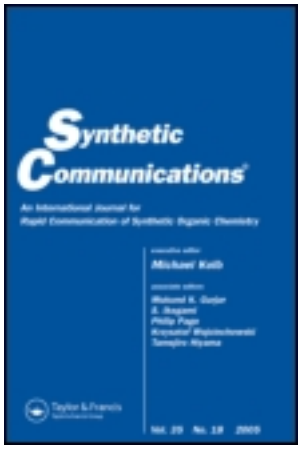

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PRACTICAL LARGE-SCALE PREPARATION OF (*R*)-ROLIPRAM USING CHIRAL NICKEL CATALYST

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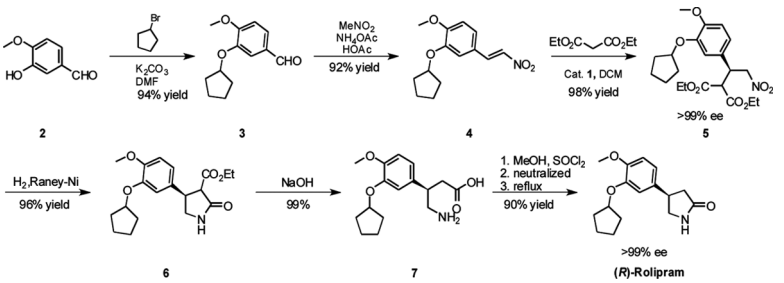
GRAPHICAL ABSTRACT



Abstract *Antidepressant drug (R)-rolipram was readily prepared on a large scale from isovanilline via a succinct route. The key reaction was carried out using a 1 mol% loading of nickel(II)-bis[(*S,S*)-N,N′-dibenzylcyclohexane-1,2-diamine]Br_2 complex as the catalyst. The* ee% *could reach to 99%, and the catalyst could be recovered and used in the next reaction cycle with high* ee%.

Keywords Asymmetric synthesis; Michael addition; (*R*)-rolipram

INTRODUCTION

(*R*)-Rolipram (Fig. 1), an antidepressant drug known to be a selective phosphodiesterase type IV inhibitor,[1] is of great interest as a therapeutic agent for the treatment of central nervous system disorders, such as depression and mental disorders.[2–4] Among the various reported synthetic strategies, the key step introducing the chiral center is still problematic, which increases the cost of this drug. Numerous

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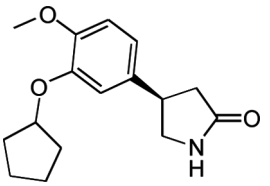


Figure 1. (R)-Rolipram.

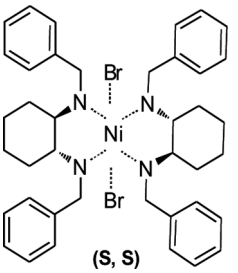


Figure 2. Nickel complex **1**.

approaches have been developed to introduce the chiral center, which include (a) conjugate addition of the chiral enolate to β-nitrostyrene,[5] (b) the conjugate addition of nucleophilic substrate to chiral α,β-unsaturated bicyclic lactam or oxazoline,[6] and (c) a Claisen rearrangment process with the transfer of chiral site.[7] Recently, the application of chiral metal catalyst and organocatalyst has created a new process for (*R*)-rolipram,[8] but loaded catalysts are expensive and difficult to recover in the following cycles. Therefore, developing a new practical symmetric synthesis of (*R*)-rolipram has become increasingly urgent.

Evans et al.[9] invented a readily prepared nickel(II)–bis[(*S,S*)-*N,N′*-dibenzylcyclohexane-1,2-diamine]Br_2 complex that could catalyze the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes to achieve high enantioselective transformation. In this article, we first applied this air- and moisture-stable nickel complex **1** (Fig. 2) to the preparation of (*R*)-rolipram. In addition, the catalyst could be recovered in 90% yield and was used in the next batch of the reaction, affording high *ee*% and yield.

RESULTS AND DISCUSSION

O-Alkylation of isovanillin (**2**) with cyclopentyl bromide, followed by standard Henry condensation of 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) with nitromethane, provided (*E*)-2-(cyclopentyloxy)-1-methoxy-4-(2-nitrovinyl) benzene(**4**) with a yield of 92%. The key Michael addition of diethyl malonate to compound **4** catalyzed by the chiral nickel catalyst was described as follows. The mixture of compound **4** (10.5 g, 40 mmol), diethyl malonate (8.3 g, 52 mmol), and nickel complex **1** (0.36 mg, 0.4 mmol) was stirred under nitrogen at 0 °C. The reaction was monitored by high-perfomance liquid chromatography (HPLC). The effect of

solvent for Michael addition of diethyl malonate to compound **4** catalyzed by nickel complex **1** is illustrated in Table 1. Generally, nickel compelx **1** could be dissolved in a range of solvents and provided perfect reactivity and enantioselectivity. In the polar solvent ethanol, the enantiomeric excess was 80%. The enantioselectivity in neat reaction was normal. Excellent reactivity and enantioselectivity could be obtained in toluene, dichloromethane, and dichloroethane. Decreasing temperature could improve the enantioselectivity slightly, but longer reaction time was required. Interestingly, the use of dichlormethane gave the best results. It might be explained by the best solubility of nickel complex **1** and compound **3** in dichloromethane. In addition, the enantioselectivity could not be improved in tetrahydrofuran (THF) or ethyl acetate.

