Stereoselective Synthesis of Mirogabalin via 1,4-Selective Addition of Lithioacetonitrile to Alkylidene Malonate

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ABSTRACT: The synthesis of mirogabalin was studied for industrial production, and an alternative to the Daiichi–Sankyo's method was established. The developed synthesis involves the introduction of a two-carbon unit with the stereoselective 1,4-selective addition of lithioacetonitrile to alkylidene malonate and one-carbon degradation by Hofmann rearrangement. The precursor for the Hofmann rearrangement was readily prepared from the 1,4-adduct via a one-pot reaction involving decarboxylation, hydrolysis, and hydration.

■ INTRODUCTION

Mirogabalin is a class of gabapentinoids originally developed by Daiichi–Sankyo Co., Ltd. These gabapentinoids function as an α2δ ligand and are derivatives of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).[1] Since its approval in Japan in 2019, mirogabalin has been marketed as a drug for the treatment of neuropathic pain under the trade name Tarlige. Other well-known gabapentinoids are pregabalin and gabapentin, which are increasingly used worldwide (Figure 1).

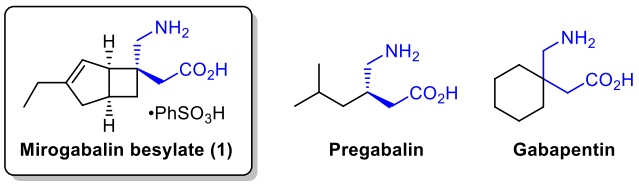


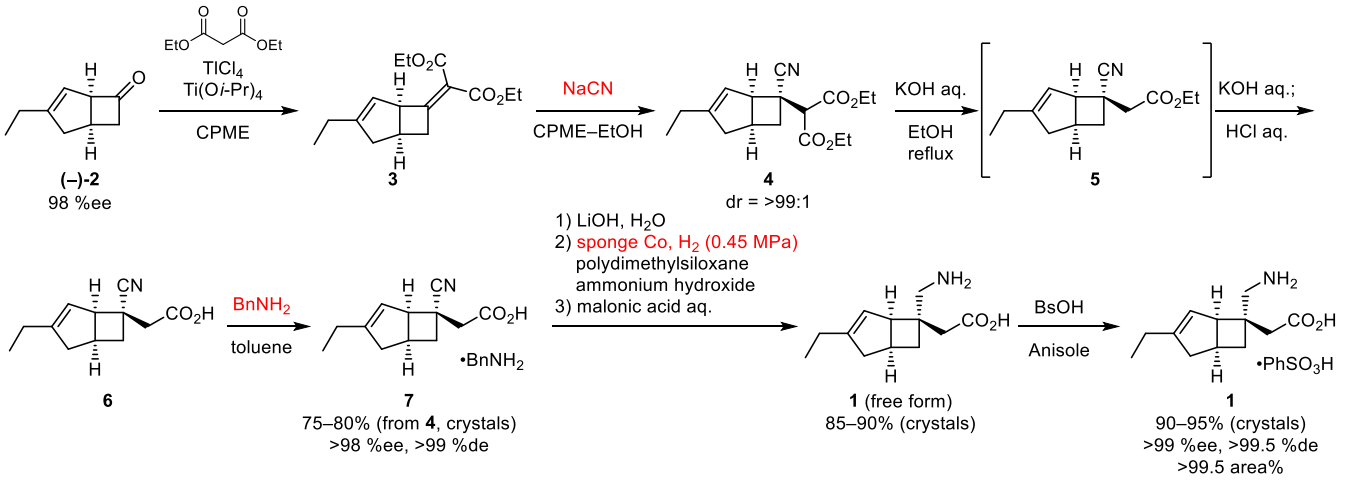
Figure 1. Structures of gabapentinoids.

From the structural viewpoint, this compound has a highly strained bicyclo[3.2.0]heptane skeleton and three contiguous stereogenic centers despite its small molecular size, making it unique and difficult to synthesize. Therefore, a sophisticated design strategy is necessary for synthesizing mirogabalin to ensure a robust commercial supply.

The original synthetic route for mirogabalin developed by Daiichi–Sankyo is shown in Scheme 1.[1] The optically active bicyclo ketone **(–)-2** was readily derived by separating its racemic form **(*rac*)-2** by various optical resolution methods (i.e., enzymatic,[2] salt crystallization,[3] and asymmetric aldol methods[4]), and the requisite **(*rac*)-2** was readily synthesized via Claisen rearrangement[5] or Aza-Claisen rearrangement.[6] **(–)-2** was transformed to diethyl cyclobutylidene malonate **3** through Knoevenagel condensation. Reportedly, the undesired precipitation of insoluble Ti complexes was suppressed by conducting the reaction in cyclopentyl methyl ether (CPME).[1] Furthermore, reports have stated that the use of $TiCl_3$(O*i*-Pr), generated in situ by mixing $TiCl_4$ and Ti(O*i*-Pr)$_4$ in a 3:1 ratio, could adjust the Lewis acidity and suppress the decomposition of **2**, while furnishing **3** in good yield. 1,4-Addition of a cyano group from the convex face of **3** yielded the 1,4-adduct **4** with perfect stereoselectivity. Aqueous KOH was slowly added to an ethanolic solution of **4**, while heating to induce decarboxylation of the ethyl malonate unit to afford **5**. Further addition of KOH solution completed the hydrolysis to furnish **6** in a one-pot manner. The resulting **6** was solidified with benzylamine via salt formation to obtain **7**. Subsequently, after the dissolution of salt **7** with LiOH, the nitrile moiety of the resulting **7** (free form) was reduced by hydrogenation under high-pressure conditions using sponge cobalt to obtain the corresponding amine moiety. After neutralizing the γ-amino acid with malonic acid, **1** (free form) was isolated as crystals. Finally, salt crystallization of **1** (free form) with benzenesulfonic acid (besylic acid) afforded mirogabalin besylate **1** in good yield with good purity.

Given the interesting and unique structure of **1**, we have also gained our interest and embarked on its process development, aiming for a robust commercial supply of **1**. Prior to the study, issues to be addressed based on Daiichi–Sankyo's original synthetic route were identified by considering scale-up. The generation of toxic HCN gas during the introduction of the cyano group was a concern, where the amount of generated gas needed to be controlled. Controlling the residual heavy metals during reduction with pyrophoric sponge cobalt was also necessary.[7] Furthermore, pressure-resistant equipment is needed for nitrile reduction to achieve efficient hydrogenation.[8] All of these requirements arise from the use of inorganic NaCN as a nucleophile for constructing the asymmetric quaternary center.

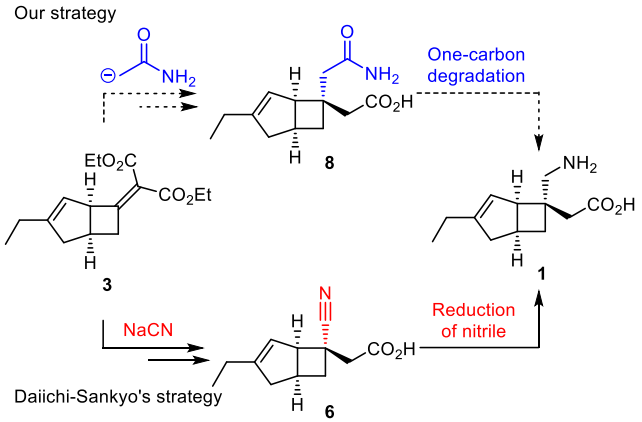
Scheme 1. Original synthetic route (Daiichi–Sankyo, Co., Ltd.)



■ RESULTS AND DISCUSSION

Based on the above background, we envisioned that these matters of concern, including controlling HCN gas, the use of a pyrophoric metal, controlling the residual metal, and facility limitations, could be avoided in a single stroke by changing the strategy to introduce a two-carbon unit bearing a carbamoyl group to obtain **8**, followed by one-carbon degradation (Scheme 2, top), instead of introducing a cyano group followed by the reduction of the nitrile (Scheme 2, bottom).

