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Chemoenzymatic total synthesis and determination of the absolute configuration of (*S*)-nebracetam

Sho Yamashita, Nobuyuki Mase, Kunihiko Takabe *

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan

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ABSTRACT

We have developed an asymmetric total synthesis of nebracetam **3** by a chemoenzymatic strategy. Diastereoselective Michael addition of nitromethane to the chiral lactam (*S*)-**9d** (>99% ee), which was prepared by lipase-catalyzed kinetic resolution, afforded the Michael product **10d** in 99% yield with 86% de. Chemical transformations of **10d** including recrystallization furnished the chiral nebracetam **3** and its derivative. The absolute configuration of the chiral (−)-nebracetam was determined to be an (*S*)-configuration.

1. Introduction

Since piracetam **1** (2-(2-oxopyrrolidin-1-yl)acetamide) was the first nootropic drug to reach clinical practice in the early 1970s, there has been an increase in the number of reports on the synthesis of pyrrolidone derivatives, as well as preclinical studies (see Fig. 1).[1] Their pharmacological properties and clinical effects are dependent on structural differences, for instance, piracetam's primary indication is cognitive enhancement, myoclonus, and post-stroke treatment, whereas levetiracetam **2** (2-(2-oxopyrrolidin-1-yl)butanamide) is used in adjunctive therapy in partial and secondarily generalized seizures.[1a] Nebracetam **3** (4-aminomethyl-1-benzylpyrrolidin-2-one), which is one of the racetam family developed in Germany and Japan, enhances cholinergic neurotransmission and acts as a partial agonist presynaptically at muscarinic receptors. It also reduces dopaminergic and serotonergic uptake, and inhibits intracellular calcium flux in response to glutaminergic stimulation.[1a] In spite of these unique properties, to the best of our knowledge, the asymmetric synthesis of **3** has not been studied. Resolution of the diastereomeric ammonium salts using L-tartaric acid is the only known route to access enantiopure nebracetam **3**,[2] but absolute configuration of **3** have not yet been determined. Herein, we report the first asymmetric synthesis of (*S*)-nebracetam (*S*)-**3** via a chemoenzymatic strategy and assignment of its absolute configuration (see Scheme 1).

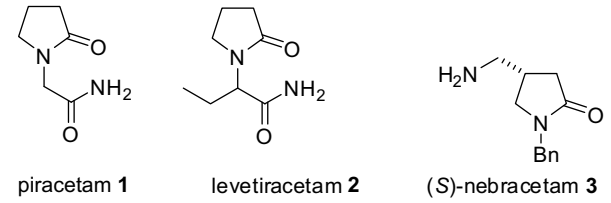
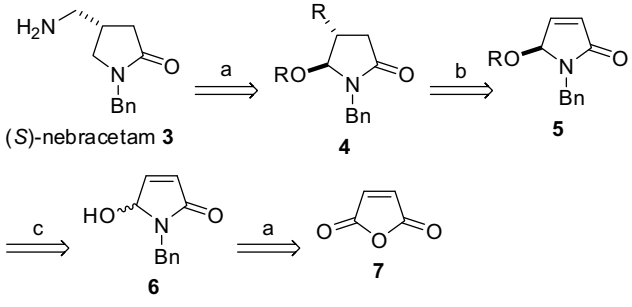


Figure 1. Pyrrolidone derivatives.



Scheme 1. Retrosynthesis of (*S*)-nebracetam (*S*)-3 from maleic anhydride **7**.

2. Results and discussion

The straightforward chemoenzymatic retrosynthesis is depicted in Scheme 1. The stereoselective Michael addition to the chiral lactam **5** is a key reaction, although the α,β-unsaturated lactam is not generally superior Michael acceptor. Chiral lactam **5** is obtained by lipase-catalyzed kinetic resolution of the racemic hydroxylactam **6** prepared from maleic anhydride **7** (see Scheme 1).

