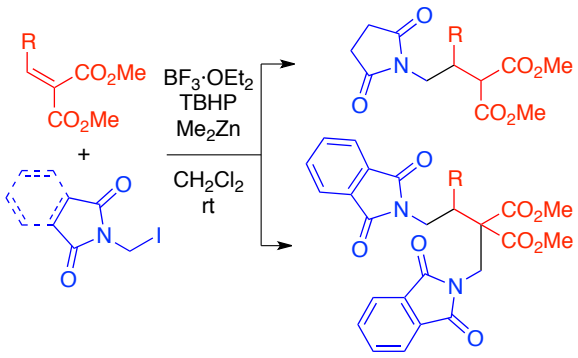
Striking Difference between Succinimidomethyl and Phthalimidomethyl Radicals in Conjugate Addition to Alkylidenemalonate Initiated by Dimethylzinc

Ken-ichi Yamada, Yusuke Matsumoto, Shintaro Fujii, Takehito Konishi, Yousuke Yamaoka, and Kiyosei Takasu*

Graduate School of Pharmaceutical Sciences, Kyoto University

Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

yamak@pharm.kyoto-u.ac.jp

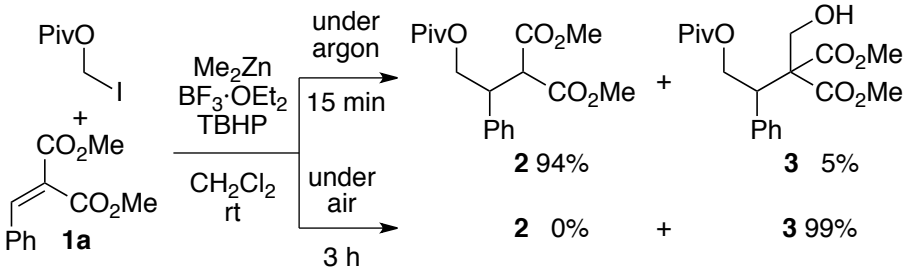


ABSTRACT: We used dimethylzinc to develop a conjugate addition reaction of imidomethyl radicals to alkylidenemalonates using dimethylzinc, in which we observed a significant difference between succinimidomethyl and phthalimidomethyl radicals. This reaction provides new access to γ-aminobutyric acid derivatives, which often function as neurotransmitters.

INTRODUCTION

The utility of conjugate addition in synthetic organic chemistry is well documented.[1,2] We previously reported the dimethylzinc-mediated conjugate addition[3] of α-oxygenated C-centered radicals to α,β-unsaturated imines [4] and alkylidenemalonates. [5] Under argon atmosphere, the reaction of benzylidenemalonate **1a** and iodomethyl pivalate provided conjugate addition product **2** as a main product in 94% yield within 15 min, while a subsequent aldol reaction of the zinc enolate intermediate with formaldehyde, which was generated by the oxidation of a pivaloyloxymethyl radical, occurred to give α-hydroxymethylated adduct **3** in 99% yield after 3 h in the presence of air under ordinary atmosphere (Scheme 1).[5c] As part of our continuing studies, we investigated the conjugate addition of imidomethyl radicals to alkylidenemalonate.[6,7] It was reported that dimethylzinc-mediated conjugate addition of imidomethyl radicals to fumarate was followed by intramolecular addition of the resulting zinc enolate intermediate to the imido carbonyl group.[7a] In contrast, the reaction of alkylidenemalonates proceeded without a subsequent intramolecular reaction and provided γ-aminobutyric acid (GABA) derivatives with a β-substituent, which often function as neurotransmitters.[8] In addition, α,β-bis imidomethylation occurred in good yield when an excess amount of *N*-iodomethylphthalimide was used as a radical source. Herein, we report the β-mono and α,β-bis imidomethylation of alkylidenemalonate using dimethylzinc-mediated conjugate addition,[9] as well as the significant difference among pivaloyloxymethyl, succinimidomethyl, and phthalimidomethyl radicals.

