Synthesis of α-(3-Indolyl)glycine Derivatives via Spontaneous Friedel–Crafts Reaction between Indoles and Glyoxylate Imines

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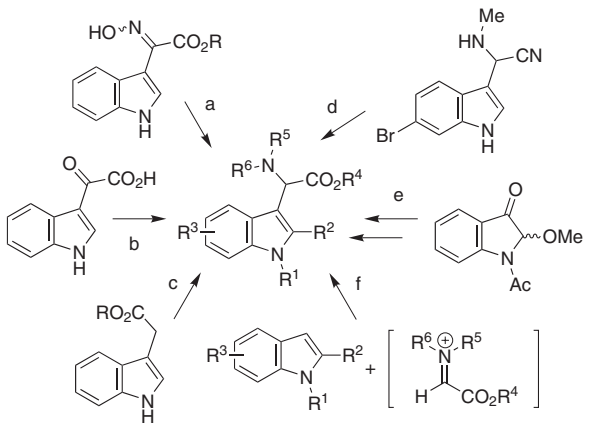
Abstract: Mannich-type Friedel–Crafts reaction between indoles and ethyl glyoxylate imines proceeded spontaneously in the absence of an acid catalyst. Ethyl α-(3-indolyl)glycinates were obtained in moderate to high yields. Reaction with (*R*)-α-methylbenzylamine derived imine afforded chiral α-(3-indolyl)glycinates with good diastereoselectivities (up to 96:4).

Key words: Friedel–Crafts reaction, indolyl glycine, indole derivative, glyoxylate imine, spontaneous reaction

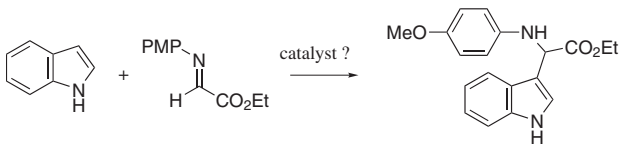
(3-Indolyl)glycine derivatives are important synthetic intermediates or building blocks for drug discovery[1] and marine bisindole alkaloid synthesis.[2] There are several methods to prepare this valuable non-proteinogenic amino acid (Scheme 1). Hydrogenation of the hydroxyimino (3-indolyl)gloxylates has been long used as a preparative method (route a).[1,2c] Recently, (3-indolyl) glycine was prepared by means of the Rh(III)-catalyzed reductive amination of 3-indoleglyoxylic acid with ammonium formate (route b).[3] Oxidation of (3-indolyl) acetate induced by $FeCl_3$ and secondary amines was also reported (route c).[4] The synthesis of bisindole alkaloid Dragmacidins and Hamacanthins involved a modified Strecker adduct as the synthetic intermediate (route d)[2b] or arose from indolin-3-ones (route e).[2d,e]



Scheme 1

Another method uses the direct coupling of indole derivatives and glyoxylate imines/iminiums or glycine cation equivalents (route f).[5] It is worth mentioning that the first total synthesis of bisindole alkaloid Dragmacidin B was achieved via the addition of indoles to cyclic α,α′-dibromo-*N*,*N*′-dimethyl glycine anhydride.[5c] Stoichiometric Lewis acid-promoted reaction between indoles and iminium salts generated in situ from glyoxylate, secondary amines, and 1*H*-benzotriazole constituted a straightforward one-pot stepwise preparation of (3-indolyl)glycinates in high yields.[6] The Cu(I)/Tol-BINAP-catalyzed addition of indoles to *N*-tosylimino esters at –78 °C provided the chiral (3-indolyl)glycinates with high enantioselectivity.[7] The Pd(II)/BIPHEP catalyzed synthesis of the racemates was also reported.[8] Optically active ethyl (3-indolyl)glycinates were obtained through the sequence of Friedel–Crafts reaction catalyzed by $Yb(OTf)_3$, hydrogenation and enzymatic resolution.[9] Highly diastereoselective synthesis was achieved by means of TFA-promoted Friedel–Crafts reaction between *N*-substituted indoles and a chiral cyclic glyoxylate imine.[10] Most of these Friedel–Crafts reactions require a catalytic to stoichiometric amount of Lewis acid or Brønsted acid (5 equiv of TFA was employed in ref.[10]).[11]

Previously, we reported a highly diastereoselective synthesis of *N*-substituted (3-indolyl)glycines based on the three-component Petasis reaction among (3-indolyl) boronic acid, glyoxylic acid hydrate and (*R*)-α-methyl benzylamine.[12] Herein, we disclose the observation of the spontaneous Friedel–Crafts reaction between indoles and ethyl glyoxylate imines without the use of an acid catalyst.[13,14]