Benzyl-protected maleimide **8** was obtained in 80% yield according to the general procedure,[3] following regioselective 1,2-reduction[4] using $NaBH_4/CeCl_3$ to afford the racemic hydroxylactam *rac*-**6** in 98% yield over two steps. Acetyl, benzyl, and/or silyl protection of the hydroxyl group were carried out by standard

* Corresponding author. Tel./fax: +81 53 478 1148.
E-mail address: tcktaka@ipc.shizuoka.ac.jp (K. Takabe).

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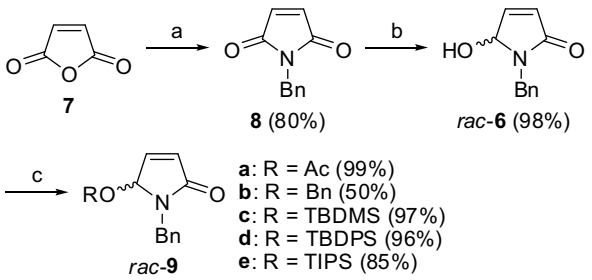
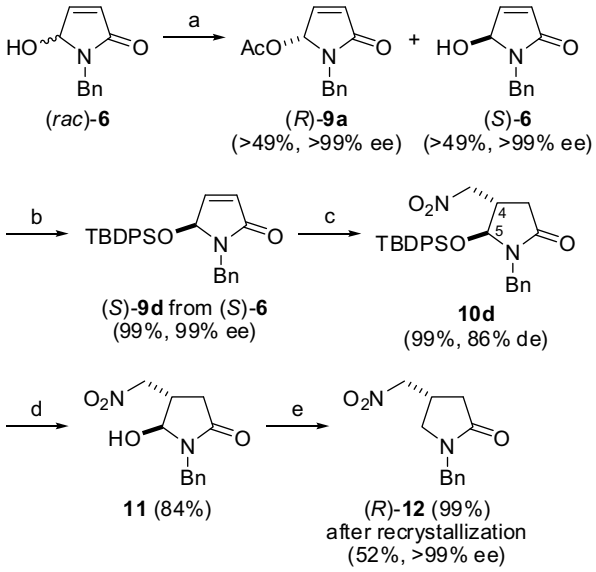


Scheme 2. Reagents and conditions: (a) $BnNH_2$, Ac_2O, NaOAc, CH_2Cl_2, 0 °C for 2 h, then 70 °C for 5 h; (b) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 0 °C, 3 h; (c) Ac_2O, pyridine, rt, 24 h for **9a**. Ag_2O, BnBr, CH_2Cl_2, rt, 18 h for **9b**. TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 17 h for **9c**. TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 24 h for **9d**. TIPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h for **9e**.



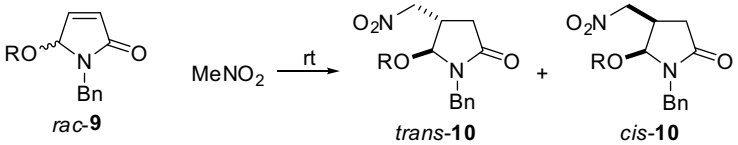
Scheme 3. Reagents and conditions: (a) AcOCH=CH_2, lipase PS-D, 1,4-dioxane, rt, 48 h; (b) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 24 h; (c) $MeNO_2$, DBU, rt, 24 h; (d) TBAF, THF, 0 °C to rt, 22 h; (e) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to rt, 14 h, then recrystallized from ethyl acetate.

reaction conditions to give the protected product **9** in good yields (Scheme 2).

