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Solvent-free organocatalytic Michael addition of diethyl malonate to nitroalkenes: the practical synthesis of Pregabalin and γ-nitrobutyric acid derivatives

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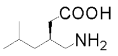
ABSTRACT

A highly enantioselective synthesis of Pregabalin **1** hydrochloride with good overall yield (44%) and enantioselectivity (98% ee) was described. The key step is an asymmetric Michael addition of equivalent of diethyl malonate and nitroalkene under solvent-free conditions using thiourea **2** as catalyst. The reaction can be applied to a variety of aromatic and aliphatic substituted nitroalkenes affording corresponding adducts in good to excellent yields (61–92%) and enantioselectivities (78–93% ee).

1. Introduction

Pregabalin (**1**), an anticonvulsant drug, which is used to treat epilepsy and neuropathic pain, is considered as one of the blockbuster drugs of the future. Thus, the development of simple and efficient synthetic processes has become an important research goal for medicinal and organic chemists. Though the initial industrial preparation of Pregabalin was a racemic synthesis followed by resolution, much attention has been focused on the development of asymmetric synthetic processes.[1] Among them, asymmetric Michael addition was considered as one of the most effective routes for constructing the chiral center of Pregabalin.[1g,2] However, most of them were catalyzed by metal complexes. Such as, Sammins and Jacobsen[2a] described a highly enantioselective route for **1** through conjugate addition of cyanide to α,β-unsaturated imide by salen Al catalysis. Shibasaki's group[1g] developed a catalytic enantioselective conjugate addition reaction of cyanide to α,β-unsaturated *N*-acylpyrrole mediated by a chiral gadoliniumcatalyst. Armstrong et al.[2b] described the synthesis of enantiopure Pregabalin through conjugate addition of cyanide to a chiral α,β-unsaturated isobutyloxazolidinone. Poe et al.[2c] also synthesized **1** by a one-pot reaction of isovaleraldehyde, nitromethane, and dimethyl malonate promoted by two microencap sulated catalysts (Fig. 1).



1
Pregabalin

Fig. 1. Structure of Pregabalin.

Although the product could be obtained in an excellent enantioselectivity and yields in the cases of metal catalysis, the drawbacks, such as the harsh reaction conditions, high toxicity or expensive catalyst could not be avoided. Recently, some effort has been directed toward the application of organocatalytic asymmetric Michael addition in the preparation of Pregabalin[3] because organocatalyzed reactions are always environmentally friendly processes with the benefits of easy operation, ready availability, and low toxicity of catalysts. For examples, Pregabalin has also been obtained by catalytic enantioselective conjugate addition of nitroalkenes to α,β-unsaturated aldehydes using diphenylprolinol silyl ether as organocatalyst.[3a] Bassas et al. described a synthetic procedure of Pregabalin, which was based on a Michael addition reaction of Meldrum's acid to a nitroalkene mediated by a quinidine derived thiourea.[3b] Unfortunately, the use of harmful organic solvents and an excess of Michael donors were required in most cases. Therefore, it is still a challenge for organic chemist to develop an environmental protective and economic synthetic procedure of Pregabalin.

In recent years, the Michael addition of malonate to nitroalkenes promoted by organocatalysts,[4] especially bifunctional thiourea catalysts,[5] have been investigated extensively and excellent