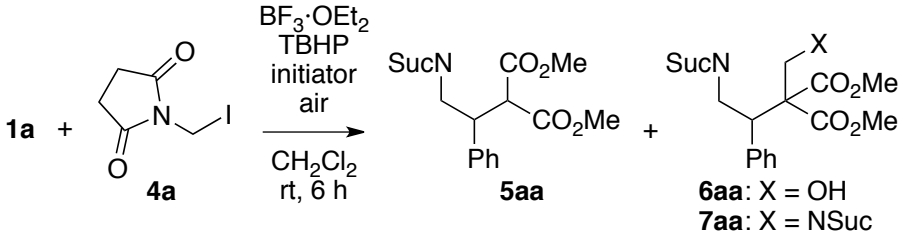
Scheme 1. Previous Work: Me_2Zn-mediated Pivaloyloxymethylation of Alkylidenemalonate.[5c]



RESULTS AND DISCUSSION

The reaction of benzylidenemalonate **1a** and *N*-iodomethylsuccinimide (**4a**) was first conducted under the conditions reported for the reaction of **1a** and iodomethyl pivalate.[5c] *tert*-Butyl hydroperoxide (TBHP) and boron trifluoride diethyl etherate (1.2 equiv each), and then dimethylzinc (3 equiv) were added to a solution of **1a** (1 mmol) and **4a** (3 equiv) in dichloromethane (5 mL), and the mixture was stirred at room temperature under argon atmosphere. The reaction was so sluggish that it failed to complete even after 24 h, giving succinimidomethyl adduct **5aa** in only 18% yield along with α-hydroxymethylated adduct **6aa** (10%), with significant recovery (59%) of **1a** (Table 1, entry 1). A plausible pathway to **6aa** is shown in Scheme 2. The reaction is initiated by the action of dimethylzinc and oxygen or TBHP to generate a methyl radical. The methyl radical abstracts an iodine atom from **4a** to give imidomethyl radical **A**, which undergoes addition to **1a**. The resulting radical intermediate **B** is trapped by dimethylzinc to give zinc enolate **C** and a methyl radical, which restarts the chain reaction. As in the reaction with iodomethyl pivalate,[5c] the formation of **6aa** is attributable to the subsequent aldol reaction of **C** with formaldehyde, which is formed by the action of imidomethyl radical **A** and oxygen that invaded into the reaction flask, via imidomethanolate **D**.[10]

Table 1. Reactions of **1a** with **2a**.[a]

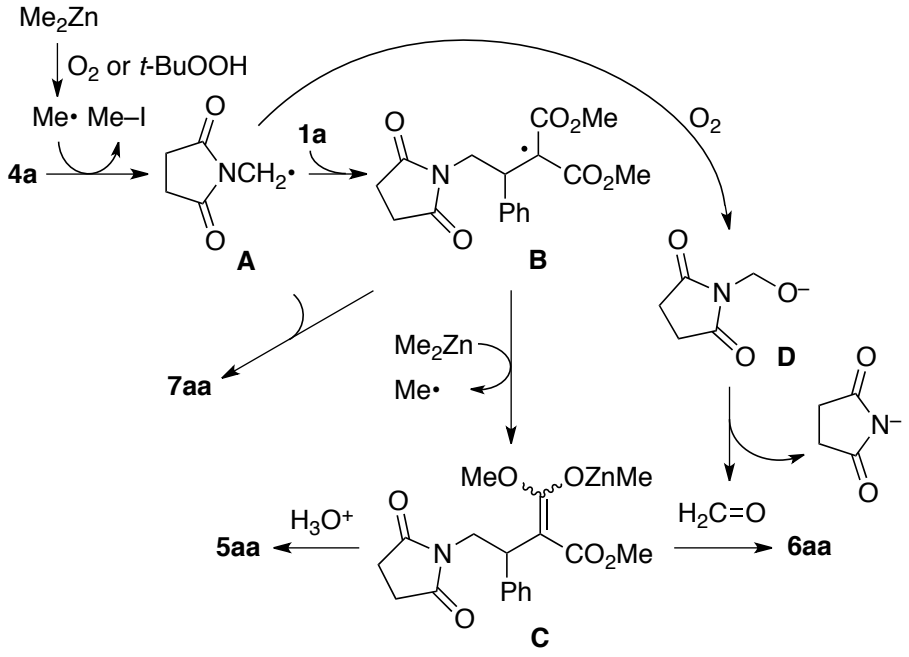


entry	initiator	**5aa** %yield	**6aa** %yield	**7aa** %yield	**1a** %recovery
1[b]	Me_2Zn	18	10	-	59
2	Me_2Zn	51	4	7	24
3	Et_2Zn	49[c]	-	-	34

