A Facile Chiral Pool Synthesis of (*S*)-6-Nitroindoline-2-carboxylic Acid from L-Phenylalanine

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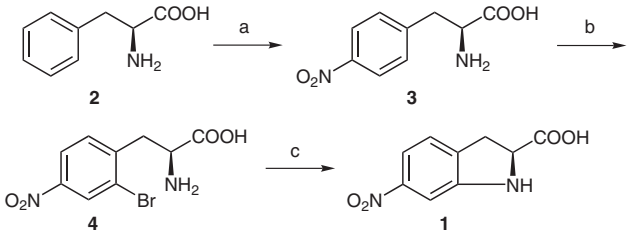
Abstract: (*S*)-6-Nitroindoline-2-carboxylic acid, a substructure occurring in numerous biologically active natural products, was synthesized with moderate yield (53%) and high enantiomeric excess (>99.5%) starting from the nitration of L-phenylalanine, which is a commercially available chiral pool compound, followed by successively bromination and intramolecular cyclization. The route was carried out in gram quantities and it is suitable for industrial application due to its convenient reaction conditions and low cost.

Key words: chiral pool synthesis, (*S*)-6-nitroindoline-2-carboxylic acid, L-phenylalanine, 2-bromo-4-nitro-L-phenylalanine, intramolecular cyclization

Indolines[1] can be found as a building block in numerous biologically active alkaloid natural products[2] and pharmaceuticals.[3] Recently, highly efficient indoline-based organic dyes for dye-sensitized solar cells have also been developed.[4]

Indoline-2-carboxylic acid (2,3-dihydro-1*H*-indole-2-carboxylic acid) has received much attention since the angiotensin converting enzyme (ACE) inhibitor perindopril was discovered[3k,l] and its analogues can be utilized in the catalysis of different organic reactions.[5] A number of elegant and useful approaches toward the synthesis of indoline-2-carboxylic acid have been developed, including the reduction of indole derivatives[6] and transition-metal-catalyzed intramolecular amination of *ortho*-halophenylalanine derivatives[7] or *ortho*-aminophenylpropanoic acid derivatives;[8] chirally pure enantiomers could be obtained after resolution of the racemic mixture of its derivatives with chiral amines[9] or acids[6b] and/or enzymes.[10] Recently, a new procedure was proposed using a radical rearrangement method.[11] However, these previous routes had yields and enantiomeric excesses that were too low for industrial applications; a facile synthesis was needed to fulfill pharmaceutical demand. (*S*)-6-Nitroindoline-2-carboxylic acid (**1**) can easily be converted into other 6-substituted (*S*)-indoline-2-carboxylic acids that can be utilized in the synthesis of pharmaceuticals.[12] It can be obtained from the nitration of (*S*)-indoline-2-carboxylic acid;[13] however, this gives a mixture of 5-nitro and 6-nitro derivatives, which cannot be easily separated.[13] Moreover, few of the methods mentioned above are chiral pool methods. L-Phenylalanine is a convenient chiral pool compound[14] due to its facile availability and, thus, it is widely used in the synthesis of natural and bioactive molecule.[14c,15] The molecular similarity between L-phenylalanine and (*S*)-indoline-2-carboxylic acid prompted us to prepare (*S*)-indoline-2-carboxylic acid via intramolecular cyclization of *ortho*-halo-L-phenylalanine, which, in the literature, was not obtained by the halogenation of L-phenylalanine. Here we report our efforts aimed at the chiral pool synthesis of (*S*)-6-nitroindoline-2-carboxylic acid (**1**) starting from L-phenylalanine (**2**) (Scheme 1).



Scheme 1 Synthesis of 6-nitro-(*S*)-indoline-2-carboxylic acid (**1**) with L-phenylalanine (**2**) as a chiral pool compound. *Reagents and conditions:* (a) HNO_3, H_2SO_4, 0–20 °C, 3 h, 81%; (b) TBCA, H_2SO_4, r.t., 5 h, 73%; (c) H_2O, K_2CO_3, CuCl (5 mol%), reflux, 4 h, 91%.

