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Practical method for the synthesis of (*R*)-homopipecolinic acid and (*R*)-homoproline esters from ω-chloroalkanoic acids and available chiral amines

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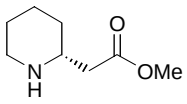
Abstract—A practical synthesis of (*R*)-homopipecolinic acid methyl ester **1** and (*R*)-homoproline methyl ester **2** was performed utilizing (i) a direct intramolecular cyclization of ω-chloro-β-enamino esters **11** and **12**, which were prepared from available (*S*)-1-phenylethylamine or (*S*)-1-(1-naphthyl)ethylamine and ω-chloro-β-keto esters **5** and **10**, respectively and (ii) a highly diastereoselective $NaBH_4$ reduction followed by hydrogenolysis. The present method is a short-step process using inexpensive and readily available substrates and reagents with fewer wasted materials.

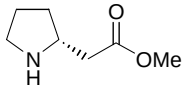
1. Introduction

Considerable attention has been focused on chiral piperidine and pyrrolidine derivatives, especially as key synthetic precursors of a variety of biologically active alkaloids. Among them, methyl (*R*)-(2-piperidino)acetate [(*R*)-homopipecolinic acid methyl ester] (**1**) and methyl (*R*)-(2-pyrrolidino)acetate [(*R*)-homoproline methyl ester] (**2**) are two attractive chiral building blocks for the synthesis of natural alkaloids[1] and useful pharmaceuticals.[2] There are several methods to synthesize these compounds;[3] the Lhommet's protocol[4] and the Michael type addition of chiral amines to α,β-unsaturated esters, followed by cyclizations utilizing either alkylation[5] or ring-closing metathesis.[6]

Lhommet and co-workers extensively investigated the synthesis of various chiral cyclic β-amino acid esters, which serve as key intermediates for the synthesis of alkaloids.[4] Their study began with the utilization of the Eschenmoser sulfide contraction,[7] which requires the tedious removal of undesirable sulfur-containing by-products, for the next Pd-catalyzed hydrogenation step.[4a–d,8] To resolve these problems, they developed three efficient alternative synthetic methods that utilize ω-chloro-2-alkynoates,[4e] ω-chloro-β-keto esters, and ω-oxo-2-alkynoates.[4f] Due to the multi-steps and/or expensive starting materials and reagents, there remains a need for an easier, more practical, and less expensive method.



1



2

As outlined in Scheme 1, we disclose a new practical synthetic method of **1** and **2**, which involves (i) the preparation of β-keto esters; (ii) β-enamino ester formation using available chiral benzylamines; (iii) regioselective cyclization; (iv) highly diastereoselective $NaBH_4$ reduction and (v) hydrogenolysis.

2. Results and discussion

The preparation of ω-chloro-β-keto ester precursors **5** and **10** is illustrated in Scheme 2. C-Acylation of Meldram's acid with 5-chloropentanoic acid (**3**) was performed using a condensation reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl), to give product **4** in 95% yield. Methanolysis of **4** gave methyl 7-chloro-3-oxoheptanoate (**5**) quantitatively, which was used for the next step without any purification procedure such as distillation or column chromatography. On the other hand, a similar reaction using 4-chlorobutanoic acid (**6**) did

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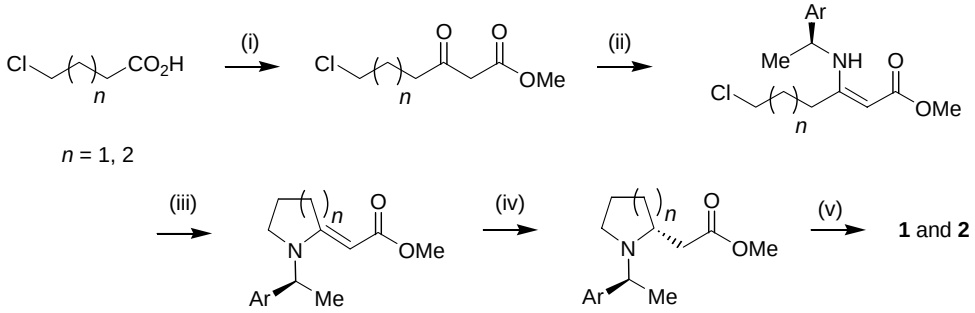
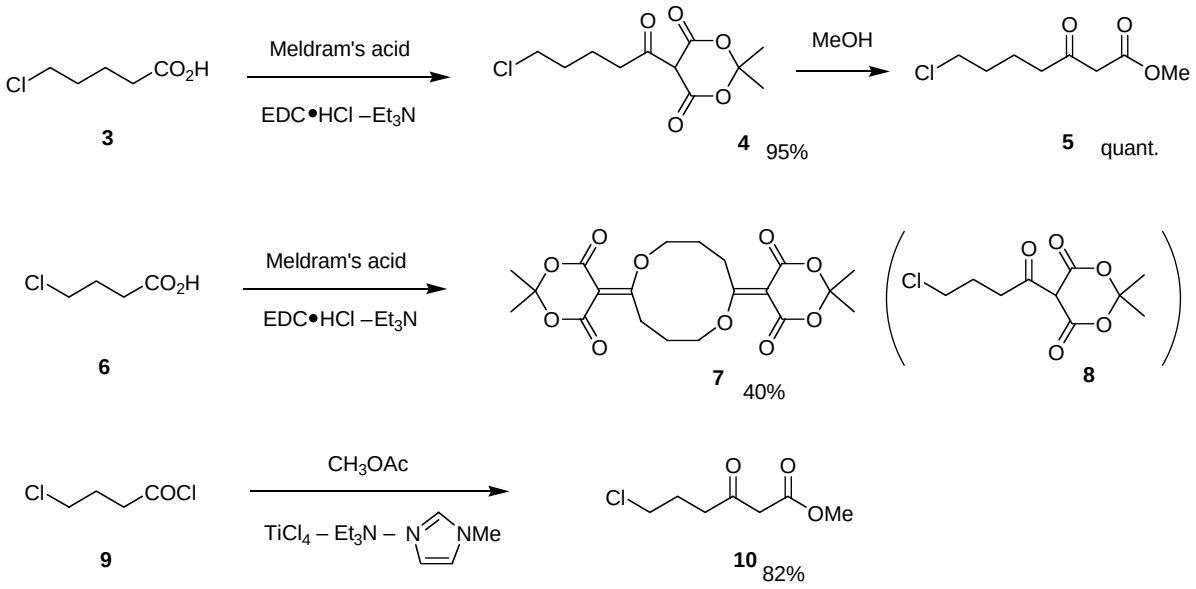


Scheme 1.