Scheme 2. Working hypothesis of this study



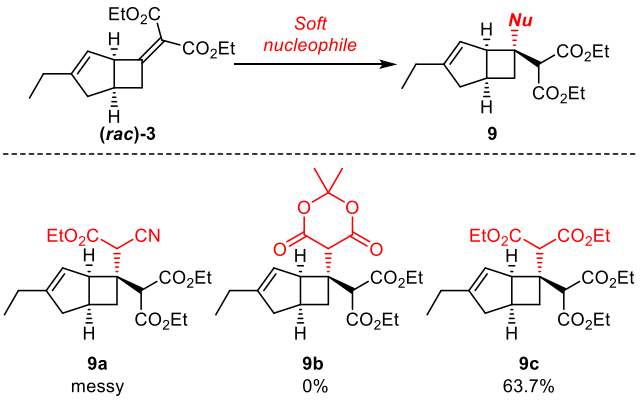
For the one-carbon degradation reaction, the Hofmann rearrangement is one of the most inexpensive and commercially effective methods. There are many similar examples of the derivation from 4-carbamoylbutyric acids to *γ*-amino acids using this reaction; therefore, this transformation is considered promising.[9]

Based on this working hypothesis, an alternative to the original Daiichi–Sankyo's synthesis was established, which is explained in detail below. The synthetic route is summarized in Scheme S1 (Supporting Information).

The Knoevenagel condensation product **(*rac*)-3** was synthesized with **(*rac*)-2** according to a method published by Daiichi–Sankyo[1] and a patent description (Scheme S2).[8]

First, various malonate-type derivatives were investigated as soft-carbon nucleophiles for the construction of quaternary centers via 1,4-addition (Scheme 3). Ethyl cyanoacetate afforded a complex mixture; however, **9a** was not obtained. When Meldrum's acid was used to generate **9b**, the reaction did not proceed and the starting material was completely recovered. When diethyl malonate was used, the target product **9c** was obtained in moderate yield; however, a high yield could not be achieved despite modification of the reaction conditions. 1,4-Addition of soft nucleophiles to **3** did not proceed efficiently because of steric hindrance near the newly formed quaternary center and undesired competition from the reverse reaction of the malonate as a good leaving group.

Scheme 3. 1,4-Addition of soft nucleophiles



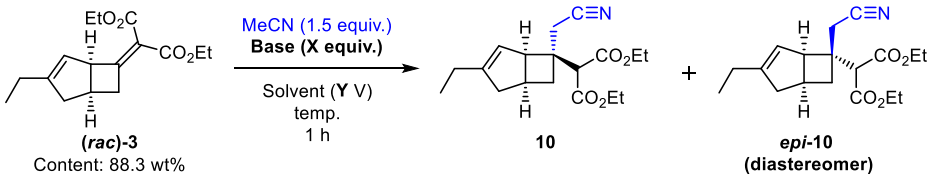
Therefore, a monoester derivative was considered as an alternative nucleophile to malonate, aiming for relaxation of the steric hindrance and suppression of reverse reactions, although a stronger base is required for deprotonation. Incidentally, to carry out the Hofmann rearrangement in the later stage of synthesis, a carbamoyl moiety is required. Herein, acetonitrile was considered the best nucleophile among the monoester derivatives, providing easy access to the carbamoyl moiety in a few steps because it already has a nitrogen atom in its chemical structure. Importantly, because the anion species generated from acetonitrile is a relatively hard nucleophile, the competitive 1,2-addition, rather than 1,4-addition, was a concern,[10] and the reactivity of this species has not been well investigated.

The results of the optimization study are shown in Tables 1 and S1–6. Upon treatment with strong bases such as lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LiTMP), and lithium hexamethyldisilazide (LHMDS) under cryogenic conditions at –78 °C, the 1,4-addition proceeded smoothly from the convex face of **3** to afford the desired **10** in high yields (entries 1–3; Table S1), in which the competitive 1,2-addition was not observed, intriguingly. Surprisingly, the same reaction was achieved using *n*-BuLi instead of lithium amide (entry 4); to a suspension of *n*-BuLi (1.5 M in hexane, 1.5 equiv.) and MeCN (1.5 equiv.) in THF (10 V), **3** (1 equiv.) was added at –78 °C, followed by stirring at 25 °C

for 1 h to obtain the desired **10** in 97.2% yield (assayed by HPLC). This result suggests that lithioacetonitrile was generated efficiently without the undesired nucleophilic addition[11] to acetonitrile or without dimerization[12] under these conditions.[13] Interestingly, when NaH was used, the desired product was not obtained (entry 5). In this case, **3** was recovered, and the active species were deactivated. To the best of our knowledge, the 1,4-selective addition of lithioacetonitrile to *β,β*-dialkyl-substituted alkylidene malonates, as in this case, is not well known. At this stage, it is difficult to conclude whether the reaction is specific to mirogabalin[14], or whether it can be generalized.

From the viewpoint of material cost, the reaction conditions in entry 4 are highly attractive and were considered provisionally optimal. Further investigations of the reaction conditions were conducted. The effect of solvents were investigated. (entries 6–10; Table S2). Interestingly, significant differences were observed in ether-based solvents. When cyclopentyl methyl ether (CPME) or 4-methyltetrahydropyran (MTHP) was used, the reaction proceeded well and furnished the target product in good yields (entries 6 and 7); however, when methyl *tert*-butyl ether (MTBE) was used, a significant decrease in the yield was observed (entry 8). Low-polarity solvents such as toluene and *n*-hexane significantly reduced the yield and gave complex mixtures (entries 9 and 10). The effect of reducing the amount of base was also examined (entries 11 and 12; Table S3). The reduction of *n*-BuLi to 1.2 equiv. reduced the yield to 89.1% (entry 11). In this case, many unidentified byproducts were obtained. Upon further reduction to 1.0 equiv, the reaction did not proceed to completion and the yield was reduced to 76.0% (entry 12). The concentrations of the reactants were also studied (entries 13 and 14; Table S4). When the solvent volume was reduced to 5 V, the product yield remained unchanged (entry 13). When the solvent volume was further reduced to 3 V, the product yield decreased slightly (entry 14). The reaction temperature was also examined (entries 15–17; Table S5). The reaction proceeded smoothly even at −78 °C, suggesting that the 1,4-addition reaction proceeds rapidly (entry 15). Increasing the temperature to −40 °C gave the desired product in relatively good yield (entry 16), whereas the reaction at −20 °C did not give the desired product (entry 17). In this case, the ester moiety was damaged. Because there is an example in which lithioacetonitrile was added at approximately room temperature,[12a,15] we were encouraged to re-examine the protocol at a temperature at which commercial production is possible (entries 18–21; Table S6). After examining the procedure for reagent addition, it was found that adding *n*-BuLi to a solution of **3** and MeCN in THF at −20 °C gave the desired product in 75.4% yield (entry 18). The amounts of *n*-BuLi and MeCN were increased to improve the yield; however, contrary to expectations, the reaction yield decreased (entry 19). Because the ratio of MeCN to *n*-BuLi seemed important, the amount of MeCN was further increased to 16 equiv, which yielded the desired product in 92.9% yield; this suggested that the deprotonation of MeCN was promoted (entry 20). The product was obtained even at 0 °C, albeit in moderate yield (entry 21). Notably, almost no diastereomers were observed and the diastereoselectivity was extremely high in every case, which is similar to the effect of adding NaCN to **3**, as reported by Daiichi–Sankyo.[1]