Diastereoselective Michael additions of nitromethane to lactam **9** were performed in the presence of DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene),[5] as shown in Table 1. In general, the reactivity of nitromethane was not sufficiently high enough to react with the α,β-unsaturated lactam compared with α,β-unsaturated ketones, aldehydes, and esters. To improve the reactivity, *N*-Boc derivatives have usually been employed as a Michael acceptor.[6] However, we found that *N*-benzyl derivatives **9** have a sufficient ability to form a carbon–carbon bond. The reaction of *O*-acetyl lactam **9a** afforded the addition product **10** with moderate diastereoselectivity in good yield (Table 1, entry 1). A better diastereoselectivity was obtained in the reaction of *O*-benzyl lactam **9b**, but unfortunately low chemical yield due to the formation of unidentified products was observed (entry 2). *O-tert*-Butyldimethylsilyl (TBDMS) lactam **9c** showed a similar reactivity to **9a** (entry 3), while high diastereoselectivity and chemical yield were observed in the reaction of *O-tert*-butyldiphenylsilyl (TBDPS) lactam **9d** (entry 4).[7] Very bulky substituents such as triisopropylsilyl (TIPS) group were not effective and the reaction did not progress (entry 5).

Next, we examined the chemoenzymatically asymmetric synthesis of nebracetam **3** (Scheme 3). The chiral lactam **6** was prepared by the recently developed lipase-catalyzed kinetic resolution of racemic lactam **6**.[8] Acetate **9a** with an (*R*)-stereochemistry in >49% yield with >99% ee, along with the recovered alcohol **6** with (*S*) stereochemistry in >49% yield with >99% ee, was obtained by lipase PS-D (*Burkholderia cepacia*, Amano Enzyme Co, Ltd) catalyzed kinetic resolution of *rac*-**6**.[9] After isolation by column chromatography, a single peak was detected by chiral HPLC analyses of both acetate **9a** and the recovered alcohol **6**. The hydroxyl function was protected as a *tert*-butyldiphenylsilyl ether with no loss of enantioselectivity.[10] Diastereoselective Michael additions of nitromethane to the chiral lactam (*S*)-**9d** were carried out in the same manner described above. The diastereomeric mixture of Michael product **10d** was obtained in 99% yield and 86% de.[11] Since the diastereomeric mixture was not separated by general column chromatography, it was used in next reaction without separation. However, in order to determine the stereochemistry, the separation of the mixture was performed by preparative HPLC. Vicinal coupling between H4–H5 was not observed with Michael product **10d**; consequently, the dihedral angle H4–C–C–H5 is approximately 90° according to the Karplus relationship.[12] Furthermore, no cross peaks between these protons were observed in a NOESY spectrum. These results indicate that the configuration of the Michael product **10d** should be *trans*. Therefore, the carbanions derived from nitromethane approached

Table 1
Stereoselective Michael addition to lactam derivatives **9**[a]



R =
a: Ac, **b**: Bn, **c**: TBDMS, **d**: TBDPS, **e**: TIPS

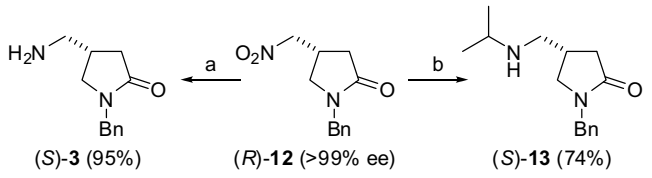
Entry	Lactam	Time (h)	**10** yield[b] (%)	**10** *trans*:*cis*[c]	de (%)
1	**9a**	30	79	75:25	50
2	**9b**	26	54	85:15	70
3	**9c**	24	78	75:25	50
4	**9d**	24	88	93:7	86
5	**9e**	24	No reaction	—	—

[a] Conditions: the lactam derivative **9** (0.15 mmol) and DBU (0.15 mmol) in nitromethane (0.3 mL) at rt with vigorous stirring.
[b] Isolated yield.
[c] Determined by HPLC using Mightysil (Kanto Chemical) and ^1H NMR analyses.

to the double bond from less hindered face to produce the *trans*-adduct.

