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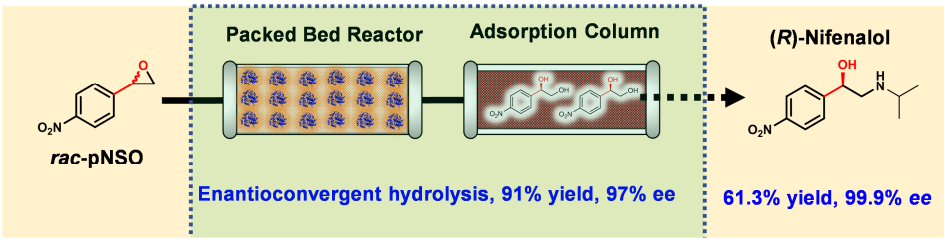

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In Memory of Professor Wei-Shan Zhou for his legacy in natural product synthesis.

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ABSTRACT

An engineered epoxide hydrolase from *Vigna radiate* (*Vr*EH2$_{M263N}$) shows near-perfect enantioconvergence in single enzyme mediated hydrolysis of racemic *p*-nitrostyrene oxide (pNSO). To explore industrial potential of the promising biocatalyst, we tried to immobilize the *Vr*EH2 variant by covalently linking onto a commercially available amino resin ECR8405F. Then a 5-mL packed bed reactor filled with the immobilized *Vr*EH2$_{M263N}$ was connected with macroporous resin NKA-11 for *in situ* product adsorption, and the product (*R*)-*p*-nitrophenyl glycol (pNPG) was harvested by methanol elution, with 91% isolated yield and 97% *ee*. The continuous reactor was operated stably for more than 100 h with a space time yield of 20 g·L^{-1}·h^{-1}. Subsequently, the β-blocker (*R*)-Nifenalol was prepared by chemically synthesized from (*R*)-pNPG, affording the product in an overall yield of 61.3% (1.5 g) and an enantiopurity of 99.9% *ee* after recrystallization.

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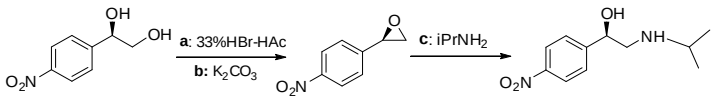
1. Introduction

(*R*)-Nifenalol is a *β*-adrenergic blocker drug endowed with anti-anginal and anti-arhythmic properties.[1,2] One of the tempting ways to this drug was to use (*R*)-*p*-nitrophenyl glycol [(*R*)-pNPG] as intermediate combining with chemical routes (Scheme 1). In the past two decades, several chemical and biological methods have been explored to obtain the intermediate (*R*)-pNPG. For example, the carbonyl reductases (RCR, 0.223 U/mg cell free extract) or organic catalysts was used to produce the chiral vicinal diols from hydroxyketone compound,[3,4] as well as oxidation of olefins by chromium Jacobsen's catalysts I or P450s (P450pyrTM, 12 $U \cdot g^{-1} \cdot cdw^{-1}$).[5,6] However, these enzymes suffered low catalytic activity and poor stability. Although chemical routes can performed in good yield, the expensive organic catalysts and harsh reaction conditions would face the environmental and safety problems.[4,7] As an alternative green route, epoxide hydrolase mediated enantioconvergent hydrolysis of styrene oxides can highly produce the corresponding vicinal diols.[8,9] Furstoss group first performed the availability to synthesize chiral (*R*)-pNPG using step-wise hydrolysis of *p*-nitrostyrene oxide (pNSO) with *An*EH and H_2SO_4, which led to satisfied yield (94%), but the *ee* value was only 80%.[10] Similarly, we utilized the native *Vr*EH2 and H_2SO_4 to step-wisely synthesize (*R*)-pNPG with 82% *ee* and 84% yield.[11] Although the preparation of (*R*)-pNPG can be performed by chemo-enzymatic routes, the degree of enantioconvergence was still unsatisfactory.



Scheme 1. Chemical synthesis of *β*-blocker (*R*)-Nifenalol based on (*R*)-*p*-nitrophenyl glycol which can be produced by enzymatic hydrolysis of epoxide.

