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ARTICLE TYPE

Enantioselective synthesis of gabapentin analogues via organocatalytic asymmetric Michael addition of α-branched aldehydes to β-nitroacrylates.

Masanori Yoshida,*[a,b] Erika Masaki,[c] Hiroto Ikehara[b] and Shoji Hara[a,b]

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Michael addition reaction of α-branched aldehydes to β-nitroacrylates was successfully carried out by using a mixed catalyst consisting of a primary amino acid, L-phenylalanine, and its lithium salt to give β-formyl-β'-nitroesters having a quaternary carbon centre in good yields (up to 85%) with high enantioselectivity (up to 98% ee). By using benzyl β-nitroacrylates as Michael acceptors, the obtained β-formyl-β'-nitroesters were converted into various 4,4-disubstituted pyrrolidine-3-carboxylic acids including analogues of gabapentin (Neurotin®) in one step from the Michael adducts in high yields.

Introduction

Michael addition of aldehydes to nitroalkenes is an effective method to create a new carbon–carbon bond for obtaining synthetically useful γ-nitroaldehydes. An asymmetric version of this reaction has been achieved by various catalytic reactions,[1] and most of them are organocatalyses that proceed via formation of an imine–enamine intermediate from an aldehyde and an amine catalyst.[1a,2] For this type of organocatalysis, secondary amines are often employed as catalysts, since an enamine, which is a real Michael donor in the reaction, is generated readily by reaction of a secondary amine with an aldehyde.[3] In the case of using sterically hindered substrates such as α-branched aldehydes, however, primary amines generally afford better results than secondary amines as catalysts, since a secondary amine catalyst needs to form a sterically hindered imine–enamine intermediate to promote the Michael addition reaction.[4,5] We recently reported that a primary amino acid salt was an effective catalyst for the Michael addition of α-branched aldehydes to nitroalkenes for the synthesis of various γ-nitroaldehydes having a quaternary carbon centre.[6] For obtaining more functionalized organic molecules, β-nitroacrylates are attractive substrates for the Michael addition reaction of aldehydes, since Michael adducts having three synthetically useful functionalities such as formyl, nitro and alcoxycarbonyl groups, namely β-formyl-β'-nitroesters, can be synthesized.[7] Although Bonne,[7a] Hayashi[7b] and Ma[7c] individually reported that asymmetric Michael addition of aldehydes to β-nitroacrylates was successfully carried out in the presence of a secondary amine catalyst, *O*-TMS diphenylprolinol, there was only one example employing an α-branched aldehyde.[7c] To show the usefulness of the Michael adducts, Ma and co-workers examined the transformation of a β-formyl-β'-nitroester into a pyrrolidine-3-carboxylic acid by multistep reactions.[7c]

On the other hand, Bryans and co-workers reported that a 4,4-disubstituted pyrrolidine-3-carboxylic acid, **1a**-***R***, has a biological activity similar to that of gabapentin (Neurotin®), which is an anticonvulsant drug (Figure 1).[8a,b] Various analogues of gabapentin have also been synthesized and their biological activities have been evaluated.[8c-f]

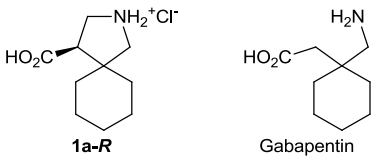


Fig. 1 Gabapentin and its analogue

In this context, we planned to use a primary amino acid salt as a catalyst for the Michael addition of α-branched aldehydes to β-nitroacrylates, and we succeeded in synthesizing β-formyl-β'-nitroesters having a quaternary carbon centre in good yields with high enantioselectivity. Furthermore, by using benzyl β-nitroacrylates as Michael acceptors, the obtained β-formyl-β'-nitroesters were readily converted into 4,4-disubstituted pyrrolidine-3-carboxylic acids including gabapentin analogues in one step from the Michael adducts. In this paper, we disclose the details of the Michael addition reaction and the transformation of the Michael adducts to 4,4-disubstituted pyrrolidine-3-carboxylic acids.

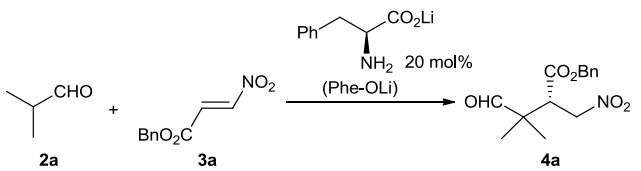
Results and discussion

Michael addition reaction of aldehydes (2) to β-nitroacrylate (3)

Initially, we examined the Michael addition of isobutyraldehyde (**2a**) to benzyl (*E*)-β-nitroacrylate (**3a**) to optimise the reaction conditions. As shown in Table 1, a solvent screen was carried out in the presence of L-phenylalanine lithium salt (Phe-OLi) as a catalyst. The results indicated that the Michael addition reaction

cleanly proceeded in haloalkanes or in aromatic solvents to provide a Michael adduct, β-formyl-β'-nitroester **4a**, in a good yield with high enantioselectivity. Compared to these solvents, relatively high-polarity solvents gave the Michael adduct in lower yields, since generation of high-polar impurities was also detected by TLC analysis. Thus, we chose dichloromethane as a solvent for further investigations by considering the balance between the yield and enantioselectivity of **4a**.

Table 1 Solvent screen for the Michael addition of **2a** to **3a**[a]



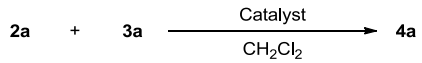
2a **3a** **4a**

Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	DMSO	11	35
2	CH_3CN	38	84
3	AcOEt	62	83
4	THF	40	82
5	Et_2O	68	81
6	$CHCl_3$	74	88
7	CH_2Cl_2	78	87
8	$(CH_2Cl)_2$	81	86
9	Toluene	76	88
10	Benzene	78	87
11	Cyclohexane	60	80

[a] The reaction was carried out with **2a** (1 mmol), **3a** (0.5 mmol) and Phe-OLi (0.1 mmol) in a solvent (1 mL) at 25 °C for 19 h. [b] Isolated yield of **4a** based on **3a**. [c] Determined by chiral HPLC analysis. The absolute configuration was determined to be (*S*), since amino acid **1b** was obtained from **4a** as shown in Scheme 1.