Scheme 2

Initially, our intention was to examine the asymmetric induction of chiral Brønsted acids in promoting this type of aza-Friedel–Crafts reaction.[15] Using CH_2Cl_2 as solvent, in which PMPN=$CHCO_2Et$ (*p*-methoxyphenylimino glyoxylate) was generated by stirring the mixture of *p*-anisidine and ethyl glyoxylate in the presence of $MgSO_4$ at room

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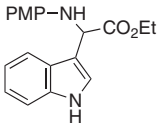
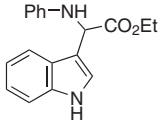
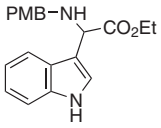
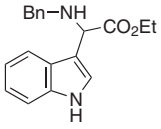
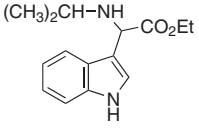
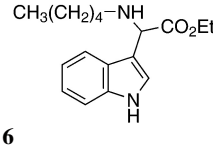
temperature for one hour, upon subsequent addition of indole, it was found that the reaction proceeded spontaneously in the absence of an acid catalyst and moderate to high yields (70–90%) of (3-indolyl)glycinate were obtained after an extension of several hours (Scheme 2).[16] Comparable yields were obtained in toluene. Reaction in ethereal solvent (THF, Et_2O) was much slower. Only a trace amount of product formed in DMSO. By lowering the temperature to –20 °C, an appreciable amount (ca. 50%) of product could be still isolated. It is noteworthy that the ethyl glyoxylate used here was obtained from the 50% solution in toluene and did not need redistillation or heating to depolymerize.[17]

As shown in Table 1, imines generated from a variety of amines were screened. Reaction with arylamine (*p*-anisidine, aniline) derived imines proceeded smoothly in high yields (entries 1 and 2). Benzylic imines were less effective electrophiles (entries 3 and 4). Much lower yields were obtained for aliphatic amine derived imines (entries 5 and 6).

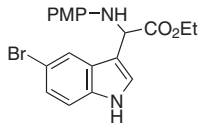
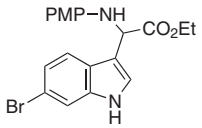
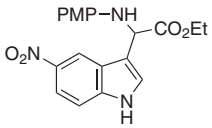
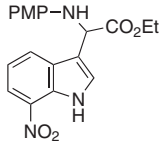
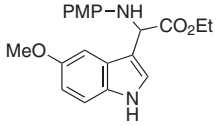
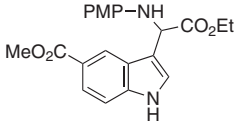
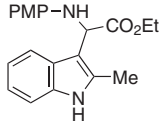
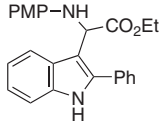
Table 1 Reaction of Indole with Imino Esters at Room Temperature[a]

Entry	Product	Time	Isolated yield
1	 **1**	12 h	89%
2	 **2**	24 h	91%
3	 **3**	72 h	46%
4	 **4**	48 h	61%
5	 **5**	72 h	33%
6	 **6**	72 h	49%

[a] Imines were preformed in toluene in the presence of $MgSO_4$.

As shown in Table 2, a variety of 2-, 5-, 6-, or 7-substituted indoles were used as nucleophiles to react with *p*-methoxyphenylimino glyoxylate. Using CH_2Cl_2 as solvent, reaction of 5-bromo indole provided 85% yield of product

Table 2 Reaction of Indoles with PMPN=$CHCO_2Et$ at Room Temperature[a]

Entry	Product	Time	Isolated yield
1	 **7**	48 h	85%
2	 **8**	48 h	92%
3	 **9**	48 h	69%
4 [b]	 **10**	7 d	44%
5	 **11**	6 h	94%
6 [c]	 **12**	72 h	26%
7	 **13**	12 h	> 99%
8	 **14**	48 h	75%

[a] PMPN=$CHCO_2Et$ was obtained from the solution (20 mg/mL) in CH_2Cl_2 (prepared as described above after removal of $MgSO_4$ by filtration and stored at r.t. for months without decomposition).
[b] Conditions: 40 °C, 36 h, < 5% yield based on ^1H NMR analysis.
[c] Conditions: 0.4 M, 48 h, 53%; 0.4 M, 40 °C, 36 h, 67% isolated yield.

