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ONE-POT PALLADIUM-CATALYZED RACEMIZATION OF (*S*)-PRAZIQUANAMINE: A KEY INTERMEDIATE FOR THE ANTHELMINTIC AGENT (*R*)-PRAZIQUANTEL

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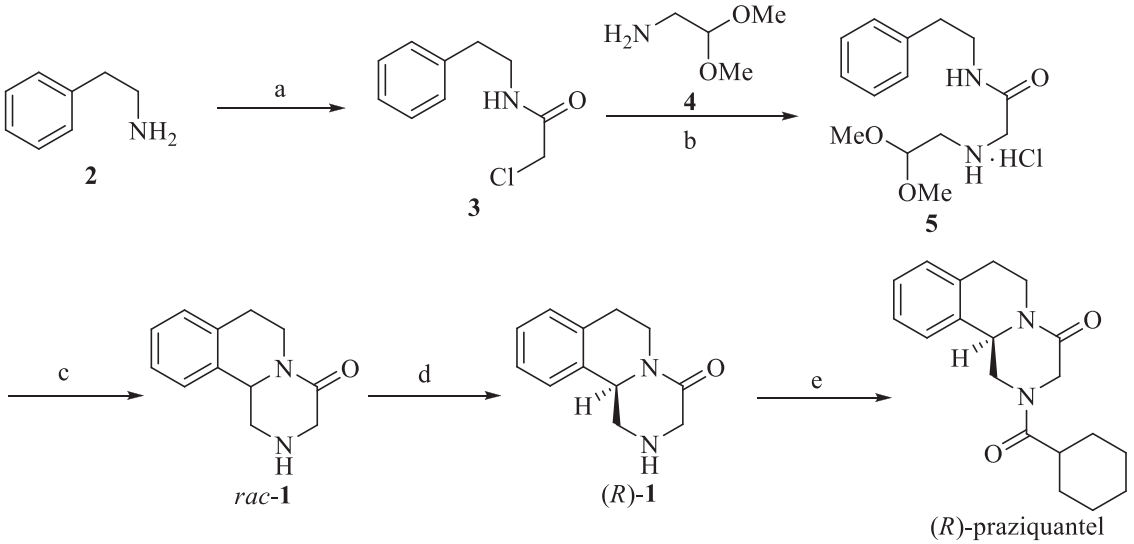
Abstract – An one-pot palladium-catalyzed procedure for racemization of (*S*)-praziquanamine, which is the undesired enantiomer and produced during the resolution step for preparing the anthelmintic drug (*R*)-praziquantel, has been developed through dehydrogenation of (*S*)-praziquanamine into 6,7-dihydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one and then hydrogenation of the double bonds. And a superior racemization method was also developed that (*S*)-praziquanamine was directly treated with Pd/C under H_2 atmosphere to obtain a racemic mixture in quantitative yield with 95% chemical purity. Such a concise and efficient approach to the racemization of (*S*)-praziquanamine can be useful to recycle the waste enantiomer into the resolution process to obtain the (*R*)-enantiomer on a large scale.

Praziquantel is a broad spectrum anthelmintic drug which is particularly applied in the treatment of schistosomiasis and plays crucial role in curbing this disease.[1] Praziquantel, a tetrahydroisoquinoline derivative, is widely used in clinic as its racemic form.[2] However, the *in vitro* and *in vivo* biological studies have demonstrated that the anthelmintic activity of praziquantel is mainly contributed by the (*R*)-enantiomer, while the inactive (*S*)-enantiomer might only cause a variety of side effects and also be primarily responsible for the extremely bitter taste of the pill.[3] (*R*)-Praziquantel was recently evaluated in the phase I clinical trial by Merck KGaA.[4]