Compared to the chemo-enzymatic combination, the enantioconvergent hydrolysis by a single and special enzyme is very attractive for preparation the product (*R*)-diols with high yield and enantiopurity. However, the perfect enantioconvergence depends on the highly specific and opposite regioselectivity of an epoxide hydrolase towards both enantiomers of the epoxide substrate, thus caused a challenge for enantioconvergent hydrolysis of epoxide hydrolase.[12-15] Fortunately, we recently obtained a single site mutant *Vr*EH2$_{M263N}$ which allowed the near-perfect enantioconvergence (>99% analytical yield, 98% *ee*) in hydrolysis of *rac*-pNSO through structure-guided regioselectivity engineering.[16] Nevertheless, the unsatisfactory operation stability of epoxide hydrolases and the spontaneous hydrolysis of racemic epoxides cannot be ignored. Under mechanical shaking condition, the stability of *Vr*EH2$_{M263N}$ was very poor, it showed no activity after 24 h. Besides, due to the spontaneous hydrolysis of *rac*-pNSO in aqueous solution, the ee_p value was decreased from 98% to 92% under high concentration of substrate (100 mM), which also limited the wide application of *Vr*EH2$_{M263N}$.

Immobilization technology is a powerful strategy for elevating enzymes' stability and recycling efficiency.[17-20] Faber group prepared the immobilized *Nocardia* EH1 through DEAE-cellulose anion adsorption, it can keep a residual activity of 55% after five batch reactions.[21] Furstoss group synthesized a stable immobilized *St*EH by the using dextran and glyoxal-agarose, which showed a 300-fold increase in thermal stability under 60 ^oC and retained high selectivity.[22] In recent years, the development of commercial resins provided new carriers for immobilization of EHs. They were more easily used by the covalently bonding the enzyme than the other carriers and have been successfully applied in recent study.[23,24] Continuous process by biocatalyst has been regarded as a green strategy for sustainable industrial production.[25] The design of continuous reactor based on the immobilized enzyme have attracted much attention for large-scale preparation of fine chemicals.[26] Packed bed reactor (PBR) is one of common continuous-flow reactors, which can improve enzyme loading per unit volume, reduce the mechanical damage to the enzyme and avoid the experimental loss of enzyme.[27,28] Herein, to develop the industrial application potential of *Vr*EH2, a number of commercial resins were used to prepare immobilized the epoxide hydrolase. A packed bed reactor with immobilized enzyme was designed for continuous preparation of (*R*)-pNPG from *rac*-pNSO. To collect the product, an adsorbed column with macroporous resin NKA-11 was connected with PBR, and thus can construct a continuously prepared apparatus. Finally, the synthesis of *β*-blocker (*R*)-Nifenalol was performed based on enzymatic enantioconvergent preparation of (*R*)-*p*-nitrophenyl glycol, with good yield and high enantiopurity.

2. Results and Discussion

2.1. Preparation of covalently immobilized VrEH2$_{M263N}$

To improve the stability of the *Vr*EH2$_{M263N}$, we selected two kinds of commercial epoxy and amino resins for immobilization. Free enzyme can be covalently bonded with the functional groups of these resins, and seven immobilized enzymes were successfully prepared. The loading and activity recovery rate (Table 1) indicate that the immobilized efficiency of amino resins was better than that of epoxy resins, and *Vr*EH2$_{M263N}$-ECR8405F exhibited the highest loading (13.2 U/g_{resin}) and activity recovery rate (57.4%). Subsequently, to investigate the wear resistant performance of these resins, the immobilized enzymes ESR-1, ESQ-1, ECR8405F and ECR8205F was selected. The immobilized resins' shapes were observed after magnetic stirring in Fig. 1. The resins ECR8405F and ECR8205F maintained the relatively overall spherical morphology, while the shapes of ESR-1 and ESQ-1 was severely destroyed. Hence, the ECR8405F and ECR8205F were selected for subsequent optimization of immobilized conditions (**Supporting information**).

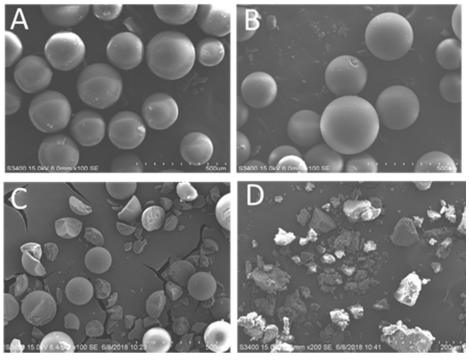


Fig. 1. The shape insights of immobilized resins after magnetic shaking (24 h). **A**) ECR8405F; **B**) ECR8205F; **C**) ESR-1; **D**) ESQ-1.