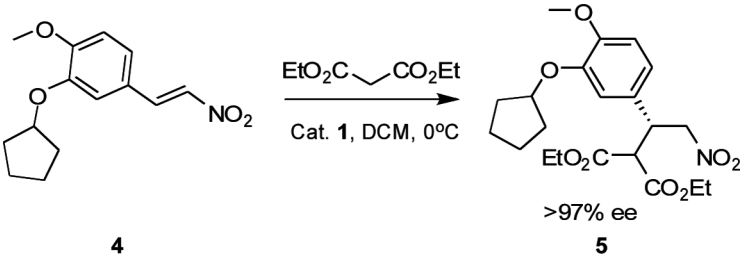
With the extended reaction time, good yield, and *ee*% were achieved by using less loaded catalyst (0.1 mol%). We turned our attention to the recovery of catalyst. The catalyst was the complex of (1*R*,2*R*)-N^1,N^2-dibenzylcyclohexane-1,2-diamine with Ni(II). Hydrochloride could decompose the complex, and the chiral ligand could be dissolved in water as hydrochloride salt, which could be extracted with organic solvent after neutralized with a base. In our experiments, we washed the mixture with 2 N hydrochloride twice, and the combined water phases were neutralized with 2 N NaOH to pH 8. The resulting water phase was extracted with dichloromethane, which resulted in the recovering the chiral ligand in 90% yield. Complex **1** could be synthesized from the recovered chiral ligand and reused. The synthesis route of compound **5** from compound **4** is shown in Scheme 1, and the catalytic asymmetric Michael reaction with catalyst recycling is presented in Table 2. The recovered complex **1** was reused several times. Although slight loss of activity was observed, the recovered complex **1** promoted the Michael reaction to obtain the desired product **5** in very high *ee* even after five runs.

The application of the Michael addition was further evaluated by performing a large-scale experiment. The Michael addition of ethyl malonate with compound **4** catalyzed by 1 mol% catalyst in dichlormethane at room temperature obtained

Table 1. Effect of solvent on enantioselective Michael addition of **4** with diethyl malonate

Entry	Solvent	Reaction temperature (°C)	Reaction time[a] (h)	Yield[b] (%)	*Ee*[c] (%)
1	THF	20	9	92	92
2	EtOAc	20	12	96	90
3	CH_2Cl_2	20	9	98	97
4	CH_2Cl_2	0	20	98	98
5	$ClCH_2CH_2Cl$	20	9	93	97
6	$ClCH_2CH_2Cl$	0	21	98	91
7	EtOH	20	24	95	80
8	Toluene	20	10	98	93
9	Toluene	0	20	98	95
10[d]	Neat	20	100	95	88

[a]All the reactions stopped with conversion of more than 99%.
[b]Isolated yield.
[c]Enantiomeric excess was determined by HPLC with chiracel AD column.
[d]Neat reaction with 1.5 equivalent of diethyl malonate.



Scheme 1. Catalytic asymmetric Michael reaction with catalyst.

Table 2. Catalytic asymmetric Michael reaction with catalyst recycling

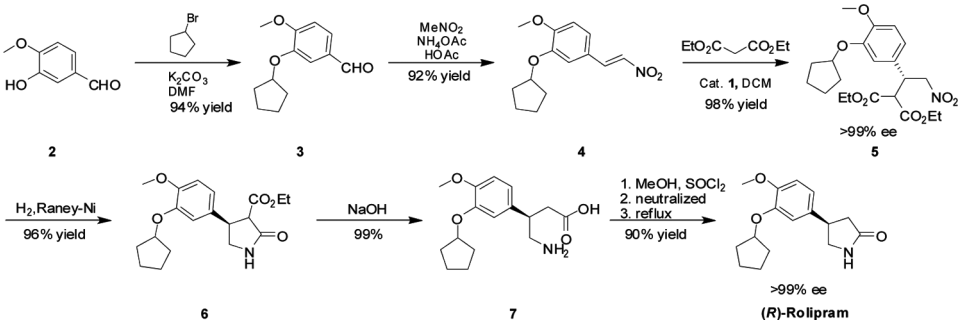
	Cycle				
Parameter	1	2	3	4	5
Yield (%)[a]	98	95	94	92	89
Ee (%)[b]	98	98	97	97	97

[a]Isolated yield.
[b]Enantiomeric excess was determined by HPLC with chiracel AD column.

