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Development and Practical Synthesis of a Triple Reuptake Inhibitor, (1*R*,2*S*)-SIPI 5357

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ABSTRACT: A new chromatography-free synthetic route to triple reuptake inhibitor (1*R*,2*S*)-SIPI 5357 was developed and demonstrated on a 300-g scale. The key feature of this route is an asymmetric induction reaction, where the (2*S*,3*S*)-aminoketone **6** was highly stereoselectively reduced to (1*R*,2*S*,3*S*)-amino alcohol **7**. After hydrogenation, chlorination, and cyclization, (1*R*,2*S*)-SIPI 5357 was prepared in 33% overall yield via seven steps from α-bromo ketone **3**.

INTRODUCTION

Depression has received considerable attention in the last decades. Notoriously, it is involved in people's thought, feeling and behavior, which can eventually lead to suicide.[1] Recently, it has been reported that triple reuptake inhibitors (TRIs, the reuptake inhibits of serotonin (5-HT), noradrenalin (NA), and dopaminergic (DA)) are promising chemical entities for the treatment of depression.[2−6] TRIs have been hypothesized to have a more rapid onset of activity and better efficacy over current antidepressants.[7] In our previous studies on such triple acting compounds,[8,9] we disclosed a series of novel and potent arylalkanol-piperazine TRI candidates such as (1*R*,2*S*)-SIPI 5357 (Scheme 1).[10] To prepare sufficient quantity of this TRI candidate for further preclinical pharmacology and safety studies, a practical synthesis is highly desired with improved overall yield and suitable pilot plant scale preparation.

The initial synthetic route to (1*R*,2*S*)-SIPI 5357 is outline in Scheme 1.[10] The major drawback of this synthetic sequence was the requirement of column separation and isolation in the last two steps. Specifically, a column chromatographic separation of 40% low yield, and a subsequent chiral HPLC isolation of about 30% yield. These two problematic steps limited itself from large-scale production of (1*R*,2*S*)-SIPI 5357.

Herein we report an alternative scale-up synthesis of (1*R*,2*S*)-SIPI 5357 in high yield without any column separation.

RESULTS AND DISCUSSION

It is recognized that the initial synthetic route involved an early preparation of diastereomeric alcohol **5**. This synthesis began with a S_N2 reaction between α-bromo ketone **3** and 1-benzylpiperazine, and subsequent reduction of piperazine-ketone **4** by sodium borohydride. To improve the synthesis and develop a chromatography-free synthetic route, an asymmetric induction route has been considered (Schemes 2 and 3) and extensively investigated in this study.

The working process was proposed in Scheme 2: (*S*)-(−)-1-phenylethylamine was introduced into compound **3** by well-documented[11] nucleophilic displacement with (*S*)-(−)-1-phenylethylamine, yielding a mixture of diastereomers amino-ketone. The HPLC analysis revealed the ratio of resulting (2*S*,3*S*)-isomer/(2*R*,3*S*)-isomer was 3/1. Therefore the S_N2 product (2*S*,3*S*)-isomer **6** can be readily obtained by recrystallization, and subsequently reduced to (1*R*,2*S*,3*S*)-amino alcohol **7** with high stereoselectivity.

It was also found that under existing reaction conditions the N-debenzylation of alcohol **7** produced a more favorable dechlorination product **10** instead of the proposed key intermediate **8**. Further investigation into the reaction conditions, such as temperature, pressure, and time with common catalysts (Pd/C and $Pd(OH)_2$) and reagents (HCO_2H, HCO_2NH_4 and H_2) confirmed that **10** was the preferred product under all conditions studied (Table 1). Therefore, the working process (Scheme 2) was adjusted and the final process route (Scheme 3) was established for the scale-up preparation of (1*R*,2*S*)-SIPI 5357.

As shown in Scheme 3, (1*R*,2*S*,3*S*)-amino alcohol **7** was hydrogenated using 10% Pd/C at 60 °C to give the key intermediate β-amino alcohol **10** in good yield (95%). **10** was then reacted with CDI to obtain 1,3-oxazolidin-2-one **11**. Subsequently, the chlorine substitution of **11** yielded compound **12**. The (1*R*,2*S*)-amino alcohol **8** can be furnished by basic hydrolysis to remove the oxazolidinone group. Finally, the coupling of (1*R*,2*S*)-amino alcohol **8** with *N*-benzyl-*N*,*N*-bis(2-chloroethyl)amine **9** gave the desired product (1*R*,2*S*)-SIPI 5357.