Table 1
The loading and activity recovery rates of the immobilized enzymes prepared with commercial resins.

Functional group	Resins	Diameter (Å)	Enzyme loading (U/g_{resin})	Activity recovery (%)
Epoxy	ECR8205F	150~300	4.3 ± 0.1	18.5
	ECR4204F	150~300	2.4 ± 0.2	10.5
	ECR8215F	150~300	0.8 ± 0.0	3.5
	ES-103	100~300	2.0 ± 0.1	8.8
Amino	ESR-1	100~300	9.9 ± 0.0	45.2
	ESQ-1	100~300	5.5 ± 0.1	25.1
	ECR8405F	150~300	13.2 ± 0.1	57.4

2.2. Thermal and operational stability of immobilized enzyme VrEH2$_{M263N}$-ECR8405F

By measuring the inactivation curves of the immobilized enzyme *Vr*EH2$_{M263N}$-ECR8405F, we found that the thermal stability of the immobilized enzyme was obviously altered comparing with the free enzyme. The residual activity of the free enzyme was only 16.3% after 96 h's incubation and the half-life ($t_{1/2}$) was 55.1 h at 30 °C, while the immobilized enzyme retained 42.3% residual activity after 200 h's incubation and its $t_{1/2}$ was improved to 193.2 h (Fig. 2A). After incubation for 20 h at 40 °C, the residual activity of free enzyme was only 18.0% with a $t_{1/2}$ of only 11.1 h, but the immobilized enzyme retained 23.8% residual activity after 150 h of incubation with an increased $t_{1/2}$ of 101.9 h, (Fig. 2B). The free enzyme showed no activity after incubation for 15 min at 50 °C, while the 21.9% residual activity was retained after 45 min for immobilized enzyme (Fig. S1). These results indicate that the immobilization of the enzyme by covalently bonding of the resin carrier can significantly improve its thermal stability.

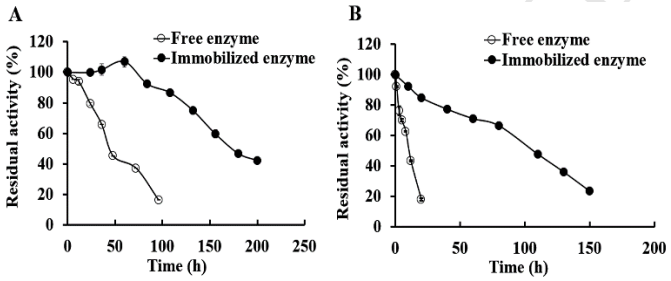


Fig. 2. The inactivation curves of immobilized enzymes and free enzymes at 30 °C (**A**) and 40 °C (**B**).

The operational stabilities of free enzyme and immobilized enzyme were also investigated. Consequently, the free enzyme lost its activity after 24 h, while the immobilized enzyme still maintained 73% of initial activity after 150 h (Fig. S2), indicating the operational stability of the epoxide hydrolase was also improved. To verify the reaction performance, a number of batches reaction for immobilized enzyme was performed, it retained a residual activity of 77% after 20 batches and the *ee* value of product can be reached to 97% (Fig. 3). The loss of activity was mainly attributed to the mechanical damage and physical recovery loss.

2.3. Synthesis of (R)-pNPG from rac-pNSO in a stirred reactor

In order to utilize the immobilized enzyme for the preparation of (*R*)-pNPG, Synthesis of (*R*)-pNPG by *Vr*EH2$_{M263N}$-ECR8405F in a stirred reactor was first explored. The substrate loading can reach to 100 mM (10% DMSO, v/v) in a 40-mL scale, the immobilized enzyme was recycled by a filtration step. After 10 batches, (*R*)-pNPG was obtained in 91% yield and 92% *ee*, with a space time yield (STY) was up to 16.7 g·L^{-1}·h^{-1}. However, the deterioration of the optical purity of the product was observed, which is possibly caused by the spontaneous hydrolysis of substrate under the high concentration (100 mM). Mechanical operation and physical loss also led to the irreversible inactivation, so the residual activity of immobilized enzyme was only 43.5 % after 10 batches.