1 kg of compound **5** in 98% yield with 97% *ee*. Optically pure compound **6** (950 g) was obtained after recrystallization in petroleum ether/methyl-*tert*-butyl ether (4:1) with a yield of 95%.

Eventually, hydrogenlysis of the compound **5** by Raney Ni catalyst gave the lactam **6**, which was further decarboxylated to give compound **7**. One-pot, ring-closure reaction gave (*R*)-rolipram as a single enantiomer in 72.5% overall yield over six steps.

In conclusion, for the first time, nickel(II)–bis[(*S,S*)-*N,N′*-dibenzylcyclohexane-1,2-diamine]Br_2 complex was used as the catalyst to make the key intermediate of (*R*)-rolipram. On a large scale, (*R*)-rolipram was prepared in a succinct route with good yield, and the *ee*% reached to 99%. This method provided an efficient, low-cost protocol to make the antidepressant drug (*R*)-rolipram (Scheme 2).



Scheme 2. General strategy for synthesis of (*R*)-rolipram.

EXPERIMENTAL

The melting point was determined on WRS-2 melting-point apparatus (Shanghai, China) and uncorrected. The NMR spectra were recorded on a Varian 400-MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Jeol AX-505 or SX-102 spectrometers. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp.

Synthesis of 3-(Cyclopentyloxy)-4-methoxybenzaldehyde, 3

To a solution of 3-hydroxy-4-methoxybenzaldehyde (50 g, 0.33 mol) and bromocyclopentane in DMF (400 mL), K_2CO_3 (68.3 g, 0.5 mol) was added and refluxed for 12 h. After completion of the reaction, the mixture was cooled to room temperature. The mixture was taken into water (200 mL), extracted with ethyl acetate (3×200 mL), dried over anhydrous Na_2SO_4, and evaporated to give the brown oily compound **3** (68.0 g); 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1 H, CHO), 7.39 (dd, $J = 8.1$, 1.7, 1 H, Ar-H), 7.33 (d, $J = 1.7$, 1 H, Ar-H), 6.96 (d, $J = 8.1$, 1 H, Ar-H), 4.85–4.74 [m, 1 H,OCH$(CH_2)_4$], 3.90 (s, 3 H, Ar-OCH_3), 2.14–1.80 (m, 6 H, cyclopentyl-H), 1.64–1.52 (m, 2 H, cyclopentyl-H); MS: m/z (M + 1) 221. The data were consistent with those reported in the literature.[10]

Synthesis of (*E*)-2-(Cyclopentyloxy)-1-methoxy-4-(2-nitrovinyl)benzene, 4

A mixture of 3-(Cyclopentyloxy)-4-methoxybenzaldehyde (68 g, 0.31 mol), ammonium acetate (40.6 g, 0.53 mol), and nitromethane (94.6 g, 1.55 mol) in acetic acid (400 mL) was refluxed for 12 h. The reaction mixture was cooled to room temperature. Water was added drop by drop. The solid was filtered and dried to give compound **4** (75.1 g); 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, $J = 13.6$, 1 H, -CH=$CHNO_2$), 7.54 (d, $J = 13.6$, 1 H, -CH=$CHNO_2$), 7.24 (dd, $J = 8.3$, 1.8, 1 H, Ar-H), 7.07 (br d, $J = 1.8$, 1 H, Ar-H), 6.87 (d, $J = 8.3$, 1 H, Ar-H), 4.81 [td, $J = 9.0$, 3.0, 1 H, -OCH$(CH_2)_4$], 3.93 (s, 3 H, Ar-OCH_3), 2.01–1.82 (m, 6 H, cyclopentyl-H), 1.72–1.61 (m, 2 H, cyclopentyl-H); MS: m/z (MNa^+) 286; mp 138.5–139.5 °C. The data were consistent with the literature.[10]

Synthesis of (*S*)-Diethyl-2-(1-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-nitroethyl)malonate, 5

Catalyst **1** (357 mg, 0.4 mmol) was added to a solution of (*E*)-2-(cyclopentyloxy)-1-methoxy-4-(2-nitrovinyl)benzene (10.5 g, 40 mmol) and diethyl malonate (8.3 g, 52 mmol) in CH_2Cl_2(10 mL) under the protection of nitrogen and stirred for 9 h at 0 °C. CH_2Cl_2 was removed under vacuum, and then water (10 mL) was introduced. The solid was filtered and dried to give compound **5**, which was the white solid (17.8 g); 98% yield. Optically pure compound **5** was obtained after recrystallization by petroleum ether/methyl *tert*-butyl ether (MTBE) (4:1). Racemic sample was prepared by racemic catalyst according to the general