4	Et_3B	21	-	20	6
5[d]	Me_2Zn	78	4	4	-
6[d,e]	Me_2Zn	92	4	3	-

[a] The reaction was conducted using **1a** (1 mmol) and **2a** (3 equiv) with $BF_3{\cdot}OEt_2$ (1.2 equiv), TBHP (1.2 equiv), and initiator (3 equiv) in CH_2Cl_2 (5 mL) unless otherwise mentioned. Suc = succinoyl [b] Under argon atmosphere for 24 h. [c] Ethyl adduct was produced in 6% yield. [d] TBHP (0.4 equiv) and Me_2Zn (1 equiv) were added every 2 h. [e] The reaction was conducted in CH_2Cl_2 (10 mL).

Scheme 2. Plausible Reaction Pathways.



This slow reaction is in great contrast to the reaction with iodomethyl pivalate, which gave pivaloyloxymethyl adduct **2** in 94% yield within 15 min under the same conditions (Scheme 1). The slow reaction seems to reflect the inferior nucleophilicity of imidomethyl radical **A** to that of the acyloxymethyl radical, and indicates difficulty in the development of its reaction with an electrophilic double bond as we previously experienced in the reaction with imine.[11] To enhance the generation of the methyl radical and increase the concentration of radical **A** in the reaction mixture, the reaction was conducted in the presence of molecular oxygen under ordinary atmosphere. As expected, the reaction

rate increased, but was still slow, and after 6 h, produced **5aa**, **6aa**, and α,β-bis imidomethylated product **7aa** in 51%, 4%, and 7% yield, respectively, with 24% recovery of **1a** (entry 2). The formation of **7aa** was due to the radical–radical coupling between radical intermediate **B** and radical **A** (Scheme 2), and indicates that **A** existed in such a concentration in the reaction mixture, probably due to the low nucleophilicity of the radical, that its reaction with radical intermediate **B** could compete with that of dimethylzinc with **B**. It is noteworthy that only a tiny amount (4%) of **6aa** was produced in the presence of oxygen, while the reaction with iodomethyl pivalate quantitatively gave α-hydroxymethylated product **3** after 3 h under ordinary atmosphere (Scheme 1). This is attributable to the stability of imidomethanolate **D**, an oxidized product of **A** that would supply formaldehyde more slowly than the $PivOCH_2O^-$ formed in the reaction with iodomethyl pivalate because of the inferior leaving-group ability of the succinimide anion compared with the pivalate anion.[12]

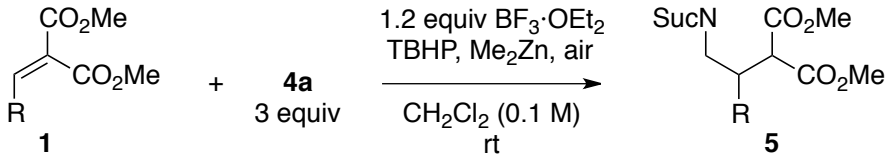
When diethylzinc was used in place of dimethylzinc, **5aa** was produced in almost the same yield (49%) with a small amount (6%) of ethyl adduct (entry 3). The lack of **7aa** production probably reflected a faster trapping of the radical intermediate **B** with diethylzinc to form zinc enolate with liberation of the ethyl radical, which was more stable than the methyl radical. In the reaction with diethylzinc, no **4a** remained in the crude mixture, and instead, a small amount (8% based on utilized **4a**) of *N*-methylsuccinimide was observed, while ca. 40% of **4a** remained unreacted after the reaction with dimethylzinc (entry 2). This is probably because the succinimidomethyl radical underwent not only addition to **1a** but also an S_H2 reaction with diethylzinc to give the succinimidomethylzinc species and ethyl radical, as previously documented.[7a] This probably contributed to reducing the concentration of the succinimidomethyl radical and resulted in suppressed **7aa** production. The reaction with triethylborane gave almost the same amount of **5aa** and **7aa** (21% and 20% yields, respectively) with unidentified byproducts (entry 4). The increased production of **7aa** and byproducts could be attributed to a slower reaction rate between radical intermediate **B** and triethylborane, as previously observed.[5]