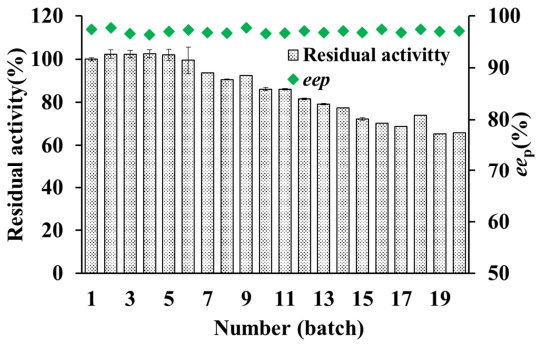


Fig. 3. Residual activity of the immobilized enzyme and *ee* value of product was determined after per batch.

2.4. Construction of PBR for continuous synthesis of (R)-pNPG

As the batch reaction cannot provide the satisfactory result, we tried to address the problem with continuous synthesis mode. A packed bed reactor (PBR) was designed and optimized in several aspects including the flow direction, space velocity and the height to diameter ratio (H-D) of the PBR (Supporting information). The performance of PBR was subsequently determined, including the stability and space time yield (STY). In a first trial, the conversion of PBR (H-D: 2:1) was only 74.7% under the equal biocatalyst loading and space velocity (SV), resulting in the STY of 41.0 g·L^{-1}·h^{-1}. Using the same enzyme amount and SV, when the H-D ratio improved by 4:1 or 8:1, a higher STY (54.9 g·L^{-1}·h^{-1}) were achieved (Table 2), which was much better than that of the stirred reactor (16.7 g·L^{-1}·h^{-1}). By measuring the stability of reactor, we found that the lower H-D

ratio of PBR, the higher residual activity of the immobilized enzyme. It was mainly because the height of the reactor increased

Table 2
Key reaction parameters of PBR with different H/D ratios.

Type (H-D)[a]	Conversion (%)	Residual activity [b]	S.T.Y. ($g{\cdot}L^{-1}{\cdot}h^{-1}$)[c]
2:1	74	>99%	41.0
4:1	99	97.4%	54.9
8:1	99	95.5%	54.9

[a] H-D: height to diameter ratio of the PBR
[b] Specific activity of immobilized enzyme after continuous operation;
[c] Space time yield normalized by the reactor volume.

the pressure at the bottom of the packed bed, resulting in the loss of enzyme activity. Compromising the productivity with the stability of biocatalyst, the H-D ratio of PBR was set to 4:1 in the following research.

2.5. Screening macroporous resins for product adsorption

Due to the poor solubility of the epoxides, the substrate concentration was limited at 5 mM with 10% DMSO in reaction. For improving the efficiency of the product recovery from large volume reactant with low concentration, an additional product adsorption column was connected with the PBR for product enrichment. Three kinds of polar macroporous adsorption resins were compared and the adsorption capacity of these resins under different space velocities were investigated (Fig. S3). It indicates that the largest adsorption capacity of resin NKA-11 was 165.5 mg/g. the adsorption efficiency of resin NKA-11 showed more than 99% at space velocity of 0.4 min^{-1}, so NKA-11 was selected for recovery of product.

Based on this mini scale continuous preparation apparatus (Fig. 4), a gram-scale preparation of (*R*)-pNPG was carried out. As expected, the PBR still maintained more than 99% conversion After 100 h continuous production and showed good operational stability (Fig. S4). Then product of adsorbed column could be readily eluted by methanol and the resin was recycled, 3.00 g (*R*)-pNPG was obtained with a yield of 91% and 99% *ee*. The STY of the continuous apparatus reached 20.0 $g{\cdot}\ L^{-1}{\cdot}h^{-1}$, which was higher than that of the stirred batch reaction. Subsequent recrystallization in chloroform gave 2.66 g highly pure (*R*)-pNPG with 87% yield and 99.9% *ee*.

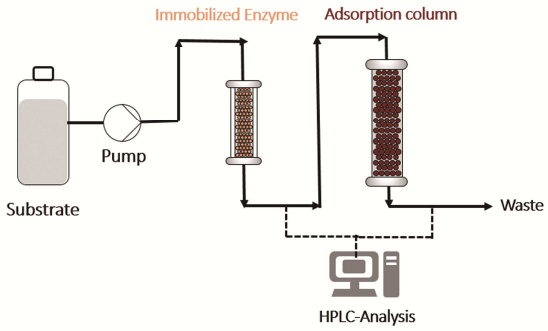


Fig. 4. Scheme of continuous synthesis apparatus, including PBR (5 mL) and a product adsorbed column (20 mL).