We then carried out a catalyst screen for the Michael addition reaction of **2a** to **3a** (Table 2). Various primary amino acid lithium salts gave the Michael adduct **4a** in good yields with high enantioselectivity; however, a secondary amino acid salt, L-proline lithium salt (Pro-OLi), was ineffective as a catalyst for the reaction (Table 2, entries 1–7). Since Phe-OLi afforded the Michael adduct **4a** in a good yield with relatively higher enantioselectivity, L-phenylalanine (Phe-OH) was chosen as a basic amino acid for investigation of the effects of the counter cation of amino acid salt. As was observed in our previous works, Phe-OH did not show catalytic activity for the Michael addition reaction (Table 2, entry 8).[6b,c] Although an alkali metal salt of Phe-OH other than lithium salt gave the Michael adduct **4a** with over 90% ee, the chemical yield was lower than that of the reaction using Phe-OLi due to the low catalytic activity (Table 2, entries 9–12). Fortunately, we found that the addition of a catalytic amount of benzoic acid to the Michael addition reaction using Phe-OLi was effective for improvement of the enantioselectivity and enhancement of the reaction rate (Table 2, entry 13). Since Phe-OLi is a base, we assumed that the addition of an acid to Phe-OLi immediately generated the corresponding amino acid, Phe-OH, in situ by an acid–base equilibrium reaction and that both Phe-OLi and Phe-OH were necessary to achieve a high yield and high enantioselectivity.[9] Indeed, the Michael addition reaction using a mixed catalyst consisting of Phe-OLi and –OH gave better results than did the reaction using Phe-OLi or Phe-OH as a sole catalyst (Table 2, entries 14–16). After detailed screening of a mixed catalyst consisting of Phe-OH and its alkali metal salt, a 1:4 mixture of Phe-OLi and Phe-OH was chosen as the catalyst for the Michael addition reaction (Table 2, entry 16).

Table 2 Catalyst screen for the Michael addition of **2a** to **3a**[a]



Entry	Catalyst[b]	Yield[c] (%)	ee[d] (%)
1	Phe-OLi	78[e]	87
2	Met-OLi	80[e]	75
3	Leu-OLi	68[e]	77
4	Ile-OLi	74[e]	83
5	Tle-OLi	68[e]	78
6	Trp-OLi	71[e]	80
7	Pro-OLi	9[e]	–
8	Phe-OH	trace	–
9	Phe-ONa	50	92
10	Phe-OK	24	94
11	Phe-ORb	19	94
12	Phe-OCs	24	95
13	Phe-OLi	60[f]	92
14	Phe-OLi/-OH (1:1)	75	90
15	Phe-OLi/-OH (1:2)	75	92
16	Phe-OLi/-OH (1:4)	80	92
17	Phe-ONa/-OH (1:1)	66	92
18	Phe-ONa/-OH (1:2)	65	92
19	Phe-ONa/-OH (1:4)	60	92
20	Phe-OK/-OH (1:4)	47	95
21	Phe-ORb/-OH (1:4)	32	95
22	Phe-OCs/-OH (1:4)	18	94

[a] Unless otherwise mentioned, the reaction was carried out with **2a** (1 mmol), **3a** (0.5 mmol) and a catalyst (0.1 mmol) in dichloromethane (1 mL) at 25 °C for 24 h. [b] Phe: L-phenylalanine; Met: L-methionine; Leu: L-leucine; Ile: L-isoleucine; Tle: L-*t*-leucine; Trp: L-tryptophane; Pro: L-proline [c] Isolated yield of **4a** based on **3a**. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out for 19 h. [f] The reaction was carried out for 5 h using benzoic acid (0.1 mmol) as an additive.

Under the reaction conditions, we investigated the substrate scope with various aldehydes (**2**) and β-nitroacrylates (**3**) (Table 3). Study of the steric effect of the alkoxycarbonyl group of **3** indicated that the yield and enantioselectivity of the Michael adduct **4** did not greatly depend on the bulkiness of the alkoxycarbonyl group (Table 3, entries 1–4). On the other hand, the Michael addition of sterically hindered aldehydes such as cyclohexane– (**2c**) and cycloheptanecarboxaldehyde (**2d**) was slower than that of less hindered substrates, and increased catalyst loading was required to complete the Michael addition reaction within a reasonable reaction time (Table 3, entries 6 and 7). Asymmetric α-branched aldehydes such as 2-methylvaleraldehyde (**2e**) and 2-phenylpropionaldehyde (**2f**) were also subjected to the Michael addition reaction, and the corresponding Michael adducts **4h–j** were synthesized in good yields with high enantioselectivity (Table 3, entries 8–10). Since the absolute configuration of a major enantiomer of **4j** was determined to be (2*S*,3*R*) by comparison of the specific rotation with that of the previous report,[7c] it was found that the Michael addition reaction proceeded *syn* selectively. Study of the substituent effect of β-nitroacrylates using benzyl (*E*)-3-nitropent-2-enoate (**3e**) and methyl (*E*)-2-methyl-3-nitroprop-2-enoate (**3f**) indicated that a substituent on the β-position did not disturb the Michael addition reaction to give the corresponding Michael adduct **4k**,[10] while a substituent on the α-position inhibited the

attack of a nucleophile upon the nitroacrylate (Table 3, entries 11 and 12).

The reaction mechanism would be similar to that of the Michael addition reaction of aldehydes to nitroalkenes catalyzed by a primary amino acid salt,[6b,c] and the addition of an acid would accelerate the formation of an imine–enamine intermediate from an aldehyde and the catalyst.[9] Seebach and Hayashi recently proposed an interesting reaction mechanism of *O*-TMS diphenylprolinol-catalyzed Michael addition of aldehydes to nitroalkens involving a cyclobutane intermediate consisting of an enamine and a nitroalkene; however, no generation of such a species was observed in our case by monitoring the reaction of **2a** to **3a** with NMR.[11]

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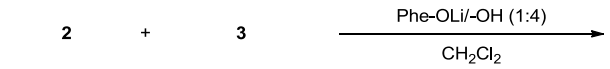
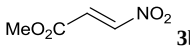
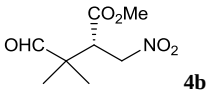
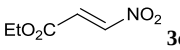
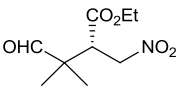
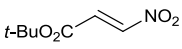
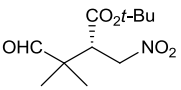
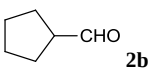
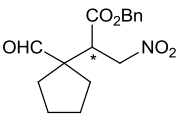
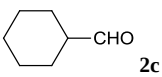
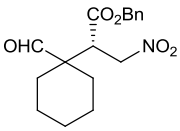
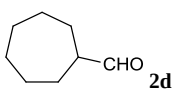
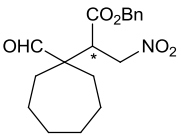
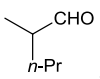
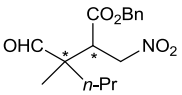
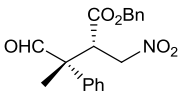
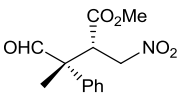
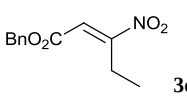
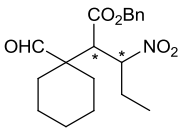
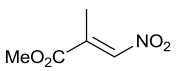
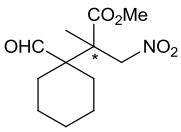
Table 3 Substrate scope in the Michael addition reaction of **2** to **3**[a]