The chlorination of **11** was further studied for the large-scale preparation even though the ortho chlorination of 2-methoxynaphthalene derivatives are well-known reactions.[12−16] As shown in Table 2, a number of chlorination reagents were explored. Specifically, by using Cl_2 as a chlorinating reagent, the starting material **11** was completely consumed but only afforded the desired chlorine-substituted compound **12** in 51% isolated yield after 15 h (entry 1). By lowering the temperature to 10 °C and shortening reaction time to 5 h, the isolated yield of **12** decreased to 38% (entry 2), and by using other chlorination reagents, such as HCl/H_2O_2, NCS, and $Ca(ClO)_2$/AcOH, low yields of **12** were observed (entries 3−5). Eventually a system of $NaClO/H^+$ was developed with

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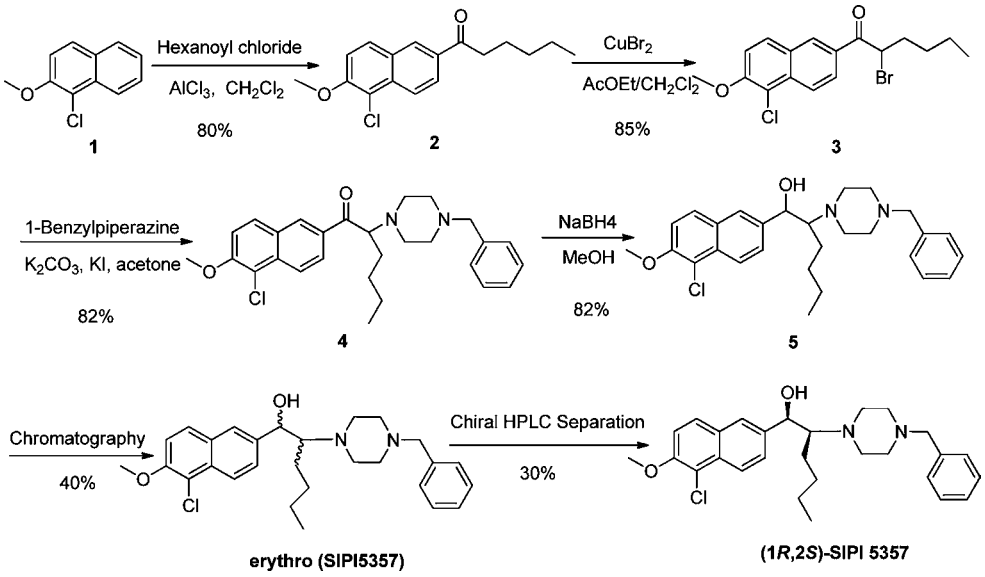
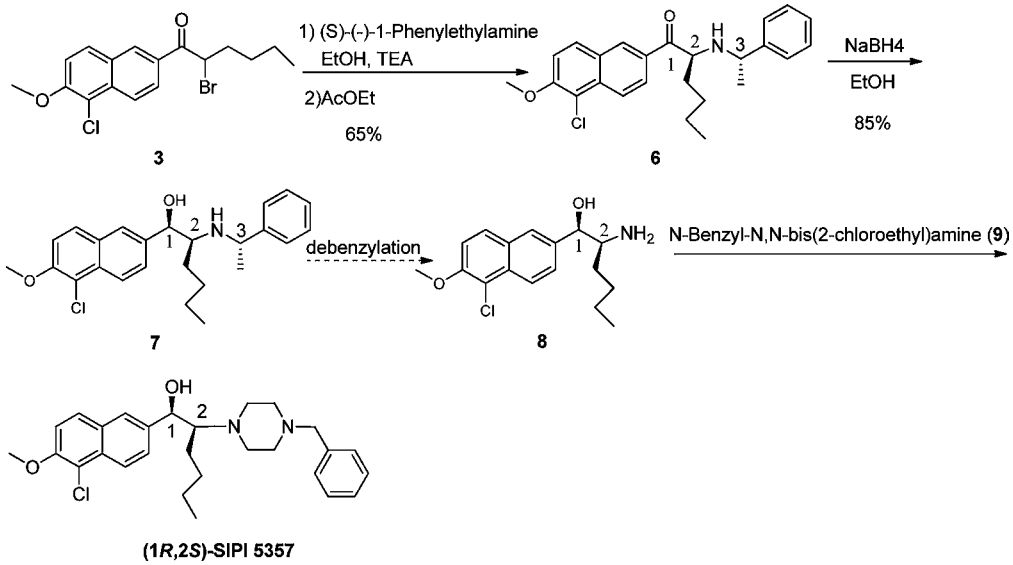
Scheme 1. Initial Synthesis of (1*R*,2*S*)-SIPI 5357



Scheme 2. Working Process for the Synthesis of (1*R*,2*S*)-SIPI 5357



satisfactory yields (entries 6−9), which was further optimised for scale-up preparation of **12** in a good yield (entry 10).