Our first attempt of the direct deoxygenation of **10d** into **12** was unsuccessful under triethylsilane/boron trifluoride etherate-mediated conditions;[13] therefore, stepwise deoxygenation was next examined. Deprotection of the silyl group using tetrabutylammonium fluoride (TBAF) furnished the hydroxyl lactam **11** in 84% yield, and subsequent deoxygenation of **11** under standard conditions gave lactam (*R*)-**12** in quantitative yield via a well-known *N*-acylpyrrolidinium ion intermediate.[14] The enantiopurity of (*R*)-**12** reached up to >99% ee by recrystallization from ethyl acetate.[15]

Finally, reduction of the nitro group was performed by hydrogenation in the presence of 10% Pd/C in THF to give the enantiopure nebracetam (*S*)-**3** in 95% yield.[16] The specific rotation of the synthesized chiral nebracetam (*S*)-**3** has a negative value $[\alpha]_D^{26} = -8.0$ (*c* 1.0, H_2O), and hence the absolute configuration of the previously resolved chiral nebracetam $[\alpha]_D = -8.4$ (*c* 1.0, H_2O) was determined to have an (*S*)-configuration. The nebracetam derivative (*S*)-**13** was also prepared by a one-pot hydrogenation and reductive amination in the presence of acetone (see Scheme 4).[17]



Scheme 4. Reagents and conditions: (a) Pd/C, H_2 (1.4 MPa), THF, rt, 8 h; (b) Pd/C, acetone, H_2 (1.4 MPa), MeOH, rt, 3 d.

3. Conclusion

In conclusion, we have developed an asymmetric total synthesis of nebracetam **3** by a chemoenzymatic strategy. Lipase-catalyzed kinetic resolution of the lactam **6** demonstrated excellent enantioselectivity. The diastereoselective Michael addition of nitromethane to the chiral lactam (*S*)-**9d** afforded the Michael product **10d** in 99% yield with 86% de. It was not necessary to additionally activate the *N*-benzyl lactam (*S*)-**9d**, which was used directly in the Michael addition. The chemical transformations of **10d**, including recrystallization, furnished the important intermediate lactam (*R*)-**12** with >99% enantioselectivity. Standard reduction of (*R*)-**12** gave the chiral nebracetam **3** and its derivative. The absolute configuration of the chiral (−)-nebracetam was determined to have an (*S*)-configuration. Further studies focusing on the synthesis of nebracetam derivatives are currently under investigation, and will be reported in due course.

Acknowledgements

We would like to thank Amano Enzyme Co, Ltd., Meito Sangyo Co, Ltd, Novozymes®, and Roche Molecular Biochemicals for a generous gift of enzymes. This work was supported in part by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science.