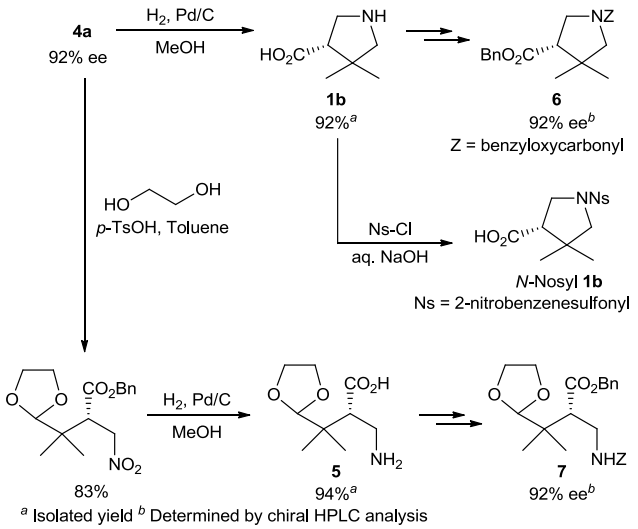


Entry	2	3	4	*t* / h	Yield[b] (%)	ee[c] (%)	dr[d]
1	**2a**	**3a**	**4a**	24	80	92 (*S*)[e]	–
2	**2a**	 **3b**	 **4b**	24	71	93 (*S*)	–
3	**2a**	 **3c**	 **4c**	24	76	92 (*S*)	–
4	**2a**	 **3d**	 **4d**	24	74	89 (*S*)	–
5	 **2b**	**3a**	 **4e**	9	68	88	–
6	 **2c**	**3a**	 **4f**	72[f]	72	87 (*S*)[g]	–
7	 **2d**	**3a**	 **4g**	72[f]	70	95	–
8	 **2e**	**3a**	 **4h**	48	75[h]	95	4:1
9	 **2f**	**3a**	 **4i**	48	85	97 (2*S*,3*R*)[i]	>20:1[j]
10	**2f**	**3b**	 **4j**	38	84	98 (2*S*,3*R*)[k]	>20:1[j]
11	**2c**	 **3e**	 **4k**	96[f]	84	92	>20:1[j]
12	**2c**	 **3f**	 **4l**	72[f]	no reaction	–	–

[a] Unless otherwise mentioned, the reaction was carried out with **2** (1 mmol), **3** (0.5 mmol) and a mixed catalyst, Phe-OLi/-OH (1:4, 0.1 mmol), in dichloromethane (1 mL) at 25 °C. [b] Isolated yield of **4** based on **3**. [c] Determined by chiral HPLC analysis. The absolute configuration of a major enantiomer of **4** is shown in parenthesis. [d] Determined by ^{1}H NMR analysis of the crude product. [e] The absolute configuration was determined to be (*S*), since the NMR spectra and specific rotation of carboxylic acids obtained by deprotection of the alkoxycarbonyl group of **4a**–**d** are in good agreement. [f] The reaction was carried out with 30 mol% of the catalyst (0.15 mmol). [g] The absolute configuration was determined to be (*S*), since amino acid **1a-*S*** was obtained from **4f** as shown in Table 4. [h] Yield of a mixture of diastereomers. [i] The absolute configuration was determined to be (2*S*,3*R*), since the NMR spectra and specific rotation of carboxylic acids obtained by deprotection of the alkoxycarbonyl group of **4i** and **4j** are in good agreement. [j] *syn*/*anti*. [k] The absolute configuration was determined by comparison of the specific rotation with that of the literature.[7c]

Synthesis of gabapentin analogues

We then attempted a transformation of β-formyl-β'-nitroesters **4** into amino acids. By subjecting **4a** to a common condition of hydrogenolysis using H_2–Pd/C, a cyclic amino acid, 4,4-dimethylpyrrolidine-3-carboxylic acid (**1b**), was successfully obtained in 92% yield (Scheme 1). Probably, removal of the benzyl group, reduction of the nitro group to an amino group, and intramolecular imine formation and its reduction would successively occur to complete the transformation. Stereochemistry of **1b** was determined to be (*S*) by carrying out X-ray analysis of *N*-nosyl **1b** (Figure 2). A linear β-amino acid **5** was also synthesized by hydrogenolysis after protecting the formyl group of **4a**. By measuring the enantiomeric excess of protected amino acids **6** and **7** obtained from **1b** and **5**, respectively, it was confirmed that no racemization occurred during the syntheses of **1b** and **5** from **4a**. Encouraged by these results, we then carried out the hydrogenolysis of Michael adducts **4** to synthesize various 4,4-disubstituted pyrrolidine-3-carboxylic acids **1**. The spiro-type gabapentin analogue **1a** was synthesized in a high yield by hydrogenolysis of **4f** and subsequent treatment with aq. HCl (Table 4, entry 1). The absolute configuration of the major enantiomer was determined to be (*S*) by comparison of the specific rotation with that of the literature.[8a] The opposite enantiomer **1a-*R*** could be obtained as a major enantiomer from Michael adduct **4f-*R***, which was synthesized by using D-phenylalanine and its lithium salt as a mixed catalyst (Table 4, entry 2). A spiro-type gabapentin analogue **1c** having a substituent on the pyrrolidine ring was also synthesized from **4k** in a high yield (Table 4, entry 3). Similarly, spiro amino acids having a five– or seven-membered ring, **1d** and **1e**, and other 4,4-disubstituted pyrrolidine-3-carboxylic acids such as **1f** and **1g** were synthesized in high yields by the present method (Table 4, entries 4–7).



Scheme 1 Transformation of **4a** to a cyclic γ-amino acid **1b** and a linear β-amino acid **5**

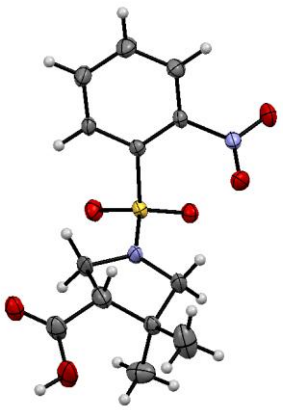
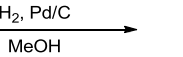
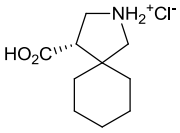
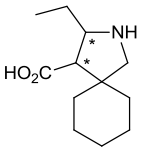
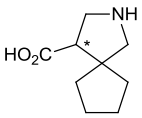
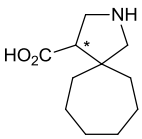
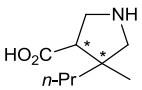
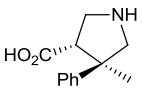


Fig. 2 ORTEP of *N*-Nosyl **1b**

Table 4 Transformation of **4** to **1**[a]



Entry	4	1	Yield[b] (%)
1	**4f**	 **1a-*S***[c]	97
2	**4f-*R***	**1a-*R***[c]	97
3	**4k**	 **1c**	93
4	**4e**	 **1d**	94
5	**4g**	 **1e**	94
6	**4h**	 **1f**	99
7	**4i**	 **1g**	90

[a] The reaction was carried out with **4** (0.5 mmol), Pd/C and H_2 (rubber balloon) in methanol (1 mL) at rt for 48 h. [b] Isolated yield of **1** based on **4**. [c] After reduction of **4f** or **4f-*R***, the obtained amino acid was treated with aq. HCl.