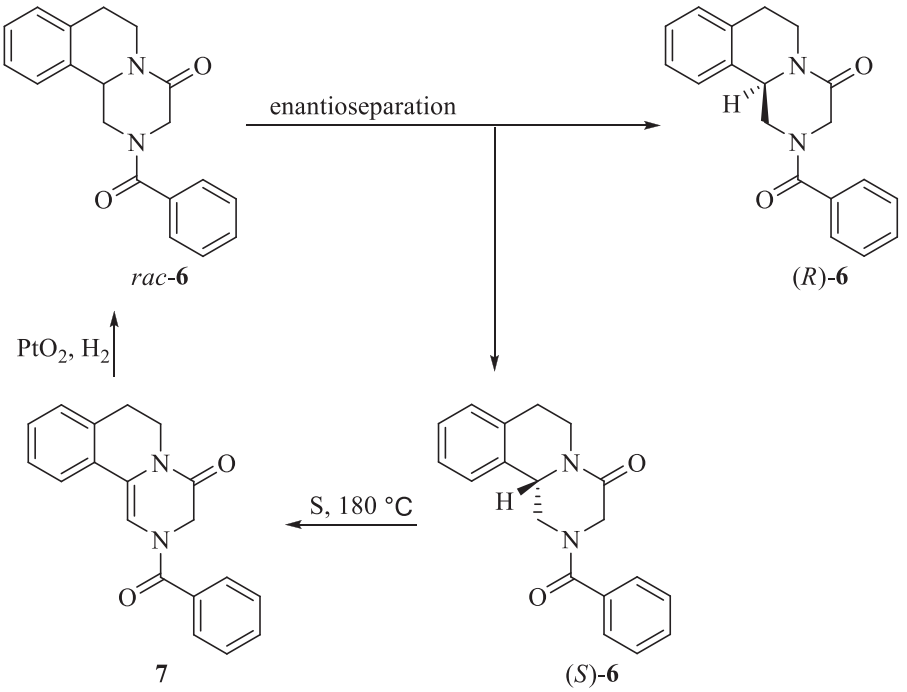
Several synthetic strategies to (*R*)-praziquantel have already been reported in the literatures including the introduction of chiral pool[5] and chiral auxiliaries,[6] directly asymmetric hydrogenation[7] as well as enantioseparation.[8] However, the classical resolution is still a good choice from the point of view of large

scale of synthesis. Todd *et al.*[9] developed a method with (–)-dibenzoyl-L-tartaric acid (L-DBTA) as the resolution agent for the separation of praziquanamine *rac*-**1** which was readily prepared from the cheap material phenylethylamine in the synthesis of *rac*-praziquantel (Scheme 1).[10]



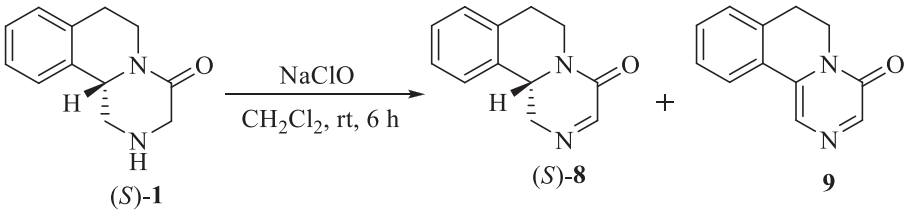
Scheme 1. Regents and conditions: (a) chloroacetyl chloride, $NaHCO_3$, CH_2Cl_2, 0 °C, 3 h, 92%; (b) (i) toluene, reflux, 2 h; (ii) HCl gas, CH_2Cl_2, 0-5 °C, 67%; (c) *conc.* H_2SO_4, rt, 3.5 h, 96%; (d) (i) L-DBTA, *i*PrOH, H_2O; (ii) NaOH, CH_2Cl_2, 33%, 99% ee; (e) cyclohexanecarbonyl chloride, Et_3N, CH_2Cl_2, rt, 14 h, 90%, 97% ee.

The (*R*)-**1** could be obtained in 33% yield with 99% ee value. It is highly important to make use of the undesired isomer in the resolution, unfortunately, there was a lack of this methodlogy in Todd report. Herein, we reported an interesting and practical racemization process for recycling (*S*)-praziquanamine.