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7. We tried to lower the reaction temperature to −25 °C, but low chemical yield (45%) and no improvement in diastereoselectivity were observed after 2 d stirring. Other organic amine base such as *N*,*N*-diisopropylethylamine was not efficient, and no reaction was observed. Michael addition of 2-nitropropane to **9d** gave the Micheal product in 95% yield as a single diastereomer.
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9. Reactivity and enantioselectivity was dependent upon the nature of the lipase, for instance, lipase A (*Aspergillus niger*, Amano Enzyme Co, Ltd), Lipase M (Mucor javanicus, Amano Enzyme Co, Ltd), Lipase MY (*Candida rugosa*, Meito Sangyo Co, Ltd), and Lipase OF (*Candida cyclindracea*, Meito Sangyo Co, Ltd) did not catalyze the reaction. Novozym 435 (*Candida antarctica*, Novozymes®) and Chirazyme®L-2 (*Candida antarctica* (lipase B), Roche molecular biochemicals) were also a practical catalyst for this kinetic resolution (>49% yield, >99% ee).
Compound (*S*)-**6**: (*R*)-323204-65-5, (*S*)-323204-78-0, (*rac*)-323204-69-9; $R_f = 0.18$ (hexane/AcOEt = 50:50); $[\alpha]_D^{27} = -35.0$ (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, DMSO) δ 4.21 (d, *J* = 15.4 Hz, 1H, $-CH_2$), 4.71 (d, *J* = 15.4 Hz, 1H, $-CH_2$), 5.26 (d, *J* = 8.6 Hz, 1H, $-CHOH$), 6.18 (d, *J* = 6.0 Hz, 1H, $-CH_\alpha$), 6.43 (d, *J* = 8.7 Hz, 1H, –OH), 7.08 (dd, *J* = 1.4, 5.9 Hz, 1H, $-CH_\beta$), 7.17–7.44 (m, 5H, Ar); ^{13}C NMR (75 MHz, DMSO) δ 169.04 (C=O), 147.91 (CH), 138.25 (C), 128.57 (CH), 127.64 (CH), 127.19 (CH), 127.13 (CH), 81.96 (CH), 41.77 (CH_2); ESI-TOFMS calcd for $C_{11}H_{11}NO_2Na$ (MNa^+) 212.0687. Found 212.0720; HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 95:5, flow rate 0.5 mL/min, λ = 254 nm) t_R = 39.48 (*R*-isomer), 44.63 (*S*-isomer) min.
Compound (*R*)-**9a**: (*R*)-323204-73-5, (*S*)-323204-67-7, (*rac*)-323204-63-3; $R_f = 0.43$ (hexane/AcOEt = 50:50); $[\alpha]_D^{27} = -44.7$ (*c* 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H, $-CH_3$), 4.41 (d, *J* = 15.2 Hz, 1H, $-CH_2-$), 4.71 (d, *J* = 15.2 Hz, 1H, $-CH_2-$), 6.30 (dd, *J* = 0.7, 6.0 Hz, 1H, –CHOAc), 6.45 (d, *J* = 1.7 Hz, 1H, $-CH_\alpha$), 6.93 (dd, *J* = 1.7, 6.0, 1H, $-CH_\beta$), 7.17–7.37 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.48 (C=O), 170.08 (C=O), 142.68 (CH), 136.96 (C), 129.90 (CH), 128.80 (CH), 128.20 (CH), 127.76 (CH), 82.53 (CH), 44.08 (CH_2), 20.54 (CH_3); ESI-TOFMS calcd for $C_{13}H_{13}NO_3Na$ (MNa^+) 254.0793. Found 254.0772; HPLC (Daicel CHIRALCEL OD-H, hexane/2-PrOH = 95:5, flow rate 0.5 mL/min, λ = 254 nm) t_R = 33.41 (*R*-isomer), 43.35 (*S*-isomer) min.
10. If the protection reaction was carried out for prolonged time in the presence of excess silyl reagent at room temperature, the enantioselectivity was decreased to around 90% ee.
Compound (*S*)-**9d**: $R_f = 0.80$ (hexane/AcOEt = 50:50); $[\alpha]_D^{25} = +15.5$ (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.52 (m, 4H, Ar), 7.50–7.17 (m, 9H, Ar), 7.16–7.00 (m, 2H, Ar), 6.49 (dd, *J* = 1.5, 6.0 Hz, 1H, CH_β), 6.03 (d, *J* = 6.0 Hz, 1H, CH_α), 5.39 (d, *J* = 1.5 Hz, 1H, –CHOSi–), 5.01 (d, *J* = 15.4 Hz, 1H, $-CH_2-$), 4.24 (d, *J* = 15.4 Hz, 1H, $-CH_2$s–), 1.05 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.57 (C=O), 145.69 (CH), 137.53 (C), 135.92 (CH), 135.85 (CH), 132.99 (C), 132.36 (C), 130.42 (CH), 128.73 (CH), 128.14 (CH), 128.06 (CH), 127.92 (CH), 127.43 (CH), 83.18 (CH), 42.57 (CH_2), 26.77 (CH_3), 19.29 (C); Elemental Anal. Calcd for $C_{27}H_{29}NO_2Si$: C, 75.84; H, 6.84; N, 3.28. Found: C, 75.56; H, 6.84; N, 3.27; HPLC (Daicel CHIRALPAK AD-H, hexane/2-PrOH = 95:5, flow rate 0.5 mL/min, λ = 254 nm) t_R = 17.06 (*R*-isomer), 13.19 (*S*-isomer) min.
11. The diastereomeric mixture of Michael product **10d** was solid. We tried to separate these diastereomers by recrystallization, but it was difficult to isolate as a single diastereomer.
Compound **10d**: Registry number unknown; $R_f = 0.50$ (hexane/AcOEt = 70:30); $[\alpha]_D^{25} = +15.46$ (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.0 Hz, 4H, Ar), 7.54–7.31 (m, 6H, Ar), 7.23–7.10 (m, 3H, Ar), 6.91–6.71 (m, 2H, Ar), 4.93 (d, *J* = 15.1 Hz, 1H, $-CH_2$Ph), 4.80 (s, 1H, –CHOSi–), 3.81 (d, *J* = 15.1 Hz, 1H, $-CH_2$Ph), 3.78 (dd, *J* = 13.4, 8.0 Hz, 1H, $-CH_2NO_2$), 3.59 (dd, *J* = 6.4, 13.4, 1H, $-CH_2NO_2$), 2.97 (dd, *J* = 17.1, 8.4 Hz, 1H, $-CH_2C$=O), 2.93–2.77 (m, 1H, $-CHCH_2NO_2$), 2.14 (d, *J* = 17.1 Hz, 1H, $-CH_2C$=O), 1.07 (s, 9H, Bu^t); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.11 (C=O), 136.27 (C), 135.97 (CH), 135.92 (CH), 132.35 (C), 132.29 (C), 130.82 (CH), 130.69 (CH), 128.94 (CH), 128.51 (CH), 128.39 (CH), 128.04 (CH), 127.89 (CH), 85.10 (CH), 75.66 (CH_2), 43.65 (CH_2), 39.72 (CH), 32.74 (CH_2), 26.85 (CH_3), 19.40 (C); Elemental Anal. Calcd for $C_{28}H_{32}N_2O_4Si$: C, 68.82; H, 6.60; N, 5.73. Found: C, 68.67; H, 6.63; N, 5.77; HPLC (Daicel CHIRALPAK IA, hexane/CH_2Cl_2 = 70:30, flow rate 0.5 mL/min, λ = 254 nm) t_R = 47.37 (*R*,*R*-isomer), 53.07 (*S*,*R*-isomer) 64.99 (*S*,*S*-isomer), 70.85 (*R*,*S*-isomer) min.
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14. *Compound* **11**: Registry number unknown; $R_f = 0.23$ (hexane/AcOEt = 50:50); ^1H NMR (300 MHz, DMSO) δ 2.10-3.22 (m, 3H), 3.94–4.17 (m, 1H), 4.34–5.30 (m, 4H), 6.39–6.58 (m, 1H, $-CHOH$), 7.17–7.43 (m, 5H, Ar); ^{13}C NMR (75 MHz, DMSO) δ 172.47 (C=O, *trans*), 171.54 (C=O, *cis*), 137.30 (C, *trans*), 137.12 (C, *cis*), 128.61 (CH, *trans*), 128.51 (CH, *cis*), 127.81 (CH, *cis*), 127.76 (CH, *trans*), 127.29 (CH, *trans*), 127.18 (CH, *cis*), 83.35 (CH, *cis*), 80.66 (CH, *trans*), 76.47 (CH_2, *cis*), 73.93 (CH_2, *trans*), 42.47 (CH_2, *trans*), 42.26 (CH_2, *cis*), 39.40 (CH, *cis*), 34.26 (CH, *trans*), 32.82 (CH_2, *cis*), 31.54 (CH_2, *trans*); ESI-TOFMS calcd for $C_{12}H_{14}N_2O_4Na$ (MNa^+) 273.0851. Found 273.0892; HPLC (Kanto Chemical Mightysil, hexane/2-PrOH = 80:20, flow rate 0.5 mL/min, λ = 254 nm) t_R = 20.08 (*trans*-isomer), 26.81 (*cis*-isomer) min.