Conclusions

We found that a mixture of L-phenylalanine and its lithium salt was an effective catalyst for the Michael addition of α-branched aldehydes to β-nitroacrylates to give β-formyl-β'-nitroesters having a quaternary carbon centre in good yields with high enantioselectivity. Michael adducts obtained from benzyl β-nitroacrylates were readily converted into 4,4-disubstituted pyrrolidine-3-carboxylic acids including gabapentin analogues in almost quantitative yield by a common hydrogenolysis using H_2–Pd/C in high yields.

Experimental

General

Aldehydes **2a**–**c,e,f** were purchased and used after distillation. Synthesis of cycloheptanecarboxaldehyde **2d** and β-nitroacrylates **3** are described in the ESI. Amino acid salts[12] and a mixture of an amino acid and its alkali metal salts[9] were prepared according to the literatures.

^{1}H NMR (400 MHz) ^{13}C NMR (100 MHz) spectra were recorded on a FT NMR. Chemical shifts, δ are referred to TMS ($CDCl_3$ and CD_3OD) or 3-(trimethylsilyl) propionic-2,2,3,3-d_4 acid sodium salt (D_2O).

General procedure for the Michael addition of aldehydes (2) to β-nitroacrylates (3)

In a 7 mL vial, benzyl β-nitroacrylate (**3a**) (103.5 mg, 0.5 mmol) and isobutyraldehyde (**2a**) (72 mg, 1 mmol) were successively added to a slurry of a mixed catalyst Phe-OLi/-OH (1:4, 16.6 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) at 25 °C. After stirring for 24 h at 25 °C, the reaction mixture was filtered through a small plug of silica gel, eluted with Et_2O (2 mL × 3) and concentrated under reduced pressure. Benzyl (*S*)-3,3-dimethyl-2-nitromethyl-4-oxobutyrate (**4a**) was isolated by column chromatography (silica gel, hexane/Et_2O) in 80% yield as clear oil. The enantioselectivity was determined by chiral HPLC analysis (92% ee). $[\alpha]_D^{19.2}$ –13.7 (c = 1.0, $CHCl_3$, 92% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol (93:7, v/v), 0.8 mL/min, 215 nm; t_r(major enantiomer) = 17.2 min, t_r(minor enantiomer) = 15.7 min]. $\delta_H(CDCl_3)$ 1.08 (3H, s), 1.13 (3H, s), 3.60 (1H, dd, *J* 3.3, 10.8 Hz), 4.46 (1H, dd, *J* 3.3, 14.9 Hz), 4.80 (1H, dd, *J* 10.8, 14.9 Hz), 5.15–5.22 (2H, m), 7.32–7.41 (5H, m), 9.43 (1H, s); $\delta_C(CDCl_3)$ 19.2, 20.2, 46.7, 47.1, 67.8, 72.5, 128.5, 128.7, 128.8, 134.9, 170.5, 201.7; γ(neat)/cm^{-1} 1732 [C(=O)H, C(=O)OBn], 1557 (NO_2); [HR ESI-MS: Calc. for $C_{14}H_{17}NO_5$+Na (*M*+Na): 302.0999. Found: M^++Na, 302.1000].

Methyl (*S*)-3,3-dimethyl-2-nitromethyl-4-oxobutyrate (4b)

Oil. $[\alpha]_D^{21.9}$ –21.5 (c = 1.0, $CHCl_3$, 93% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol (93:7, v/v), 0.8 mL/min, 215 nm; t_r(major enantiomer) = 18.0 min, t_r(minor enantiomer) = 14.9 min]. $\delta_H(CDCl_3)$ 1.14 (3H, s), 1.17 (3H, s), 3.57 (1H, dd, J 3.3, 10.5 Hz), 3.77 (3H, s), 4.47 (1H, dd, J 3.3, 14.3 Hz), 4.80 (1H, dd, J 10.5, 14.3 Hz), 9.47 (1H, s); $\delta_C(CDCl_3)$ 19.1, 20.0, 46.4, 46.9, 52.5, 72.3, 170.9, 201.5; γ(neat)/cm^{-1} 1732 [C(=O)H, C(=O)OMe], 1558 (NO_2); [HR ESI-MS: Calc. for $C_8H_{13}NO_5$+Na (*M*+Na): 226.0686. Found: M^++Na, 226.0689].

Ethyl (*S*)-3,3-dimethyl-2-nitromethyl-4-oxobutyrate (4c)

Oil. $[\alpha]_D^{22.3}$ –17.5 (c = 1.0, $CHCl_3$, 92% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol (98:2, v/v), 0.8 mL/min, 215 nm; t_r(major enantiomer) = 23.1 min, t_r(minor enantiomer) = 21.8 min]. $\delta_H(CDCl_3)$ 1.14 (3H, s), 1.16 (3H, s), 1.28 (3H, t, *J* 7.4 Hz), 3.55 (1H, dd, *J* 3.3, 10.6 Hz), 4.22 (2H, q, *J* 7.4 Hz), 4.46 (1H, dd, *J* 3.3, 14.9 Hz), 4.80 (1H, dd, *J* 10.6, 14.9 Hz), 9.48 (1H, s); $\delta_C(CDCl_3)$ 13.9, 19.1, 19.8, 46.4, 47.0, 61.8, 72.3, 170.2, 201.5; γ(neat)/cm^{-1} 1732 [C(=O)H,C(=O)OEt], 1559 (NO_2); [HR ESI-MS: Calc. for $C_9H_{15}NO_5$+Na (*M*+Na): 240.0842. Found: M^++Na, 240.0846].

t-Butyl (*S*)-3,3-dimethyl-2-nitromethyl-4-oxobutyrate (4d)

Oil. $[\alpha]_D^{22.3}$ –17.0 (c = 1.0, $CHCl_3$, 89% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol (99:1, v/v), 0.7 mL/min, 208 nm; t_r(major enantiomer) = 21.8 min, t_r(minor enantiomer) = 23.0 min]. $\delta_H(CDCl_3)$ 1.13 (3H, s), 1.14 (3H, s), 1.45 (9H, s), 3.47 (1H, dd, *J* 3.5, 10.8 Hz), 4.41 (1H, dd, *J* 3.5, 14.5 Hz), 4.76 (1H, dd, *J* 10.8, 14.5 Hz), 9.50 (1H, s); $\delta_C(CDCl_3)$ 19.2, 19.5, 27.7, 46.4, 47.8, 72.2, 83.2, 169.1, 201.5; γ(neat)/cm^{-1} 1732 [C(=O)H, C(=O)O*t*-Bu], 1559 (NO_2); [HR ESI-MS: Calc.

for $C_{11}H_{19}NO_5$+Na (*M*+Na): 268.1155. Found: M^++Na, 268.1159].