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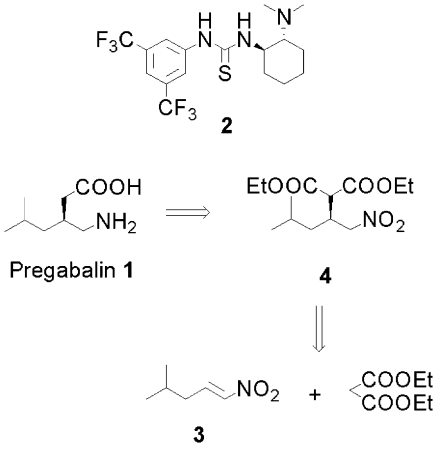
enantioselectivity and yields have been achieved. For examples, Deng[4a] reported that cinchona alkaloids could catalyze this reaction in nearly solvent-free condition with high yield and ee value; Takemoto's group[5a,b] developed a Michael addition of malonate to nitroalkenes promoted by chiral thiourea catalysts. Enlightened by their work, we achieved to form the stereocenter of Pregabalin via an enantioselective Michael addition reaction catalyzed by thiourea **2**[6] as depicted in Scheme 1. Meanwhile, the drawbacks of previous synthetic methodology have been successfully overcome by avoiding the use of organic solvent and reducing the amount of Michael donors in order to meet the requirements of green chemistry. Herein, we present a practical synthesis of Pregabalin via solvent-free organocatalytic Michael addition of equivalent of diethyl malonate and nitroalkene.

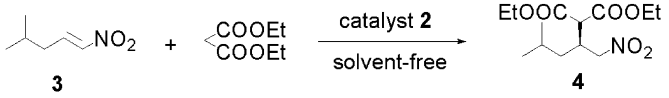


Scheme 1. Retrosynthetic analysis of Pregabalin.

2. Results and discussion

Previously, we found that the organocatalytic aldol reaction of aldehydes and ketones could be performed in alkaline Al_2O_3 with considerable satisfying results.[7] This result aroused our interest to explore the organocatalytic asymmetric Michael addition of malonate to nitroalkene in solid media. Initially we screened a number of solid media for the reaction of diethyl malonate with nitroalkene (**3**) in the ratio of 2:1 using 20 mol % of thiourea **2** as catalyst at room temperature (Table 1, entries 1–4). It showed that good yield (73%) and moderate enantioselectivity (67% ee) were obtained in the presence of bentonite. Much to our delight, the enantioselectivity was obviously improved in the absence of solid media (Table 1, entry 5, 74% yield, 77% ee). Accordingly, we next turned our attention to the investigation of solvent-free reaction. Under solvent-free conditions, reaction temperature, catalyst loading and ratio of the substrates were systematically examined and the selected findings were detailed in Table 1. It is clear that reaction temperature of −20 °C is more suitable (Table 1, entry 7, 71% yield, 89% ee). The catalyst loading screening revealed that 10 mol % and 20 mol % of catalyst gave the almost similar results (Table 1, entries 7 and 9). Reducing catalyst loading to 5 mol % led to a great decrease of yield (Table 1, entry 10). Notably, reducing the amount of diethyl malonate from 2 to 1 equiv did not lead to any significant influence on both the yield and enantioselectivity (Table 1, entries 9 and 11). Thus, it could be concluded that the best compromise between reaction rate and enantioselectivity was achieved by using equivalent mole of diethyl malonate and nitroalkene in the presence of 10 mol % of thiourea **2** at −20 °C.

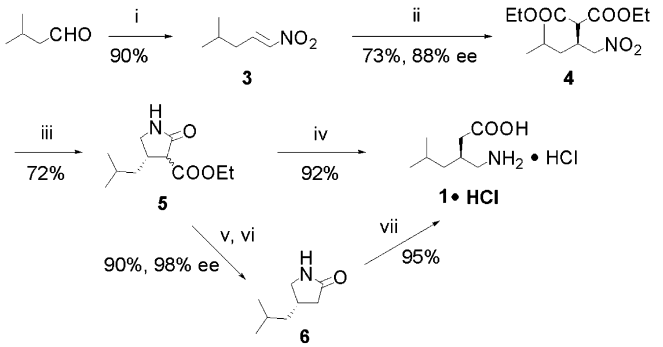
Table 1
Reaction conditions screening[a]



Entry	Media	Catalyst loading (mol %)	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	Alkaline Al_2O_3	20	rt	72	0
2	Neutral Al_2O_3	20	rt	61	0
3	Silica gel	20	rt	68	20
4	Bentonite	20	rt	73	67
5	Solvent-free	20	rt	74	77
6	Solvent-free	20	0	73	75
7	Solvent-free	20	−20	71	89
8	Solvent-free	20	−30	54	85
9	Solvent-free	10	−20	73	88
10	Solvent-free	5	−20	38	87
11[d]	Solvent-free	10	−20	72	88

[a] Unless specified, the reaction was conducted with **3** (0.1 mmol), diethyl malonate (0.2 mmol), and catalyst **2** for 24 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] Diethyl malonate (0.1 mmol) was used.