In addition, the coupling of (1*R*,2*S*)-amino alcohol **8** and *N*-benzyl-*N*,*N*-bis(2-chloroethyl)amine (**9**) was explored in this study for optimal coupling conditions (Table 3). Under base-free conditions (entries 1−3), (1*R*,2*S*)-SIPI 5357 was obtained in poor yields (35−55%), and similar yields were achieved in the presence of an inorganic base such as K_2CO_3 and $NaHCO_3$ (entries 4−5). In contrast, by switching from inorganic to organic bases (TEA and DIEA), the desired product can be afforded in good yields (69−76%) (entries 6−7), which was further optimised from 76% to 87% by increasing the molar ratio of **9**/**8** from 1.1 to 1.3 (entries 8−9).

CONCLUSION

In conclusion, we have developed an efficient and scalable seven-step process for the preparation of (1*R*,2*S*)-SIPI 5357 and improved the overall yield from 8% to 33% (from α-bromo ketone **3**). We have achieved this by successfully introducing an asymmetric induction reaction where (2*S*,3*S*)-aminoketone **6** can be highly stereoselectively reduced to (1*R*,2*S*,3*S*)-amino alcohol **7**. In addition, we have demonstrated the optimal conditions for the chlorination of **11** and the coupling of compounds **8** and **9**.

EXPERIMENTAL SECTION

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian INOVA-400 spectrometer with TMS as an internal standard. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. ESI mass spectra were performed on an Agilent 6210 TOF spectrometer. Elemental analyses were performed on an MOD-1106 instrument and are consistent with theoretical values within ±0.3%. Uncorrected melting points were determined on an electrothermal melting point apparatus. Optical rotations were measured with an Autopol V Plus polarimeter. Solvents and reagents were used without any pretreatment. Reaction progress and chemical purity were evaluated by HPLC analysis

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Scheme 3. Final process route for the synthesis of (1*R*,2*S*)-SIPI 5357

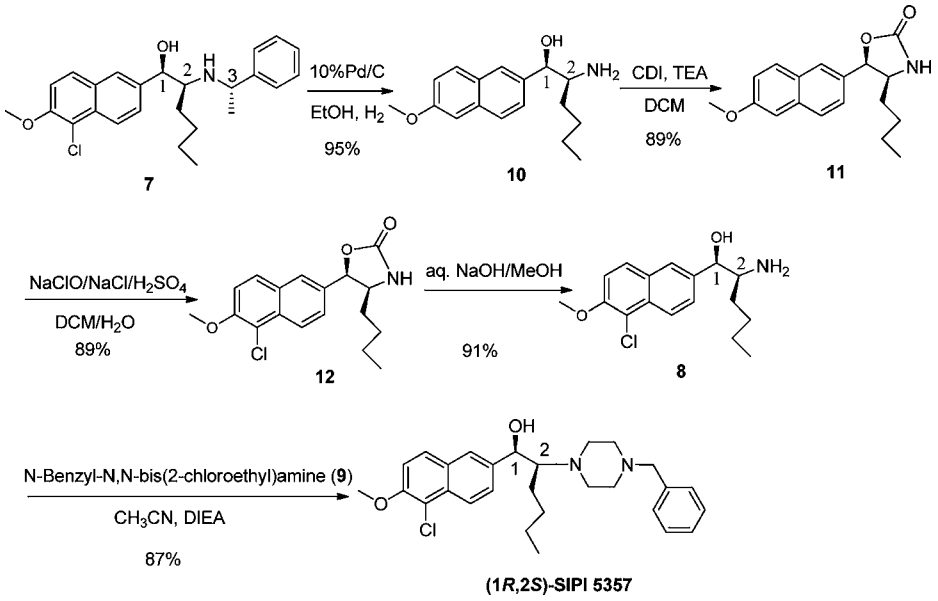
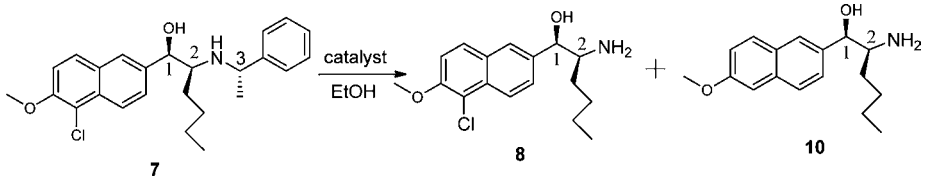


Table 1. N-Debenzylation of 7 under different reaction conditions



entry	catalyst	regent	temp (°C)	pressure (MPa)	time (h)	7 (area %)[a]	8 (area %)[a]	10 (area %)[a]
1	10% Pd/C	H_2	60	0.5	6	0	0.1	99.9
2	10% Pd/C	H_2	60	0.3	4	0.2	0.5	99.3
3	5% Pd/C	H_2	30	0.1	4	0.5	1.5	98.0
4	5% Pd/C	H_2	30	0.1	2	7.9	4.5	87.6
5	10% Pd/C	HCO_2H	60	0.1	4	0	1.3	98.7
6	5% Pd/C	HCO_2NH_4	60	0.1	2	0	2.2	97.8
7	20% $Pd(OH)_2$	H_2	60	0.5	4	0	0.5	99.5
8	10% $Pd(OH)_2$	H_2	30	0.1	4	3.5	6.4	90.1
9	10% $Pd(OH)_2$	H_2	30	0.1	2	12.6	11.2	76.2