(entry 1). The 6-bromo indole afforded 92% yield of 6-bromo indol-3-yl glycinate, which is an important synthetic intermediate for marine bisindole alkaloid synthesis (entry 2).[2] 5-Nitro indol-3-yl glycinate was isolated in 69% yield, whereas only 44% yield of 7-nitro indol-3-yl glycinate could be obtained after seven days of reaction time (entries 3 and 4). The sluggish rate and low yield for 7-nitro indole might be caused by the possible intramolecular hydrogen bond between the indole NH moiety and the neighboring nitro group. Reaction of electron-donating 5-methoxy substituted indole proceeded more rapidly giving 94% yield after six hours (entry 5). The 5-methoxycarbonyl indole gave only 26% yield at room temperature. Moderate yields were obtained at higher substrate concentration and elevated temperature (entry 6). Reaction of 2-methyl indole went smoothly with high yield, whereas the 2-phenyl substitution slightly retarded the reaction (entries 7 and 8). It should be noted that the addition of *N*-substituted indoles (*N*-TBDMS, *N*-Ts, etc) to glyoxylate imines did not occur without acid catalysis. The free indole NH moiety probably contributed to forming a cyclic transition state, activating the imino group in situ, and promoting the aza-Friedel–Crafts reaction in the absence of an acid catalyst (Figure 1).[18]

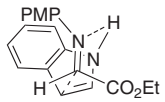
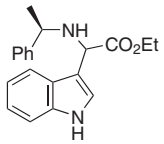
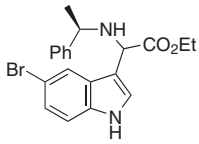
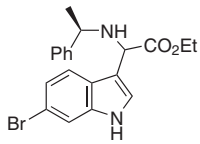
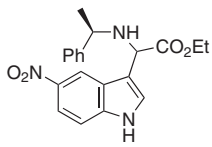
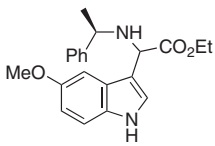
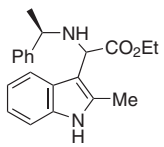


Figure 1

Based on these results, the diastereoselectivity of this reaction between indoles and chiral imines was then studied. As shown in Table 3, the aza-Friedel–Crafts reaction of indole and the chiral (*E*)-2-(α-methylbenzyl imino)glyoxylate also proceeded smoothly in the absence of an acid catalyst. The diastereoselectivities varied in different solvents. The yield in CH_2Cl_2 was 58% with a disappointing 1:1 diastereoisomer ratio. Reaction in THF provided 52% yield with 6:1 diastereoselectivity. The best result (92% yield and 12:1 dr) was obtained in toluene (entry 1). Other solvents ($CHCl_3$, MeCN) gave moderate yields and stereoselectivities. Reaction of 5-bromo indole provided 42% yield with 9:1 diastereoselectivity, while the yield and isomer ratio for the 6-bromo (3-indolyl) glycinate were 62% and 6.5:1, respectively (entries 2 and 3). However, 5-nitro indole gave rather poor result: 33% yield and 2:1 diastereoselectivity (entry 4). The best diastereoselectivity (24:1) was obtained for the electron-donating 5-methoxy substituted indole (entry 5). The fastest rate was observed for 2-methyl indole (entry 6). Reactions of other indoles (7-nitro-, 5-methoxycarbonyl-, 2-phenyl- etc.) were sluggish. And hardly any product was formed in reaction of *N*-substituted indoles and the chiral imine.

In summary, the spontaneous Friedel–Crafts reaction between indoles and glyoxylate imines in the absence of an acid catalyst was observed. A variety of substituted (3-indolyl) glycinates were obtained in moderate to high yields. Reaction of the chiral (*E*)-2-(α-methylbenzylimino)glyoxylate afforded optically active (3-indolyl) glycinate derivatives with moderate to high diastereoselectivities.[19] *N*-Substituted indoles were ineffective in this reaction without acid catalysis. The free indole NH moiety probably contributed to activating the imino group by intermolecular hydrogen bonding and promoting the aza-Friedel–Crafts reaction in the absence of an acid catalyst.