Scheme 2. Racemization of (*S*)-**6** by dehydrogenation and hydrogenation

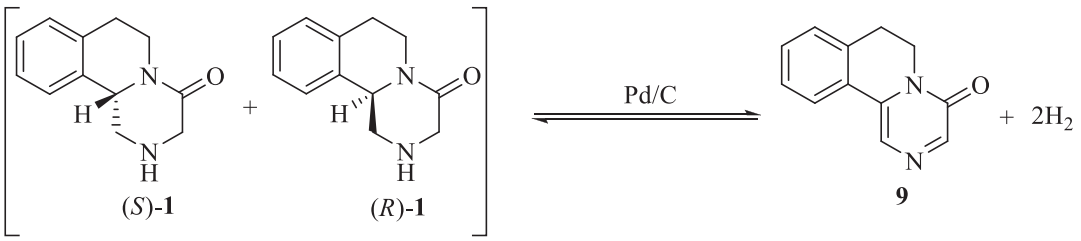
A review of the literatures showed that the unwanted enantiomer (*S*)-**6** as a praziquantel analogue could be converted to a racemic mixture in two steps, dehydrogenation of the (*S*)-**6** with melted sulfur at 180 °C under N_2 to provide **7** after column chromatography, followed by catalytic hydrogenation to afford *rac*-**6** in poor yield (Scheme 2).[11] Due to the similarity, an attractive strategy for the racemization of (*S*)-**1** was envisaged that constructed a carbon-carbon double bond at C_1 and C_{11b} positions, which would cause the C_{11b} stereogenic center to be racemized through a catalytic hydrogenation of the unsaturated compound. With this design in mind, when the drastic method with melted sulfur was applied to (*S*)-**1** which was synthesized according to the Todd's procedure,[12] however, no desired product was detected in the reaction mixture. Treatment of (*S*)-**1** with a slight excess of 5% NaClO aqueous solution[13] in CH_2Cl_2 at room temperature for 6 h gave imine (*S*)-**8** as a major product, being accompanied by the formation of a very small amount of byproduct which was identified as a conjugated compound **9** (Scheme 3).[11c,14] And when (*S*)-**1** was reacted with 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) as dehydrogenating agent in toluene at 80 °C for 1 h, only traces of **9** was detected in the reaction mixture. Under these investigated conditions none of the reagents were able to achieve C=C double bond formation with acceptable conversion.



Scheme 3. Dehydrogenation of (*S*)-**1** with NaClO

The unsuccessful dehydrogenation of (*S*)-**1** under the above conditions led us to explore other possible chemistry in order to obtain the desired **9** with higher conversion. The metal catalysts, especially Pd/C, are frequently regarded as a powerful, atom-economical and environmentally friendly choice for dehydrogenation of organic compounds, whilst avoiding the use of stoichiometric amounts of harmful oxidants such as DDQ. Usually, hash conditions with high temperature for Pd/C catalyzed dehydrogenation were well documented,[15] thus we firstly treated the (*S*)-**1** to dehydrogenation with catalytic amount of Pd/C at 180 °C under N_2 atmosphere. After 5 h the reaction mixtures were detected by HPLC using achiral C18 column, which indicated that 70.7% of **9** was observed with 18.2% of "undehydrogenated" praziquanamine without conversion (Table 1, entry 1). When the reaction time was increased to 10 h, the praziquanamine almost disappeared, but the content of impurities increased up to 23.8% (entry 2). In addition, incomplete reaction was also observed by using solvents such as xylene and toluene under refluxing conditions (entries 3 and 4). Surprisingly, chiral HPLC examination of the above

reaction mixtures indicated that the undehydrogenated praziquanamine had been converted to a near racemic mixture, which meant dehydrogenation of (*S*)-**1** to the desired **9** was accompanied by the racemization of (*S*)-**1**. A possible reaction mechanism for the palladium-catalyzed dehydrogenation of (*S*)-**1** concomitant with racemization was shown in Scheme 4. The dehydrogenation of amine (*S*)-**1** as a hydrogen donor could gave the corresponding compound **9** that can also act as a hydrogen acceptor and be reduced to either amine enantiomer. The reaction might proceed via hydrogen transfer between amine and **9**. To test this hypothesis, an additional experiment was carried out by adding styrene as a competing hydrogen acceptor to the reaction mixture, and in the presence of styrene the racemization was completely inhibited (entry 5), meanwhile the reductive product ethylbenzene was also detected by HPLC.