Based on TLC monitoring of the reaction with dimethylzinc (entry 2), the reaction proceeded

intensively at the beginning and rapidly became slower, and most of the dimethylzinc seemed to be consumed within 2 h. Therefore, radical initiators, i.e., TBHP and dimethylzinc, were added in three portions (0.4 × 3 and 1 × 3 equiv, respectively) at 2-h intervals. To our delight, **1a** was totally consumed after 6 h, and **5aa**, **6aa**, and **7aa** were obtained in 78%, 4%, and 4% yield, respectively (entry 5). The yield of **5aa** was further improved to 92% when the reaction was conducted in a more diluted condition with 10 mL CH_2Cl_2 (entry 6; Method A).

The scope of Method A was investigated using other alkylidenemalonates (Table 2). The reaction also proceeded with **1b**, bearing an electron-withdrawing group, to give **5ba** in 66% yield (entry 2). With **1c**, bearing an electron-donating group, adduct **5ca** was produced in 85% yield (entry 3). The reaction was slightly retarded with sterically hindered substrate **1d** bearing an *ortho*-tolyl group to provide adduct **5da** in 70% yield with 8% recovery of **1d** (entry 4). The reaction with aliphatic substrate **1e** proceeded smoothly and afforded adduct **5ea** in 84% yield after 2 h (entry 5).

Table 2. Conjugate Addition of Alkylidenemalonates with Method A.[a]

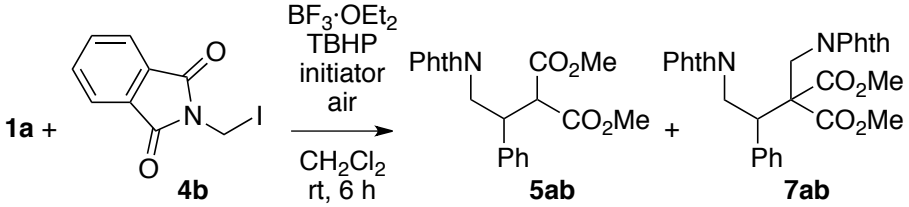


entry	**1**	R	TBHP equiv	Me_2Zn equiv	time h	**5**	% yield
1[b]	**1a**	Ph	1.2	3	6	**5aa**	92
2	**1b**	4-ClC_6H_4	1.6	4	8	**5ba**	66[c]
3	**1c**	4-$MeOC_6H_4$	1.6	4	8	**5ca**	85
4	**1d**	2-MeC_6H_4	1.6	4	8	**5da**	70[d]
5	**1e**	*i*-Bu	0.4	1	2	**5ea**	84

[a] Method A: TBHP (0.4 equiv) and Me_2Zn (1 equiv) were added every 2 h for the indicated reaction time. Suc = succinoyl [b] Data from Table 1, entry 6 for comparison. [c] With 2% recovery of **1d**. [d] With 8% recovery of **1d**.

In contrast to the reaction with **4a**, that with *N*-iodomethylphthalimide (**4b**) was much faster and produced much more bis-imidomethylated product **7ab**. When the reaction was conducted under the conditions shown in Table 1, entry 2 using **4b** in place of **4a**, **1a** was completely consumed within 6 h, and **7ab** was mainly produced in 76% yield along with adduct **5ab** in 14% yield (Table 3, entry 1; Method B). The production of a significant amount (76%) of **7ab** indicates that a high concentration of the phthalimidomethyl radical existed in the reaction mixture. NMR analysis of the crude mixture showed that a much smaller amount (9%) of **4b** than **4a** remained unreacted after this reaction under the same conditions (40% in Table 1, entry 2). These results clearly indicate that the methyl radical should react with **4b** faster than with **4a**, probably because of the higher stability of the phthalimidomethyl radical than of the succinimidomethyl radical. Indeed, the following isodesmic reaction indicated that the phthalimidomethyl radical was more stable by 1.3 kcal/mol than the succinimidomethyl radical at the B3LYP/6-311++G(3df,3pd)//B3LYP/6-31+G* level of theory (Scheme 3).[13] Importantly, this radical–radical cross-coupling occurred highly selectively, and no homo coupling products such as *N*,*N*'-ethylenebisphthalimide were detected by ^{1}H NMR of the crude mixture, suggesting that the phthalimidomethyl radical should be present in a much smaller amount in the reaction mixture than the radical intermediate **B**, the homo coupling of which could be sterically prevented.[14]