Initially, we intended to synthesize an *ortho*-halo-substituted L-phenylalanine by halogenation of L-phenylalanine (**2**) (Scheme 2).

Unfortunately, both the regioselectivity and the yields of the halogenations were low regardless of the chloro and bromo substitution and, moreover, the main product was the *para*-substitution product regardless of the reagent employed. To obtain higher regioselectivity for the *ortho*-halo-substitution of L-phenylalanine, the *para*-substitution had to be blocked by an auxiliary, which could be removed readily and had a *meta*-directing effect. Thus, the nitro group was chosen for its strong *meta*-directing effect and because after its reduction to the amino group, the amino group undergoes facile conversion into either a hetero, carbon, or hydrogen atom, via a diazotization reaction or other reactions. However, the nitro group was sufficiently electron-withdrawing that it deactivated the benzene ring to halogenation by the electrophilic substitution process, but recently reported methods for the efficient and simple bromination of deactivated aromatics[16] made the route feasible as the intramolecular cyclization (Ullmann reaction) catalyzed by transition metal has been well documented to give high yields and enantiomeric excess.

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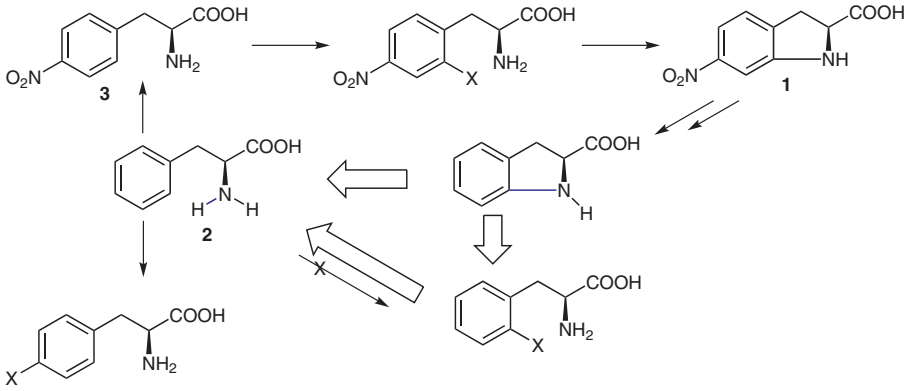

Scheme 2 The retrosynthesis of (*S*)-6-nitroindoline-2-carboxylic acid (**1**)

We began our synthesis from the nitration of L-phenylalanine (**2**), which has been well documented in literature despite its low yield,[17] which was easily overcome using a previously modified procedure.[18] In the nitration of L-phenylalanine (**2**) with mixed acid as nitrating reagent, a byproduct with a much lower melting point was found. After confirmation by IR and ^{1}H and ^{13}C NMR spectroscopy, it was regarded as the coupling product of two L-phenylalanine molecules with sulfuric acid. To suppress the side reaction, we use a tubular reactor instead of the traditional batch reactor and this gave **3** in 81% yield.

As 4-nitro-L-phenylalanine (**3**) has poor solubility in common organic solvent, concentrated sulfuric acid was chosen as the solvent for the halogenations. Bromination, rather than chlorination, was chosen due to the lower reaction temperature required and the resultant bromine atom is easier to cleave. Different bromination reagents were used to improve the yield and enantiomeric excess, including *N*-bromosuccinimide,[16a] sodium bromate,[16h,i] and tribromoisocyanuric acid (TBCA)[16j] and sodium tribromoisocyanurate (Na-TBCA)[19] (Table 1).

Table 1 Bromination of 4-Nitro-L-phenylalanine (**3**) with Different Reagents

Entry	Bromination reagent	Yield[a] (%)	ee (%)
1	$NaBrO_3$, H_2SO_4	11	55
2	NBS, H_2SO_4	14	63
3	TBCA, H_2SO_4	73	>99
4	Na-TBCA, H_2SO_4	44	95

[a] Isolated yield.