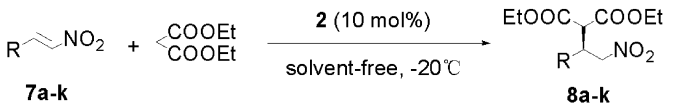
After established the optimal reaction conditions, we then applied this efficient enantioselective Michael reaction to the synthesis of Pregabalin. As outlined in Scheme 2, the nitroalkene **3**, prepared from the condensation of isopropylaldehyde with nitromethane, reacted with diethyl malonate in the presence of 10 mol % of catalyst **2** under solvent-free conditions at −20 °C for 24 h affording the key intermediate **4** in 73% yield with 88% ee. Then, hydrogenation of **4** in the presence of Raney-Ni gave the (*S*)-ethyl 4-isobutyl-2-oxopyrrolidine-3-carboxylate **5** as a white solid in 72% yield after crystallization from hexane. Finally, **5** was refluxed for 18 h in 6 N HCl affording Pregabalin as its hydrochloric salt (**1**·**HCl**) in 92% yield. The overall yield is 44% through four steps starting from isopropylaldehyde. Meanwhile, the key intermediate **6** from **5** to **1**·**HCl** was also obtained in 90% yield with 98% ee. The excellent enantioselectivity of **6** should be attributable to the effective crystallization of **5**. The optical purity of Pregabalin could be indirectly evaluated according to the enantioselectivity of **6**, because the last step did not involve the chiral center. Consequently, we succeeded in the synthesis of Pregabalin by this simple procedure with high enantioselectivity.



Scheme 2. Enantioselective synthetic route of Pregabalin hydrochloride. Reagents and conditions: (i) (1) CH_3NO_2, NaOH, EtOH, 0 °C; (2) DCC, CuCl, Et_2O, rt; (ii) diethyl malonate, **2** (10 mol %), −20 °C, 24 h; (iii) Raney-Ni, H_2, MeOH, rt, 24 h; (iv) 6 N HCl, reflux for 18 h; (v) NaOH, EtOH, rt; (vi) toluene, reflux for 6 h; (vii) 6 N HCl, reflux for 10 h.

In order to test the versatility of the protocol, various aromatic and aliphatic substituted nitroalkenes as substrates were examined under optimized reaction conditions (Table 2). To our pleasure, good yields and enantioselectivities could be obtained in the cases of aliphatic nitroalkenes as receptors (Table 2, entries 1–6), which is reluctant to undergo Michael addition reaction according to the previous literatures.[5c,d] The length of R groups in aliphatic nitroalkenes does not

Table 2
Enantioselective Michael addition of diethyl malonate to substituted nitroalkenes under solvent-free conditions[a]



7a-k **8a-k**

Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	CH_3CH_2–	**8a**	78	78
2	$CH_3(CH_2)_2$–	**8b**	77	87
3	$CH_3(CH_2)_3$–	**8c**	74	87
4	$CH_3(CH_2)_4$–	**8d**	71	89
5	$CH_3(CH_2)_9$–	**8e**	61	83
6	$(-CH_2-)_5CH$–	**8f**	76	86
7[d]	C_6H_5–	**8g**	88	90
8[d]	4-Me–C_6H_4–	**8h**	86	89
9[d]	4-CH_3O–C_6H_4–	**8i**	67	85
10[d]	4-F–C_6H_4–	**8j**	92	88
11[d]	2-Thienyl–	**8k**	91	93

[a] Unless specified, the reaction was conducted with **7** (0.1 mmol), diethyl malonate (0.1 mmol), and catalyst **2** (0.01 mmol) under solvent-free conditions at −20 °C for 24 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.
[d] Diethyl malonate (0.2 mmol) was used.

obviously influence the enantioselectivities. For the aryl-substituted nitroalkenes, all the tested examples afforded the corresponding Michael adducts in good to excellent yields and enantioselectivities (Table 2, entries 7–11).