Table 3 Reaction of Indoles with the Chiral Imine at Room Temperature[a]

Entry	Product	Time	Isolated yield	dr[b] and $[\alpha]_D^{20}$
1[c]	 **15**	48 h	92%	92:8 92° (*c* = 0.92)
2	 **16**	98 h	42%	90:10 57° (*c* = 0.90)
3	 **17**	98 h	62%	87:13 70° (*c* = 0.85)
4	 **18**	98 h	33%	67:33 33° (*c* = 0.85)
5	 **19**	72 h	79%	96:4 90° (*c* = 0.85)
6	 **20**	24 h	84%	89:11 89° (*c* = 1.40)

[a] The chiral imine was preformed in toluene in the presence of $MgSO_4$.
[b] The dr was determined by ^1H NMR and the solvent for $[\alpha]_D^{20}$ measurement (mixture of diastereomers) was $CHCl_3$.
[c] Conditions: 40 °C, 36 h; 80% isolated yield, 40:60 dr.

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Varian Mercury 300 spectrometer using $CDCl_3$ as solvent. IR spectra (film of $CDCl_3$ solution) were recorded on a Bio-Rad FTS-185 spectrometer. EI–MS and HRMS were obtained on an Agilent

5973N MSD and an Ionspec 4.7 Tesla FTMS spectrometer. ESI MS data were obtained on an APEXIII 7.0 Tesla FTMS spectrometer.

General Procedure

$MgSO_4$ (200 mg), ansidine (41 mg) and ethyl glyoxylate (70 μL, 50% solution in toluene) were mixed in CH_2Cl_2 or toluene (2 mL) and stirred at r.t. for 1 h. Into the resulting iminoester solution, indole (39 mg) was added and stirred for 12 h. Flash chromatography of the reaction mixture on silica (hexane–EtOAc, 4:1) afforded the product as a slightly yellow oil in 89% yield.

Ethyl 2-(1*H*-Indol-3-yl)-2-(4-methoxyphenylamino)acetate (1)

Slightly yellow oil.

IR: 3405, 2984, 1734, 1513, 1239, 1043, 823, 746 cm^{-1}.

^1H NMR: δ = 8.26 (s, 1 H), 7.83 (d, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.23 (m, 1 H), 7.17 (m, 1 H), 6.75 (d, *J* = 9.0 Hz, 2 H), 6.62 (d, *J* = 9.0 Hz, 2 H), 5.33 (s, 1 H), 4.28–4.09 (m, 2 H), 3.72 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.8, 152.4, 140.7, 136.4, 125.8, 123.0, 122.4, 119.9, 119.5, 114.80, 114.77, 112.6, 111.4, 61.5, 55.7, 55.1, 14.1.

EI–MS: *m*/*z* (%) = 324 (27) [M^+].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_3^+$: 325.1547; found: 325.1529.

Ethyl 2-(1*H*-Indol-3-yl)-2-(phenylamino)acetate (2)

Slightly yellow oil.

IR: 3409, 2983, 1730, 1603, 1505, 1313, 1194, 1018, 747 cm^{-1}.

^1H NMR: δ = 8.15 (s, 1 H), 7.84 (d, *J* = 8.1 Hz, 1 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 7.26–7.12 (m, 5 H), 6.72 (m, 1 H), 6.64 (d, *J* = 8.1 Hz, 2 H), 5.40 (s, 1 H), 4.77 (br, 1 H), 4.30–4.10 (m, 2 H), 1.22 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR: δ = 172.7, 146.4, 136.3, 129.2, 125.6, 123.2, 122.3, 119.8, 119.3, 118.0, 113.3, 111.9, 111.4, 61.5, 54.1, 14.0.

EI–MS: *m*/*z* (%) = 294 (16) [M^+].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{18}N_2O_2Na^+$: 317.1260; found: 317.1262.

Ethyl 2-(1*H*-Indol-3-yl)-2-(4-methoxybenzylamino)acetate (3)

Slightly yellow oil.

IR: 3406, 2929, 1732, 1612, 1513, 1458, 1249, 1180, 1107, 1032, 818, 744 cm^{-1}.

^1H NMR: δ = 8.16 (s, 1 H), 7.71 (d, *J* = 8.1 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.28–7.18 (m, 4 H), 7.12 (t, *J* = 7.2 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 4.69 (s, 1 H), 4.26–4.10 (m, 2 H), 3.81 (s, 3 H), 3.76 (d, *J* = 2.4 Hz, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 173.5, 158.6, 136.3, 131.6, 129.6, 125.9, 123.0, 122.1, 119.7, 119.3, 113.7, 112.8, 111.3, 61.0, 57.2, 55.2, 50.1, 14.1.

EI–MS: *m*/*z* (%) = 339 (2) [M + H]$^+$.

HR–MS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{22}N_2O_3Na^+$: 361.1523; found: 361.1523.