Table 1. Optimization of 1,4-addition

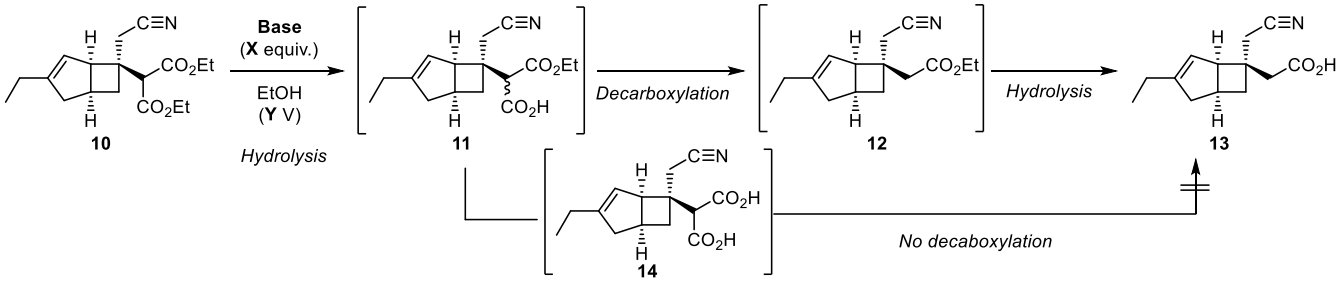


entry	**Base** (**X** equiv.)	**Solvent** (**Y** V)	temp. (°C)	Conv. (%)[a]	**3** (%)[b]	**10** (%)[b]	***epi*-10** (%)[b]
1[c]	LDA (1.5)	THF (10 V)	–78 to 25	99.8	0.2	95.3	1.8
2[d]	LiTMP (1.5)	THF (10 V)	–78 to 25	99.7	0.2	95.9	1.9
3	LHMDS (1.5)	THF (10 V)	–78 to 25	82.8	7.7	80.0	0.0
4	***n*-BuLi (1.5)**	**THF (10 V)**	**–78 to 25**	**98.6**	**0.6**	**97.2**	**1.0**
5	NaH (1.5)	THF (10 V)	–78 to 25	0.0	54.6	0.0	0.0
6	*n*-BuLi (1.5)	CPME (10 V)	–78 to 25	97.0	2.2	72.1	0.1
7	*n*-BuLi (1.5)	MTHP (10 V)	–78 to 25	97.9	1.9	89.5	0.6
8	*n*-BuLi (1.5)	MTBE (10 V)	–78 to 25	62.4	14.4	24.2	0.5
9	*n*-BuLi (1.5)	toluene (10 V)	–78 to 25	72.1	5.8	15.0	0.0
10	*n*-BuLi (1.5)	hexane (10 V)	–78 to 25	18.4	11.1	2.5	0.0
11	*n*-BuLi (1.2)	THF (10 V)	–78 to 25	99.3	0.3	89.1	0.9
12	*n*-BuLi (1.0)	THF (10 V)	–78 to 25	77.4	10.2	76.0	0.5
13	*n*-BuLi (1.5)	THF (5 V)	–78 to 25	99.0	0.5	97.1	0.5
14	*n*-BuLi (1.5)	THF (3 V)	–78 to 25	98.9	0.5	91.3	0.4
15	*n*-BuLi (1.5)	THF (10 V)	–78	99.5	0.2	95.6	0.6
16	*n*-BuLi (1.5)	THF (10 V)	–40 to 25	98.9	0.4	89.3	1.0
17	*n*-BuLi (1.5)	THF (10 V)	–20 to 25	100	0.0	0.4	0.2
18[e]	*n*-BuLi (1.5)	THF (10 V)	–20 to 25	87.0	5.5	75.4	1.2
19[e,f,h]	*n*-BuLi (2.0)	THF (10 V)	–20 to 25	91.4	6.5	67.8	1.4
20[e,g,h]	***n*-BuLi (2.0)**	**THF (10 V)**	**–20 to 25**	**97.3**	**2.6**	**92.9**	**1.0**
21[e,f]	*n*-BuLi (2.0)	THF (10 V)	0 to 25	82.4	7.5	73.3	1.5

[a]Determined by HPLC [(area^{10} + area$^{epi\text{-}10}$)/(area^{3} + area^{10} +area$^{epi\text{-}10}$)].
[b]Quantified using external standard method.
[c]LDA (1.5 equiv) was prepared *in situ* from diisopropylamine (1.5 equiv) and *n*-BuLi (1.5 equiv) at −78 °C for 30 min.
[d]LiTMP (1.5 equiv) was prepared *in situ* from 2,2,6,6-tetramethylpiperidine (1.5 equiv) and *n*-BuLi (1.5 equiv) at −78 °C for 30 min.
[e]*n*-BuLi was added to the solution containing **3** and MeCN in THF.
[f]MeCN (2.0 equiv) was used instead of MeCN (1.5 equiv). [g]MeCN (16.0 equiv.) was used instead of MeCN (1.5 equiv).
[h]Reaction time was 30 min.

Encouraged by the successful 1,4-selective addition of lithioacetonitrile to **3** with good yield and stereoselectivity, which was achieved using only inexpensive *n*-BuLi and MeCN, we focused on the decarboxylation and hydrolysis of **10** to **13** (Tables 2 and S7).

Table 2. Optimization of one-pot process (decarboxylation and hydrolysis)



entry	**Base** (**X** equiv.)	Base solution in dropping funnel	EtOH total (**Y** V)	**10** (%)[a]	**11** (%)[a]	**12** (%)[a]	**13** (%)[a]	**14** (%)[a]	**12+13** (%)
1	KOH (1.5)	45% aq. solution	9	0.0	2.1	20.1	69.4	11.5	89.5
2[b]	KOH (1.5)	EtOH (4 V)	9	0.0	0.0	16.4	74.3	9.2	90.7
3[c]	LiOH (1.5)	insoluble	9	42.4	3.2	52.4	0.0	0.0	52.4
4[b]	NaOH (1.5)	EtOH (4 V)	9	7.2	0.0	16.6	73.6	2.9	90.2
5[b]	$CsOH·H_2O$ (1.5)	EtOH (4 V)	9	0.0	0.0	0.0	84.2	15.3	84.2
6[c]	KOH (1.5)	EtOH (4 V)	20	0.0	0.0	5.8	88.9	8.0	94.7
7[d]	**KOH (1.2)**	EtOH (4 V)	**20**	**0.0**	**2.3**	**49.9**	**49.2**	**3.8**	**99.1**

[a]Quantified using external standard method.
[b]Base in EtOH (4 V) was added to a solution of **10** in EtOH (5 V). Total volume of EtOH was 9 V.
[c]LiOH was added to a solution of **10** in EtOH (9 V).
[d]KOH in EtOH (4 V) was added to a solution of **10** in EtOH (16 V). Total volume of EtOH was 20 V.

Referring to the report by Daiichi–Sankyo,[1] a 45% aqueous KOH solution was added to a solution of **10** in EtOH (9 V) over 4 h under reflux conditions (entry 1). Hydrolysis and decarboxylation occurred simultaneously, yielding a mixture of monoester **12** (20.1%) and the target carboxylic acid **13** (69.4%). In this case, 11.5% of dicarboxylic acid **14** was generated as a byproduct, but this compound was not decarboxylated under the reaction conditions and was not converted to **13**.[16] Compounding the issue, **14** was difficult to remove by liquid separation or crystallization, which led to lower purity and lower yields of the products, including **12** and **13**. Therefore, the generation of **14** was minimized by strictly controlling the reaction conditions.

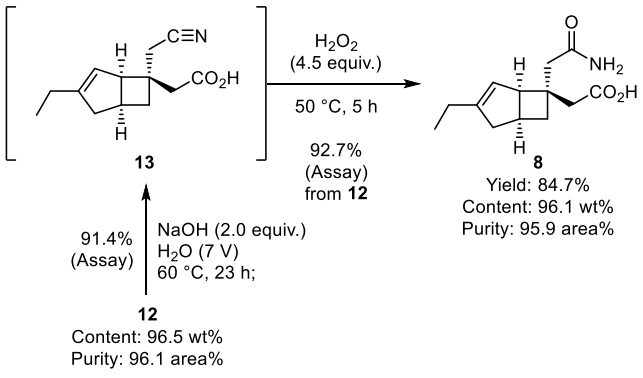
To suppress the generation of the undesired byproduct dicarboxylic acid **14**, the amount of H_2O was first reduced (entry 2); a KOH solution in dehydrated EtOH (4 V, 5.6 wt% solution) was used instead of the original 45% KOH aqueous solution. This solution was then added to a solution of **10** in EtOH (5 V) over 4 h (the total EtOH volume was 9 V). In this case, the production of **14** was slightly suppressed.

Bases were then examined (entries 2–5). When less basic LiOH or NaOH was used, the generation of byproduct **14**, formed by the hydrolysis of **11**, was suppressed. The hydrolysis of **10** to **11** was also suppressed, and the net reaction was dramatically delayed (entries 3 and 4). When excess base was added to complete the reaction, a non-negligible amount of **14** was formed (data not shown). $CsOH·H_2O$ as a stronger base was found to increase the formation of **14** (entry 5).

Therefore, to slow the intermolecular conversion of **11** to **14** and relatively accelerate the intramolecular conversion of **11** to **12**, the reaction mixture was diluted by increasing the amount of total EtOH from 9 to 20 V, which slightly improved the reaction yield, and the formation of **14** was reduced as expected (entry 6). From this point, we further reduced the amount of base to 1.2 equiv, which successfully minimized the generation of **14** to 3.8%, while allowing **10** to be completely consumed (entry 7). The resulting mixture of **12** and **13** at 25 °C was fully converted to carboxylic acid **13** by further addition of KOH to the solution.

