *J* = 8 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 49.8, 52.2, 54.6, 66.8, 109.1, 109.8, 118.9, 119.5, 122.0, 126.7, 126.9, 127.6, 128.2, 128.5, 128.8, 136.4, 136.6, 137.5, 155.8, 172.4.

Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92; N, 6.33. Found: C, 73.28; H, 6.04; N, 6.31.

α-[(Benzyloxycarbonylamino)methyl]-1-benzylindole-3-acetic Acid Methyl Ester (12b)

$[\alpha]_D^{26}$ +51.0 (*c* = 0.28, $CHCl_3$).

IR (KBr): 3348, 2950, 1725, 1515, 1455, 1336, 1249, 1063 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.68 (3 H, s, CO_2CH_3), 3.66–3.82 (2 H, m, C*H*$_2$NH), 4.20 (1 H, dd, *J* = 8, 6.5 Hz, ArC*H*), 5.07 (1 H, d, *J* = 12 Hz, OC*H*$_A$H$_B$Ph), 5.11 (1 H, d, *J* = 12 Hz, OCH$_A$*H*$_B$Ph), 5.16 (1 H, m, CH_2N*H*), 5.26 (2 H, s, NC*H*$_2$Ph of indole), 7.04–7.42 (14 H_{arom}, m), 7.69 (1 H_{arom}, d, *J* = 7.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.2, 50.2, 52.1, 66.7, 109.9, 119.3, 119.8, 122.2, 126.5, 126.9, 127.0, 127.7, 128.1, 128.5, 128.8, 136.6, 137.1, 156.3, 173.7.

HRMS (FAB): *m*/*z* calcd for $C_{27}H_{27}N_2O_4$ (M + H) 442.1893, found 443.1936.

***N*$^{\alpha}$-(Benzyloxycarbonyl)-4-chloro-L-tryptophan Methyl Ester (13a)**

$[\alpha]_D^{24}$ –5.6 (*c* = 0.77, $CHCl_3$).

IR (KBr): 3340, 2953, 1706, 1522, 1436, 1341, 1219, 1047, 936 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.37 (1 H, dd, *J* = 15, 8 Hz, C*H*$_A$H$_B$CHC), 3.64 (1 H, dd, *J* = 15, 5.5 Hz, ArCH$_A$*H*$_B$CH), 3.71 (3 H, s, CO_2CH_3), 4.73 (1 H, td, *J* = 8, 5.5 Hz, C*H*NHCbz), 5.03 (2 H, s, C*H*$_2$Ph), 5.38 (1 H, br d, *J* = 8 Hz, N*H*Cbz), 6.96 (1 H, s, H-2 of indole), 7.02–7.36 (8 H_{arom}, m), 8.32 (1 H, br s, NH of indole).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8, 52.3, 55.3, 66.8, 110.2, 110.6, 120.9, 122.7, 123.1, 124.1, 124.4, 126.1, 128.1, 128.5, 136.3, 137.7, 155.9, 172.9.

Anal. Calcd for $C_{20}H_{19}ClN_2O_4$: C, 62.10; H, 4.95; N, 7.24. Found: C, 61.96; H, 5.16; N, 7.14.

α-[(Benzyloxycarbonylamino)methyl]-4-chloroindole-3-acetic Acid Methyl Ester (13b)

$[\alpha]_D^{25}$ +14.1 (*c* = 0.29, $CHCl_3$).

IR (KBr): 3335, 2951, 1706, 1522, 1436, 1341, 1255, 1046 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.70 (3 H, s, CO_2CH_3), 3.78 (2 H, m, CHC*H*$_2$NH), 4.80 (1 H, t, *J* = 7 Hz, ArC*H*), 5.04 (1 H, d, *J* = 12 Hz, C*H*$_A$H$_B$Ph), 5.10 (1 H, d, *J* = 12 Hz, CH$_A$*H*$_B$Ph), 5.21 (1 H, m, CH_2N*H*Cbz), 7.06–7.38 (9 H_{arom}, m), 8.32 (1 H, br s, NH of indole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.8, 44.4, 52.2, 66.7, 110.2, 111.3, 121.3, 122.9, 124.0, 125.9, 128.0, 128.1, 128.5, 137.5, 156.3, 174.1.

HRMS (FAB): *m*/*z* calcd for $C_{20}H_{20}ClN_2O_4$ (M + H) 386.1033, found 386.1109.

***N*$^{\alpha}$-(Benzyloxycarbonyl)-5-nitro-L-tryptophan Methyl Ester (14a)**

$[\alpha]_D^{26}$ +71.0 (*c* = 0.39, $CHCl_3$).

IR (KBr): 3333, 2955, 1716, 1522, 1335, 1217, 1062 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.34 (1 H, dd, *J* = 15, 5 Hz, ArC*H*$_A$CH$_B$CH), 3.42 (1 H, dd, *J* = 15, 5 Hz, ArCH$_A$C*H*$_B$CH), 3.75 (3 H, s, CO_2CH_3), 4.74 (1 H, dt, *J* = 8, 5 Hz, CH_2C*H*), 5.12 (2 H, s, C*H*$_2$Ph), 5.36 (1 H, br d, *J* = 8 Hz, CHN*H*), 7.11 (1 H, d, *J* = 2.5 Hz, H-2 of indole), 7.28–7.42 (7 H_{arom}, m), 8.11 (1 H_{arom}, dd, *J* = 9, 2 Hz), 8.45 (1 H, br s, NH of indole), 8.51 (1 H, d, *J* = 2 Hz, H-4 of indole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.2, 50.1, 52.1, 66.7, 109.9, 119.3, 119.8, 122.2, 126.5, 126.9, 127.0, 127.7, 128.1, 128.5, 128.8, 136.6, 137.1, 156.3, 173.7.

HRMS (FAB): *m*/*z* calcd for $C_{20}H_{20}N_3O_6$ (M + H) 398.1352, found 398.1334.

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