[a]Determined by HPLC analysis.

using a Waters symmetry column, C18 (5 μm, 250 mm × 4.6 mm); with a mobile phase A (MeOH + 0.05% TFA) and B (0.3% TEA), 88:12 v/v; detection at 230 nm; flow: 1.0 mL/min; temp 25 °C. Chiral purity was evaluated by HPLC analysis using a Daicel 100 OJ-H chiral column (5 μm, 250 mm × 4.6 mm) with isocratic mobile phase *N*-hexane/isopropanol/diethylamine, 80:20:0.1 v/v/v; and detection at 230 nm; flow: 1.0 mL/min; and temp 30 °C.

1-(5-Chloro-6-methoxynaphthalen-2-yl)hexan-1-one (2). To a stirred solution of 1-chloro-2-methoxynaphthalene (**1**) (800 g, 4.2 mol) in dichloromethane (4 L) was added anhydrous aluminum chloride (665 g, 5 mol) portion-wise at room temperature. The reaction mixture was stirred at the same temperature for 1 h. After cooling to 0−5 °C, a solution of hexanoyl chloride (617 g, 4.6 mol) in dichloromethane (500 mL) was added dropwise, and then the mixture was stirred at room temperature for 10 h. The reaction was completed as determined by thin layer chromatography (TLC) with EtOAc/hexane (1:15, v/v). The reaction mixture was poured slowly onto ice water (3 L); after the mixture stirred for 2 h, the organic layer was washed with water (1 L) and brine (1 L), dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure (~30 mmHg). The light-yellow solid was crystallised from 95% aqueous ethanol (1 L) to afford 967 g of the product 1-(5-chloro-6-methoxynaphthalen-2-yl)hexan-1-one (**2**) as a white solid (80% yield). Mp 89−90 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.48 (s, 1H), 8.25−8.22 (d, J = 12 Hz, 1H), 8.14−8.11 (dd, J_1 = 4 Hz, J_2 = 12 Hz, 1H), 7.90−7.88 (d, J = 8 Hz, 1H),7.34−7.31 (dd, J_1 = 4 Hz, J_2 = 12 Hz, 1H), 4.05 (s, 3H), 3.97−3.93 (t, J = 8 Hz, 2H), 1.73−1.51 (m, 4H), 1.48−1.34 (m, 2H), 0.95−0.91 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.5, 155.2, 134.0, 130.4, 128.4, 125.6, 124.1, 122.6, 116.5, 113.6, 56.6, 40.3, 32.5, 26.6, 21.3, 13.8; MS m/z 291 $[M + H]^+$.

2-Bromo-1-(5-chloro-6-methoxynaphthalen-2-yl)-hexan-1-one (3). To a stirred solution of **2** (900 g, 3.1 mol) in AcOEt/CH_2Cl_2 (2 L/2 L) was added $CuBr_2$ (830 g, 3.7 mol). The reaction mixture was slowly heated to reflux, and the refluxing was continued for 4 h. After the mixture was cooled to room temperature and filtered, the solvent was removed under

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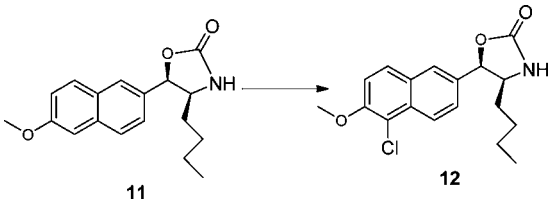
Table 2. Chlorination conditions of 11



11 12

entry	scale (**11**) (g)	reagent	solvent	temp (°C)	time (h)	yield (%)[a]
1	1	Cl_2	$CHCl_3$	20	15	51
2	1	Cl_2	$CHCl_3$	10	5	38
3	1	HCl/H_2O_2	MeOH	60	12	58
4	1	NCS	CH_3CN	50	5	48
5	1	$Ca(ClO)_2$/ AcOH	10/10 (v/v) acetone/H_2O	0	4	33
6	1	NaClO/HCl	2/1 (v/v) CH_2Cl_2/H_2O	0	5	68
7	1	NaClO/ NaCl/ H_2SO_4	2/1 (v/v) CH_2Cl_2/H_2O	0	5	78
8	1	NaClO/HCl	2/1 (v/v) CH_2Cl_2/H_2O	20	3	75
9	1	NaClO/ NaCl/ H_2SO_4	2/1 (v/v) CH_2Cl_2/H_2O	20	2	88
10	50	NaClO/ NaCl/ H_2SO_4	2/1 (v/v) CH_2Cl_2/H_2O	20	2	89