Results showed that the bromination of 4-nitro-L-phenylalanine (**3**) did not give a high yield with *N*-bromosuccinimide in sulfuric acid (entry 2). The unprotected 4-nitro-L-phenylalanine (**3**) was prone to oxidative decarboxylation and dimerization with *N*-bromosuccinimide under the acidic conditions,[20] which could also be found in the case of sodium bromate in sulfuric acid (entry 1). According to Gopalakrishnan, oxidative decarboxylation with *N*-bromosuccinimide is followed by the formation of the acyl hypobromite;[20] protection of the amino group seemed insufficient to prevent this side reaction. Furthermore, decarboxylation in the bromination with *N*-bromosuccinimide in sulfuric acid was not the major side reaction compared to dimerization. In other words, only traces of 2-bromo-4-nitrophenylacetaldehyde or 4-nitrophenylacetaldehyde resulting from decarboxylation were found in the products. The product distribution of the bromination of unprotected 4-nitro-L-phenylalanine (**3**) with *N*-bromosuccinimide in sulfuric acid was 2-bromo-4-nitro-L-phenylalanine (**4**), 2-bromo-4-nitrophenylacetonitrile, and the dibromination dimerization product. Protection of the carboxylic acid group reduced the side reaction to the maximum extent, but deprotection made the entire synthesis too complicated. Thus, we turned to another bromination reagent, tribromoisocyanuric acid (TBCA) (entry 3), which gave **4** in high yield and enantiomeric excess and used mild reaction conditions with an easy workup. Bromination with sodium tribromoisocyanurate[16j,19] (entry 4) was carried out several times, but the yield was scarcely more than 45% and the reasons for this were unclear.

The intramolecular cyclization of 2-bromo-4-nitro-L-phenylalanine (**4**) catalyzed by copper(I) bromide in water, similar to the conditions used by De Vries et al.,[7] gave the (*S*)-6-nitroindoline-2-carboxylic acid (**1**) in 91% yield and >99.5% ee. The solvent employed in the cyclization was crucial for the reason that the 2-bromo-4-nitro-L-phenylalanine (**4**) can potentially undergo a racemization reaction that would reduce the enantiomeric excess when an organic solvent was chosen (Table 2). It was believed that water suppressed the racemization and decomposition of 2-bromo-4-nitro-L-phenylalanine (**4**), which was in good

Table 2 Different Solvents Employed in the Cyclization of 2-Bromo-4-nitro-L-phenylalanine (**4**)

Entry	Solvent	Yield (%)	ee (%)
1	H_2O	91	>99.5
2	DMSO	77	45.2
3	NMP	65	13.2
4	DMF	36	0

agreement with Yokoyama et al.[19,21] The base used in the cyclization was either potassium carbonate or tripotassium phosphate; this made little difference. Other stronger bases may cause racemization even in water.

In conclusion, we have demonstrated a facile synthetic proposal for the chiral pool synthesis of (*S*)-6-nitroindoline-2-carboxylic acid (**1**) starting from L-phenylalanine in a total yield of 53%. The convenient reaction condition makes the proposal readily for industrial application.

All reagents were obtained commercially and used without further purification. Melting points were determined on a WSR-2 capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker 400 MHz spectrometer operating near 400 (^{1}H) or 100 (^{13}C) MHz in D_2O or DMSO-d_6 solutions and TMS as internal standard for calibration. IR spectra were recorded on a Nicolet E.S.P560 apparatus. LC-MS were recorded on an Agilent 6000 apparatus. Optical rotations were measured with a Perkin-Elmer 341 polarimeter in a 1 dm cell. Chiral HPLC were obtained on a Waters Alliance 2695 HPLC using a Waters Atlantis C18 column. Elemental analyses were recorded on a Vario E1 III elementary analyzer.

4-Nitro-L-phenylalanine (3)

Prepared in 81% yield following our previous work;[18] mp 241.5–242.4 °C (dec) [Lit.[17a] 235–240 °C (dec)].

$[\alpha]_D^{20}$ –7.9 (*c* 1.01, 1 M HCl) [Lit.[17a] –8.9 (*c* 2.41, 1 M HCl)].

IR (KBr): 3425(br s), 1695 (s), 1535 (s), 1345 cm^{-1} (s).