Benzyl 2-(1-formylcyclopentyl)-3-nitropropionate (4e)

Oil. $[\alpha]_D^{21.8}$ –12.0 (c = 1.0, $CHCl_3$, 88% ee). HPLC [Daicel CHIRALCEL AS-H, hexane/isopropanol (97:3, v/v), 0.7 mL/min, 215 nm; t_r(major enantiomer) = 54.3 min, t_r(minor enantiomer) = 58.5 min]. $\delta_H(CDCl_3)$ 1.49–1.74 (5H, m), 1.79–1.86 (1H, m), 1.94–2.00 (2H, m), 3.58 (1H, dd, *J* 3.1, 10.7 Hz), 4.44 (1H, dd, *J* 3.1, 14.8 Hz), 4.83 (1H, dd, *J* 10.7, 14.8 Hz), 5.15–5.21 (2H, m), 7.33–7.41 (5H, m), 9.40 (1H, s); $\delta_C(CDCl_3)$ 25.2, 25.6, 30.9, 31.7, 43.4, 47.1, 57.3, 67.8, 73.4, 128.6, 128.7, 134.8, 170.6, 201.1; γ(neat)/cm^{-1} 1731 [C(=O)H, C(=O)OBn], 1557 (NO_2); [HR ESI-MS: Calc. for $C_{16}H_{19}NO_5$+Na (*M*+Na): 328.1155. Found: M^++Na, 328.1153].

Benzyl (*S*)-2-(1-formylcyclohexyl)-3-nitropropionate (4f)

Oil. $[\alpha]_D^{21.2}$ –15.0 (c = 1.0, $CHCl_3$, 87% ee). HPLC [Daicel CHIRALCEL AS-H, hexane/isopropanol/ethanol (98.5:1.0:0.5 v/v/v), 0.8 mL/min, 229 nm; t_r(major enantiomer) = 45.5 min, t_r(minor enantiomer) = 48.1 min]. $\delta_H(CDCl_3)$ 1.14–1.36 (4H, m), 1.48–1.70 (4H, m), 1.89–1.92 (1H, m), 1.99–2.01 (1H, m), 3.33 (1H, dd, *J* 2.9, 11.4 Hz), 4.47 (1H, dd, *J* 2.9, 14.5 Hz), 4.76 (1H, dd, *J* 11.4, 14.5 Hz), 5.16–5.23 (2H, m), 7.34–7.41 (5H, m), 9.53 (1H, s); $\delta_C(CDCl_3)$ 22.1, 22.2, 24.8, 29.2, 29.9, 48.8, 49.6, 67.6, 72.4, 128.51, 128.54, 128.6, 134.6, 170.0, 204.0; γ(neat)/cm^{-1} 1735 [C(=O)H, C(=O)OBn], 1560 (NO_2); [HR ESI-MS: Calc. for $C_{17}H_{21}NO_5$+Na (*M*+Na): 342.1312. Found: M^++Na, 342.1314].

Benzyl (*R*)-2-(1-formylcyclohexyl)-3-nitropropionate (4f-*R*)

$[\alpha]_D^{21.5}$ +16.0 (c = 1.0, $CHCl_3$, 87% ee).

Benzyl 2-(1-formylcycloheptyl)-3-nitropropionate (4g)

Oil. $[\alpha]_D^{20.5}$ –26.5 (c = 1.0, $CHCl_3$, 95% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol/ethanol (97.5:2.0:0.5 v/v/v), 1.0 mL/min, 229 nm; t_r(major enantiomer) = 31.5 min, t_r(minor enantiomer) = 33.6 min]. $\delta_H(CDCl_3)$ 1.33–1.74 (10H, m), 1.83–1.95 (2H, m), 3.47 (1H, dd, *J* 2.9, 11.0 Hz), 4.42 (1H, dd, *J* 2.9, 14.8 Hz), 4.80 (1H, dd, *J* 11.0, 14.8 Hz), 5.12–5.23 (2H, m), 7.33–7.41 (5H, m), 9.47 (1H, s); $\delta_C(CDCl_3)$ 23.1, 23.3, 30.3, 30.4, 30.5, 31.2, 48.5, 52.9, 67.9, 72.8, 128.66, 128.68, 134.7, 170.6, 202.1; γ(neat)/cm^{-1} 1732 [C(=O)H, C(=O)OBn], 1559 (NO_2); [HR ESI-MS: Calc. for $C_{18}H_{23}NO_5$+Na (*M*+Na): 356.1468. Found: M^++Na, 356.1470].

Benzyl 3-formyl-3-methyl-2-nitromethylhexanoate (4h)

Oil. $[\alpha]_D^{21.5}$ –11.0 (c = 1.0, $CHCl_3$, dr = 4:1, 95% ee). HPLC [Daicel CHIRALCEL AS-H, hexane/isopropanol (97:3, v/v), 0.8 mL/min, 215 nm; t_r(major enantiomer) = 22.9 min, t_r(minor enantiomer) = 24.8 min]. $\delta_H(CDCl_3)$ 0.77 (3H, t, *J* 7.0 Hz), 1.11 (3H, s), 1.35–1.48 (4H, m), 3.61 (1H, dd, *J* 3.1, 11.4 Hz), 4.45 (1H, dd, *J* 3.1, 14.3 Hz), 4.78 (1H, dd, *J* 11.4, 14.3 Hz), 5.14–5.27 (2H, m), 7.34–7.39 (5H, m), 9.34 (1H, s); $\delta_C(CDCl_3)$ 14.1, 16.5, 16.9, 37.3, 45.1, 49.9, 67.5, 72.9, 128.5, 128.6, 134.8, 170.5, 202.2; γ(neat)/cm^{-1} 1731 [C(=O)H, C(=O)OBn], 1557 (NO_2); [HR ESI-MS: Calc. for $C_{16}H_{21}NO_5$+Na (*M*+Na): 330.1312. Found: M^++Na, 330.1316].