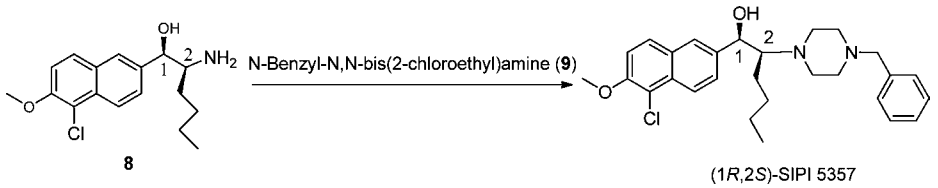
[a]Isolated yield.

reduced pressure (~30 mmHg). The crude residue was washed with water (500 mL), and then the light-yellow solid was crystallised from ethanol (1 L) to afford 970 g of 2-bromo-1-(5-chloro-6-methoxynaphthalen-2-yl) hexan-1-one (**3**) as a white solid (85% yield). Mp 106–108 °C; ^{1}H NMR (400 Hz, $CDCl_3$) δ 8.49 (s, 1H), 8.26–8.23 (d, J = 12 Hz, 1H), 8.13–8.10 (dd, J_1 = 4 Hz, J_2 = 12 Hz, 1H), 7.90–7.88 (d, J = 8 Hz, 1H),7.36–7.28 (dd, J_1 = 12 Hz, J_2 = 20 Hz, 1H), 5.30–5.27 (t, J = 8 Hz, 1H), 4.06 (s, 3H), 2.32–2.14 (m, 2H), 1.69–1.51 (m, 2H), 1.49–1.34 (m, 2H), 0.97–0.94 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 192.7, 154.8, 133.4, 130.1, 128.1, 125.8, 124.1, 122.9, 116.7, 114.0, 56.8, 47.5, 33.3, 29.7, 22.4, 14.0; MS m/z 370 $[M + H]^+$.

(*S*)-1-(5-Chloro-6-methoxynaphthalen-2-yl)-2-(((*S*)-1-phenylethyl)amino)hexan-1-one (6). To a stirred solution of (*S*)-(−)-1-phenylethylamine (375 g, 3.1 mol) and Et_3N (390 g, 3.9 mol) in ethanol (5 L) was added **3** (950 g, 2.6 mol) at room temperature. The mixture was heated to reflux for 15 h and cooled to room temperature. The solution was concentrated under reduced pressure (~30 mmHg) to give a light-yellow oil. AcOEt (4 L) was added to the residue, and the mixture was heated to reflux for 30 min, then cooled to room temperature, stirred for 3 h, and filtered. The filter cake was dried under vacuum to afford the desired (2*S*,3*S*)-isomer **6** as a white solid (686 g, 65% yield) with 99.0% purity and 98.2% ee. $[\alpha]^{25}_D$ −72.1 (MeOH, *c* 1.0); mp 210–212 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 10.53 (br, 1H), 9.36 (s, 1H), 8.79 (s, 1H), 8.20–7.96 (m, 2H), 7.72–7.60 (m, 3H), 7.21 (m, 3H), 5.47 (m, 1H), 4.42 (m, 1H), 4.06 (s, 3H), 2.12 (m, 2H), 1.76 (m, 3H), 1.16–1.04 (m, 4H), 0.70 (m, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 195.3, 155.6, 137.2, 134.0, 132.4, 131.4, 130.2, 129.3, 129.2, 128.9, 128.1, 125.7, 123.7, 115.7, 115.3, 59.9, 58.4, 57.4, 30.8, 36.4, 22.4, 19.5, 14.0; MS m/z 410 $[M + H]^+$.

(1*R*,2*S*)-1-(5-Chloro-6-methoxynaphthalen-2-yl)-2-(((*S*)-1-phenylethyl)amino)hexan-1-ol (7). The (2*S*,3*S*)-aminoketone **6** (650 g, 1.6 mol) was dissolved in EtOH (4 L) and cooled below 10 °C. To this stirred solution was added $NaBH_4$ (30 g, 0.8 mol) portionwise over a period of 30 min. After the final addition of $NaBH_4$, the mixture was allowed to stir at 25 °C for 30 min. The resulting solution was quenched into 3 N hydrochloric acid (300 mL) to crystallise. The mixture was heated to reflux for 30 min, then cooled to room temperature and filtered. The filter cake was washed with EtOH (300 mL), dried under vacuum to afford the (1*R*,2*S*,3*S*)-amino alcohol **7** as a white solid (555 g, 85% yield) with 99.2% purity and 98.6% ee. $[\alpha]^{25}_D$ −22.6 (MeOH, *c* 1.0); mp 189–191 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 7.98–7.96 (d, J = 8 Hz, 1H), 7.94–7.96 (d, J = 8 Hz, 1H), 7.85–7.83 (d, J = 8 Hz, 2H), 7.78 (s, 1H), 7.55–7.43 (m, 4H), 7.24–7.22 (d, J = 8 Hz, 1H), 6.36–6.35 (d, J = 4 Hz, 1H), 5.30 (s, 1H), 4.58 (br, 1H), 3.42 (s, 1H), 2.96 (br, 1H), 1.76–1.75 (d, J = 4 Hz, 1H), 1.57–1.54