Scheme 4. A possible mechanism for the palladium-catalyzed dehydrogenation of (*S*)-**1** along with racemization

On the other hand, when reaction temperature in the dehydrogenation was droped to 95 °C, a major product with molecular weight 200 was obtained and identified as (*S*)-**8** by optical rotation, ^{1}H- and ^{13}C-NMR spectra. Moreover, no racemization of (*S*)-**1** or (*S*)-**8** was observed (entry 6). The results seemed to suggest that the catalytic dehydrogenation of (*S*)-**1** proceeded via (*S*)-**8**. And then if the reaction was conducted at higher temperature, (*S*)-**8** would be transformed into the more stable product **9** in which benzene ring, carbonyl group and double bonds formed much larger conjugated system. Only hydrogenation of **9** rather than (*S*)-**8** could lead to the conversion of (*S*)-**1** to the racemic **1**.

Obviously, the dehydrogenation reaction endpoint was determined by degree of racemization of (*S*)-**1** rather than achieving complete conversion to **9**. Consequently, although the racemization rate in toluene was slower compared to the that with the use of xylene and decalin, target products **9** and *rac*-**1** were obtained with excellent conversion at relatively low reaction temperature (entry 4). In the subsequent step, N_2 gas was replaced with H_2 to reduce **9** into *rac*-**1**, which was performed under 5 atmospheres of hydrogen at 50-60 °C for 4 h to afford a racemic mixture of (*R*)-**1**/(*S*)-**1** (49.8%/50.2%) as a deep yellow solid in quantitative yield with 92% purity.

Based on the mechanism for the racemization of (*S*)-**1**, a superior and one-pot racemization method was also found that treatment (*S*)-**1** with Pd/C under 24 atmospheres of H_2 at 130 °C for 48 h straightly

accomplished a near racemic mixture in quantitative yield with 95% chemical purity (entry 7). Unlike existing methods, the approach for the racemization of (*S*)-**1** was involved with hydrogen transfer between amine and **9** and showed a remarkable advantage over Seubert's procedure[11] which could be achieved by acylation with benzoyl chloride, dehydrogenation with sulfur, and catalytic reduciton of the intermediate **7**.

Table 1. Dehydrogenation of (*S*)-**1** using Pd/C[a]

Entry	Solvent	Temp (°C)	Time (h)	**9** (%)[b]	**1**[b] ((*R*)-**1**/(*S*)-**1**)[c] (%)	**8** (%)[b]	Byproducts (%)[b]
1	decalin	180	5	70.7	18.2 (48.0/52.0)	ND[d]	11.1
2	decalin	180	10	75.5	0.7 (51.5/48.5)	ND	23.8
3	xylene	139	12	64.8	28.7 (49.7/50.3)	0.1	6.4
4	toluene	110	24	55.5	40.9 (49.8/50.2)	0.3	3.3
5[e]	toluene	110	48	5.1	52.7 (0.5/99.5)	11.2[f]	31.0
6	toluene	95	48	4.6	80.0 (0.5/99.5)	11.9[f]	3.5
7[g]	toluene	130	48	ND	95.5 (48.4/51.6)	ND	4.5

[a] Reaction conditions: 0.1 g/mL (*S*)-**1** in solvents with 10% Pd/C (10% wt) under N_2 atmosphere. [b] Measured by HPLC on a Waters XBridge C18 column. [c] Measured by HPLC on a Chiralpak IC-3 column. [d] ND = not detected. [e] Addition of 4 equiv of styrene. [f] The stereochemical structure of **8** was identified as an *S* configuration. [g] The reaction was performed under 24 atmospheres of H_2.

In conclusion, we have developed an one-pot process in quantitative yield with 92% chemical purity, which racemizes (*S*)-**1** via dehydrogenation and imine reduction using Pd/C. Furthermore, a superior racemization method was also developed that (*S*)-**1** could be excellently converted to a racemic mixture in quantitative yield with 95% chemical purity after treatment with Pd/C under H_2 atmosphere. As the (*R*)-**1** which is the key intermediate in the synthesis of anthelmintic drug (*R*)-praziquantel is prepared by classical resolution of the racemate, such a concise and efficient procedure can be applied on a large scale to racemize and to recycle the undesired enantiomer and is of great importance for (*R*)-praziquantel manufacture without a significant increase in cost compared with *rac*-praziquantel.