Ethyl 2-(Benzylamino)-2-(1*H*-indol-3-yl)acetate (4)[9]

Colorless oil.

^1H NMR: δ = 8.19 (s, 1 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.37–7.13 (m, 8 H), 4.71 (s, 1 H), 4.23–4.11 (m, 2 H), 3.82 (s, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 173.5, 139.4, 136.3, 128.38, 128.37, 127.1, 125.9, 123.1, 122.1, 119.7, 119.2, 112.6, 111.4, 61.0, 57.4, 51.5, 14.1.

Ethyl 2-(1*H*-Indol-3-yl)-2-(isopropylamino)acetate (5)

Colorless oil.

IR: 3145, 2970, 1727, 1458, 1303, 1185, 1021, 738 cm^{-1}.

^1H NMR: δ = 8.14 (s, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.24–7.12 (m, 3 H), 4.79 (s, 1 H), 4.26–4.09 (m, 2 H), 2.84 (sept, *J* = 6.6 Hz, 1 H), 1.23 (t, *J* = 6.9 Hz, 3 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 1.11 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR: δ = 174.0, 136.3, 125.9, 122.7, 122.2, 119.7, 119.1, 113.2, 111.3, 61.0, 55.9, 46.5, 23.0, 22.6, 14.1.

EI–MS: *m*/*z* (%) = 260 (0.2) [M^+].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}N_2O_2Na^+$: 283.1417; found: 283.1421.

Ethyl 2-(1*H*-Indol-3-yl)-2-(pentylamino)acetate (6)

Colorless oil.

IR: 3408, 2931, 2859, 1734, 1458, 1186, 1024, 742 cm^{-1}.

^1H NMR: δ = 8.70 (s, 1 H), 7.76 (d, *J* = 7.2 Hz, 1 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 7.21–7.10 (m, 2 H), 7.07 (d, *J* = 2.4 Hz, 1 H), 4.69 (s, 1 H), 4.25–4.09 (m, 2 H), 2.70–2.59 (m, 2 H), 1.55 (m, 2 H), 1.32 (m, 4 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR: δ = 173.7, 136.2, 125.9, 122.8, 122.1, 119.6, 119.2, 112.9, 111.3, 61.0, 58.5, 48.0, 29.6, 29.4, 22.5, 14.1, 14.0.

EI–MS: *m*/*z* (%) = 289 (6) [M + H]$^+$, 6%).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{24}N_2O_2Na^+$: 311.1730; found: 311.1729.

Ethyl 2-(5-Bromo-1*H*-indol-3-yl)-2-(4-methoxyphenylamino)acetate (7)

Yellow oil.

IR: 3396, 2984, 1731, 1513, 1462, 1239, 1035, 822 cm^{-1}.

^1H NMR: δ = 8.34 (s, 1 H), 7.97 (s, 1 H), 7.28 (m, 1 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 6.61 (d, *J* = 8.7 Hz, 2 H), 5.26 (s, 1 H), 4.29–4.11 (m, 2 H), 3.72 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.5, 152.6, 140.5, 135.1, 127.4, 125.3, 124.2, 122.1, 114.9, 114.8, 113.2, 112.8, 112.3, 61.7, 55.7, 55.0, 14.1.

EI–MS: *m*/*z* (%) = 402 (15.4) [M^+], 404 (12.6) [M + 2]$^+$.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{19}N_2O_3BrNa^+$: 425.0471; found: 425.0484.

Ethyl 2-(6-Bromo-1*H*-indol-3-yl)-2-(4-methoxyphenylamino)acetate (8)

Slightly yellow oil.

IR: 3393, 2835, 1730, 1513, 1239, 1035, 821 cm^{-1}.

^1H NMR: δ = 8.27 (s, 1 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.43 (s, 1 H), 7.22 (m, 1 H), 7.11 (d, *J* = 2.4 Hz, 1 H), 6.71 (d, *J* = 7.5 Hz, 2 H), 6.55 (d, *J* = 7.5 Hz, 2 H), 5.24 (s, 1 H), 4.21–4.07 (m, 2 H), 3.68 (s, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.5, 152.6, 140.5, 137.2, 124.7, 123.6, 123.3, 120.8, 116.0, 114.9, 114.8, 114.3, 113.0, 61.7, 55.7, 55.0, 14.1.

EI–MS: *m*/*z* (%) = 402 (3.5) [M^+], 404 (2.7) [M + 2]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_2O_3Br^+$: 403.0652; found: 403.0658.

Ethyl 2-(4-Methoxyphenylamino)-2-(5-nitro-1*H*-indol-3-yl)acetate (9)

Yellow oil.