Table 3. Reagents and conditions for coupling 8 with 9



8 (1*R*,2*S*)-SIPI 5357

entry	**9**/**8** ratio[a]	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	1.1:1	none	EtOH	75	10	35
2	1.1:1	none	BuOH	115	8	42
3	1.1:1	none	CH_3CN	75	12	55
4	1.1:1	K_2CO_3	EtOH	75	5	45
5	1.1:1	$NaHCO_3$	CH_3CN	75	5	58
6	1.1:1	TEA	CH_3CN	75	5	69
7	1.1:1	DIEA	CH_3CN	75	5	76
8	1.2:1	DIEA	CH_3CN	75	5	87
9	1.3:1	DIEA	CH_3CN	75	5	86

[a]Mole ratio. [b]Isolated yield.

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(m, 2H), 0.95−0.88 (m, 2H), 0.86−0.81 (m, 1H), 0.64−0.57 (m, 1H), 0.48−0.44 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 152.6, 140.9, 133.8, 103.8, 130.4, 129.2, 129.0, 128.8, 127.0, 125.2, 122.6, 115.2, 114.8, 70.2, 69.7, 60.3, 57.2, 51.5, 47.6, 29.7, 23.5, 22.5, 14.2; MS m/z 412 $[M + H]^+$. Anal. Calcd for $C_{25}H_{30}ClNO_2$: C, 72.89; H, 7.34; N, 3.40. Found: C, 72.88; H, 7.28; N, 3.42.

(1*R*,2*S*)-2-Amino-1-(6-methoxynaphthalen-2-yl)-hexan-1-ol (10). A 5 L hydrogenation reactor was charged with Pd/C (10% Pd content, 10 g), EtOH (3 L) and (1*R*,2*S*,3*S*)-amino alcohol **7** (500 g, 1.2 mol). The reactor was pressurised with hydrogen (0.5 MPa) and then warmed to 60 °C for 6 h. The reaction mixture was filtered to remove catalyst, and the solvent was concentrated under reduced pressure (∼30 mmHg) to give a light-yellow solid. The solid was added to AcOEt (600 mL) and stirred for 1 h. After the mixture was filtered, the filter cake was washed with AcOEt (500 mL) and dried under vacuum to afford the β-amino alcohol **10** as a white solid (315 g, 95% yield) with 99.5% purity and 99.0% ee. $[\alpha]^{25}_D$ −32.7 (MeOH, c 2.0); mp 152−154 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 7.85−7.76 (m, 3H), 7.49−7.47 (d, J = 8 Hz, 1H), 7.32 (s, 1H), 7.17−7.11 (dd, J_1 = 4 Hz, J_2 = 16 Hz, 1H), 6.17−6.16 (d, J = 4 Hz, 1H), 5.20 (br, 1H), 3.87 (s, 3H), 3.35 (br, 2H), 3.12 (m, 1H), 1.50−1.47 (m, 2H), 1.39−1.30 (m, 2H), 1.15−1.02 (m, 2H), 0.71−0.67 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 157.7, 136.7, 134.1, 129.8, 128.6, 127.1, 125.8, 125.1, 119.2, 106.3, 71.9, 56.4, 55.8, 27.6, 26.3, 22.3, 14.1; MS m/z 274 $[M + H]^+$; Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.52; H, 8.43; N,5.07.

(4*S*,5*R*)-4-Butyl-5-(6-methoxynaphthalen-2-yl)-oxazolidin-2-one (11). To a stirred solution of β-amino alcohol **10** (300 g, 1.1 mol) and Et_3N (166 g, 1.6 mol) in DCM (2 L) was added *N*,*N*′-carbonyldiimidazole (267 g, 1.6 mol) at room temperature. The reaction mixture was stirred for 12 h, H_2O (500 mL) was added, and the mixture stirred for 20 more min. The organic phase was then washed with 10% hydrochloric acid (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in reduced pressure (∼30 mmHg). The residue was crystallised from AcOEt (800 mL) to afford 292 g of 1,3-oxazolidin-2-one **11** as a white solid (89% yield) with 99.3% purity and 98.7% ee. $[\alpha]^{25}_D$ −27.8 (CH_2Cl_2, c 1.0); mp 178−179 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.53 (br, 1H), 7.83−7.76 (m, 3H), 7.50−7.48 (d, J = 8 Hz, 1H), 7.34 (s, 1H), 7.18−7.14 (dd, J_1 = 4 Hz, J_2 = 12 Hz, 1H), 6.32−6.31(d, J = 4 Hz, 1H), 3.85 (s, 3H), 3.15 (m, 1H), 1.52−1.48 (m, 2H), 1.32−1.25 (m, 2H), 1.16−1.01 (m, 2H), 0.67−0.63 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 165.3, 157.8, 136.4, 134.0, 129.9, 128.3, 127.0, 125.9, 125.3, 119.1, 106.1, 73.1, 56.1, 55.2, 27.4, 26.0, 22.1, 13.8; MS m/z 300 $[M + H]^+$; Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.19; H, 7.03; N, 4.61.