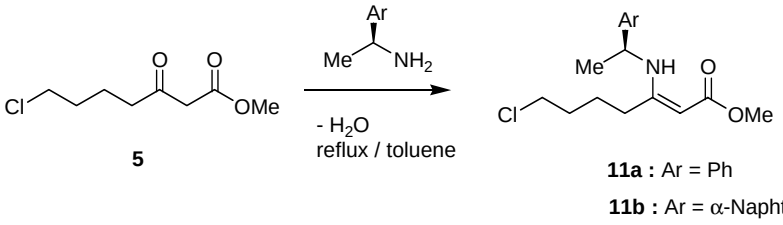


Scheme 2.

not result in the formation of the desired product **8**, but rather in the side formation of dimerized product **7** mainly under the identical conditions. We attribute this unexpected result to the fact that intermediate **8** is very labile due to the high reactivity of the 4-(γ-)chloro atom (neighboring group participation).[9] To solve the problem, we utilized Ti-Crossed Claisen condensation of acid chloride **9** with methyl acetate, which successfully afforded the desired β-keto ester **10** in good yield.[10]

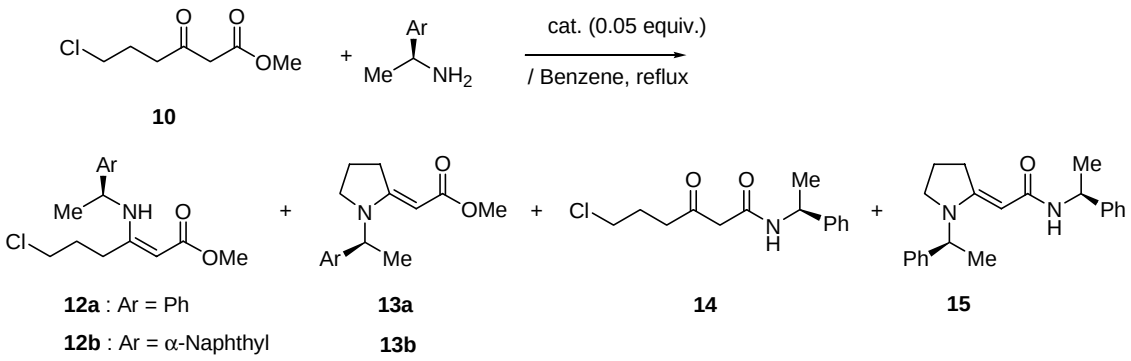
According to the reported method,[11] the condensation of **5** with readily available chiral amines, (*S*)-1-phenylethylamine and (*S*)-1-(1-naphthyl)ethylamine, smoothly proceeded to give the corresponding β-enamino esters **11a** (64%) and **11b** (69%), respectively, using the *p*-TsOH·H_2O catalyst (0.05 equiv) in toluene under convenient azeotropic conditions (Scheme 3). Note that, due to the instability of **11a** and **11b** against SiO_2 column chromatographic purification, one-pot procedure for the subsequent cyclization leading to **16a** and **16b**, respectively, should be desired (see Section 3).

A similar reaction between **10** and (*S*)-1-phenylethylamine gave the desired β-enamino ester **12a** and cyclized-homoproline ester **13a**; however, both resulted in poor yields, with considerable amounts of undesirable β-keto amides **14** and **15** (Table 1, entry 1). A longer reaction period did not improve the total yield of **12a** and **13a**, and increased the formation of **15** (entry 2), probably because the reactivity of the ketone function of **10** paralleled that of the ester. To solve this problem, we applied the $TiCl_4$-catalyzed method for β-enamino ester formation:[12] the side



Scheme 3.

Table 1.



10

12a : Ar = Ph
12b : Ar = α-Naphthyl

13a
13b

14

15

Entry	Cat.	Ar / Me / NH$_2$ (equiv)	Time (h)	Yield (%)[a]				
				12a	**13a**	**14**	**15**	Recovery of **10**
1[b]	TsOH·H$_2$O	1.5	1	28	6	18	6	42
2[b]			4	20	16	11	44	8
3	TiCl$_4$	1.2	4	50	8	Trace	Trace	35
4		1.4	4	61	15	Trace	Trace	24
5		1.5	4	73	15	Trace	Trace	12
6	SnCl$_4$	1.5	4	68	14	Trace	Trace	18
7	TiCl$_4$		6	78	19	Trace	Trace	Trace
8[c]			6	94	4	Trace	Trace	Trace
9[c,d]			6	96 (**12b**)	3 (**13b**)	—	—	Trace

[a] Determined by ^{1}H NMR.
[b] Toluene was used as a solvent and refluxed with removal of H$_2$O using Dean–Starks apparatus.
[c] Cyclohexane was used as a solvent.
[d] (*S*)-1-(1-Naphthyl)ethylamine was used instead of (*S*)-1-phenylethylamine.

formation of **14** and **15** was completely suppressed (entries 3–5). The use of $SnCl_4$ was somewhat inferior to that of $TiCl_4$ (entry 6). Under optimized conditions, the desired enamine **12a** (or its analog, **12b**) together with homoproline **13a** (or **13b**) resulted in a total 97% (or 99%) yield (entries 8 and 9).

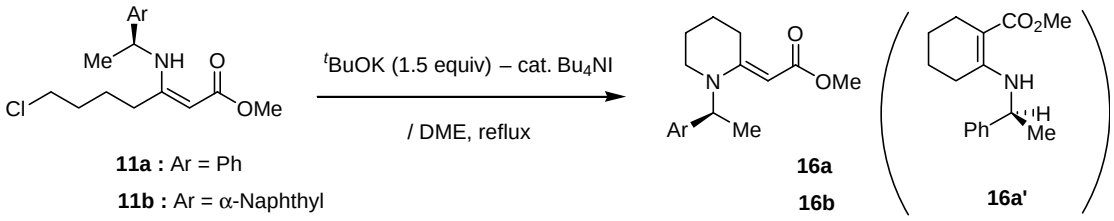
Next, we investigated the cyclization reaction of β-enamino ester **11a** and **11b** into homopipecolinic acid esters **16a** and **16b**, respectively, using ^{t}BuOK as a base (Table 2). The use of ^{t}BuOK alone resulted in slow conversion of the reaction with poor yield of **16a** (entry 1). To facilitate the reaction, 0.1 equiv of Bu_4NI was used as a co-catalyst and remarkable effects were observed; a shorter reaction time (1 h) and higher yield (55%) (entry 2). An increase in the number of Bu_4NI equivalents (0.2 and 0.4 equiv) did not affect the reaction yield, but rather the reaction became sluggish; that is, the purity of **16a** decreased (entries 3 and 4). The naphthyl analog **16b** also underwent the reaction smoothly (entry 5). Note that homoproline esters **13a** and **13b** were synthesized in better yield than **16a** and **16b** (entries 6 and 7), probably because of the advantageous five-membered ring formation.