^{1}H NMR (400 MHz, D_2O): δ = 8.05 (d, *J* = 8.8 Hz, 2 H, H3, H5), 7.36 (d, *J* = 8.8 Hz, 2 H, H2, H6), 4.27 (t, *J* = 6.0 Hz, 1 H, CH), 3.24 (ddd, *J* = 6.0, 7.2, 14.4 Hz, 2 H, CH_2).

^{13}C NMR (101 MHz, D_2O): δ = 170.7, 147.2, 141.9, 130.5, 124.1, 53.4, 35.2.

LC-MS: *m*/*z* (%) = 211 (100, [M + 1]).

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.76; N, 13.33. Found: C, 51.44; H, 4.75; N, 13.34.

2-Bromo-4-nitro-L-phenylalanine (4)

To a well-stirred soln of **3** (21.0 g, 0.10 mol) in 98% H_2SO_4 (50 mL) in an ice-water bath was added TBCA (0.74 mmol) slowly portionwise over a period of 30 min. The reaction was monitored (TLC) and, after 5 h, the mixture was poured onto crushed ice (250 g). The isocyanic acid was filtered off and the filtrate was carefully neutralized with concd aq NH_3 (~150 mL). The product precipitated out and was recrystallized (H_2O) to give **4** as a white solid; yield: 21.9 g (73%); mp 206.8–208.4 °C (dec).

$[\alpha]_D^{20}$ –12.1 (*c* 0.1, 1 M HCl).

IR (KBr): 3420, 3115 (br s), 1733, 1553, 1344, 1054, 883 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ = 8.14 (s, 1 H, H3), 7.81 (d, *J* = 8.4 Hz, 1 H, H5), 7.22 (d, *J* = 8.4 Hz, 1 H, H6), 4.09 (t, *J* = 7.6 Hz, 1 H, CH), 3.13 (ddd, *J* = 7.2, 8.0, 14.0 Hz, 2 H, CH_2).

^{13}C NMR (101 MHz, D_2O): δ = 170.2, 147.3, 141.3, 132.2, 127.9, 124.4, 122.7, 51.9, 35.8.

Anal. Calcd for $C_9H_9N_2O_4Br$: C, 37.37; H, 3.11; N, 9.69. Found: C, 37.40; H, 3.15; N, 9.71.

(*S*)-6-Nitro-2,3-dihydro-1*H*-indole-2-carboxylic Acid (1)

To a soln of **4** (14.5 g, 0.05 mol) in H_2O (200 mL) was added K_2CO_3 (7.0 g) and CuCl (0.3 g). The result mixture was heated to reflux and kept at this temperature for an additional 4 h. The content was filtered to remove the impurities as soon as the reaction finished. The pH of the filtrate was adjusted to 3–4 with 1 M HCl and the resultant soln was extracted with EtOAc (3 × 50 mL). The combined organic phases were successively washed with dilute HCl, H_2O, and brine, decolorized with charcoal, dried ($MgSO_4$), and concentrated in vacuo. Recrystallization (EtOAc–petroleum ether) gave **1** as a yellow solid; yield: 9.4 g (91%); >99.5% ee; mp 168.2–169.7 °C (dec.).

$[\alpha]_D^{20}$ –39.8 (*c* 0.1, DMSO).

IR (KBr): 3396 (s), 3113 (br s), 1727 (s), 1521 (s), 1335 cm^{-1} (s).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.84 (br s, 1 H, COOH), 7.43 (dd, *J* = 2.4, 8.0 Hz, 1 H, H5), 7.25 (d, *J* = 2.4 Hz, 1 H, H7), 7.22 (d, *J* = 8.0 Hz, 1 H, H4), 6.67 (s, 1 H, NH), 4.44 (dd, *J* = 5.6, 10.4 Hz, 1 H, CH), 3.37 (ddd, *J* = 5.6, 10.8, 18.4 Hz, 2 H, CH_2).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 175.0, 152.9, 148.3, 135.6, 124.8, 113.1, 101.6 (Ar-C7), 60.1, 33.3.

LC-MS: *m*/*z* (%) = 209 (100%, [M + 1]).

Anal. Calcd for $C_9H_8N_2O_4$: C, 51.92; H, 3.85; N, 13.46. Found: C, 51.93; H, 3.86; N, 13.43.

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