(4*S*,5*R*)-4-Butyl-5-(5-chloro-6-methoxynaphthalen-2-yl)oxazolidin-2-one (12). 1,3-Oxazolidin-2-one **11** (290 g, 0.97 mol) was dissolved in DCM (1.5 L), and to this solution were added sodium chloride (67 g, 1.2 mol) and 40% sulfuric acid (280 mL). Then a solution of 11% sodium hypochlorite (980 mL) was added dropwise over a period of 30 min at room temperature. After this mixture stirred for 2 h, the organic phase was separated, then washed with brine (1 L), and concentrated in reduced pressure (∼30 mmHg) at 35 °C to give a crude product. The crude residue was crystallised from AcOEt (500 mL) to afford 287 g of chlorine substitute **12** as a white solid (89% yield) with 99.5% purity and 98.9% ee. $[\alpha]^{25}_D$ −28.1 (CH_2Cl_2, c 1.0); ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.41 (s, 1H), 8.24−8.22 (d, J = 8 Hz, 1H), 8.13−8.10 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 7.88−7.86 (d, J = 8 Hz, 1H),7.35−7.32 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 6.30−6.29 (d, J = 4 Hz, 1H), 3.87 (s, 3H), 3.13 (m, 1H), 1.51−1.48 (m, 2H), 1.30−1.25 (m, 2H), 1.14−1.00 (m, 2H), 0.61−0.57 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 165.6, 157.8, 136.9, 135.2, 131.2, 129.0, 127.7, 126.1, 120.2, 106.6, 72.1, 55.4, 54.9, 28.3, 25.8, 21.4, 13.7; MS m/z 334 $[M + H]^+$; Anal. Calcd for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; N, 4.20. Found: C, 64.69; H, 6.07; N, 4.18.

(1*R*,2*S*)-2-Amino-1-(5-chloro-6-methoxynaphthalen-2-yl)hexan-1-ol (8). Chlorine substitute **12** (285 g, 0.85 mol) was dissolved in MeOH (1 L). To this mixture was added 2 N sodium hydroxide solution (640 mL). The reaction mixture was heated to reflux for 5 h. MeOH was removed in vacuo, and DCM (1 L) was added and stirred for 30 min. The organic phase was separated and concentrated in vacuo (∼30 mmHg) at 35 °C. The residue was crystallised from 90% aqueous ethanol to afford 239 g of (1*R*,2*S*)-amino alcohol **8** as a white solid (91% yield) with 99.6% purity and 99.1% ee. $[\alpha]^{25}_D$ −24.2 (MeOH, c 2.0); mp 161−162 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.42 (s, 1H), 8.23−8.21 (d, J = 8 Hz, 1H), 8.12−8.10 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 7.89−7.87 (d, J = 8 Hz, 1H),7.34−7.32 (dd, J_1 = 4 Hz, J_2 = 8 Hz, 1H), 6.18−6.17 (d, J = 4 Hz, 2H), 5.21 (br, 1H), 3.88 (s, 3H), 3.37 (br, 2H), 3.15 (m, 1H), 1.52−1.48 (m, 2H), 1.40−1.32 (m, 2H), 1.13−1.02 (m, 2H), 0.68−0.66 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 158.9, 137.8, 135.3, 131.1, 128.9, 127.8, 126.2, 125.6, 119.8, 106.9, 71.8, 56.3, 55.9, 28.1, 26.5, 22.4, 14.0; MS m/z 308 $[M + H]^+$; Anal. Calcd for $C_{17}H_{22}ClNO_2$: C, 66.33; H, 7.20; N, 4.55. Found: C, 66.21; H, 7.23; N, 4.58.