The reaction between **5** and (*S*)-1-phenylethylamine using two different reagents (Na_2SO_4–Na_2HPO_4–cat. I_2[13] and Na_2CO_3–cat. Bu_4NI) resulted in competitive C-cyclization to give mainly compound **16a′**,[4f] a regioisomer of **16a**. The mechanism underlying the successful result of the desired regioselectivity using ^{t}BuOK–cat. Bu_4NI is not clear at present. We assume that the reported reaction proceeds via the enamine C-alkylation pathway, whereas ^{t}BuOK is sufficiently strong enough to eventually deprotonate amine hydrogen via the N-alkylation pathway. Wang and co-workers described another notable N-cyclization, which seems to be a back-to front mode of the present reaction; that is, N-alkylation occurs first, followed by enamine formation.[3f]

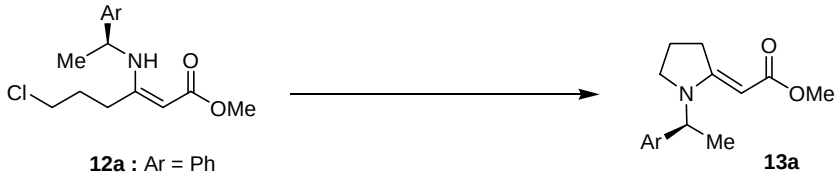
Next, we discuss diastereoselective reduction of *N*-protected homopipecolinic acid esters **16a**, **16b**, and homoproline esters **13a**, and **13b**, followed by deprotection, leading to (*R*)-homoproline methyl esters **2** and (*R*)-homopipecolinic acid methyl esters **1**. Catalytic hydrogenation of *N*-protected homoproline esters using the PtO_2 catalyst was previously reported.[4a,f] The MeCH(Cl)OCOCl mediated deprotection method is also documented.[5] We examined the reduction using readily available $NaBH_4$ of **16a**, **16b**, **13a**, and **13b**, which proceeded smoothly to give the desired products **17a**, **17b**, **18a**, and **18b**, respectively, with high stereoselectivity (Table 3). Compared with reported methods (entries 1–3),[14] $NaBH_4$ reduction in DME–AcOH mixed solvent gave almost similar results (entry 4). Compound **17b** (84% de) was isolated by its HCl salt, which was purified by recrystallization in 2-propanol to give pure product **17b** (98% de) in 56% total isolated yield. Note that naphthyl analogs **17b** and **18b** were obtained in good yield with excellent de (entries 6 and 8). This result would be a promising method to avoid column chromatographic purification from starting substrates **3** and **6**.

A proposed mechanism for the present stereoselective reduction, exemplified by naphthyl β-enamino ester **16b**,

Table 2. Intramolecular cyclization of β-enamino esters **11a**, **11b**, **12a**, and **12b**



11a : Ar = Ph
11b : Ar = α-Naphthyl
16a
16b
16a'

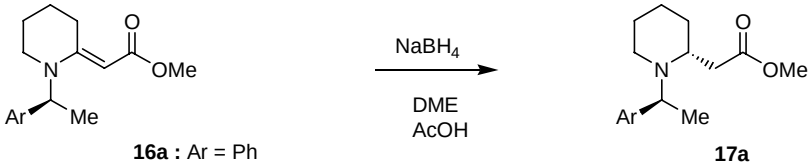


12a : Ar = Ph
12b : Ar = α-Naphthyl
13a
13b

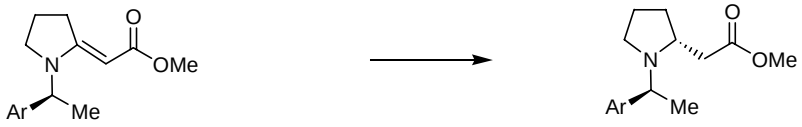
Entry	β-Enamino ester	Bu_4NI (equiv)	Time (h)	Product	Purity (%)[a]	Yield (%)[b]
1	**11a**	None	4	**16a**	—	27
2	**11a**	0.1	1	**16a**	97	55[c]
3	**11a**	0.2	1	**16a**	89	56[c]
4	**11a**	0.4	1	**16a**	86	55[c]
5	**11b**	0.1	1	**16b**	—	68
6	**12a**	0.1	1	**13a**	—	84
7	**12b**	0.1	1	**13b**	—	89

[a] Quantitative HPLC analysis: Column (YMC ODS-AM302; 5 μm, 4.6 mm×150 mm), mobil phase (H_2O/CH_3CN=30:70).
[b] Isolated yield.
[c] Calculated yield based on the purity of both starting material and product.

Table 3. Diastereoselective reduction of cyclized enamines **13** and **16** using $NaBH_4$[a]



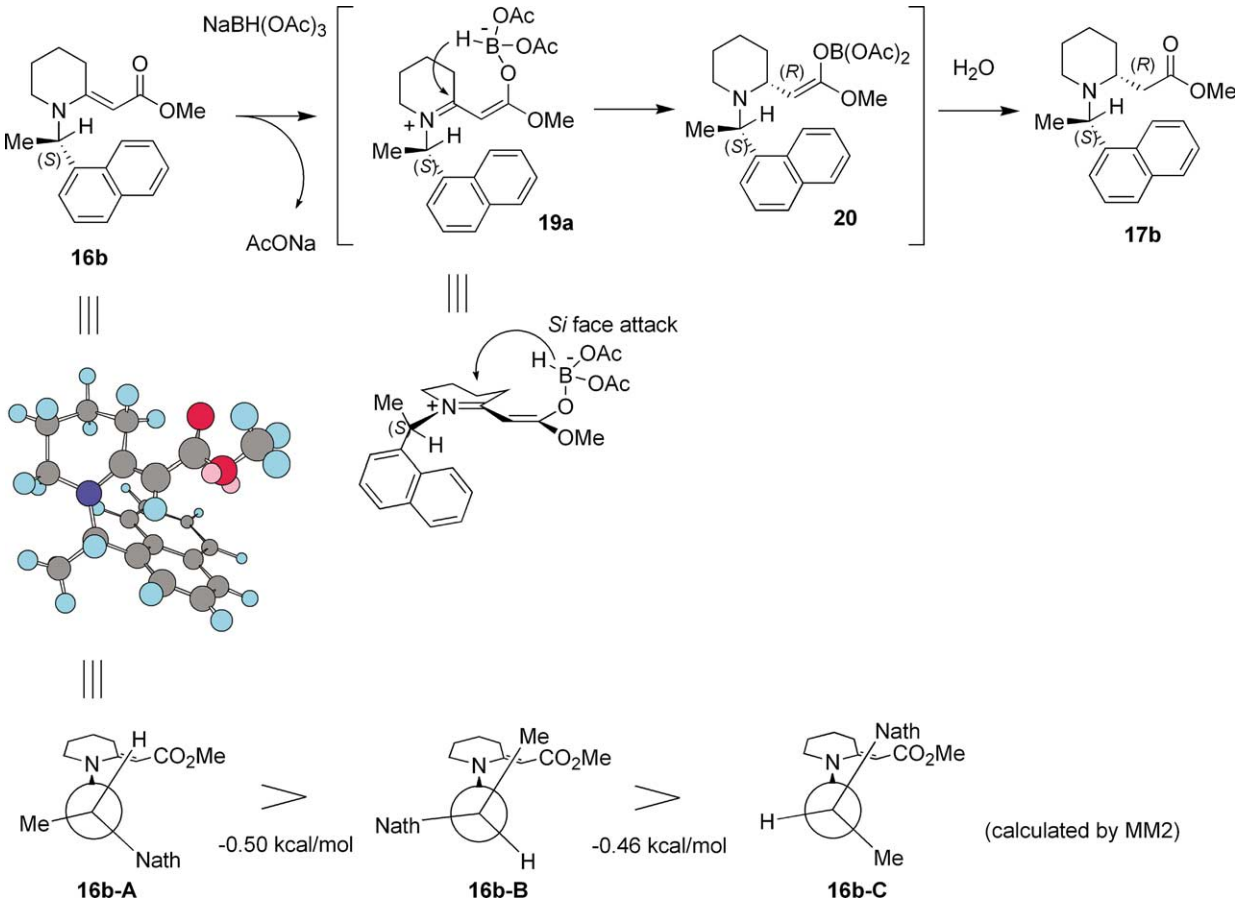
16a : Ar = Ph
16b : Ar = α-Naphthyl
17a
17b