3. Conclusion

In summary, we have developed an efficient and practical asymmetric synthesis of (*S*)-3-aminomethyl-5-methylhexanoic acid (Pregabalin) using isopropylaldehyde, nitromethane, and diethyl malonate as starting materials in 44% overall yield and 98% ee through four steps. The key organocatalytic Michael addition of equivalent of diethyl malonate to nitroalkene for constructing chiral center of Pregabalin was carried out under solvent-free conditions. Moreover, the versatility and potent of this solvent-free organocatalytic Michael addition have been demonstrated by a broad scope of substrates.

4. Experimental

4.1. General experimental

Melting point data were recorded on an X-4 micro-melting point instrument. NMR spectra were registered on Varian Mercury-300 and JEOL JNM-LA400 using TMS as an internal standard. High-resolution mass spectra were recorded on a ZAB-HS instrument using an electrospray source (ESI). Elemental analyses were performed on a Vario EL III (Germany). Optical rotations were measured in H_2O with an Optical Activity Ltd. AA-10R digital polarimeter. Thin-layer chromatography (TLC) was carried out using Silica gel 60. Enantiomer ratios were determined by chiral HPLC using an Agilent 1100 HPLC systems with column Daicel Chiralpak AD-H (5 μm 4.6×250 mm) and Daicel Chiralcel OD-H (5 μm 4.6×250 mm).

4.2. General procedure for reaction condition screening

Nitroalkene (12.8 mg, 0.1 mmol) was added to a stirred solution of diethyl malonate (32 mg, 0.2 mmol) and thiourea-catalyst **2** in 1 g solid carrier or in solvent-free condition. After being stirred for 24 h, the reaction mixture was directly purified by column chromatography on silica gel (ethyl acetate/petroleum ether=1:3) to afford desired product.

4.3. Total synthesis of hydrochloride of Pregabalin

*4.3.1. (E)-4-Methyl-1-nitro-1-pentene (**3**)*[8]. An aqueous 10 M sodium hydroxide solution (9 mL, 90 mmol) was added dropwise under mechanical stirring (to prevent the formation of a solid mass) to a solution of isovaleraldehyde (7.81 g, 90 mmol) and nitromethane (5.6 g, 90 mmol) in EtOH (150 mL) at 0 °C. After 10 min, the crude mixture was warmed to room temperature and stirred overnight. Then, acetic acid (5.2 mL, 90 mmol) was added. The aqueous layer was extracted with diethyl ether (3×50 mL). The extracts were washed with water until the pH of the washings was 6. The residue was dried, filtrated, and concentrated in vacuo affording crude 3-methyl-1-(nitromethyl)butanol, which was used without further purification. Then DCC (20.5 g, 0.1 mol) and CuCl (200 mg, 2 mmol) were added successively to a solution of 3-methyl-1-(nitromethyl)butanol (15.84 g, 90 mmol) in anhydrous ether (50 mL). The reaction mixture was stirred overnight at room temperature and cooled to 0 °C. Hexane (100 mL), water (20 mL), and acetic acid (8.2 mL) were added. The mixture was warmed to room temperature and stirred until completion of the reaction. The organic phase was washed with water, saturated with aqueous ammonium chloride solution and brine, then dried. After filtration and evaporation in vacuo, the residue was purified by column chromatography (ethyl acetate/petroleum ether=1:3) affording compound **3** (6.04 g, 90%). Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22–7.29 (m, 1H), 6.96–7.00 (m, 1H), 2.13–2.17 (m, 2H), 1.81–1.87 (m, 1H), 0.97 (d, *J*=7.2 Hz, 6H).