Benzyl (2*S*,3*R*)-3-methyl-3-phenyl-2-nitromethyl-4-oxobutyrate (4i)

Oil. $[\alpha]_D^{21.5}$ –128.7 (c = 1.0, $CHCl_3$, 97% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol (90:10, v/v), 0.6 mL/min, 215 nm; t_r(major enantiomer) = 21.3 min, t_r(minor enantiomer) = 19.8 min]. $\delta_H(CDCl_3)$ 1.63 (3H, s), 3.98 (1H, dd, *J* 2.7, 11.2 Hz), 4.56–4.65 (2H, m), 4.80–4.90 (2H, m), 6.93–7.38 (10H, m), 9.31 (1H, s); $\delta_C(CDCl_3)$ 14.4, 47.6, 54.0, 67.1, 73.1, 127.2, 128.1, 128.2, 128.48, 128.52, 129.1, 134.4, 135.2, 170.7, 197.8; γ(neat)/cm^{-1} 1720 [C(=O)H, C(=O)OBn], 1559 (NO_2); [HR ESI-MS: Calc. for $C_{19}H_{19}NO_5$+Na (*M*+Na): 364.1155. Found: M^++Na, 364.1159].

Methyl (2*S*,3*R*)-3-methyl-3-phenyl-2-nitromethyl-4-oxobutyrate (4j)

Oil. $[\alpha]_D^{19.8}$ –158.0 (c = 1.0, $CHCl_3$, 98% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol (93:7, v/v), 0.8 mL/min, 215 nm; t_r(major enantiomer) = 16.4 min, t_r(minor enantiomer) = 14.5 min]. $\delta_H(CDCl_3)$ 1.64 (3H, s), 3.29 (3H, s), 3.92 (1H, dd, *J* 2.5, 11.2 Hz), 4.60 (1H, dd, *J* 2.5, 14.3 Hz), 4.81 (1H, dd, *J* 11.2, 14.3 Hz), 7.17–7.44 (5H, m), 9.36 (1H, s); $\delta_C(CDCl_3)$ 14.6, 47.7, 52.0, 54.1, 73.1, 127.1, 128.5, 129.1, 135.5, 171.3, 198.0; γ(neat)/cm^{-1} 1731 [C(=O)H, C(=O)OMe], 1559 (NO_2).

Spectroscopic data are in agreement with the published data.[7c]

Benzyl 2-(1-formylcyclohexyl)-3-nitropentanoate (4k)

Oil. $[\alpha]_D^{20.3}$ –4.0 (c = 1.0, $CHCl_3$, 92% ee). HPLC [Daicel CHIRALCEL AS-H, hexane/isopropanol (95:5 v/v), 1.0 mL/min, 229 nm; t_r(major enantiomer) = 10.7 min, t_r(minor enantiomer) = 15.9 min]. $\delta_H(CDCl_3)$ 0.83 (3H, t, *J* 7.6 Hz), 1.06–1.16 (3H, m), 1.28–1.37 (1H, m), 1.47–1.68 (5H, m), 1.71–1.83 (1H, m), 1.97–2.00 (2H, m), 3.33 (1H, d, *J* 8.4 Hz), 4.70–4.76 (1H, m), 5.13–5.19 (2H, m), 7.33–7.40 (5H, m), 9.56 (1H, s); $\delta_C(CDCl_3)$ 6.4, 10.1, 22.3, 24.9, 25.8, 29.1, 30.2, 49.8, 56.0, 67.5, 86.5, 128.7, 128.8, 134.5, 169.5, 204.4; γ(neat)/cm^{-1} 1731 [C(=O)H, C(=O)OBn], 1555 (NO_2); [HR ESI-MS: Calc. for $C_{19}H_{25}NO_5$+Na (*M*+Na): 370.1625. Found: M^++Na, 370.1628].

General procedure for hydrogenolysis of 4: synthesis of (*S*)-4,4-dimethylpyrrolidine-3-carboxylic acid (1b).[7c]

In a round bottom flask, 10 % Pd/C (200 mg) was placed, and the flask was flushed with N_2. Then a methanol solution (10 mL) of benzyl (*S*)-3,3-dimethyl-2-nitromethyl-4-oxobutyrate (**4a**) (139.5 mg, 0.5 mmol) was poured into the flask. A balloon charged with H_2 was attached to the flask, and the atmosphere in the flask was replaced with H_2. After the reaction mixture was stirred for 48 h at room temperature, Pd/C was filtered off with Celite. The obtained organic layer was concentrated under reduced pressure to give (*S*)-4,4-dimethylpyrrolidine-3-carboxylic acid (**1b**) in 92% yield (65.8 mg, 0.46 mmol) as white solid. M.p. 165.0–166.0 °C. $[\alpha]_D^{18.3}$ –5.0 (c = 1.0, CH_3OH). $\delta_H(D_2O)$ 1.07 (3H, s), 1.25 (3H, s), 2.74–2.78 (1H, m), 3.09–3.24 (2H, m), 3.52–3.62 (2H, m),; $\delta_C(D_2O)$ 24.3, 28.5, 43.8, 50.4, 58.0, 59.6, 180.8; γ(KBr)/cm^{-1} 1574 [C(=O)O^-]; [HR ESI-MS: Calc. for $C_7H_{12}NO_2$ (*M*–H): 142.0874. Found: M^+–H, 142.0870].

The enantiomeric excess (92% ee) was confirmed after protection of the amino acid moiety: benzyl *N*-benzyloxycarbonyl (*S*)-4,4-dimethylpyrrolidine-3-carboxylate (**6**). Oil. $[\alpha]_D^{19.3}$ –4.0 (c = 1.0, $CHCl_3$, 92% ee). HPLC [Daicel CHIRALPAK AS-H, hexane/isopropanol (90:10, v/v), 0.7 mL/min, 210 nm; t_r(major

enantiomer) = 24.9 min, t_r(minor enantiomer) = 32.4 min]. $\delta_H(CDCl_3)$ 0.96 (3H, s), 1.19–1.21 (3H, s×2, rotamer), 2.75–2.83 (1H, m), 3.17–3.22 (1H, m), 3.33–3.41 (1H, m), 3.65–3.84 (2H, m), 5.09–5.18 (4H, m), 7.31–7.36 (10H, m); $\delta_C(CDCl_3)$ 22.05–22.10 (rotamer), 26.3–26.4 (rotamer), 40.6–41.5 (rotamer), 46.9–47.4 (rotamer), 52.0–52.8 (rotamer), 58.9–59.3 (rotamer), 66.49–66.54 (rotamer), 66.78–66.80 (rotamer), 127.80, 127.82, 127.9, 128.38, 128.42, 128.6, 135.5, 136.7, 154.7–154.8 (rotamer), 171.25–171.34 (rotamer); γ(neat)/cm^{-1} 1731 [C(=O)OBn], 1703 [NC(=O)OBn]; [HR ESI-MS: Calc. for $C_{22}H_{25}NO_4$+Na (*M*+Na): 390.1676. Found: M^++Na, 390.1675].

Synthesis of (*S*)-*N*-(2-nitrophenylsulfonyl)-4,4-dimethylpyrrolidine-3-carboxylic acid (*N*-nosyl 1b).