IR: 3363, 2934, 1731, 1610, 1514, 1333, 1242, 822, 740 cm^{-1}.

^{1}H NMR: δ = 8.94 (s, 1 H), 8.84 (s, 1 H), 8.11 (d, *J* = 9.0 Hz, 1 H), 7.37 (m, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 6.62 (d, *J* = 8.7 Hz, 2 H), 5.36 (s, 1 H), 4.30–4.13 (m, 2 H), 3.72 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.0, 152.7, 141.8, 140.2, 139.6, 126.3, 125.2, 118.0, 117.1, 115.4, 115.0, 114.8, 111.5, 62.0, 55.7, 54.9, 14.0.

EI–MS: *m*/*z* (%) = 369 (48) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_3O_5^+$: 370.1397; found: 370.1413.

Ethyl 2-(4-Methoxyphenylamino)-2-(7-nitro-1*H*-indol-3-yl)acetate (10)
Yellow oil.

IR: 3392, 2917, 1733, 1515, 1327, 1235, 1099, 1035, 823, 738 cm^{-1}.

^{1}H NMR: δ = 9.93 (s, 1 H), 8.19 (t, *J* = 8.7 Hz, 2 H), 7.43 (s, 1 H), 7.26 (t, *J* = 8.1 Hz, 1 H), 6.74 (d, *J* = 8.7 Hz, 2 H), 6.61 (d, *J* = 8.7 Hz, 2 H), 5.35 (s, 1 H), 4.29–4.12 (m, 2 H), 3.71 (s, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.0, 152.7, 140.2, 133.0, 129.9, 129.6, 128.0, 125.5, 119.7, 119.4, 114.9, 114.8, 114.6, 61.8, 55.6, 54.9, 14.1.

EI–MS: *m*/*z* (%) = 369 (15) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_3O_5^+$: 370.1397; found: 370.1412.

Ethyl 2-(5-Methoxy-1*H*-indol-3-yl)-2-(4-methoxyphenylamino)acetate (11)
Colorless oil.

IR: 3402, 2833, 1731, 1513, 1239, 1031, 824 cm^{-1}.

^{1}H NMR: δ = 8.12 (s, 1 H), 7.23 (m, 3 H), 6.88 (d, *J* = 8.7 Hz, 1 H), 6.76 (d, *J* = 9.0 Hz, 2 H), 6.62 (d, *J* = 9.0 Hz, 2 H), 5.28 (s, 1 H), 4.26–4.11 (m, 2 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.8, 154.2, 152.4, 140.7, 131.5, 126.1, 123.7, 114.78, 114.75, 112.8, 112.12, 112.10, 100.9, 61.4, 55.8, 55.6, 55.2, 14.1.

EI–MS: *m*/*z* (%) = 354 (6) [M$^+$].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{22}N_2O_4Na^+$: 377.1472; found: 377.1495.

Ethyl 2-(5-Methoxycarbonyl-1*H*-indol-3-yl)-2-(4-methoxyphenylamino)acetate (12)
Slightly yellow oil.

IR: 3315, 2952, 1722, 1686, 1620, 1516, 1438, 1242, 1016, 823, 769 cm^{-1}.

^{1}H NMR: δ = 8.61 (s, 1 H), 8.47 (s, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 7.27 (m, 1 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 6.61 (d, *J* = 8.4 Hz, 2 H), 5.37 (s, 1 H), 4.28–4.11 (m, 2 H), 3.94 (s, 3 H), 3.72 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.5, 168.0, 152.5, 140.5, 139.1, 125.5, 124.3, 123.9, 122.6, 122.1, 114.9, 114.8, 114.4, 111.1, 61.7, 55.7, 54.9, 51.9, 14.0.

EI–MS: *m*/*z* (%) = 382 (19) [M$^+$].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{22}N_2O_5Na^+$: 405.1421; found: 405.1411.

Ethyl 2-(4-Methoxyphenylamino)-2-(2-methyl-1*H*-indol-3-yl)acetate (13)
Slightly yellow oil.

IR: 3383, 2837, 1730, 1575, 1513, 1460, 1240, 1176, 1039, 752 cm^{-1}.