13a : Ar = Ph
13b : Ar = α-Naphthyl
18a
18b

Entry	Enamine	Reaction condition	Solvent	Product de (%)[b]	Yield (%)[c]
1	**16a**	H_2 (balloon), PtO_2 (0.2W) rt, 18 h	DME	**17a** 86	77[d]
2	**16a**	$NaBH(OAc)_3$ (100 mol%) rt, 18 h	DME	**17a** 84	72
3	**16a**	$NaBH(OAc)_3$ (100 mol%) rt, 7 h	DME	**17a** 80	80[e]
4	**16a**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**17a** 84	68
5	**16a**	$NaBH_4$ (400 mol%) rt, 3 h	MeOH	**17a** 62	69
6	**16b**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**17b** 94	88
7	**13a**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**18a** 62	79
8	**13b**	$NaBH_4$ (100 mol%) rt, 2 h	DME–AcOH (4/1)	**18b** 92	89

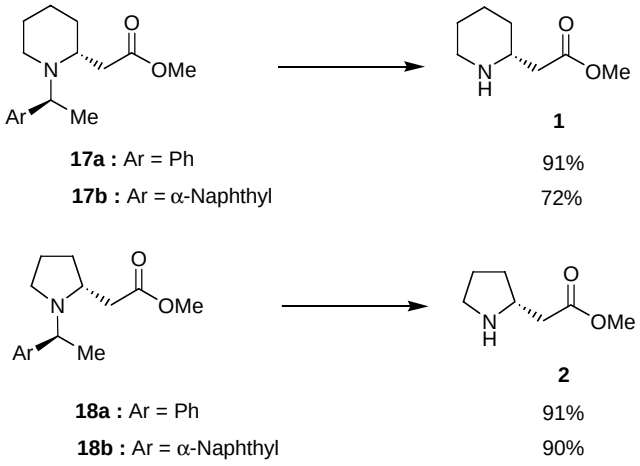
[a] The reaction conversion and diastereomeric excess were checked by either HPLC analysis: Column (YMC ODS-AM302; 5 μm, 4.6 mm×150 mm), mobil phase (H_2O/CH_3CN=70:30) or ^1H NMR integration for **18a**.
[b] de was checked before a chromatographic purification.
[c] Calculated yield based on the product purity.
[d] The reaction did not complete after 18 h.
[e] Conversion of HPLC analysis.



Scheme 4.

is as follows (Scheme 4). Ester **16b** has a preferential conformation of **16b-A** rather than **16b-B** or **16b-C**; Computer-assisted conformation analysis supports this assumption [MM2 force field, Chem3D 5.0 Windows, CambridgeSoft Corporation (Cambridge Scientific Computing, Inc.), Cambridge, Massachusetts, USA]. Initially, the reaction of **16b-A** with $NaBH(OAc)_3$, generated by $NaBH_4$ and AcOH, produces (*Z*)-β-iminium borate **19a**, which was in turn transformed into β-amino boron-enolate **20** by the intramolecular reduction; bulky naphthyl group hangs over the *Re* face of **19a** and hydride transfer occurs from less hindered *Si* face. Final hydrolysis of **20** affords the desired β-amino ester **17b**.

Final stage of the present syntheses, that is, deprotection of **17a** and **17b** was performed by catalytic hydrogenation using H_2–10% Pd–C to give (*R*)-homopipecolinic acid methyl ester **1** in good yield in contrast to the reported description (Scheme 5).[5] The analytical data of **1** was identical with that of the authentic sample[12] with high optical purity (98% ee). (*R*)-homoproline methyl ester (**2**) was obtained in a similar manner (91% ee).



Scheme 5.

In conclusion, we performed an efficient practical method for the synthesis of two useful chiral building brocks, (*R*)-homopipecolinic acid methyl ester **1** and (*R*)-homoproline methyl ester **2**.

3. Experimental

3.1. General

All reagents and solvents were commercially available. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). ^{1}H NMR spectra were recorded on a Bruker AC200P (200 MHz), or a on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and were uncorrected. NMR spectra were recorded Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 (Δ 589 nm). Mass spectra were measured on a JEOL JMS-T100LC spectrometer. HPLC analyses were performed using a Shimadzu 10A apparatus.

3.1.1. 2,2-Dimethyl-5-(5-chloropentanoyl)-1,3-dioxane-4,6-dione (4). Meldram's acid (10.0 g, 69 mmol) was added to a stirred solution of 5-chlorohexanoic acid (**1b**, 9.5 g, 69 mmol), 4-dimethylaminopyridine (2.1 g, 17 mmol), Et_3N (14.0 g, 139 mmol), and EDC hydrochloride (14.6 g, 76 mmol) in CH_2Cl_2 (200 mL) at 0–5 °C. After stirring at 20–25 °C for 24 h, the mixture was concentrated, and extracted with AcOEt (200 mL). The organic phase was washed with 1 M HCl (200 mL), water, brine, dried ($MgSO_4$), and concentrated to give the desired product **4** (17.4 g, 95%).

Viscid yellowish oil. Leaving the oil at room temperature it solidified; mp 40–41 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.74 (s, 6H), 1.85–1.95 (m, 4H), 3.08–3.16 (m, 2H), 3.52–3.64 (m, 2H), 15.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.16, 26.77, 31.90, 34.77, 44.23, 91.40, 104.90, 197.08; HRMS (ESI) calcd for $C_{11}H_{15}ClO_5$ ($M-H^+$) 261.0530, found 261.0529. Anal. Calcd for $C_{11}H_{15}ClO_5$: C, 50.29; H, 5.76. Found: C, 49.9; H, 5.5.

3.1.2. 2,7-Bis(4,4-dimethyl-3,5-dioxo-2,6-dionecyclohexylidene)[1,6]dioxetane (7). Following the procedure for the preparation of **4**, the reaction of **6** (5.0 g, 40 mmol) gave not the desired product but dimeric compound **3b** (3.45 g, 40%) as a main product.