2.6. Synthesis of (R)-Nifenalol from (R)-pNPG

According to the reported method of Furstoss group,[10] the gram-scale synthesis of (*R*)-Nifenalol was performed, which led to the (*R*)-Nifenalol in 61.3% overall yield after recrystallization.

3. Conclusion

In this study, the key intermediate of (*R*)-Nifenalol, (*R*)-pNPG, was successfully prepared by *Vr*EH2 in an enantioconvergent manner. The immobilized *Vr*EHs were prepared by covalently cross-linking with a commercially available amino resin ECR8405F. A simple continuous manufacturing module was subsequently established to prepare the valuable intermediate, the STY of the reactor can reach 20.0 $g{\cdot}L^{-1}{\cdot}h^{-1}$ with high enantiopurity (99% *ee*) after recrystallization. This allowed the preparation of enantiopure (*R*)-Nifenalol combination of chemical method with a 61.3% overall yield.

4. Experimental section

4.1 General

Substrate *rac*-pNSO was prepared according to the reported method.[29] All the biological and chemical reagents were commercial available. Immobilized resins were provided from Tianjin Nankai Hecheng Science and Technology Co., Ltd and Purolite (China) Co., Ltd. The NMR spectra ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ solution on Brucker-400 MHz. The chemical shift (δ) of ^{1}H NMR and ^{13}C NMR was given in ppm relative to solvent residual peak according to the reference 30. The optical rotation of (*R*)-Nifenalol was measured by Autopol I (Rudolph, American). The *ee* value of product was determined by chiral OD-H column as previously described.[16] High resolution mass spectra were determined on Waters GCT Premier (EI-OA-TOF).

4.2. Enzyme Immobilization

Genes of *Vr*EH2$_{M263N}$ were constructed with pET-28a(+) and expressed in *Escherichia coli* BL21 (DE3). The methods for cells cultivation, enzyme expression and purification were described previously.[16] The collected recombinant cells were disrupted by a high-pressure homogenizer and centrifuged, clear lysate was lyophilized by a freeze dryer. The lyophilized enzyme powder (50 mg) was dissolved in 10 mL of phosphate buffer (pH 7.0, 100 mM) and mixed with 1.0 g amino resins (activated by 2% (v/v) glutaraldehyde) or epoxy resins. The mixture was reacted in a shaker (16 °C, 180 rpm) for 12 h. The immobilized enzyme was obtained by filtration and washed with buffer carefully to avoid the remaining of glutaraldehyde. The activity recovery rate was calculated by the activity of immobilized enzyme and the initial activity of free enzyme.

4.3. Thermostability and operational stability of immobilized enzyme

Investigation the wear resistance of different resins. In 10-mL reactor (KPB buffer, pH 7.0, 100 mM), 1 g epoxy resins or amino resins was stirred (400 rpm, 30 °C) for 24 h. Then morphological

shapes of the immobilized carrier were observed by using a Cryo-SEM (Scanning Electron Microscope).

Thermostability of the immobilized enzyme. In 1 mL KPB buffer (pH 7.0, 100 mM), 0.2 g immobilized enzyme was incubated at different temperatures (30 °C, 40 °C and 50 °C). The residual activities were measured at different time intervals and the inactivation curves were then made.

Operational stability of the immobilized enzyme. In 1 mL KPB buffer (pH 7.0, 100 mM), 0.2 g immobilized enzyme was shaken in a constant temperature mixer (1000 rpm. 30 °C). The residual activities were measured under different time intervals.

Immobilized enzyme for batch reaction. In 10 mL KPB buffer (pH 7.0, 100 mM), substrate *rac*-pNSO was dissolved with 10% DMSO (v/v) as a final concentration of 10 mM, and 1 g immobilized enzyme was used. The reaction was performed in a shaker (200 rpm, 30 °C) until the substrate was converted completely. Then the immobilized enzyme was recycled for the next batch reaction. After each batch, the *ee* value of product and the residual activity of immobilized enzyme were measured.