^{1}H NMR: δ = 7.90 (s, 1 H), 7.79 (m, 1 H), 7.27 (m, 2 H), 7.12 (m, 2 H), 6.73 (d, *J* = 6.9 Hz, 2 H), 6.58 (d, *J* = 6.9 Hz, 2 H), 5.22 (s, 1 H), 4.26–4.04 (m, 2 H), 3.71 (s, 3 H), 2.49 (s, 3 H), 1.17 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.6, 152.2, 140.6, 135.0, 133.4, 126.6, 121.2, 119.7, 118.6, 114.7, 114.5, 110.5, 107.3, 61.3, 55.6, 54.8, 14.0, 11.8.

EI–MS: *m*/*z* (%) = 338 (32) [M$^+$].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{22}N_2O_3Na^+$: 361.1523; found: 361.1531.

Ethyl 2-(4-Methoxyphenylamino)-2-(2-phenyl-1*H*-indol-3-yl)acetate (14)
Slightly yellow oil.

IR: 3005, 1716, 1421, 1363, 1223, 1093, 904 cm^{-1}.

^{1}H NMR: δ = 8.32 (s, 1 H), 7.91 (d, *J* = 7.5 Hz, 1 H), 7.65 (d, *J* = 7.5 Hz, 2 H), 7.48–7.41 (m, 3 H), 7.38–7.07 (m, 4 H), 6.61 (d, *J* = 8.4 Hz, 2 H), 6.38 (d, *J* = 8.7 Hz, 2 H), 5.38 (s, 1 H), 4.30–4.06 (m, 2 H), 3.64 (s, 3 H), 1.19 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 172.7, 152.2, 140.5, 137.4, 135.8, 132.0, 128.9, 128.8, 128.5, 126.5, 122.5, 120.3, 120.1, 114.60, 114.58, 111.0, 108.5, 61.5, 55.6, 55.6, 54.7, 14.0.

EI–MS: *m*/*z* (%) = 400 (3.3) [M$^+$].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{24}N_2O_3Na^+$: 423.1679; found: 423.1673.

Ethyl 2-(1*H*-Indol-3-yl)-2-[(*R*)-1-phenylethylamino]acetate (15)
Colorless oil.

IR: 3409, 2979, 1733, 1457, 1186, 1025, 744 cm^{-1}.

^{1}H NMR: δ = 8.19 (s, 1 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.37–7.06 (m, 9 H), 4.53 (s, 1 H), 4.14–3.98 (m, 2 H), 3.71 (q, *J* = 6.6 Hz, 1 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 1.12 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 173.4, 144.7, 136.3, 128.4, 127.0, 126.9, 125.9, 123.5, 122.1, 119.6, 119.4, 112.6, 111.3, 61.0, 55.9, 55.1, 24.1, 13.9.

EI–MS: *m*/*z* (%) = 322 (0.2) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_2^+$: 323.1754; found: 323.1752.

Ethyl 2-(5-Bromo-1*H*-indol-3-yl)-2-[(*R*)-1-phenylethylamino]acetate (16)
Slightly yellow oil.

IR: 3329, 2979, 1736, 1450, 1184, 1024, 886, 702 cm^{-1}.

^{1}H NMR: δ = 8.34 (s, 1 H), 7.80 (d, *J* = 1.8 Hz, 1 H), 7.41–7.20 (m, 8 H), 7.09 (d, *J* = 2.7 Hz, 1 H), 4.49 (s, 1 H), 4.18–4.01 (m, 2 H), 3.70 (q, *J* = 6.6 Hz, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 173.1, 144.6, 135.0, 128.5, 127.8, 127.2, 126.9, 125.2, 124.4, 122.2, 113.1, 113.0, 112.7, 61.2, 55.7, 55.2, 24.1, 14.0.

EI–MS: *m*/*z* (%) = 401 (0.68) [M + H]$^+$, 403 (0.63).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_2O_2Br^+$: 401.0859; found: 401.0853.

Ethyl 2-(6-Bromo-1*H*-indol-3-yl)-2-[(*R*)-1-phenylethylamino]acetate (17)
Slightly yellow oil.

IR: 3340, 2927, 1730, 1454, 1186, 803, 701 cm^{-1}.

^{1}H NMR: δ = 8.44 (s, 1 H), 7.56 (s, 1 H), 7.38–7.20 (m, 8 H), 7.07 (d, *J* = 2.4 Hz, 1 H), 4.49 (s, 1 H), 4.12–3.97 (m, 2 H), 3.67 (q, *J* = 6.6 Hz, 1 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 1.10 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR: δ = 173.2, 144.5, 137.2, 128.5, 127.1, 126.9, 124.9, 123.9, 123.0, 120.8, 115.8, 114.2, 113.2, 61.2, 55.7, 55.1, 24.1, 14.0.