Colorless solid; mp 145–148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (s, 12H), 2.18–2.34 (m, 4H), 3.53 (t, 4H, J=7.9 Hz), 4.78 (t, 4H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.80, 26.88, 36.16, 77.42, 91.57, 103.22, 159.83, 162.95, 190.35; IR (KBr) 3430, 2986, 1741, 1707, 1537, 1304, 1209 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}O_{10}$ ($M+Na^+$) 447.1267, found 447.1270. Anal. Calcd for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70. Found: C, 56.8; H, 5.9.

3.1.3. Methyl 6-chloro-3-oxohexanoate (10).[3a,4f] 4-Chlorobutanoyl chloride (**9**; 5.07 g, 30 mmol) was added to a stirred solution of AcOMe (3.56 g, 48 mmol) and *N*-methylimidazole (2.96 g, 36 mmol) in toluene (90 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred at the same temperature for 10 min. $TiCl_4$ (18.78 g, 99 mmol) and *N*,*N*-diisopropylethylamine (13.96 g, 108 mmol) were successively added to the mixture at 0–5 °C, which was stirred at same temperature for 30 min. Water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (6.00 g). Purification by silica gel column chromatography (hexane/AcOEt=20:1) gave the desired product **10** (4.39 g, 82%).

Yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.08 (quin, 2H, J=6.5 Hz), 2.76 (t, 2H, J=6.9 Hz), 3.48 (s, 2H), 3.59 (t, 2H, J=6.5 Hz), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.85, 39.43, 43.90, 48.82, 52.16, 167.27, 201.46; IR (neat) 2957, 1748, 1719, 1439, 1408, 1325, 1265 cm^{-1}; HRMS (ESI) calcd for $C_7H_{11}ClO_3$ ($M+Na^+$) 201.0294, found 201.0300.

3.1.4. Methyl 3-[1(*S*)-phenylethylamino]-7-chlorohept-2-enoate (11a). Methyl 7-chloro-3-oxoheptanoate (**5**; 96 mg, 0.50 mmol) was added to a stirred solution of (*S*)-phenylethylamine (91 mg, 0.75 mmol) and *p*-TsOH·H_2O (5 mg, 0.03 mmol) in toluene (1.5 mL). After reflux for 1 h using Dean–Stark apparatus with continual removal of water, water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (~100% ^{1}H NMR conversion yield), which was purified by silica gel column chromatography (hexane/AcOEt=10:1) gave the desired product **11a** (95 mg, 64%). Because **11a** was somewhat labile to silica gel column chromatography, the isolated yield decreased. One-pot reaction improved the yield (See the preparation of **16a**).

Yellowish oil; $[\alpha]_D^{27}$ +403.9 (*c* 1.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.41–1.51 (1H, m), 1.53 (3H, d, J=7.2 Hz), 1.56–1.86 (3H, m), 1.87–2.05 (1H, m), 2.10–2.22 (1H, m), 3.42 (2H, t, J=6.2 Hz), 3.67 (3H, s), 4.50 (1H, s), 4.64 (1H, quin, J=7.2 Hz), 7.20–7.38 (4H, m), 8.95–9.07 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.10, 31.43, 31.78, 44.34, 50.04, 52.47, 82.20, 125.34, 127.14, 128.80, 145.03, 164.58, 171.10; IR (neat) 3279, 2948, 1655, 1607, 1258 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}ClNO_2$ ($M+Na^+$) 318.1237, found 318.1232.

3.1.5. Methyl 3-[1(*S*)-naphthylethylamino]-7-chlorohept-2-enoate (11b). Following the procedure for the preparation of **11a**, the reaction using **5** (96 mg, 0.50 mmol) and (*S*)-naphthylethylamine (128 mg, 0.75 mmol), gave the desired product **11b** (120 mg, 69%). (~100% ^{1}H NMR conversion yield). **11b** was somewhat labile to silica gel column chromatography.

Yellowish oil; $[\alpha]_D^{24}$ +443.0 (*c* 1.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.40–1.62 (4H, m), 1.66 (3H, d, J=7.2 Hz), 1.82–1.95 (1H, m), 2.00–2.13 (1H, m), 3.30 (2H, t, J=6.2 Hz), 3.72 (3H, s), 4.55 (1H, s), 5.45 (1H, quin, J=

7.2 Hz), 7.42–7.62 (4H, m), 7.72–7.80 (1H, m), 7.87–7.93 (1H, m), 8.00–8.06 (1H, m), 9.17–9.25 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.12, 25.06, 31.41, 31.71, 44.26, 48.54, 50.09, 82.61, 121.81, 122.41, 125.64, 125.85, 126.38, 127.61, 129.15, 129.73, 133.78, 140.80, 164.60, 171.20; IR (neat) 3283, 2948, 1653, 1605, 1262 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}ClNO_2$ ($M+Na^+$) 368.1393, found 368.1397.

3.1.6. Methyl 3-[1(*S*)-phenylethylamino]-6-chlorohex-2-enoate (12a) (Table 1, entry 8). $TiCl_4$ (3 μL, 0.03 mmol) was added to a stirred solution of **10** (89 mg, 0.5 mmol) and (*S*)-phenylethylamine (81 mg, 0.75 mmol) in cyclohexane (2.0 mL) at 20–25 °C. The reaction mixture was refluxed for 6 h. Water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (94% ^{1}H NMR conversion yield), which was purified by silica gel column chromatography (hexane/AcOEt=10:1) to give the desired product **12a** (104 mg, 74%). Compound **12a** was somewhat labile to silica gel column chromatography.

Yellowish oil; $[\alpha]_D^{26}$ +299.9 (*c* 1.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.53 (3H, d, *J*=7.2 Hz), 1.73–1.98 (2H, m), 2.03–2.20 (1H, m), 2.26–2.41 (1H, m), 3.37–3.57 (2H, m), 3.67 (3H, s), 4.51 (1H, s), 4.67 (1H, quin, *J*=7.2 Hz), 7.19–7.39 (5H, m), 8.96–9.08 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.07, 29.37, 30.80, 44.00, 50.06, 52.47, 82.51, 125.36, 127.16, 128.80, 144.88, 163.66, 171.02.

3.1.7. Methyl 3-[1(*S*)-naphthylethylamino]-6-chlorohex-2-enoate (12b) (Table 1, entry 9). Following the procedure for the preparation of **12a**, the reaction using **10a** (89 mg, 0.5 mmol) and (*S*)-naphthylethylamine (128 mg, 0.75 mmol), gave the desired product **12b** (96% ^{1}H NMR conversion yield) (130 mg, 78%). Compound **12b** was somewhat labile to silica gel column chromatography.