(1*R*,2*S*)-2-(4-Benzylpiperazin-1-yl)-1-(5-chloro-6-methoxynaphthalen-2-yl)hexan-1-ol ((1*R*,2*S*)-SIPI 5357). A solution of (1*R*,2*S*)-amino alcohol **8** (230 g, 0.75 mol) and Et_3N (91 g, 0.9 mol) in acetonitrile (800 mL) was stirred at room temperature, and then *N*-benzyl-*N*,*N*-bis(2-chloroethyl)-amine **9** (207 g, 0.9 mol) was added. The reaction mixture was heated to reflux and stirred for 8 h. The mixture was concentrated in vacuo, and DCM (1 L) and water (500 mL) were added and stirred vigorously for 30 min. The phases were separated, and the organic layer was washed with brine (300 mL). The DCM was distilled, and the residue was crystallised from AcOEt (500 mL) to afford 303 g of **(1*R*,2*S*)-SIPI 5357** as a white solid (87% yield) with 99.6% purity and 99.3% ee. $[\alpha]^{25}_D$ −12.1 (MeOH, c 0.5); mp 218−220 °C; ^{1}H NMR (400 Hz, DMSO-d_6) δ 8.04−8.01(d, J = 12 Hz, 1H), 7.96−7.96 (d, J = 8 Hz, 1H), 7.92 (s, 1H), 7.63−7.61 (d, J = 8 Hz, 1H), 7.54−7.52 (d, J = 8 Hz, 1H), 7.47−7.46 (m, 2H), 7.41−7.34 (m, 3H), 5.22 (s, 1H), 3.98 (s, 3H), 3.93 (s, 2H), 3.10 (m, 4H), 2.97−2.85 (m, 5H), 1.61−1.41 (m, 2H), 1.23−1.12 (m, 1H), 1.09−0.97 (m, 2H), 0.89 (m, 1H), 0.62 (t, J = 8 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 152.6, 140.9, 133.8, 130.8, 130.4, 129.2, 129.0, 128.8, 127.0, 125.2, 122.6, 115.2, 114.8, 70.2, 69.7, 60.3, 57.2, 51.5, 47.6, 29.7, 23.5, 22.5, 14.2; MS m/z 467 $[M + H]^+$; Anal. Calcd for $C_{28}H_{35}ClN_2O_2$: C, 72.01; H, 7.55; N, 6.00. Found: C, 72.10; H, 7.53; N, 5.92.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Dilsaver, S. C.; Chen, Y. W.; Swann, A. C.; Shoaib, A. M.; Krajewski, K. J. *Am. J. Psychiatry* **1994**, *151* (9), 1312−1315.
(2) Micheli, F.; Cavanni, P.; Andreotti, D.; Arban, R.; Benedetti, R.; Bertani, B.; Bettati, M.; Bettelini, L.; Bonanomi, G.; Braggio, S. *J. Med. Chem.* **2010**, *53* (13), 4989−5001.
(3) Tran, P.; Skolnick, P.; Czobor, P.; Huang, N.; Bradshaw, M.; McKinney, A.; Fava, M. *J. Psychiatr. Res.* **2012**, *46* (1), 64−71.
(4) Tian, J. W.; Jiang, W. L.; Zhong, Y.; Meng, Q.; Gai, Y.; Zhu, H. B.; Hou, J.; Xing, Y.; Li, Y. X. *Neuroscience* **2011**, *196*, 124−130.
(5) Shao, L.; Hewitt, M. C.; Malcolm, S. C.; Wang, F.; Ma, J.; Campbell, U. C.; Spicer, N. A.; Engel, S. R.; Hardy, L. W.; Jiang, Z. D. *J. Med. Chem.* **2011**, *54* (15), 5283−5295.
(6) Deschamps, N. M.; Elitzin, V. I.; Liu, B.; Mitchell, M. B.; Sharp, M. J.; Tabet, E. A. *J. Org. Chem.* **2011**, *76* (2), 712−715.
(7) Chen, Z.; Skolnick, P. *Expert Opin. Invest. Drugs* **2007**, *16* (9), 1365−1377.
(8) Zheng, Y. Y.; Guo, L.; Zhen, X.; Chu, Li, J. Q. *Eur. J. Med. Chem.* **2012**, *54*, 123−136.
(9) Weng, Z. J.; Li, J. Q. *Bioorg. Med. Chem. Lett.* **2010**, *20* (3), 1256−1259.
(10) Li, J. Q.; Lv, N.; Jin, H.; Weng, Z. J.; Zheng, Y. Y. The 1-butyl-2-hydroxyarylalkyl piperazine derivatives and the uses as anti-depression medicine thereof. U.S. Patent 2011,183,996, 2009.
(11) Nishiyama, A.; Kishimoto, N.; Nagashima, N. Process for producing optically active s-amino alcohol. EP Patent 1512677, 2005.
(12) Nwaukwa, S. O.; Keehn, P. M. *Synth. Commun.* **1989**, *19* (5−6), 799−804.
(13) Piccolo, O.; Spreafico, F.; Visentin, G.; Valoti, E. *J. Org. Chem.* **1987**, *52* (1), 10−14.
(14) Chang, Y. S.; Deinzer, M. L. *Synth. Commun.* **1990**, *20* (16), 2501−2506.
(15) Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44* (21), 4085−4088.
(16) Moseley, J. D.; Brown, D.; Firkin, C. R.; Jenkin, S. L.; Patel, B.; Snape, E. W. *Org. Process Res. Dev.* **2008**, *12* (6), 1044−1059.