EXPERIMENTAL

All solvents and reagents were purchased from commercial sources and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. The solvents used for NMR spectroscopy were $CDCl_3$, using TMS as the internal reference. HRMS-spectra were obtained on Bruker maXis 4G. Method of ionization was ESI (Electron Spray Ionization). Melting points were measured on a Yice WRS-1B melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel 60 (54-74 μm). Optical rotations values were measured with an Anton Paar MCP 500 polarimeter at 20 °C, 589 nm (sodium ray), and concentrations are given in 1.0 g/100 mL. The chemical purity was determined on a Dionex UItiMate 3000 chromatograph using a Waters XBridge C18,

4.6 mm × 150 mm, 3.5 μm column, acetonitrile and water (containing 0.1% CF_3CO_2H) as eluent, a column temperature of 35 °C, a flow rate of 1.0 mL/min, and measuring at 210 nm (Table 2). The retention times of **1** is 10.1 min and **9** is 13.3 min. The optical purity and racemic ratio of (*R*)-**1**/(*S*)-**1** were determined on a Dionex UItiMate 3000 chromatograph at 210 nm, using a Chiralpak IC-3 column (4.6 mm × 250 mm, 3.0 μm) at 30 °C with flow rate of 0.4 mL/min and run time of 70.0 min with *n*-hexane (containing 0.1% Et_2NH) and 2-propanol (30:70) as eluent. The retention time of (*R*)-**1** is 30.2 min and (*S*)-**1** is 34.5 min. The optical purity and racemic ratio of (*R*)-**8**/(*S*)-**8** were determined on a Dionex UItiMate 3000 chromatograph at 210 nm, using a Chiralpak IC-3 column (4.6 mm × 250 mm, 3.0 μm) at 30 °C with flow rate of 1.0 mL/min and run time of 35.0 min with *n*-hexane (containing 0.1% Et_2NH and 0.1% CF_3CO_2H) and 2-propanol (90:10) as eluent. The retention time of (*R*)-**8** is 19.8 min and (*S*)-**8** is 24.3 min. The purities of the compounds were based on the area of HPLC UV.

Table 2. The standard gradient

Time (min)	Acetonitrile (%)	Water (containing 0.1% TFA) (%)
0	5	95
3	5	95
8	20	80
20	70	30
24	70	30
24.1	5	95
30	5	95

(*S*)-1,2,3,6,7,11*b*-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one ((*S*)-1). *Rac*-**1** (110.4 g, 545.9 mmol) and (+)-dibenzoyl-D-tartaric acid (195.6 g, 545.9 mmol) were dissolved in a mixture of 2-propanol (2.2 L) and water (220 mL) by heating at reflux. The solution was slowly cooled to 60 °C over 1 h and stirred at this temperature for 3 h. And then the suspension was cooled from 60 °C to room temperature at a rate of 5 K/h. The resulting slurry was stirred overnight. The white solid was isolated by filtration, washed with cold 2-propanol (2 × 300 mL). The solid was then suspended in water (300 mL) and the pH of the mixture was adjusted to 12 by addition of 1 N sodium hydroxide solution. When the salt was completely dissolved the solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (2 × 150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give (*S*)-**1** (31.0 g, 28% yield, 99% ee); a off-white solid; mp 118.2-118.9 °C; $[\alpha]_D^{20}$ +300 (*c* 1.0, CH_2Cl_2) (lit.,[12] $[\alpha]_D^{20}$ +284 (*c* 1.0, CH_2Cl_2)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.10 (m, 4H), 4.87 (ddd, *J* = 12.5, 5.1, 2.6 Hz, 1H), 4.80 (dd, *J* = 10.0, 4.6 Hz, 1H), 3.73 (ddd, *J* = 13.0, 4.7, 1.3 Hz, 1H), 3.60 (ABq, *J* = 17.4 Hz, 2H), 3.05 – 2.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ

167.29, 134.97, 134.26, 129.40, 127.03, 126.64, 124.71, 56.88, 50.07, 49.84, 38.81, 28.84; HRMS *m/z* [M + H]$^+$ calcd for $C_{12}H_{14}N_2O$: 203.1179; found: 203.1184.