Yellowish oil; $[\alpha]_D^{24}$ +325.4 (*c* 1.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.65 (3H, d, *J*=6.9 Hz), 1.68–1.94 (2H, m), 1.96–2.08 (1H, m), 2.19–2.32 (1H, m), 3.23–3.34 (1H, m), 3.36–3.48 (1H, m), 3.71 (3H, s), 4.58 (1H, s), 5.48 (1H, quin, *J*=6.9 Hz), 7.40–7.59 (4H, m), 7.71–7.79 (1H, m), 7.85–7.91 (1H, m), 7.94–8.07 (1H, m), 9.09–9.31 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.07, 29.19, 30.74, 43.73, 48.55, 50.07, 82.89, 121.89, 122.26, 125.60, 125.74, 126.29, 127.59, 129.05, 129.64, 133.73, 140.63, 163.66, 171.07; IR (neat) 3281, 2948, 1653, 1607, 1262 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}ClNO_2$ ($M+Na^+$) 354.1237, found 354.1233.

3.1.8. *p*-TsOH·H_2O catalyzed reaction of methyl 6-chloro-3-oxohexanoate (10) with (*S*)-phenylethylamine (Table 1, entry 2). Methyl 6-chloro-3-oxohexanoate **10** (179 mg, 1.0 mmol,) was added to a stirred solution of (*S*)-phenylethylamine (182 mg, 1.5 mmol) and *p*-TsOH·H_2O (10 mg, 0.05 mmol) in toluene (3 mL) at room temperature. After reflux for 4 h using Dean–Stark apparatus with continual removal of water, water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil [^{1}H NMR conversion yields; **12a** (20%), **13a** (16%), **14** (11%), **15** (44%)]. The mixture was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give the products **12a** (28 mg, 10%), **13a** (29 mg, 12%), **14** (27 mg, 10%), **15** (117 mg, 35%).

3.1.9. 6-Chloro-3-oxo-*N*-[1(*S*)-phenylethyl]hexanamide (14). Yellowish oil; $[\alpha]_D^{26}$ −64.7 (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (3H, d, *J*=7.2 Hz), 4.67 (2H, quin, *J*=6.2 Hz), 2.71–7.77 (2H, m), 3.42–3.44 (1H, m), 3.56 (2H, t, *J*=6.2 Hz), 5.12 (1H, quin, *J*=6.2 Hz), 7.20–7.39 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.26, 22.04, 25.87, 40.48, 43.94, 49.04, 49.18, 65.83, 126.05, 127.38, 128.70, 142.93, 164.31, 205.67; IR (KBr) 3283, 3061, 2973, 2928, 1721, 1495, 1547 cm^{-1}.

3.1.10. 1-(1(*S*)-Phenylethyl)-2-[(1(*S*)-phenylethylaminocarbonyl)methylidene]pyrrolidine (15). Yellowish oil; $[\alpha]_D^{26}$ −176.4 (*c* 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.46 (d, 3H, *J*=6.2 Hz), 1.52 (d, 3H, *J*=7.0 Hz), 1.76–1.99 (m, 2H), 3.00–3.44 (m, 4H), 4.49 (s, 1H), 4.77 (br s, 1H), 5.13 (br s, 2H), 7.16–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.16, 16.84, 21.22, 22.39, 32.29, 46.58, 47.99, 52.64, 65.72, 81.01, 126.12, 126.41, 126.66, 127.15, 128.32, 128.47, 140.81, 144.76, 161.84; IR (neat) 3293, 2975, 1638, 1580, 1213, 1177 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}N_2O$ ($M+Na^+$) 357.1943, found 357.1939.

3.1.11. 1-[(1*S*)-Phenylethyl]-2-[(methoxycarbonyl)-methylidene]piperidine (16a).[4a,15] (one-pot reaction from 1,3-dioxane-4,6-dione 4) 1,3-Dioxane-4,6-dione **4** (3.00 g, 11 mmol) was added to a stirred solution of MeOH (30 mL) and the mixture was refluxed for 2 h. After cool down to room temperature the mixture was concentrated to give methyl 7-chloro-3-oxoheptanoate (**5**). To the residual oil of was added toluene (45 mL), (*S*)-phenylethylamine (1.66 g, 14 mmol), and *p*-TsOH·H_2O (0.13 g, 0.68 mmol). After reflux for 1 h using Dean–Stark trap with continual removal of water, the mixture was concentrated to give product **11a**, to which was added DME (45 mL), ^{t}BuOK (1.92 g, 17 mmol), and Bu_4NI (0.42 g, 1.1 mmol). After reflux for 1 h, the mixture was concentrated and dissolved with AcOEt (100 mL), which was extracted with 0.2 M HCl (15 mL×3). Separated combined aqueous phase was adjusted to pH 8–9 using Na_2CO_3, and then re-extracted with AcOEt (25 mL×2). Combined separated organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the desired product **16a** (1.68 g, 57%).

Yellowish orange solid; mp 50–52 °C; $[\alpha]_D^{25}$ −126.0 (*c* 0.88, CH_2Cl_2); {lit.,[4e] $[\alpha]_D^{20}$ −121 (*c* 1.10, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.53 (d, 3H, *J*=6.9 Hz), 1.54–1.74 (m, 4H), 2.75–2.90 (m, 1H), 2.90–3.06 (m, 1H), 3.10–3.30 (m, 2H), 3.61 (s, 3H), 4.87 (s, 1H), 5.13 (q, 1H, *J*=6.9 Hz), 7.20–7.40 (m, 5H); Mass (TIC, *m*/*z*): 282 (M+Na); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.2, 19.3, 23.0, 26.3, 41.9, 49.9, 55.2, 81.4, 126.9, 127.4, 128.6, 140.4, 164.0, 169.8; IR (KBr) 2949, 2868, 1684, 1589, 1142 cm^{-1}.

3.1.12. 1-[(1*S*)-Naphthylethyl]-2-[(methoxycarbonyl)-methylidene]piperidine (16b). Following the procedure

for the preparation of **16a**, use of (*S*)-naphthylethylamine (445 mg, 2.6 mmol) and **4** (545 mg, 2.0 mmol) gave the desired product **16b** (418 mg, 68%).

Pale yellow solid; mp 146–148 °C; $[\alpha]_D^{25}$ −153.3 (*c* 1.58, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.20–1.60 (m, 4H), 1.65 (d, 3H, *J*=6.8 Hz), 2.35–2.50 (m, 1H), 2.80–2.98 (m, 1H), 3.22 (t, 2H, *J*=6.4 Hz), 3.69 (s, 3H), 5.12 (s, 1H), 5.61 (q, 1H, *J*=6.8 Hz), 7.42–7.60 (m, 4H), 7.62–7.74 (m, 1H), 7.78–7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ*: 13.7, 18.9, 22.9, 26.3, 41.5, 50.0, 52.6, 80.9, 123.6, 124.7, 124.8, 126.0, 126.9, 128.7, 128.9, 131.9, 133.7, 135.5, 162.9, 169.9. Mass (TIC, *m*/*z*): 332 (M+Na). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.3; H, 7.2; N, 4.3.