In a 7 mL vial, a solution of 2-nitrobenzenesulfonyl chloride (40 mg, 0.180 mmol) in Et_2O (1 mL) was added to a solution of **1b** (25 mg, 0.175 mmol) in 1N-NaOH (0.5 mL) at room temperature. After stirring for 1 h at room temperature, Et_2O was removed under reduced pressure. The resulting solution was acidified to pH 3 by adding 1N-HCl, and extracted with EtOAc (2 mL × 3). Combined organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Recrystallization from 2-propanol/hexane gave (*S*)-*N*-(2-nitrophenylsulfonyl)-4,4-dimethylpyrrolidine-3-carboxylic acid (*N*-nosyl **1b**) (28.3 mg, 0.073 mmol) as colourless crystal. M.p. 157–158 °C. $[\alpha]_D^{20.6}$ –7.2 (c = 1.0, CH_3OH). $\delta_H(CD_3OD)$ 0.96 (3H, s), 1.21 (3H, s), 2.83 (1H, *t*, *J* 7.9 Hz), 3.22 (1H, d, *J* 9.7 Hz), 3.37 (1H, d, *J* 9.8 Hz), 3.65–3.77 (2H, m), 7.73–7.83 (3H, m), 8.04–8.07 (1H, m); $\delta_C(CD_3OD)$ 21.9, 26.1, 42.3, 49.9, 53.8, 61.5, 125.2, 131.6, 132.2, 132.8, 135.2, 149.7, 174.2; γ(KBr)/cm^{-1} 1695 [C(=O)OH], 1538 (NO_2); [HR ESI-MS: Calc. for $C_{13}H_{16}N_2O_6S$+Na (*M*+Na): 351.0621. Found: M^++Na, 351.0620].

Crystal data for *N*-Nosyl **1b**: $C_{13}H_{16}N_2O_6S$, *M* = 328.34, Triclinic, *a* = 7.5722(4) Å, *b* = 9.8018(4) Å, *c* = 10.6602(5) Å, *α* = 75.7440(10)°, *β* = 72.7350(10)°, *γ* = 80.7840(10)°, *V* = 729.04(6) $Å^3$, *T* = 123(2) K, space group *P*1, *Z* = 2, *μ*(MoKα) = 0.254 mm^{-1}, 7153 reflections measured, 5411 independent reflections (R_{int} = 0.0156). The final R_1 values were 0.0440 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1186 ($I > 2\sigma(I)$). The final R_1 values were 0.0468 (all data). The final $wR(F^2)$ values were 0.1235 (all data). The goodness of fit on F^2 was 1.090. Flack parameter = 0.02(8). CCDC number ####.

Synthesis of (*S*)-2-aminomethyl-3-[1,3]dioxolan-2-yl-3-methyl butyric acid (5).

In a round bottomed flask equipped with a Dien-Stark trap, ethylene glycol (1 mL) and *p*-toluenesulfonic acid mono hydrate (5.7 mg, 0.03 mmol) were successively added to a toluene solution (15 mL) of benzyl (*S*)-3,3-dimethyl-2-nitromethyl-4-oxobutyrate (**4a**) (2.5 mmol) at room temperature. The reaction mixture was refluxed for 16 h, and cooled then to room temperature. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Benzyl (*S*)-3-[1,3]dioxolan-2-yl-2-nitromethyl-3-methyl butyrate was isolated by column chromatography (silica gel, hexane/Et_2O) in 83% yield (888 mg, 2.08 mmol) as yellow oil. In a round bottom flask, 10 % Pd/C (250 mg) was placed, and the flask was flushed with N_2. A methanol solution (40 mL) of benzyl (*S*)-3-[1,3]dioxolan-2-yl-2-nitromethyl-3-methyl butyrate (239 mg, 0.56 mmol) was poured into the flask. A balloon charged with H_2 was attached to the flask, and the atmosphere in the flask was replaced with H_2. After the reaction mixture was stirred for 24 h at room temperature, Pd/C was filtered off with Celite. The obtained organic layer was concentrated under reduced pressure to give (*S*)-2-aminomethyl-3-[1,3]dioxolan-2-yl-3-methyl butyric acid (**5**) in 94 % yield (108 mg, 0.53 mmol) as white solid. M.p. 270 °C (decomp.). $[\alpha]_D^{18.8}$ –2.0 (c = 0.5, H_2O). $\delta_H(D_2O)$ 1.01 (3H, s), 1.02 (3H, s), 2.64–2.71 (1H, m), 3.25–3.34 (2H, m), 3.90–4.02 (4H, m), 4.76 (1H, s); $\delta_C(D_2O)$ 21.4, 21.5, 39.7, 40.2, 50.1, 66.36, 66.38, 109.3, 177.1; γ(KBr)/cm^{-1} 1627 [C(=O)O^-]; [HR ESI-MS: Calc. for $C_9H_{18}NO_4$ (*M*+H): 204.1230. Found: M^++H, 204.1230].

The enantiomeric excess (92% ee) was confirmed after protection of the amino acid moiety: benzyl *N*-benzyloxycarbonyl (*S*)-2-aminomethyl-3-[1,3]dioxolan-2-yl-3-methyl butyrate (**7**). Oil. $[\alpha]_D^{19.6}$ +18.3 (c = 1.0, $CHCl_3$, 92% ee). HPLC [Daicel CHIRALPAK AD-H, hexane/isopropanol (80:20, v/v), 0.8 mL/min, 209 nm; t_r(major enantiomer) = 16.9 min, t_r(minor enantiomer) = 13.4 min]. $\delta_H(CDCl_3)$ 0.98 (3H, s), 1.05 (3H, s), 2.88 (1H, dd, *J* 4.1, 11.0 Hz), 3.33–3.41 (1H, m), 3.70–3.96 (5H, m), 4.61 (1H, s), 4.82–4.86 (1H, m), 5.02–5.14 (4H, m), 7.28–7.36 (10H, m); $\delta_C(CDCl_3)$ 20.4, 20.6, 39.4, 39.8, 50.9, 65.1, 65.2, 66.3, 66.6, 108.4, 127.99, 128.03, 128.1, 128.2, 128.4, 128.5, 135.8, 136.5, 156.1, 173.6; γ(neat)/cm^{-1} 1731 [C(=O)OBn, NC(=O)OBn]; [HR ESI-MS: Calc. for $C_{24}H_{29}NO_6$+Na (*M*+Na): 450.1887. Found: M^++Na, 450.1884].