Subsequently, the hydration reactions of nitriles targeting amide **8** were studied separately.

Scheme 4. Hydration of nitrile on 13

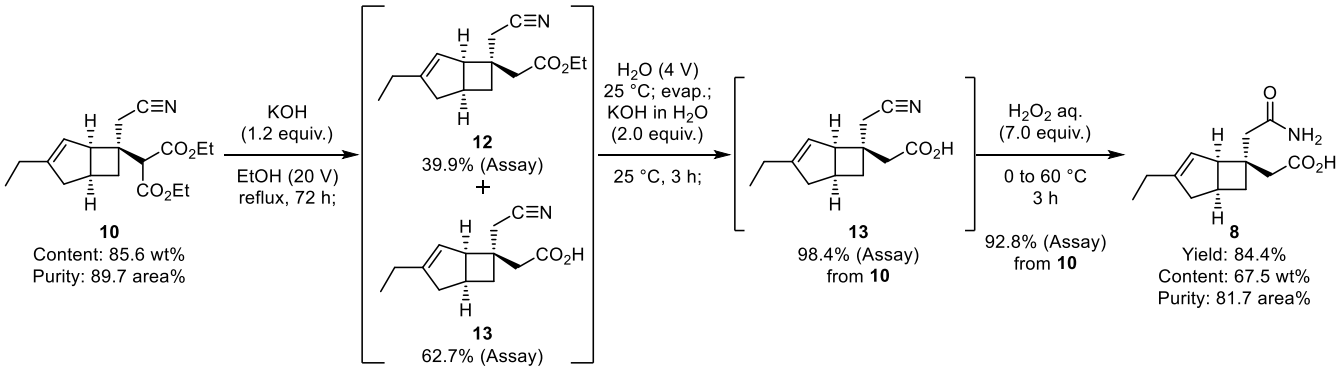


Several reaction conditions have been reported for nitrile hydration.[17] Under acidic conditions, the olefin moiety of **13** was damaged prior to hydration, whereas under basic conditions, the resulting carbamoyl group underwent overhydrolysis, yielding a non-negligible amount of symmetric dicarboxylic acid. Undesired overhydrolysis could not be suppressed despite several efforts. Gratifyingly, the hydration of nitriles could be induced in high yields under

mild conditions with the Radziszewskii reaction,[18] in which aqueous hydrogen peroxide was added under basic conditions. Hydrolysis of ester **12**, followed by hydration of the resulting **13**, proceeded smoothly to furnish **8** in good yield in a one-pot manner (Schemes 4 and S7).

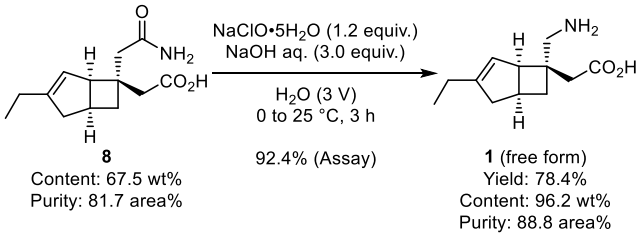
The transformations, including decarboxylation, hydrolysis, and hydration, were also conducted and examined in a one-pot process (Schemes 5 and S8). After the decarboxylation, the solvent was exchanged from EtOH to water to facilitate liquid separation. Subsequently, hydrolysis was conducted in one pot, yielding **13** in 98.4% assayed yield. Aqueous H_2O_2 was added to this basic aqueous solution to afford **8** in 92.8% assay yield. After workup, a residue containing **8** was obtained in 84.4% yield, 81.7 area% as an oil. Purity of the crude was rather low due to byproducts derived from the residue containing **10** and high-polar unidentified impurities generated through reactions. The crude oil was used for the next step without further purification to simplify the operation and reduce production costs. Since pure **8** is a solid, it would be possible to increase the purity of **8** by solidification at this step.

Scheme 5. One-pot transformation



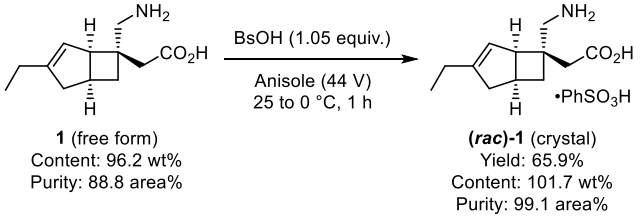
With **8** in hand, which was readily obtained from **10** via a one-pot transformation, the Hoffman rearrangement was subsequently investigated (Schemes 6 and S9). One of the least expensive reagents, $NaClO\cdot 5H_2O$, was used as the oxidant. The reaction proceeded smoothly under the standard reaction conditions. After completion of the reaction, hydrochloric acid was added to adjust the pH to 6. Neutralization and crystallization proceeded, and γ-amino acids were precipitated from the aqueous solution and isolated as a solid in high yield. Through this solidification process, both the purity and content of the resulting solid were improved compared to those of crude **8**. Notably, the isolation of **1** (free form) as a solid is required only once, which simplifies the process and reduces the operating time.

Scheme 6. Hofmann rearrangement



The remaining step was the salt crystallization of **1** (free form) (Schemes 7 and S10). As in Daiichi-Sankyo's patent,[8] besylic acid was added to a suspension of **1** (free form) in anisole to obtain target product ***(rac)*-1** with good purity.

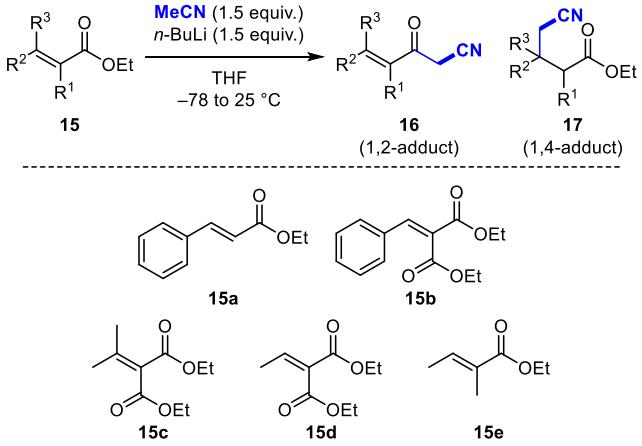
Scheme 7. Salt formation with besylic acid



■ DISCUSSION OF 1,4-SELECTIVE ADDITION

The key to the developed synthesis of mirogabalin was the successful 1,4-selective addition of lithioacetonitrile to alkylidene malonates. As mentioned above, lithioacetonitrile seems to be a relatively hard nucleophile, and 1,2-additions are expected to be preferential; however, 1,4-selective addition occurred even under kinetic reaction conditions. To ascertain whether this phenomenon is specific to mirogabalin or can be generalized, various electrophiles were explored to investigate the selectivity and discuss its origin (Tables 3 and S8).

Table 3. Investigation of selectivity



entry	**15**	**16** (%)[a]	**17** (%)[a]	Others
1	**15a**	79	ND	
2	**15b**	ND	87	
3	**15c**	13	54	olefin isomer: 14%
4	**15d**	ND	93	
5	**15e**	73	ND	

[a]Isolated yield.
[b]"ND" stands for "not detected".

When the reaction conditions (Table 1, entry 4) were employed for cinnamic acid ester **15a**, only the 1,2-adduct **16a** was obtained; the

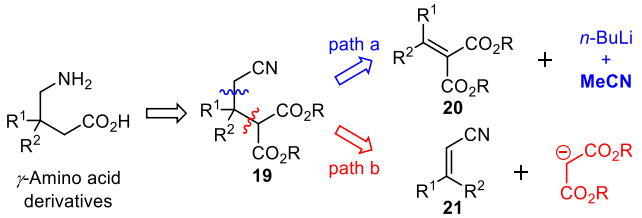
1,4-adduct **17a** was not observed (entry 1). On the other hand, quite interestingly, when applied to benzylidene malonate **15b**, only the 1,4-adduct **17b** was obtained in 87% yield, suggesting that the activation of the double bond by two ester groups accelerates the 1,4-addition reaction (entry 2). A competition experiment between **15a** and **15b** also supported this observation.[19]

When the reaction conditions were employed for isopropylidene malonate **15c** bearing the *β*,*β*-dialkylsubstituted olefin, 1,2-addition and 1,4-addition competed, with isomerization of the olefin occurring in addition to these reactions (entry 3; Table S8). With **15d**, which is ethylidene malonate with less steric hindrance around the reaction site, only the 1,4-adduct **17d** was obtained in high yield (entry 4). With **15e** bearing a methyl group at the *α*-position, only the 1,2-addition product **16e** was observed in spite of the steric hindrance around the reaction site, suggesting that the second ester behaves as an activator of the double bond and does not play the role of a bulky substituent (entry 5).