*4.3.2. (S)-Diethyl-2-(4-methyl-1-nitropentan-2-yl-) malonate (**4**)*[9]. Ni troalkene **3** (2.06 g, 16 mmol) was added to a stirred solution of diethyl malonate (2.56 g, 16 mmol) and thiourea-catalyst **2** (0.66 g, 1.6 mmol) at −20 °C. After being stirred for 24 h, the reaction mixture was directly purified by column chromatography on silica gel (ethyl acetate/petroleum ether=1:3) to afford desired product **4** (3.65 g, 73%). Yellow oil; 88% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 4.65 (dd, *J*=13.2, 4.8 Hz, 1H), 4.46 (dd, *J*=13.2, 6.4 Hz, 1H), 4.13–4.19 (m, 4H), 3.55 (d, *J*=5.6 Hz, 1H), 2.87–2.92 (m, 1H), 1.57–1.63 (m, 1H), 1.20–1.29 (m, 8H), 0.85–0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 167.7, 76.8, 61.7, 61.6, 52.6, 38.9, 34.7, 25.0, 22.2, 22.1, 13.9, 13.8; Chiral HPLC (Daicel Chiralcel OD-H) hexanes/2-propanol=98:2; flow rate: 1.0 mL/min; λ=210 nm; t_{minor}=6.2 min, t_{major}=8.6 min.

*4.3.3. Ethyl-4-isobutyl-2-oxopyrrolidine-3-carboxylate (**5**)*[10]. A solution of **4** (1.59 g, 8 mmol) in 2 mL THF and 10 mL EtOH was added to a hydrogenation bottle containing Raney-Ni (0.16 g). The resulting black suspension was stirred at room temperature under H_2 at 4 atm for 24 h. After completion of the reaction, the resulting mixture was filtered and the solvent was evaporated under vacuum. The crude product was purified by column chromatography (ethyl acetate/petroleum ether=1:3 as eluent) to give colorless oil. After crystallization from petroleum ether, white crystal (700 mg, 72%) was obtained. White crystal; mp 72–73 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 4.21–4.28 (m, 2H), 3.52–3.58 (m, 1H), 2.89–2.06 (m, 3H), 1.51–1.61 (m, 1H), 1.34–1.46 (m, 2H), 1.30 (t, *J*=7.2 Hz, 3H), 0.90 (t, *J*=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 169.9, 61.4, 54.9, 46.8, 43.2, 37.4, 25.8, 22.5, 22.4, 14.1.

*4.3.4. (S)-4-Isobutylpyrrolidin-2-one (**6**)*[11]. NaOH (1 N, 20 mL) was added to the solution of **5** (2.87 g, 13.5 mmol) in EtOH (60 mL) at room temperature. After stirring for 30 min, the reaction mixture was concentrated in vacuo. To the residue was added H_2O and 5 N HCl, and the aqueous phase was extracted with $CHCl_3$ (3×50 mL).

The extract was dried over $MgSO_4$, filtrated, and concentrated in vacuo to afford the corresponding carboxylic acid, which was used without further purification. After refluxing in toluene (30 mL) for 6 h, the reaction mixture was purified by column chromatography on silica gel (ethyl acetate/petroleum ether=1:6 as eluent) to afford desired product **6** (1.71 g, 90%). Colorless oil; 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (s, 1H), 3.48 (dd, J=8.8 Hz, 1H), 2.99 (dd, J=7.2, 2.4 Hz, 1H), 2.50–2.58 (m, 1H), 2.42 (dd, J=8.8, 8 Hz, 1H), 1.97 (dd, J=8.8, 8 Hz, 1H), 1.53–1.61 (m, 1H), 1.31–1.37 (m, 2H), 0.89–0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8, 48.3, 43.8, 37.1, 32.8, 26.1, 22.6, 22.4; Chiral HPLC (Daicel Chiralpak AD-H) hexanes/2-propanol=96:4; flow rate: 1.0 mL/min; λ=210 nm; t_{major}=12.8 min, t_{minor}=14.6 min.