(*S*)-1,6,7,11*b*-Tetrahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one ((*S*)-8). To a solution of (*S*)-**1** (5.0 g, 24.7 mmol) in CH_2Cl_2 (50 mL) was added 5% NaClO aqueous solution (40.0 g, 26.9 mmol), followed by stirring the mixture at room temperature for 6 h. The organic layer was separated, washed with water (100 mL) and concentrated at reduced pressure. And then CH_2Cl_2 (35 mL) was stripped off under vacuum to afford (*S*)-**8** (92% area purity by HPLC) as a yellow solution in CH_2Cl_2. To the solution was added EtOAc (50 mL) and the mixture stood at room temperature for 5-6 h. The solid was isolated by filtration, washed with EtOAc, and then dried under vacuum at 25 °C for 3 h to give (*S*)-**8** (2.8 g, 56% yield, 99% ee); a off-white solid; mp 163 °C (decomposed); $[\alpha]_D^{20}$ +470 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 3.3, 1.1 Hz, 1H), 7.31 – 7.19 (m, 4H), 4.83 (dd, *J* = 13.5, 4.2 Hz, 1H), 4.75 – 4.68 (m, 1H), 4.41 (ddd, *J* = 17.0, 4.2, 0.9 Hz, 1H), 3.39 (ddd, *J* = 17.0, 13.5, 3.3 Hz, 1H), 3.01 – 2.84 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.17, 155.81, 134.34, 132.03, 129.39, 127.42, 127.08, 125.65, 55.83, 52.24, 37.22, 29.08; HRMS *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}N_2O$: 201.1022; found: 201.1018.

6,7-Dihydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (9). A solution of (*S*)-**1** (1.0 g, 4.94 mmol) in toluene (10 mL) was stirred with 10% Pd/C (0.1 g, 10% wt) at reflux under N_2 atmosphere. After 48 h the reaction mixture was cooled to room temperature and then filtered. The filtrates were purified by column chromatography on silica gel eluting with petroleum ether/EtOAc (2:1) to give **9** (0.55 g, 56%); a yellow solid; mp 146.5-146.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.86 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.35 (m, 2H), 7.34 – 7.26 (m, 1H), 4.28 – 4.18 (m, 2H), 3.08 – 2.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 155.56, 146.49, 135.21, 135.14, 130.90, 128.37, 127.91, 126.71, 125.09, 120.53, 38.60, 27.34; HRMS *m/z* [M + H]$^+$ calcd for $C_{12}H_{10}N_2O$: 199.0866; found: 199.0863.

(±)-1,2,3,6,7,11*b*-Hexahydro-4*H*-pyrazino[2,1-*a*]isoquinolin-4-one (*rac*-1). Method A: A solution of (*S*)-**1** (5.0 g, 24.7 mmol) in toluene (50 mL) was stirred with 10% Pd/C (0.5 g, 10% wt) at reflux under N_2 atmosphere. After 24 h the reaction mixture was cooled to room temperature, and then N_2 was replaced by 4.0 atmospheres of H_2. The mixture was heated to 50-60 °C for 4 h, then cooled to room temperature. The catalyst was removed by filtration, and the filtrates were concentrated in vacuo to give a racemic mixture of (*R*)-**1**/(*S*)-**1** (49.8%/50.2%) as a deep yellow solid (5.0 g) in quantitative yield with 92% chemical purity. An analytical sample as a white solid was obtained by crystallization with EtOAc and *n*-hexane. mp 116.7-117.4 °C (lit.,[10] mp 118-119 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.13 (m, 4H), 4.90 (ddd, *J* = 12.5, 5.1, 2.6 Hz, 1H), 4.83 (dd, *J* = 10.0, 4.6 Hz, 1H), 3.76 (dd, *J* = 13.0, 4.7 Hz, 1H), 3.63 (ABq, *J* = 17.4 Hz, 2H), 3.07 – 2.73 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 167.30, 134.98, 134.25, 129.40, 127.04, 126.64, 124.71, 56.89, 50.08, 49.85, 38.82, 28.84; HRMS *m/z* [M + H]$^+$ calcd for $C_{12}H_{14}N_2O$: 203.1179; found: 203.1180.

Method B: A solution of (*S*)-**1** (5.0 g, 24.7 mmol) in toluene (50 mL) was stirred with 10% Pd/C (0.5 g, 10% wt) at 130 °C under 24 atmospheres of H_2. After 48 h the reaction mixture was cooled to room temperature. The catalyst was removed by filtration, and the filtrates were concentrated in *vacuo* to give a racemic mixture of (*R*)-**1**/(*S*)-**1** (48.4%/51.6%) as a white solid (5.0 g) in quantitative yield with 95% chemical purity.

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