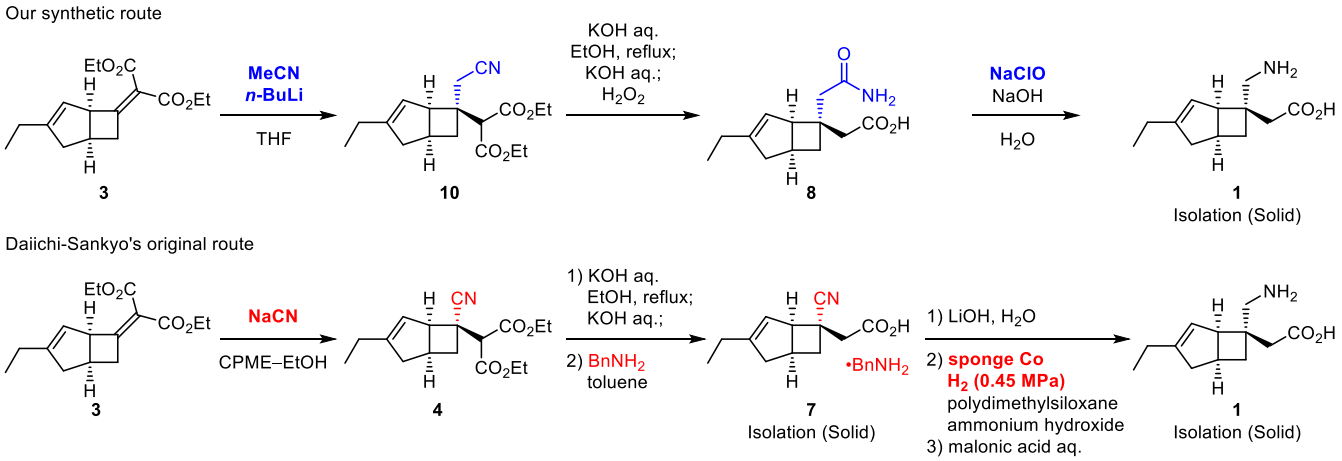
Based on the above, the 1,4-selective addition reaction of **3** proceeds with high efficiency, mainly due to the synergistic effect of the electronic activation of the olefins by the two ester groups and the suppression of the 1,2- addition by steric hindrance around the reaction site. The fact that olefin isomerization does not occur because of the ring strain of the cyclobutene ring and that the ring strain is partly released by the transformation from sp^2 to sp^3-hybridization also contributes to the high efficiency.

Other than malonate addition to unsaturated nitriles **21** (Scheme 8, path b), this 1,4-selective addition of lithioacetonitrile to alkylidene malonate is expected to provide an inexpensive alternative for accessing cyanoethylmalonate derivatives **19**, which are important intermediates for synthesizing *γ*-amino acid derivatives (Scheme 8, path a).

Scheme 8. Alternative retrosynthesis



Scheme 9. Summary of the developed synthetic route



■ CONCLUSION

An alternative to Daiichi–Sankyo's method was established for the commercial production of mirogabalin (Scheme 9). The developed synthesis involves the introduction of a two-carbon unit, followed by one-carbon degradation. The method features the introduction of a two-carbon unit by the stereo- and 1,4-selective addition of lithioacetonitrile to alkylidene malonate, which can be generated from inexpensive *n*-BuLi and acetonitrile. This novel transformation potentially broadens the scope of retrosynthesis of GABA derivatives. The one-pot transformation, including decarboxylation, hydrolysis, and hydration, enables easy access to the precursor of the Hofmann rearrangement.

■ EXPERIMENTAL SECTION

General Information

All reactions were performed under a nitrogen atmosphere unless otherwise indicated. All manipulations of air- and/or moisture-sensitive compounds were performed using standard Schlenk techniques. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained from measurements at ambient temperature on a JEOL 500SS spectrometer (JNM-ECA500). Chloroform–d_1 ($CDCl_3$) containing 0.03% tetramethylsilane (TMS) (99.8%D, KANTO Chemical Co., Inc.) was used as a solvent for NMR measurements at room temperature. Chemical shifts (δ) are given in parts per million (ppm) downfield from the signal of TMS in $CDCl_3$ (δ 0.00 ppm for ^{1}H NMR) or $CDCl_3$ (δ 77.0 ppm for ^{13}C NMR) as an internal standard, and as an external standard with coupling constants (*J*) in hertz (Hz). Abbreviations s, d, t, q, sep, m, and br signify singlet, doublet, triplet, quartet, septet, multiplet, and broad, respectively.

HPLC Method

High performance liquid chromatography (HPLC) was performed by LC-2050C Plus with 5C18-AR-II column (250 × 4.6 mm I.D., 5.0 μm). The column oven was set at 40 °C. The UV detector was set at 210 nm. Mobile phases A (0.1% phosphoric acid aq.) and B (acetonitrile) were utilized at a flow rate of 1.4 mL/min. Mobile phase B was increased linearly from 50% to 70% over 3.2 min, held at 70% for 6 min, increased linearly from 70% to 100% over 4.8 min, and held at 100% for 4.8 min.

Retention times: **2** (5.19 min), **3** (9.56 min), **10** (9.20 min), ***epi*-10** (8.97 min), **12** (7.58 min), **13** (4.32 min), **14** (3.26 min), **8** (2.91 min), **1** (1.58 min), BsOH (2.39 min).

Preparation for (*rac*)-3 (Knoevenagel Condensation)

To a stirred solution of Ti(O*i*-Pr)$_4$ (3.50 mL, 11.8 mmol, 0.40 equiv.(gross basis)) in CPME (32.0 mL, 8.0 V (gross basis)) was added $TiCl_4$ (3.52 mL, 32.3 mmol, 1.1 equiv.(gross basis)) dropwise at 20 °C. After stirring for 30 min at 10 °C, diethyl malonate (4.93 mL, 32.3 mmol, 1.1 equiv.(gross basis)) was added at the same temperature. After stirring at 5 °C for 15 min, **(*rac*)-2** (gross: 4.00 g, net: 3.96 g, content: 99.0 wt%, purity: 98.8 area%, 29.4 mmol, 1 equiv.(basis)) was added at the same temperature. After stirring at 30 °C for 3 h [conversion: 93.7%, yield: 95.8% (HPLC)], to the reaction mixture was added H_2O (20 mL, 5.0 V (gross basis)) at 5 °C. The organic phase was separated and washed by 3.8% HCl (8 mL, 2.0 V (gross basis)) and 3.0% $NaHCO_3$ (8 mL, 2.0 V (gross basis)). The organic phase was concentrated under reduced pressure and dried in vacuo at 25 ℃ for 18 h to afford **(*rac*)-3** (gross: 8.07 g, net: 7.59 g, content: 92.4 wt%, purity: 94.5 area%, 27.3 mmol, 93.8% yield) as reddish oil.

Preparation for (*rac*)-10 (1,4-addition of lithioacetonitrile)

To a solution of *n*-BuLi (1.6 M in hexane, 11.2 mL, 18.0 mmol, 1.5 equiv.(net basis)) in THF (36 mL, 10 V (gross basis)) was added MeCN (0.937 mL, 18.0 mmol, 1.5 equiv.(net basis)) at –78 °C. After stirring for 30 min, **(*rac*)-3** (gross: 3.60 g, net: 3.33 g, content: 92.4 wt%, purity: 94.5 area%, 12.0 mmol, 1 equiv.(basis)) was added dropwise at the same temperature. After stirring at 25 ℃ for 1 h [conversion: 100%, yield: 102.6% (HPLC)], to the reaction mixture was added sat. NH_4Cl aq. (18 mL, 5 V (gross basis)) at the same temperature. The organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (18 mL, 5 V (gross basis)) twice. The combined organic phases were concentrated under reduced pressure and dried in vacuo at 25 ℃ for 18 h to afford **(*rac*)-10** (gross: 4.17 g, net: 3.57 g, content: 85.6 wt%, purity: 89.7 area%, 1.47 mmol, 91.1% yield.) as reddish oil.