*4.3.5. (S)-3-Aminomethyl-5-methyl-hexanoic acid (Pregabalin) hydrochloride (**1**·**HCl**)[2a].* Compound **5** (1.7 g, 121 mmol) and 6 N HCl aqueous (40 mL) were heated at 100 °C for 18 h. Upon cooling, the mixture was extracted with EtOAc (4×10 mL). The aqueous layer was concentrated in vacuo to give product **1**·**HCl** (1.78 g, 92%).

The product could also be obtained from **6**: the solution of **6** (107 mg, 0.55 mmol) in 6 N HCl (2.7 mL) was refluxed at 100 °C for 10 h. The reaction mixture was concentrated in vacuo to afford hydrochloride of Pregabalin **1**·**HCl** (129 mg, 95%). White solid; $[\alpha]_D^{20}$ +7.15(*c* 1.1, H_2O) (Ref. 2a $[\alpha]_D^{20}$ +7.0(*c* 1.1, H_2O)); ^{1}H NMR (400 MHz, CD_3OD): δ 2.96–2.98 (m, 1H), 2.37–2.48 (m, 1H), 2.18–2.24 (m, 1H), 1.66–1.73 (m, 1H), 1.25–1.29 (m, 1H), 0.92–0.96 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz): δ=175.7, 44.4, 41.9, 37.2,32.4, 26.0, 23.1, 22.6.

4.4. General procedure for enantioselective Michael addition of diethyl malonate to nitroalkenes

To a stirred solution of diethyl malonate (1.0 equiv, 0.1 mmol) and thiourea-catalyst **2** (0.1 equiv, 0.01 mmol) was added nitroalkene (1.0 equiv, 0.1 mmol) at −20 °C. After being stirred for 24 h, the mixture was directly purified by column chromatography on silica gel (ethyl acetate/petroleum ether=1:3 as eluent) to afford desired product.

*4.4.1. (S)-Diethyl 2-(1-nitrobutan-2-yl)malonate (**8a**).* Colorless oil; 78% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.72 (dd, J=8.7, 4.8 Hz, 1H), 4.46 (dd, J=7.2, 6.0 Hz, 1H), 4.19–4.26 (m, 4H), 3.63 (d, J=5.7 Hz, 1H), 2.81–2.87 (m, 1H), 1.48–1.58 (m, 2H), 1.28 (t, J=7.2 Hz, 6H), 1.00 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 167.7, 76.3, 61.9, 61.7, 52.4, 38.4, 29.6, 23.1, 14.0, 11.1; HRMS (ESI): m/z calcd for $C_{11}H_{19}NNaO_6$ [M+Na^+]: 284.11046. Found: 284.11055; Chiral HPLC (Daicel Chiralpak OD-H) hexanes/2-propanol=98:2; flow rate: 1.0 mL/min; λ=210 nm; t_{minor}=7.2 min, t_{major}=8.2 min.

*4.4.2. (S)-Diethyl 2-(1-nitropentan-2-yl)malonate (**8b**).* Colorless oil; 87% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (dd, J=8.7, 4.8 Hz, 1H), 4.54 (dd, J=6.9, 6.3 Hz, 1H), 4.19–4.26 (m, 4H), 3.62 (d, J=5.7 Hz, 1H), 2.88–2.94 (m, 1H), 1.35–1.49 (m, 4H), 1.28 (t, J=7.2 Hz, 6H), 0.92 (t, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 167.8, 76.7, 61.9, 61.7, 52.6, 36.6, 32.1, 29.6, 19.8, 14.0, 13.7; HRMS (ESI): m/z calcd for $C_{12}H_{21}NNaO_6$ [M+Na^+]: 298.12611. Found: 298.12632; Chiral HPLC (Daicel Chiralpak OD-H) hexanes/2-propanol=98:2; flow rate: 1.0 mL/min; λ=210 nm; t_{minor}=8.5 min, t_{major}=12.6 min.