15. *Compound* **12**: R_f = 0.19 (hexane/AcOEt = 50:50); $[\alpha]_D^{29}$ = +13.7 (*c* 0.50, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.11 (m, 5H, Ar), 4.55–4.25 (m, 4H, $-CH_2Ar$, $-CH_2NO_2$), 3.52 (dd, *J* = 7.2, 9.6 Hz, 1H, $-CH_2N-$), 3.25–2.97 (m, 2H, –CH, $-CH_2N-$), 2.73 (dd, *J* = 9.0, 17.1 Hz, 1H, $-CH_2C{=}O$), 2.25 (dd, *J* = 6.7, 17.1 Hz, 1H, $-CH_2C{=}O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.93 (C=O), 135.76 (C), 128.86 (CH), 128.16 (CH), 127.90 (CH), 77.52 ($-CH_2NO_2$), 49.39 (CH_2), 46.45 (CH_2), 34.28 (CH_2), 29.58 (CH); EI-MS *m/e* 234 (M^+, 4), 118 (16), 104 (13), 91 (100); Elemental Anal. (%) calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.67; H, 6.03; N, 12.04; HPLC (Daicel CHIRALPAK AD-H, hexane/2-PrOH = 90:10, flow rate 0.5 mL/min, λ = 254 nm) t_R = 56.30 (*R*-isomer), 62.12 (*S*-isomer) min.