procedure. ^{1}H NMR ($CDCl_3$/300 MHz) δ 6.81–6.72 (m, 3H), 4.90 (dd, $J = 12.9$, 1H), 4.82 (dd, $J = 12.9$, 1H), 4.73–4.69 (m, 1H), 4.29–4.14 (m, 3H), 4.05 (q, 2H), 3.76 (s, 3H), 3.79 (d, 1H), 2.02–1.79 (m, 5H), 1.64–1.59 (m, 3H), 1.29 (t, 3H), 0.91 (t, 3H); MS: m/z (MNH_4^+) 441; mp 94.5–95.5 °C; $[\alpha]^D$: 30–9.4 (c 1.15 $CHCl_3$), $ee > 99\%$. Chiral HPLC condition: Agilent 1200 HPLC, Chiracel AD column (250 × 4.6 mm i.d.) with a mixture of hexane and 2-propanol (95:5) at a flow rate 1.0 ml/min as the mobile phase, oven temperature 25 °C, 210 nm, $t_{major} = 20.22$ min, $t_{minor} = 26.22$ min. The data were consistent with literature.[11]

Synthesis of (4*R*)-Ethyl-4-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylate, 6

Raney nickel (5 g, washed with 95% MeOH) was placed in a flask equipped with a magnetic stirrer and charged with a solution of compound **5** (19.9 g, 47 mmol) in MeOH (500 mL) under a nitrogen atmosphere. The reaction system was then flushed and filled with H_2. After stirring the mixture at room temperature for 12 h, the catalyst was filtered off and the filtrate was condensed to produce a light-grey oily compound. Then, petroleum ether was added to give target product **6** (15.7 g); 96% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.74 (br s, 1 H, NH), 6.86–6.68 (m, 3 H, Ar-H), 4.78–4.69 (br m, 1 H, Ar-*CH), 4.23 (q, $J = 7.1$, 2 H, OCH_2CH_3), 3.42 (dd, $J = 18.0$, 8.6, 1 H, CHAHB-NH), 3.85–3.71 (m, 4 H, Ar-OCH_3 and CHAHB-NH), 3.51 (d, $J = 9.8$, 1 H, CH-*C), 3.39 [t, $J = 9.0$, 1 H, $OCH(CH_2)_2$], 1.96–1.73 (m, 6H, cyclopentyl-H), 1.62–1.51 (m, 2 H, cyclopentyl-H), 1.26 (t, $J = 7.1$, 3 H, OCH_2CH_3); MS: m/z (MH^+) 348. The data were consistent with the literature.[10]

Synthesis of (*R*)-Rolipram

The mixture of compound **6** (15.6 g, 45 mmol) in THF (50 mL) and 2 N NaOH aqueous solution (50 mL, 100 mmol) was refluxed for 2 h. The pH value of the resulting solution was adjusted to 1 with 1 N HCl and extracted with CH_2Cl_2(100 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in MeOH (50 mL), and thionly chloride (10 mL) was added in an ice bath. It was stirred at room temperature for 2 h. The mixture was evaporated into dryness and diluted with toluene (50 mL). The resulting solution was neutralized with 2 N NaOH aqueous solution, and the water was decanted. The resulting toluene solution was refluxed for 2 h and evaporated to oil, which was titrated to give yellow solid (*R*)-Rolipram (11.2 g, 90% overall yield); ^{1}H NMR (400 MHz, $CDCl_3$): 7.23 (br s, 1 H, NH), 6.82 (d, $J = 8.5$, 1H, Ar-H), 6.75–6.71 (m, 2 H, Ar-H), 4.75 [m, 1 H, $OCH(CH_2)_2$], 3.82 (s, 3 H, Ar-OCH_3), 3.75 (app. t, $J = 8.9$, 1 H, CHAHB-NH), 3.64–3.56 (m, 1 H, Ar-*CH), 3.37 (dd, $J = 9.4$, 7.7, 1 H, CHAHB-NH), 2.70 (dd, $J = 16.9$, 8.9, 1 H, CHAHBCO), 2.47 (dd, $J = 16.9$, 8.9, 1 H, CHAHBCO), 1.93–1.75 (m, 6 H, cyclopentyl-H), 1.66–1.51 (m, 2 H, cyclopentyl-H); m/z (MH^+) 276; mp 131.5–132.5 °C $[\alpha]^D$: 25–31 (c 1.05, MeOH); $ee > 99\%$. Chiral HPLC condition: Agilent 1200 HPLC, Chiracel AD-H column (250 × 4.6 mm i.d.) with a mixture of hexane and 2-propanol (90:10) at a flow rate of 1.0 ml/min as the mobile phase, oven temperature was 28 °C, 210 nm, $t_{major} = 10.22$ min, $t_{minor} = 10.65$ min. The data were consistent with those reported in the literature.[10]

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