*4.4.3. (S)-Diethyl 2-(1-nitrohexan-2-yl)malonate (**8c**).* Colorless oil; 87% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (dd, J=8.4, 4.8 Hz, 1H), 4.53 (dd, J=6.9, 6.3 Hz, 1H), 4.18–4.26 (m, 4H), 3.62 (d, J=5.7 Hz, 1H), 2.89 (m, 1H), 1.44–1.51 (m, 2H), 1.26–1.35 (m, 10H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 167.8, 76.7, 61.8, 61.7, 52.6, 36.8, 29.6, 28.6, 22.3, 13.9, 13.9, 13.7; HRMS (ESI): m/z calcd for $C_{13}H_{23}NNaO_6$ [M+Na^+]: 312.14176. Found: 312.14205; Chiral HPLC (Daicel Chiralcel OD-H) hexanes/2-propanol=98:2; flow rate: 1.0 mL/min; λ=210 nm; t_{minor}=5.8 min, t_{major}=6.7 min.

*4.4.4. (S)-Diethyl 2-(1-nitroheptan-2-yl)malonate (**8d**)[5a].* Colorless oil; 89% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (dd, J=8.4, 4.8 Hz, 1H), 4.53 (dd, J=7.2, 6.3 Hz, 1H), 4.18–4.26 (m, 4H), 3.63 (d, J=5.7 Hz, 1H), 2.86–2.92 (m, 1H), 1.26–1.49 (m, 14H), 0.88 (t, J=6.6 Hz, 3H); Chiral HPLC (Daicel Chiralcel OD-H) hexanes/2-propanol=98:2; flow rate: 1.0 mL/min; λ=210 nm; t_{minor}=7.4 min, t_{major}=11.1 min.

*4.4.5. (S)-Diethyl 2-(1-nitrododecan-2-yl)malonate (**8e**).* Colorless oil; 83% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.71 (dd, J=8.7, 4.8 Hz, 1H), 4.53 (dd, J=6.9, 6.3 Hz, 1H), 4.19–4.26 (m, 4H), 3.62 (d, J=6.0 Hz, 1H), 2.86–2.92 (m, 1H), 1.25–1.45 (m, 24H), 0.88 (t, J=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 167.8, 76.7, 61.9, 61.7, 52.6, 36.9, 31.8, 30.0, 29.5, 29.4, 29.2, 26.5, 22.6, 14.0, 14.0; HRMS (ESI): m/z calcd for $C_{19}H_{35}NNaO_6$ [M+Na^+]: 395.23566. Found: 395.23587; Chiral HPLC (Daicel Chiralcel OD-H) hexanes/2-propanol=98:2; flow rate: 1.0 mL/min; λ=210 nm; t_{minor}=7.0 min, t_{major}=10.7 min.

*4.4.6. (S)-Diethyl 2-(1-cyclohexyl-2-nitroethyl)- malonate (**8f**).* Color less oil; 86% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.73 (dd, J=10.5, 4.2 Hz, 1H), 4.61 (dd, J=8.1, 6.6 Hz, 1H), 4.17–4.25 (m, 4H), 3.71 (d, J=5.1 Hz, 1H), 2.85–2.93 (m, 1H), 1.66–1.74 (m, 4H), 1.41–1.50 (m, 1H), 1.28 (t, J=6.9 Hz, 6H), 0.94–1.19 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 168.1, 75.4, 61.9, 61.6, 51.4, 41.9, 39.6, 30.1, 29.7, 26.2, 26.1, 25.9, 13.8; HRMS (ESI): m/z calcd for $C_{15}H_{25}NNaO_6$ [M+Na^+]: 338.15741. Found: 298.15727; Chiral HPLC (Daicel Chiralcel OD-H) hexanes/2-propanol=98:2; flow rate: 1.0 mL/min; λ=210 nm; t_{minor}=7.2 min, t_{major}=14.5 min.