4.4 Synthesis of (*R*)-pNPG from *rac*-pNSO in a stirred reactor

In 36 mL KPB buffer (pH 7.0, 100 mM), substrate *rac*-pNSO was dissolved with 10% DMSO (v/v) as a final concentration of 100 mM, and 4 g immobilized enzyme was added. The reaction was performed in a 100-mL reactor (400 r/min, 30 °C) until the substrate was converted completely, then the immobilized enzyme was recycled for the next batch reaction.

4.5 Resin screening for the product adsorption

30 mg macroporous resin (NKA-11, NKA-9, AS-17) and 500 μL product solution (100 mM) was added in 2 mL EP tube, then the adsorption was performed in a shaker (500 rpm, 30 °C) for 5 h. When the adsorption reached saturation, the largest adsorption capacity of resin was calculated. In a packed bed column (H: 60 mm; D: 15mm), 2 g macroporous resins was washed and equilibriumed with KP buffer. The product solution (5 mM) was continuously fed into the reactor from top to bottom by peristaltic pump with different space velocities (0.1 min^{-1}, 0.2 min^{-1}, 0.4 min^{-1} and 0.5 min^{-1}), and the eluent solution was detected for calculating the adsorption efficiency.

4.6 Synthesis of (*R*)-pNPG from *rac*-pNSO in PBR

The substrate solution (5 mM) was continuously fed into the PBR (H: 60 mm, D: 15 mm) from top to bottom by peristaltic pump at space velocity 0.4 min^{-1}. Connected with the PBR, a glass column (H: 200 mm, D: 15 mm) filled with 20 g macroporous resins was used to adsorb the product (*R*)-pNPG. Then the product was eluted with methanol, and the macroporous resins can be recovered. The methanol elution was evaporated and the resultant product was dissolved with ethyl acetate. Then ethyl acetate solution was washed with saturated NaCl solution, and dried over anhydrous Na_2SO_4 for 12 h, concentrated in vacuum, and the resulting residual was recrystallization by chloroform.

4.7 Preparation of (*R*)-Nifenalol from (*R*)-pNPG in a gram-scale

In a 50-mL reaction flask, enantiopure (*R*)-pNPG (2.0 g, 10.9 mmol) was slowly dropped by 33% hydrobromide acetic acid solution on ice-bath. After the diols was completely dissolved, the system was reacted at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into ice water, the reaction pH was adjusted to neutral condition with saturated sodium hydrogen carbonate, and then extracted with ethyl acetate. The organic phase was washed with saturated NaCl, dried over anhydrous sodium sulfate and evaporated. The resulting residual was dissolved in methanol (20 mL) and anhydrous K_2CO_3 (2.0 g, was added. The mixture was reacted at room temperature for 1 h, the reaction mixture was concentrated in vacuum after filtration and affording (*R*)-pNSO (1.6 g, 89% yield).

(*R*)-pNSO (1.6 g, 9.8 mmol) was dissolved in absolute ethanol (20 mL), and then 6 mL isopropylamine (4 g) were added drop-wise. The reaction was reacted and refluxed under 50 °C for 24 h. When the reaction was completed, the ethanol and the remaining isopropylamine were evaporated to obtain a crude product. The final crude product was recrystallized in *n*-hexane/ethyl acetate to afford (*R*)-Nifenalol (61.3% yield, 99.9% *ee*).

(*R*)-Nifenalol ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.59 (s), 147.25 (s), 126.50 (s), 123.60 (s), 71.02 (s), 54.27 (s), 48.75 (s), 23.05 (d, *J* = 16.9 Hz). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.12 (m, 2H), 7.55 (dd, *J* = 6.9, 1.9 Hz, 2H), 4.72 (dd, *J* = 8.8, 3.8 Hz, 1H), 3.01 (ddd, *J* = 12.3, 3.8, 1.4 Hz, 1H), 2.83 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.57 (dd, *J* = 12.2, 8.8 Hz, 1H), 1.67 (s, 2H), 1.09 (t, *J* = 5.7 Hz, 6H). $[\alpha]_D^{20}$ = -11.3 (c 1.0, EtOH) lit 31. $[\alpha]_D^{30}$ = -11.0 (c 1.0, EtOH). HRMS: $[M]^+$, found 223.1057. $C_{11}H_{16}N_2O_3$ requires 223.1088.

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Supplementary Material

Supplementary data related to this article can be found in the online version.

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