3.1.13. 1-[(1*S*)-Phenylethyl]-2-[(methoxycarbonyl)-methylidene]pyrrolidine (13a).[4a,15] $TiCl_4$ (65 mg, 0.25 mmol) was added to a stirred solution of β-keto ester **10** (894 mg, 5.00 mmol) and (*S*)-phenylethylamine (916 mg, 7.50 mmol) in cyclohexane (20 mL) at 20–25 °C. The reaction mixture was refluxed for 6 h. After cool down to room temperature, water was added to the mixture, which was extracted three times with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give product sufficiently pure β-enamine **12a**, to which was added DME (20 mL), ^{t}BuOK (841 mg, 7.50 mmol), and Bu_4NI (185 mg, 0.50 mmol). After reflux for 1 h, the reaction mixture was concentrated and dissolved with AcOEt (20 mL) and then extracted with 0.2 M HCl (15 mL×3). Combined separated aqueous phase was adjusted to pH 8–9 using Na_2CO_3, and then re-extracted with AcOEt (25 mL×2). Combined separated organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the desired product **13a** (1.06 g, 86%).

Yellowish orange solid; mp 68–70 °C; $[\alpha]_D^{25}$ −251.1 (*c* 0.94, EtOH); {lit.,[4e] $[\alpha]_D^{20}$ −256 (*c* 1.10, EtOH)}; ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 1.55 (d, 3H, *J*=6.9 Hz), 1.75–2.02 (m, 2H), 3.05–3.23 (m, 2H), 3.23–3.40 (m, 2H), 3.61 (s, 3H), 4.68 (s, 1H), 4.87 (q, 1H, *J*=6.9 Hz), 7.19–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 16.73, 20.84, 32.77, 47.13, 49.91, 52.87, 77.82, 126.51, 127.40, 128.57, 140.31, 164.90, 169.91; IR (KBr) 2949, 2868, 1684, 1589, 1142 cm^{-1}.

3.1.14. 1-[(1*S*)-Naphthylethyl]-2-[(methoxycarbonyl)-methylidene]pyrrolidine (13b). Following the procedure for the preparation of **13a**, the reaction using **10** (0.72 g, 4.0 mmol) and (*S*)-naphthylethylamine (1.30 g, 6.0 mmol) gave the desired product **13b** (1.32 g, 89%).

Yellowish orange solid; mp 123–125 °C; $[\alpha]_D^{25}$ −197.3 (*c* 1.82, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) *δ*: 1.66 (d, 3H, *J*=6.9 Hz), 1.72–1.90 (m, 2H), 2.48–2.59 (m, 1H), 3.06–3.33 (m, 3H), 3.69 (s, 3H), 4.94 (s, 1H), 5.44 (q, 1H, *J*=6.9 Hz), 7.42–7.55 (m, 4H), 7.66–7.74 (m, 1H), 7.79–7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 14.26, 20.76, 32.87, 47.13, 49.58, 50.06, 77.36, 123.01, 123.68, 124.99, 125.99, 126.96, 128.76, 131.67, 133.64, 135.28, 164.17, 170.12; IR (KBr) 2973, 2940, 1678, 1582, 1140 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}NO_2$ ($M+Na^+$) 318.1470, found 318.1472. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.1; H, 6.9; N, 4.6.

3.1.15. Methyl[(1*S*)-phenylethyl]-2(*R*)-piperidylacetate (17a).[4g] $NaBH_4$ (29 mg, 0.77 mmol) was added to a stirred solution of **16a** (200 mg, 0.77 mmol) in DME (8 mL) and CH_3CO_2H (2 mL) at 10–15 °C. After stirring at 20–25 °C for 2 h, the mixture was concentrated and then 10% NaOH aqueous solution (20 mL) was added to the mixture, which was extracted with AcOEt (15 mL×2). Combined separated organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give crude oil (248 mg). Purification by silica gel column chromatography (hexane/AcOEt=5:1) gave the desired product **17a** (137 mg, 68, 84% de).

The de was checked by HPLC analysis [UV (wave length, 230 nm), Mobil phase (H_2O/CH_3CN=70:30), Column (YMC ODS-AM302; 5 μm, 4.6 mm×150 mm), Column temperature (40 °C), Flow rate (1 mL/min)]. The retention times of (1*S*,2*S*)-isomer and (1*S*,2*R*)-isomer were 7.2 and 9.8 min, respectively. Further purification using column chromatography gave pure (1*S*,2*R*)- and (1*S*,2*S*)-isomers. (1*S*,2*R*)-Isomer: $[\alpha]_D^{24}$ −35.3 (*c* 1.84, $CHCl_3$); colorless oil; ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.29 (d, 3H, *J*=6.7 Hz), 1.35–1.68 (m, 5H), 1.68–1.88 (m, 1H), 2.14–2.40 (m, 2H), 2.50–2.60 (m, 2H), 3.42–3.55 (m, 1H), 3.68 (s, 3H), 3.70 (q, 1H, *J*=6.7 Hz), 7.18–7.40 (m, 5H); IR (neat) 3050, 2971, 2876, 1736 cm^{-1}; ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 17.86, 20.77, 25.57, 29.96, 31.93, 44.92, 51.53, 52.34, 59.26, 126.49, 127.25, 128.11, 146.11, 173.60; IR (neat) 3407, 2934, 1736, 1443, 1161 cm^{-1}; Mass (TIC, *m*/*z*): 262 (M+1). (1*S*,2*S*)-Isomer: ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.33 (d, 3H, *J*=6.7 Hz), 1.38–1.74 (m, 6H), 2.39–2.75 (m, 4H), 3.10–3.26 (m, 1H), 3.60 (s, 3H), 3.82 (q, 1H, *J*=6.7 Hz), 7.18–7.37 (m, 5H). Mass (TIC, *m*/*z*): 262 (M+1).

3.1.16. Methyl[(1*S*)-naphthylethyl]-2(*R*)-piperidylacetate (17b). Following the procedure for the preparation of **17a**, the reaction using **16b** (160 mg, 0.517 mmol) gave the desired product **17b** (142 mg, 88, 94% de). The retention times of (1*S*,2*S*)- and (1*S*,2*R*)-isomers, using HPLC analysis described above, were 11.7 and 13.3 min, respectively. Further purification using column chromatography gave a pure (1*S*,2*R*)-isomer.

Colorless oil; $[\alpha]_D^{27}$ −83.2 (*c* 1.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 1.26–1.40 (m, 1H); 1.46 (d, 3H, *J*=6.6 Hz); 1.61–1.70 (m, 6H); 2.18–2.33 (m, 1H); 2.33–2.48 (m, 1H); 2.60–2.86 (m, 2H); 3.60–3.77 (m, 1H); 3.70 (s, 3H); 4.42 (q, 1H, *J*=6.6 Hz); 7.38–7.55 (m, 3H); 7.60–7.90 (m, 3H); 8.40–8.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 18.18, 20.21, 25.62, 29.63, 30.51, 45.07, 51.53, 52.12, 56.90, 123.94, 124.53, 125.14, 125.24, 125.41, 127.10, 128.64, 131.57, 134.00, 141.36, 173.69; IR (KBr) 2934, 1736, 1437, 1161 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}NO_2$ ($M+H^+$) 312.1964, found 312.1696.