*4.4.7. (R)-Diethyl 2-(2-nitro-1-phenylethyl)- malonate (**8g**)[5a].* White solid; mp 43–45 °C (Ref. 4a mp 45–47 °C); 90% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.27 (m, 5H), 4.75–4.89 (m, 2H), 4.11–4.20 (m, 3H), 3.90–3.97 (m, 2H), 3.71 (d, J=9.3 Hz, 1H), 1.19 (t, J=6.9 Hz, 3H), 0.97 (t, J=6.9 Hz, 3H); Chiral HPLC (Daicel Chiralpak AD-H) hexanes/2-propanol=90:10; flow rate: 1.0 mL/min; λ=254 nm; t_{major}=8.3 min, t_{minor}=20.5 min.

*4.4.8. (R)-Diethyl 2-(2-nitro-1-p-tolylethyl)-malonate (**8h**)[11].* Colorless oil; 89% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (s, 4H), 4.79–4.91 (m, 2H), 4.17–4.26 (m, 3H), 3.98–4.05 (m, 2H), 3.79 (d, J=9.3 Hz, 1H), 2.30 (s, 3H), 1.26 (t, J=6.9 Hz, 3H), 1.06 (t, J=6.9 Hz, 3H); Chiral HPLC (Daicel Chiralpak AD-H) hexanes/2-propanol=95:5; flow rate: 1.0 mL/min; λ=215 nm; t_{major}=13.57 min, t_{minor}=35.6 min.

*4.4.9. (R)-Diethyl 2-(1-(4-methoxyphenyl)-2-nitroethyl)malonate (**8i**)[11].* Yellow oil; 85% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, J=8.4 Hz, 2H), 6.83 (d, J=8.1 Hz, 2H), 4.81–4.90 (m, 3H), 4.16–4.26 (m, 2H), 3.77–3.80 (m, 4H), 1.24–1.29 (m, 3H), 1.05–1.10 (m, 3H); Chiral HPLC (Daicel Chiralpak AD-H) hexanes/2-propanol=70:30; flow rate: 0.5 mL/min; λ=210 nm; t_{major}=10.6 min, t_{minor}=36.8 min.

*4.4.10. (R)-Diethyl 2-(1-(4-fluorophenyl)-2-nitroethyl)malonate (**8j**)[5a].* Colorless oil; 88% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.27 (m, 2H), 7.01 (t, 2H), 4.78–4.94 (m, 2H), 4.17–4.26 (m, 3H), 3.98–4.05 (m, 2H), 3.79 (d, J=9.3 Hz, 1H), 1.26 (t, J=6.9 Hz, 3H), 1.06 (t, J=6.9 Hz, 3H); Chiral HPLC (Daicel Chiralpak AD-H) hexanes/2-propanol=90:10; flow rate: 1.0 mL/min; λ=254 nm; t_{major}=8.5 min, t_{minor}=29.2 min.

*4.4.11. (S)-Diethyl 2-(2-nitro-1-(thiophen-2-yl)-ethyl)malonate (**8k**)[5a].* Colorless oil; 93% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.26 (m, 1H), 6.91–6.95 (m, 2H), 4.90–4.93 (m, 2H), 4.52–4.59 (m, 1H), 4.19–4.27 (m, 2H), 4.08–4.15 (m, 2H), 3.87 (d, J=8.1 Hz, 1H), 1.26 (t, J=6.9 Hz, 3H), 1.16 (t, J=6.9 Hz, 3H); Chiral HPLC (Daicel Chiralpak AD-H)

hexanes/2-propanol=90:10; flow rate: 1.0 mL/min; λ=254 nm; t_{major}=8.2 min, t_{minor}=15.1 min.

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Supplementary data

The original spectra of ^{1}H NMR, ^{13}C NMR, and HPLC of all products are supplied. The supplementary data files are to be used as an aid for the refereeing of the paper only. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.053. These data include MOL files and InChIKeys of the most important compounds described in this article.

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