Preparation for (*rac*)-8 (one-pot transformation)

To a solution of **(*rac*)-10** (gross: 4.05 g, net: 3.47 g, content: 85.6 wt%, purity: 89.7 area%, 10.9 mmol, 1 equiv.) in EtOH (55.5 mL, 16 V (net basis)) was added KOH (5.6 wt% solution, 730 mg, 13.0 mmol, 1.2 equiv.) in EtOH (15.6 mL, 4 V (net basis)) at reflux temperature over 4 h. After stirring for 72 h [yields: **10** (0.0%), **12** (39.9%), **13** (62.7%) (HPLC)], the reaction mixture was cooled to 25 ℃. To the mixture was added H_2O (13.9 mL, 4 V (net basis)) at the same temperature. The reaction mixture was concentrated under reduced pressure (30 ℃, 50 mmHg) to afford an aqueous solution (total weight: 24.4 g). To the mixture was added aq. KOH (20% solution, 1.22 g, 21.7 mmol, 2.0 equiv.) at the same temperature. After stirring at the same temperature for 3 h [yields: **12** (0.0%), **13** (98.4%)], the reaction mixture was cooled to 0 ℃. To the mixture was added aq. H_2O_2 (30% solution, 2.58 g, 76.0 mmol, 7.0 equiv.) at the same temperature. After stirring at 60 °C for 3 h [yields: **13** (1.0%), **8** (92.8%) (HPLC)], the reaction mixture was cooled to 25 ℃. To this mixture was added toluene (20.3 mL, 5 V (gross basis)) at the same temperature. The phases were separated. To the aqueous phase was added HCl aq. (17.5% solution, 2.35 mL) at room temperature. The aqueous solution was extracted by EtOAc (40.5 mL, 10 V (gross basis)) three times. The combined organic phases were concentrated under reduced pressure and dried in vacuo at 25 ℃ for 18 h to afford **(*rac*)-8** (gross: 3.20 g, net: 2.17 g, content: 67.5 wt%, purity: 81.7 area%, 12.5 mmol, 84.4% yield) as a viscous yellow oil.

Preparation for (*rac*)-1 (free form) (Hofmann rearrangement)

To a stirred suspension of **(*rac*)-8** (gross: 1.00 g, net: 675 mg, content: 67.5 wt%, purity: 81.7 area%, 2.85 mmol, 1 equiv.(basis)) in H_2O (3 mL, 3 V (gross basis)) were added NaOH aq. (20% in H_2O, 8.53 mmol, 3.0 equiv. (net basis)) and $NaClO \cdot 5H_2O$ (561 mg, 3.41 mmol, 1.2 equiv. (net basis)) at 0 ℃. After stirring for 1 h at the same temperature, the reaction mixture was warmed up to 25 ℃. After stirring for 3 h at the same temperature [(conversion: 100%, yield: 92.4% (HPLC)], the reaction mixture was cooled to 0 ℃. To the mixture was added HCl (17.5 wt% in H_2O, 1.78 g) until reaching pH6 to afford precipitation. Then NaCl (1.04 g, 17.8 mmol) was added to the reaction mixture. After stirring at the same temperature for 1 h, the resulting slurry solution was filtered off. The resulting wet crystal was washed with iced water (2 mL, 2 V (gross basis)) twice, and dried in vacuo at 40 ℃ for 20 h to afford **(*rac*)-1** (free form) as a white crystal (gross: 483 mg, net: 465 mg, content: 96.2 wt%, purity: 88.8 area%, 2.22 mmol, 78.4% yield).

Preparation for (*rac*)-1 (Salt formation)

To a suspension of **(*rac*)-1** (free form) (gross: 100 mg, net: 96.2 mg, content: 96.2 wt%, purity: 88.8 area%, 0.460 mmol, 1 equiv.(basis)) in anisole (4.0 mL, 40 V (gross basis)) was added a solution of besylic acid (79.5 mg, 0.483 mmol, 1.05 equiv.(net basis)) in anisole (0.40 mL, 4.0 V (gross basis)) at 25 ℃. The reaction mixture was cooled to 0 ℃. After stirring at the same temperature for 1 h, the resulting suspension was filtered off. The wet crystal was washed with acetone (0.50 mL, 5.0 V (gross basis)) once and dried in vacuo at 40 ℃ for 20 h to afford **(*rac*)-1** as a white solid (gross: 111 mg, net: 113 mg, content: 101.7 wt%, purity: 99.1 area%, 0.303 mmol, 65.9% yield).

General Procedure for 1,4-addition of lithioacetonitrile

To a solution of *n*-BuLi (1.5 M in *n*-hexane, 5.00 mL, 7.50 mmol, 1.5 equiv.) in THF (10 mL, 0.5 M) was added MeCN (0.392 mL, 7.50 mmol, 1.5 equiv.) dropwise at –78 ℃. After stirring at the same temperature for 30 min, **15** (5.00 mmol, 1 equiv.(basis)) was added dropwise at the same temperature. The reaction mixture was warmed up to 25 ℃. After stirring at the same temperature for 1 h, 1 M HCl (10 mL) was added to the mixture. The mixture was extracted by EtOAc (10 mL) three times. The combined organic phase was dried over Na_2SO_4, and filtered. The resulting organic phase was concentrated under the reduced pressure to afford a residue. The residue was purified by silica-gel column chromatography to afford the products.

Characterization

(1R,5S)-3-Ethylbicyclo[3.2.0]hept-3-en-6-one (**2**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.24–5.22 (m, 1H), 4.21–4.18 (m, 1H), 3.24–3.17 (m, 1H), 2.85–2.76 (m, 3H), 2.35–2.29 (m, 1H), 2.14 (q, *J* = 7.5 Hz, 2H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 209.1 (1C), 150.1 (1C), 117.1 (1CH), 73.3 (1CH), 53.1 ($1CH_2$), 42.7 ($1CH_2$), 26,1 (1CH), 24.2 ($1CH_2$), 12.2 ($1CH_3$).

Diethyl 2-((1R,5S)-3-ethylbicyclo[3.2.0]hept-3-en-6-ylidene)malonate (**3**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.37–5.35 (m, 1H), 4.29–4.23 (m, 1H), 4.26 (qd, *J* = 7.2, 1.4 Hz, 2H), 4.21 (qd, *J* = 7.2, 0.9 Hz, 2H), 3.32 (ddd, *J* = 18.9, 8.6, 3.7 Hz, 1H), 2.95–2.89 (m, 1H), 2.72 (ddd, *J* = 18.9, 5.8, 3.7 Hz, 1H), 2.66 (dd, *J* = 16.8, 8.2 Hz, 1H), 2.22 (dd, *J* = 16.8, 3.4 Hz, 1H), 2.11 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.1 (1C), 164.5 (1C), 164.2 (1C), 148.8 (1C), 121.0 (1CH), 118.2 (1C), 60.6 ($1CH_2$), 60.6 ($1CH_2$), 58.3 (1CH), 42.7 ($1CH_2$), 39.7 ($1CH_2$), 32.7 (1CH), 24.3 ($1CH_2$), 14.22 ($1CH_3$), 14.20 ($1CH_3$), 12.2 ($1CH_3$).

1,3-Diethyl 2-[(1R,5S,6R)-(6-cyanomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]propanedioate (**10**). Colorless oil; 1H NMR ($CDCl_3$) δ 5.28–5.26 (m, 1H), 4.22 (qd, *J* = 7.2, 3,4 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 1H), 3.30 (br s, 1H), 3.08–3.02 (m, 1H), 3.01 (d, *J* = 2.9 Hz, 2H), 2.54 (dd, *J* = 16.6, 8.0 Hz, 1H), 2.31 (ddd, *J* = 13.0, 8.9, 2.7 Hz, 1H), 2.19–2.12 (m, 2H), 2.07 (d, *J* = 16.6 Hz, 1H), 1.70 (dd, *J* = 13.0, 7.5 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.0 (1C), 167.8 (1C), 151.8 (1C), 121.0 (1CH), 118.9 (1C), 61.52 ($1CH_2$), 61.47 ($1CH_2$), 55.7 (1CH), 55.1 (1CH), 43.8 (1C), 42.6 ($1CH_2$), 37.9 ($1CH_2$), 31.4 (1CH), 24.5 ($1CH_2$), 24.4 ($1CH_2$), 14.01 ($1CH_3$), 13.99 ($1CH_3$), 12.4 ($1CH_3$).