Synthesis of (*S*)-aza-spiro[4,5]decane-4-carboxylic acid hydrochloride (1a-*S*)

In a round bottomed flask, 10 % Pd/C (200 mg) was placed, and the flask was flushed with N_2. A methanol solution (10 mL) of benzyl (*S*)-2-(1-formylcyclohexyl)-3-nitropropionate (**4f**) (159.5 mg, 0.5 mmol) was poured into the flask. A balloon charged with H_2 was attached to the flask, and the atmosphere in the flask was replaced with H_2. After the reaction mixture was stirred for 48 h at room temperature, Pd/C was filtered off with Celite. The obtained organic layer was concentrated under reduced pressure, and aqueous 3N-HCl (2 mL) was added to the residue. After the mixture was stirred for 2 h, resulting aqueous solution was washed with Et_2O (2 mL × 3). The obtained aqueous layer was concentrated under reduced pressure to give (*S*)-aza-spiro[4,5]decane-4-carboxylic acid hydrochloride (**1a-*S***) in 97 % yield (106.5 mg, 0.49 mmol). white solid. M.p. 109–110 °C. $[\alpha]_D^{23.0}$ –30.0 (c = 1.0, CH_3OH). $\delta_H(D_2O)$ 1.30–1.70 (10H, m), 3.03–3.06 (1H, m), 3.29–3.37 (2H, m), 3.56–3.67 (2H, m); $\delta_C(D_2O)$ 25.4, 25.5, 27.8, 33.5, 37.7, 48.9, 49.1, 54.8, 55.5, 178.1.; γ(KBr)/cm^{-1} 1724 [C(=O)OH]; [HR ESI-MS: Calc. for $C_{10}H_{17}NO_2$+H (*M*+H): 184.1332. Found: M^++H, 184.1335]. The absolute configuration was determined by comparison of the specific rotation with that of the literature.[8a]

(*R*)-Aza-spiro[4,5]decane-4-carboxylic acid hydrochloride (1a-*R*)

$[\alpha]_D^{22.4}$ +29.5 (c = 1.0, CH_3OH).

Aza-spiro[4,5]decane-3-ethyl-4-carboxylic acid (1c)

Very pure **1c** was obtained after the product synthesized by the

general procedure for hydrogenolysis was washed with acetone. white solid. M.p. 215 °C (decomp.). $[\alpha]_D^{22.6}$ –4.0 (c = 1.0, CH_3OH). $\delta_H(D_2O)$ 1.00 (3H, t, *J* 7.5 Hz), 1.14–1.36 (4H, m), 1.55–1.81 (8H, m), 2.41 (1H, d, *J* 10.6 Hz), 3.19–3.41 (2H, m), 3.73–3.80 (1H, m); $\delta_C(D_2O)$ 9.5, 13.1, 24.9, 26.2, 27.9, 34.2, 39.2, 47.6, 55.2, 65.5, 66.0, 179.8; γ(KBr)/cm^{-1} 1560 [C(=O)O$^-$]; [HR ESI-MS: Calc. for $C_{12}H_{21}NO_2$+H (*M*+H): 212.1645. Found: M^++H, 212.1646].

Aza-spiro[4,4]nonane-4-carboxylic acid (1d)

white solid. M.p. 201 °C (decomp.). $[\alpha]_D^{22.6}$ –16.5 (c = 1.0, CH_3OH). $\delta_H(D_2O)$ 1.53–1.80 (8H, m), 2.81–2.84 (1H, m), 3.16–3.35 (2H, m), 3.45–3.58 (2H, m); $\delta_C(D_2O)$ 26.5, 26.7, 34.9, 39.8, 51.0, 55.2, 56.4, 57.7, 181.8.; γ(KBr)/cm^{-1} 1572 [C(=O)O$^-$]; [HR ESI-MS: Calc. for $C_9H_{15}NO_2$+Na (*M*+Na): 192.0995. Found: M^++Na, 192.0997].

Aza-spiro[4,6]undecane-4-carboxylic acid (1e)

white solid. M.p. 162 °C (decomp.). $[\alpha]_D^{22.6}$ –12.5 (c = 1.0, CH_3OH). $\delta_H(D_2O)$ 1.38–1.86 (12H, m), 2.75–2.78 (1H, m), 3.13–3.31 (2H, m), 3.45–3.56 (2H, m); $\delta_C(D_2O)$ 25.9, 26.0, 32.1, 32.2, 36.1, 41.1, 50.5, 51.4, 58.4, 58.6, 181.3; γ(KBr)/cm^{-1} 1579 [C(=O)O$^-$]; [HR ESI-MS: Calc. for $C_{11}H_{19}NO_2$+H (*M*+H): 198.1489. Found: M^++H, 198.1489].

4-Methyl-4-propylpyrrolidine-3-carboxylic acid (1f)

white solid. M.p. 151–152 °C. $[\alpha]_D^{22.3}$ –16.1 (c = 0.9, CH_3OH). $\delta_H(D_2O)$ 0.92 (3H, t, *J* 7.4 Hz), 1.05 (3H, s), 1.19–1.48 (4H, m), 2.73–2.82 (1H, m), 3.18 (2H, s), 3.47–3.60 (2H, m); $\delta_C(D_2O)$ 18.8, 20.3, 21.9, 44.1, 47.1, 50.1, 56.9, 58.1, 180.9; γ(KBr)/cm^{-1} 1583 [C(=O)O$^-$]; [HR ESI-MS: Calc. for $C_9H_{17}NO_2$+Na (*M*+Na): 194.1152. Found: M^++Na, 194.1153].

(3*S*,4*R*)-4-Methyl-4-phenylpyrrolidine-3-carboxylic acid (1g)

white solid. M.p. 157 °C (decomp.). $[\alpha]_D^{22.2}$ –34.5 (c = 1.0, CH_3OH). $\delta_H(D_2O)$ 1.47 (3H, s), 2.92–3.68 (4H, m), 3.78–3.85 (1H, m) , 7.32–7.58 (5H, m); $\delta_C(D_2O)$ 24.8, 50.4, 51.2, 58.1, 58.8, 128.7, 130.2, 131.8, 146.1, 180.4.; γ(KBr)/cm^{-1} 1585 [C(=O)O$^-$]; [HR ESI-MS: Calc. for $C_{12}H_{15}NO_2$+Na (*M*+Na): 228.0995. Found: M^++Na, 228.0996].

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Notes and references

[a] *Division of Chemical Process Engineering, Faculty of Engineering, Hokkaido University, Kita 13-jo Nishi 8, Kita-ku, Sapporo, Hokkaido 060-8628 Japan. Fax: +81 11 706 6557; Tel:+81 11 706 6557; E-mail: myoshida@eng.hokudai.ac.jp*

[b] *Molecular Chemistry and Engineering Course, Graduate School of Chemical Sciences and Engineering, Hokkaido University*

[c] *Department of Applied Science and Engineering, School of Engineering, Hokkaido University*

† Electronic Supplementary Information (ESI) available: [Synthesis of cycloheptanecarboxaldehyde **2d** and β-nitroacrylates **3** , HPLC data of **4**, **6** and **7**, ^{1}H and ^{13}C NMR spectra of **1**, **4**–**7** and *N*-nosyl **1b**, X-ray structure report for *N*-nosyl **1b**, noe analysis of **1c**]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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