16. *(S)-Nebracetam (S)*-**3**: (*rac*)-103295-65-4, (*rac*)-103295-62-1, (*rac*)-97205-34-0; R_f = 0.17 (MeOH); $[\alpha]_D^{26}$ = −8.0 (*c* 1.00, H_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.10 (m, 5H, Ar), 4.41 (s, 2H, $-CH_2Ph$), 3.37 (dd, *J* = 8.0, 9.9 Hz, 1H, $-CH_2N-$), 3.00 (dd, *J* = 5.5, 9.9 Hz, 1H, $-CH_2N-$), 2.82–2.44 (m, 3H, $-C\underline{H}_2NH_2$, $-CH_2C{=}O$), 2.43–2.27 (m, 1H, –CH), 2.19 (dd, *J* = 6.3, 16.5 Hz, 1H, $-CH_2C{=}O$), 1.34 (br s, 2H, $-NH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.87 (C=O), 136.31 (C), 128.52 (CH), 127.95 (CH), 127.41 (CH), 49.94 (CH_2), 46.24 (CH_2), 45.59 (CH_2), 35.04 (CH_2), 33.96 (CH).

17. Weber, K. H.; Walther, G.; Schneider, C.; Hinzen, D.; Kuhn, F. J.; Lehr, E.; Boehringer Ingelheim K.-G., Fed. Rep. Ger. Application: US, 1988, 11 pp. *Compound (S)*-**13**: Registry number: (*rac*)-120656-67-9; R_f = 0.30 (MeOH); $[\alpha]_D^{30}$ = −7.5 (*c* 1.01, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* =6.3 Hz, 3H, $-CH_3$), 1.01 (d, *J* = 6.3 Hz, 3H, CH_3), 1.30–1.50 (br s, 1H, NH), 2.19 (dd, *J* = 6.2, 16.5 Hz, 1H, $-CH_\alpha$), 2.30–2.49 (m, 1H, $-CH_\beta$), 2.48–2.67 (m, 3H), 2.72 (sept, *J* = 6.3 Hz, 1H, $-CHMe_2$), 3.37 (dd, *J* = 7.8, 9.8 Hz, 1H, $-NCH_2$), 3.02 (dd, *J* = 5.4, 9.8 Hz, 1H, $-NCH_2$), 4.44 (s, 2H, $-CH_2$), 7.17–7.37 (m, 5H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.31 (C=O), 136.73 (C), 128.89 (CH), 128.37 (CH), 127.76 (CH), 51.47 (CH_2), 50.91 (CH_2), 48.91 (CH), 46.63 (CH_2), 36.01 (CH_2), 32.14 (CH), 23.13 (CH_3), 22.89 (CH_3).