1,3-Diethyl 2-[(1R,5S,6S)-(6-cyanomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]propanedioate (3:2 mixture of diastereomixture, ***epi*-10** is a minor product) (***epi*-10**). Colorless oil; ^{1}H NMR ($CDCl_3$) (minor) δ 5.39–5.38 (m, 1H), 4.27–4.21 (m, 4H), 3.80 (s, 1H), 3.35 (br s, 1H), 2.80 (s, 2H), 2.76–2.71 (m, 1H), 2.55–2.48 (m, 2H), 2.19–2.12 (m, 3H), 1.66 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.32–1.27 (m, 6H), 1.10 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) (minor) δ 167.9 (1C), 166.6 (1C), 152.1 (1C), 120.5 (1CH), 118.4 (1C), 61.7 ($1CH_2$), 61.6 ($1CH_2$), 57.4 (1CH), 53.4 (1CH), 43.7 (1C), 41.7 ($1CH_2$), 36.6 ($1CH_2$), 30.5 (1CH), 24.4 ($1CH_2$), 22.5 ($1CH_2$), 14.01 ($1CH_3$), 13.99 ($1CH_3$), 12.3 ($1CH_3$).

1-Ethyl 2-[(1R,5S,6S)-(6-cyanomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]propanedioate (3:2 mixture of diastereomixture) (**11**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.85 (br s, 1H), 5.34 [s, (2/5)1H], 5.27 [s, (3/5)1H], 4.29–4.18 (m, 2H), 3.78 [s, (2/5)1H], 3.77 [s, (3/5)1H], 3.31 (br s, 1H), 3.09–3.01 (m, 1H), 3.01 [s, (2/5)2H], 3.00 [s, (3/5)2H], 2.54 (dd, *J* = 16.0, 7.9 Hz, 1H), 2.36–2.29 (m, 1H), 2.19–2.13 (m, 2H), 2.07 (d, *J* = 16.0 Hz, 1H), 1.74 [dd, *J* = 12.5, 7.5 Hz, (3/5)1H], 1.70 [dd, *J* = 12.5, 7.5 Hz, (2/5)1H], 1.31 [t, *J* = 7.5 Hz, (3/5)3H], 1.28 [t, *J* = 7.5 Hz, (2/5)3H], 1.09 [t, *J* = 7.5 Hz, (2/5)3H], 1.08 [t, *J* = 7.5 Hz, (3/5)3H]; ^{13}C NMR ($CDCl_3$) δ 173.3 [(3/5)1C], 173.0 [(2/5)1C], 167.9 [(2/5)1C], 167.7 [(3/5)1C], 152.3 [(3/5)1C], 152.2 [(2/5)1C], 121.1 [(2/5)1CH], 120.9 [(3/5)1CH], 118.8 (1C), 62.01 [(2/5)1CH_2], 61.96 [(3/5)1CH_2], 55.6 [(3/5)1CH], 55.4 [(2/5)1CH], 55.3 [(2/5)1CH], 55.1 [(3/5)1CH], 43.8 (1C), 42.7 ($1CH_2$), 38.1 [(3/5)1CH_2], 37.9 [(2/5)1CH_2], 31.6 [(2/5)1CH], 31.5 [(3/5)1CH], 24.6 ($1CH_2$), 24.54 [(3/5)1CH_2], 24.52 [(2/5)1CH_2], 14.10 [(2/5)1CH_3], 14.07 [(3/5)1CH_3], 12.52 [(2/5)1CH_3], 12.47 [(3/5)1CH_3].

Ethyl (1R,5S,6S)-6-(cyanomethyl)-3-ethylbicyclo[3.2.0]hept-3-ene-6-acetate (**12**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.29–5.27 (m, 1H), 4.12 (qd, *J* = 7.2, 2.3 Hz, 2H), 3.13 (br s, 1H), 2.92–2.86 (m, 1H), 2.82 (s, 2H), 2.51 (d, *J* = 2.3 Hz, 2H), 2.50 (dd, *J* = 16.4, 8.7 1H), 2.17–2.11 (m, 3H), 2.04 (d, *J* = 16.4 Hz, 1H), 1.57 (dd, *J* = 13.0, 7.5 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4 (1C), 150.7 (1C), 121.2 (1CH), 118.7 (1C), 60.4 ($1CH_2$), 54.4 (1CH), 42.2 ($1CH_2$), 41.6 (1C), 38.8 ($1CH_2$), 37.9 ($1CH_2$), 31.0 (1CH), 27.3 ($1CH_2$), 24.4 ($1CH_2$), 14.2 ($1CH_3$), 12.4 ($1CH_3$).

(1R,5S,6S)-6-(Cyanomethyl)-3-ethylbicyclo[3.2.0]hept-3-ene-6-acetic acid (**13**). White solid (mp 84.4–85.4 °C); ^{1}H NMR (CD_3OD-d_4) δ 5.36–5.35 (m, 1H), 3.11 (br s, 1H), 2.95–2.87 (m, 1H), 2.91 (s, 2H), 2.51 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.45 (d, *J* = 4.5 Hz, 2H), 2.17–2.11 (m, 1H), 2.17 (q, *J* = 7.5 Hz, 2H), 2.07 (d, *J* = 16.5 Hz, 1H), 1.57 (dd, *J* = 12.6, 7.5 Hz, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD-d_4) δ 174.8 (1C), 151.6 (1C), 122.7 (1CH), 120.0 (1C), 55.8 (1CH), 43.0 ($1CH_2$), 42.6 (1C), 39.8 ($1CH_2$), 38.9 ($1CH_2$), 32.2 (1CH), 27.5 ($1CH_2$), 25.3 ($1CH_2$), 12.8 ($1CH_3$).

2-[(1R,5S,6R)-6-(Cyanomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]propanedioic acid (**14**) .White solid; ^{1}H NMR ($CDCl_3$) δ 5.38–5.36 (m, 1H), 3.64 (s, 1H), 3.28 (br s, 1H), 3.10 (dd, *J* = 17.0, 0.6 Hz, 1H), 3.04 (d, *J* = 17.0 Hz, 1H), 3.06–3.00 (m, 1H), 2.54 (dd, *J* = 16.6, 8.0 Hz, 1H), 2.31 (ddd, *J* = 12.9, 9.0, 2.3 Hz, 1H), 2.18 (q, *J* = 7.5 Hz, 2H), 2.11 (d, *J* = 16.6 Hz, 1H), 1.73 (dd, *J* = 12.9, 7.5 Hz, 1H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5 (1C), 171.3 (1C), 152.7 (1C), 122.6 (1CH), 120.3 (1C), 57.0 (1CH), 56.5 (1CH), 44.6 (d, *J* = 10.2 Hz, 1C), 43.4 ($1CH_2$), 39.1 (d, *J* = 6.0 Hz, $1CH_2$), 32.7 (1CH), 25.3 ($1CH_2$), 25.0 ($1CH_2$), 12.8 ($1CH_3$).

(1R,5S,6S)-6-(2-Amino-2-oxoethyl)-3-ethylbicyclo[3.2.0]hept-3-ene-6-acetic acid (**8**). White solid (mp 137.8–138.9 °C); ^{1}H NMR (CD_3OD-d_4) δ 5.39–5.38 (m, 1H), 3.16 (br s, 1H), 2.87–2.81 (m, 1H), 2.67 (d, *J* = 14.0 Hz, 1H), 2.63 (d, *J* = 14.0 Hz, 1H), 2.51 (s, 2H), 2.48 (dd, *J* = 16.3, 7.7 Hz, 1H), 2.21 (ddd, *J* = 12.3, 8.8, 2.6 Hz, 1H), 2.15 (q, *J* = 7.5 Hz, 2H), 2.03 (d, *J* = 16.3 Hz, 1H), 1.49 (dd, *J* = 12.3, 7.5 Hz,1H), 1.10 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD-d_4) δ 177.4 (1C), 176.2 (1C), 150.7 (1C), 123.6 (1CH), 56.5 (1CH), 44.1 ($1CH_2$), 43.1 ($1CH_2$+1C), 40.3 ($1CH_2$), 39.5 ($1CH_2$), 32.4 (1CH), 25.4 ($1CH_2$), 12.9 ($1CH_3$).