3.1.17. Methyl 1-[(1*S*)-phenylethyl]-(2*R*)-pyrrolidyl-acetate (18a). Following the procedure for the preparation of **17a**, the reaction using **13a** (245 mg, 1.0 mmol) gave the desired product **18a** (195 mg, 79% yield, 62% de).

Yellowish oil (diastreomixtures); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.38 (d, 2.43H, J=6.5 Hz), 1.43 (d, 0.57H, J=6.9 Hz), 1.50–2.03 (m, 5H), 2.06–2.86 (m, 4H), 3.08–3.02 (m, 0.19H), 3.23–3.38 (m, 0.81H), 3.60 (s, 2.43H), 3.65 (m, 0.19H), 3.67–3.80 (m, 1H), 7.18–7.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.03, 18.03, 20.82, 22.08, 22.70, 30.71, 39.08, 40.00, 49.50, 50.00, 51.11, 56.64, 57.84, 60.17, 60.38, 60.63, 126.70, 127.39, 127.58, 127.96, 128.04, 142.97, 144.92, 170.87, 172.76; IR (neat) 3028, 2971, 2876, 1738 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}NO_2$ ($M+H^+$) 248.1651, found 248.1648. The retention times of (1*S*,2*S*)- and (1*S*,2*R*)-isomers, using HPLC analysis described above, were same 4.83 min. Further purification using column chromatography gave a pure (1*S*,2*R*)-isomer; $[\alpha]_D^{25}$ −10.2 (*c* 0.97, $CHCl_3$).

3.1.18. Methyl 1-[(1*S*)-Naphthylethyl]-2(*R*)-pyrrolidyl-acetate (18b). Following the procedure for the preparation of **18a**, the reaction using **13b** (295 mg, 1.0 mmol) gave the desired product **18b** (260 mg, 89% yield, 92% de). The retention times of (1*S*,2*S*)- and (1*S*,2*R*)-isomers, using HPLC analysis described above, were 13.3 and 11.7 min, respectively. Further purification using column chromatography gave a pure (1*S*,2*R*)-isomer.

Colorless oil; $[\alpha]_D^{24}$ −7.6 (*c* 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (d, 3H, J=6.9 Hz), 1.53–1.62 (m, 1H), 1.63–1.75 (m, 2H), 1.90–2.08 (m, 1H), 2.20 (dd, 1H, J=9.6 Hz, J_{gem}=14.5 Hz), 2.52 (dd, 1H, J=4.1 Hz, J_{gem}=14.5 Hz), 2.56–2.68 (m, 1H), 3.33–3.45 (m, 1H), 3.58 (s, 3H), 4.53 (q, 1H, J=6.9 Hz), 7.37–7.52 (m, 3H), 7.53–7.60 (m, 1H), 7.69–7.76 (m, 1H), 7.79–7.88 (m, 1H), 8.37–8.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.15, 22.35, 30.90, 38.32, 49.03, 51.26, 56.27, 58.15, 124.10, 124.54, 125.15, 125.21, 125.36, 127.39, 128.59, 131.48, 133.91, 140.64, 172.95; IR (neat) 3050, 2971, 2876, 1736 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}NO_2$ ($M+H^+$) 298.1807, found 298.1805.

3.1.19. Methyl(*R*)-(2-piperidino)acetate[(*R*)-homopipecolinic acid methyl ester] (1).[3d,g] Compound **17a** (233 mg, 0.892 mmol, >99% de) was added to a stirred suspension of 10% Pd–C (50% wet, 47 mg) in DME (15 mL) at 20–25 °C with a H_2 balloon. After stirring for 17 h, the reaction mixture was filtered through a plug Celite®, and concentrated to give the desired product **1** (127 mg, 91% yield, 98% ee).

In the case of this method using **17b** (307 mg, 0.98 mmol, 99% de), an additional work-up process was necessary for the isolation of **1**. After concentration, 0.2 M aqueous HCl was added to a residual oil, which was washed with AcOEt to eliminate 1-ethylnaphthalene. Successive neutralization of the aqueous phase with Na_2CO_3, which was reextracted with AcOEt, followed by the concentration of the organic phase to give the desired product **1** (111 mg, 72% yield, 98% ee). The enantioselectivity was checked by the chiral derivatization to *N*-*R*-(+)-1-phenylethylcarbamate of **1** using *N*-succinimidyl *R*-(+)-1-phenylethyl carbamate[16] and HPLC analysis [UV (wave length; 220 nm), Mobile phase (pH 6.5 phosphoric acid buffer/CH_3CN=70:30), Column (ULTRON VX-ODS; 5 μm, 4.6 mm×150 mm), Column temperature (25 °C)]. Colorless oil; $[\alpha]_D^{24}$ −16.5 (*c* 1.00, MeOH); {lit.,[3g] $[\alpha]_D^{26}$ +3.9 (*c* 0.64, $CHCl_3$), the antipodal (*S*) isomer}, ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.05–1.85 (m, 6H), 1.95–2.08 (br s, 1H), 2.30–2.42 (m, 2H), 2.58–2.76 (m, 1H), 2.80–3.10 (m, 2H), 3.68 (s, 3H); Mass (TIC, *m*/*z*): 158 (M+1).

3.1.20. Methyl (*R*)-(2-pyrrolidino)acetate [(*R*)-homoproline methyl ester] (2).[17] Compound **18a** (247 mg, 1 mmol, 62% de) was added to a stirred suspension of 10% Pd–C (50% wet, 108 mg) in MeOH (3 mL) at 20–25 °C with a H_2 balloon. After stirring for 14 h, the reaction mixture was filtered through a plug Celite®, and concentrated to give crude oil (154 mg). Purification by Florisil® column chromatography (hexane to MeOH/Et_3N=10:1) to give the desired product **2** (130 mg, 91, 62% ee). The enantioselectivity was checked by the chiral derivatization and HPLC analysis described above. Yellowish oil; $[\alpha]_D^{25}$ −4.3 (*c* 1.01, $CHCl_3$); {lit.,[18] $[\alpha]_D$ +7.0 (*c* 2.6, $CHCl_3$), the antipodal (*S*) isomer}.

Following the procedure for the preparation of **2**, the reaction using **18b** (297 mg, 1 mmol, 92% de) gave **2** (128 mg, 90, 91% ee), $[\alpha]_D^{25}$ −6.3 (*c* 1.85, $CHCl_3$).

Yellowish oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.27–1.42 (m, 1H), 1.64–1.85 (m, 2H), 1.87–2.01 (m, 1H), 2.43 (dd, 1H, J=7.9 Hz, J_{gem}=15.5 Hz), 2.50 (dd, 1H, J=5.50 Hz, J_{gem}=15.5 Hz), 2.83–2.94 (m, 1H), 2.95–3.05 (m, 1H), 3.36–3.48 (m, 1H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.88, 31.11, 40.52, 46.18, 51.42, 54.84, 172.80; IR (neat) 3401, 2957, 1736, 1620, 1418 cm^{-1}.

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