EI–MS: *m*/*z* (%) = 327 (29) [M – CO_2Et]$^+$, 329 (27).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{21}N_2O_2BrNa^+$: 423.0679; found: 423.0669.

Ethyl 2-(5-Nitro-1*H*-indol-3-yl)-2-[(*R*)-1-phenylethylamino]acetate (18)
Yellow oil.

IR: 3116, 2979, 1725, 1520, 1476, 1335, 1234, 1112, 817, 739 cm^{-1}.

^{1}H NMR (major isomer): δ = 8.86 (s, 1 H), 8.67 (d, *J* = 2.1 Hz, 1 H), 8.11 (m, 1 H), 7.43–7.26 (m, 7 H), 4.59 (s, 1 H), 4.30–4.03 (m, 2 H), 3.72 (q, *J* = 6.6 Hz, 1 H), 1.40 (d, *J* = 6.6 Hz, 3 H), 1.17 (t, *J* = 6.9 Hz, 3 H).

^{1}H NMR (minor isomer): δ = 8.80 (s, 1 H), 8.55 (d, *J* = 2.1 Hz, 1 H), 8.08 (m, 1 H), 7.40–7.30 (m, 7 H), 4.48 (s, 1 H), 4.35–4.10 (m, 2 H), 3.88 (q, *J* = 6.6 Hz, 1 H), 1.43 (d, *J* = 6.6 Hz, 3 H), 1.28 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR: δ = 172.9, 114.3, 141.7, 138.4, 128.7, 127.5, 127.2, 126.3, 125.5, 117.9, 117.1, 116.0, 111.4, 61.5, 56.9, 55.6, 23.9, 14.0.

EI–MS: *m*/*z* (%) = 368 (0.8) [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_3O_4^+$: 368.1605; found: 368.1605.

Ethyl 2-(5-Methoxy-1*H*-indol-3-yl)-2-[(*R*)-1-phenylethylamino]acetate (19)
Colorless oil.

IR: 3407, 2930, 1733, 1488, 1456, 1456, 1214, 1176, 1027, 703 cm^{-1}.

^{1}H NMR: δ = 8.32 (s, 1 H), 7.35–7.19 (m, 7 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 7.02 (d, *J* = 2.7 Hz, 1 H), 6.84 (dd, *J* = 9.0, 2.4 Hz, 1 H), 4.51 (s, 1 H), 4.15–4.98 (m, 2 H), 3.81 (s, 3 H), 3.73 (q, *J* = 6.6 Hz, 1 H), 1.33 (d, *J* = 6.6 Hz, 3 H), 1.13 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR: δ = 173.4, 154.0, 144.8, 131.4, 128.4, 127.02, 126.96, 126.5, 123.9, 112.64, 112.60, 112.0, 100.9, 61.0, 55.76, 55.72, 55.0, 24.3, 14.0.

EI-MS: *m*/*z* (%) = 352 (1.3) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2O_3^+$: 353.1860; found: 353.1869.

Ethyl 2-(2-Methyl-1*H*-indol-3-yl)-2-[(*R*)-1-phenylethylamino]acetate (20)
Slightly yellow oil.

IR: 3398, 2978, 1730, 1461, 1193, 1024, 744 cm^{-1}.

^{1}H NMR: δ = 7.83 (s, 1 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.36–7.23 (m, 7 H), 7.08 (m, 2 H), 4.42 (s, 1 H), 4.24–3.99 (m, 2 H), 3.91 (q, *J* = 6.3 Hz, 1 H), 2.25 (s, 3 H), 1.39 (d, *J* = 6.3 Hz, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 173.2, 144.9, 135.1, 134.0, 128.3, 126.85, 126.83, 126.82, 121.0, 119.5, 118.8, 110.4, 107.5, 60.9, 55.0, 54.2, 24.8, 14.0, 11.4.

EI–MS: *m*/*z* (%) = 336 (1.2) [M$^+$].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2O_2^+$: 337.1910; found: 337.1909.

Ethyl 2-Amino-2-(1*H*-indol-3-yl)acetate (21)
$[\alpha]_{20}^{D}$ = +90 (*c* = 1.10, $CHCl_3$); [Lit.: –88 (antipode in ref.[9])].

^{1}H NMR: δ = 8.73 (s, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.26–7.09 (m, 3 H), 4.91 (s, 1 H), 4.28–4.06 (m, 2 H), 2.42 (s, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 174.4, 136.4, 125.3, 122.4, 122.2, 119.7, 119.1, 114.8, 111.4, 61.3, 51.7, 14.1.

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