(1R,5S,6S)-6-(Aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-ene-6-acetic acid (**1** (free form)). White solid (mp 165 °C (decomp.)); ^{1}H NMR (CD_3OD-d_4) δ 5.37–5.35 (m, 1H), 3.17 (d, *J* = 13.2 Hz, 1H), 3.13 (d, *J* = 13.2 Hz, 1H), 3.09 (br s, 1H), 2.87–2.81 (m, 1H), 2.50–2.45 (m, 1H), 2.49 (d, *J* = 16.0 Hz, 1H), 2.45 (d, *J* = 16.0 Hz, 1H), 2.14 (q, *J* = 7.5 Hz, 2H), 2.07–2.02 (m, 2H), 1.46 (dd, *J* = 12.3, 7.5 Hz, 1H), 1.09 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD-d_4) δ 180.3 (1C), 151.0 (1C), 122.8 (1CH), 53.7 (1CH), 48.5 ($1CH_2$), 46.1 ($1CH_2$), 43.3 (1C), 43.0 ($1CH_2$), 37.8 ($1CH_2$), 32.3 (1CH), 25.4 ($1CH_2$), 12.8 ($1CH_3$).

Mirogabalin besylate (**1**). White solid (mp 174 °C (decomp.)); ^{1}H NMR (CD_3OD-d_4) δ 7.85–7.82 (m, 2H), 7.46–7.41 (m, 3H), 5.32 (s, 1H), 3.34 (d, *J* = 13.2 Hz, 1H), 3.29 (d, *J* = 13.2 Hz, 1H), 3.13 (br s, 1H), 2.91–2.84 (m, 1H), 2.52 (dd, *J* = 16.0, 6.9 Hz, 1H), 2.51 (s, 2H), 2.20–2.13 (m, 3H), 2.09 (d, *J* = 16.0 Hz, 1H), 1.50 (dd, *J* = 12.6, 7.5 Hz, 1H), 1.11 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD-d_4) δ 175.5 (1C), 152.1 (1C), 146.3 (1C), 131.3 (1CH), 129.3 (2CH), 126.9 (2CH), 122.0 (1CH), 53.7 (1CH), 47.7 ($1CH_2$), 43.2 ($1CH_2$), 42.9 (1C), 38.5 ($1CH_2$), 37.3 ($1CH_2$), 32.4 (1CH), 25.3 ($1CH_2$), 12.8 ($1CH_3$).

(4E)-3-Oxo-5-phenyl-4-pentenenitrile (**16a**). Off-white solid (mp 99.2–99.6 °C); ^{1}H NMR ($CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.61–7.58 (m, 2H), 7.49–7.42 (m, 3H), 6.88 (d, *J* = 16.0 Hz, 1H), 3.73 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 186.3 (1C), 146.6 (1CH), 133.3 (1C), 131.7 (1CH), 129.2 (2CH), 128.8 (2CH), 122.3 (1CH), 114.0 (1C), 30.8 ($1CH_2$).

1,3-Diethyl 2-(2-cyano-1-phenylethyl)propanedioate (**17b**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.35–7.27 (m, 5H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.99–3.93 (m, 2H), 3.86 (d, *J* = 10.3 Hz, 1H), 3.73 (ddd, *J* = 10.3, 8.2, 4.6 Hz, 1H), 2.92 (dd, *J* = 16.9, 8.2 Hz, 1H), 2.86 (dd, *J* = 16.9, 4.6 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.6 (1C), 166.9 (1C), 137.9 (1C), 128.9 (2CH), 128.2 (1CH), 127.7 (2CH), 117.6 (1C), 62.1 ($1CH_2$), 61.7 ($1CH_2$), 55.9 (1CH), 41.2 (1CH), 22.8 ($1CH_2$), 14.0 ($1CH_3$), 13.7 ($1CH_3$).

Ethyl 3-methyl-2-(2-cyanoacetyl)-2-butenoate (**16c**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 4.29 (q, *J* = 7.2 Hz, 2H), 3.68 (s, 2H), 2.22 (s, 3H), 2.02 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 189.8 (1C), 164.3 (1C), 160.0 (1C), 129.0 (1C), 113.6 (1C), 61.4 ($1CH_2$), 32.6 ($1CH_2$), 24.4 ($1CH_3$), 23.5 ($1CH_3$), 14.1 ($1CH_3$).

1,3-Diethyl 2-(2-cyano-1,1-dimethylethyl)propanedioate (**17c**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 4.21 (q, *J* = 7.2 Hz, 4H), 3.41 (s, 1H), 2.81 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 6H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 167.5 (2C), 118.0 (1C), 61.5 ($2CH_2$), 58.9 (1CH), 35.0 (1C), 27.9 ($1CH_2$), 25.5 ($2CH_3$), 14.0 ($2CH_3$).

1,3-Diethyl 2-(1-methylethenyl)propanedioate (**18c**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.09–5.08 (m, 1H), 4.99 (br s, 1H), 4.27–4.18 (m, 4H), 4.09 (s, 1H), 1.90–1.89 (m, 3H), 1.29 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 167.9 (2C), 137.6 (1C), 117.1 ($1CH_2$), 61.5 ($2CH_2$), 59.4 (1CH), 20.9 ($1CH_3$), 14.0 ($2CH_3$).

1,3-Diethyl 2-(2-cyano-1-methylethyl)propanedioate (**17d**). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 4.26–4.19 (m, 4H), 3.39 (d, *J* = 7.5 Hz, 1H), 2.66–2.53 (m, 3H), 1.288 (t, *J* = 7.2 Hz, 3H), 1.285 (t, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 167.71 (1C), 167.68 (1C), 118.0 (1C), 61.7 ($2CH_2$), 55.5 (1CH), 30.2 (1CH), 22.2 ($1CH_2$), 17.3 ($1CH_3$), 14.00 ($1CH_3$), 13.98 ($1CH_3$).

(4E)-4-Methyl-3-oxo-4-hexenenitrile (**16e**). White solid (mp 49.3–50.0 °C); ^{1}H NMR ($CDCl_3$) δ 6.74 (qq, *J* = 6.9, 1.4 Hz, 1H), 3.80 (s, 2H), 1.94 (dq, *J* = 6.9, 1,4 Hz, 3H), 1.83 (q, *J* = 1.4 Hz, 3H); ^{13}C

NMR ($CDCl_3$) δ 188.1 (1C), 141.4 (1CH), 137.0 (1C), 114.4 (1C), 28.2 ($1CH_2$), 15.1 ($1CH_3$), 11.0 ($1CH_3$).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the Publications website.

General remarks, HPLC conditions, Summary of synthetic route, Knoevenagel condensation, Stereoselective 1,4-addition of lithioacetonitrile, Synthesis of diastereomer for ***epi*-10**, Optimization of decarboxylation, One-pot transformation including decarboxylation, hydrolysis, hydration, Hofmann rearrangement, Salt formation, Investigation of the selectivity of lithioacetonitrile, Competition experiments, Characterization of compounds, References for supporting information, ^1H and ^{13}C NMR spectra of compounds (PDF)

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Author Contributions

H.O. directed this project and designed the experiments. H.O., T.M., and M.S. conducted experiments. H.O. drafted and edited manuscript and supporting information. A.N. supervised. All authors have read and given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

LDA, Lithium diisopropylamide;
LiTMP, Lithium tetramethylpiperidide;
LHMDS, Lithium hexamethyldisilazide;
CPME, Cyclopentyl methyl ether;
MTHP, 4-Methyltetrahydropyran;
MTBE, Methyl *tert*-butyl ether.

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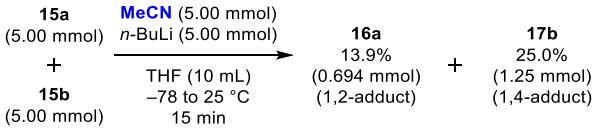
(19) The competition experiment between **15a** and **15b**, showed that 1,4-adduct was obtained in preference to 1,2-adduct (for detail, see Supporting Information S9).



(20) A prior version of this work was deposited as a preprint, see: Ochiai,H.; Taiki, M.; Sasagawa, M.; Nishiyama, A. Stereoselective Synthesis of Mirogabalin via 1,4-Selective Addition of Lithioacetonitrile to Alkylidene Malonate. *ChemRxiv*, Nov 29, 2024, ver. 1. DOI: 10.26434/chemrxiv-2024-vnwg3. https://doi.org/10.26434/chemrxiv-2024-vnwg3