Table 3. Reactions of **1a** with **4b**.[a]

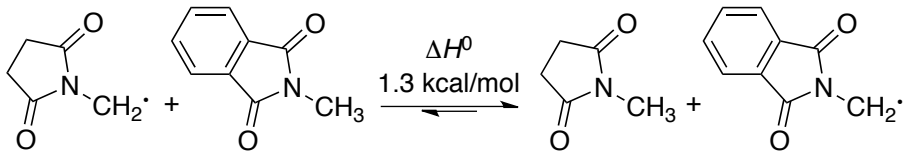


entry	**4b** equiv	initiator	**5ab** % yield	**7ab** % yield	**1a** % recovery
1	3	Me_2Zn	14	76	-

2	3	Et_2Zn	49[b]	4	-
3	3	Et_3B	36	17	12
4	1.2	Me_2Zn	81	9	-
5	1.2	Et_2Zn	23[c]	-	6
6	1.2	Et_3B	34	16	26

[a] The reaction was conducted using **1a** (0.5 mmol) with $BF_3{\cdot}OEt_2$ (1.2 equiv), TBHP (1.2 equiv), and initiator (3 equiv) in CH_2Cl_2 (2.5 mL). Phth = phthaloyl [b] Ethyl adduct was produced in 37% yield. [c] Ethyl adduct was produced in 62% yield.

Scheme 3. Relative Stability of Succinimidomethyl and Phthalimidomethyl Radicals at the B3LYP/6-311++G(3df,3pd)//B3LYP/6-31+G* Level of Theory.

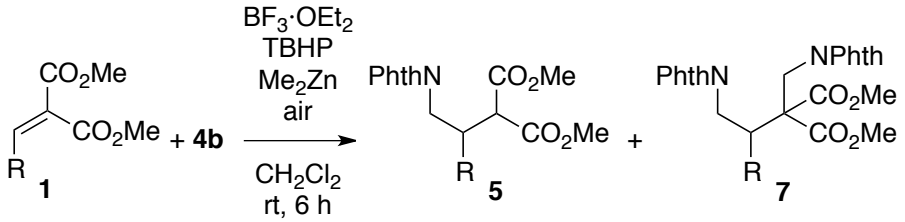


In contrast, the reaction using diethylzinc in place of dimethylzinc gave **5ab** as a major product in 49% yield along with ethyl adduct in 37% yield, and **7ab** was a minor product in 4% yield (Table 3, entry 2). The decreased production of **7ab** was probably due to the higher reactivity of diethylzinc toward the radical intermediate, corresponding to **B**, and toward the phthalimidomethyl radical than that of dimethylzinc to decrease the concentration of these radical species in the reaction mixture and suppress the radical–radical coupling. In this reaction, much more ethyl adduct (37%) was produced than that in the reaction with **4a** (6% in Table 1, entry 4). These results suggest that the phthalimidomethyl radical was less nucleophilic and thus less competitive with the ethyl radical than the succinimidomethyl radical. The use of triethylborane in place of diethylzinc resulted in an increased production of **7ab** (17%) as well as a decreased yield of **5ab** (36%) with 12% recovery of **1a** (Table 3, entry 3). The result is again attributable to the insufficient rate of the reaction between the radical intermediate, corresponding to **B**, and triethylborane.[5]

When the amount of **4b** used was decreased to 1.2 equiv, the reaction mainly provided **5ab** in 81% yield, and **7ab** was produced in only 9% yield (entry 4; Method C). Therefore, the concentration of the imidomethyl radical in the reaction mixture seems highly dependent on the amount of iodide **4** added to the reaction mixture. The use of diethylzinc under this condition produced mainly ethyl adduct in 62% yield with **5ab** in 23% yield, and 6% of **1a** was recovered (entry 5). The reaction with triethylborane gave almost the same results (**5ab** in 36% and 34% yields, and **7ab** in 17% and 16% yields, respectively) in the reactions using 3 and 1.2 equiv of **4b** (entries 3 and 6).

Using Method C or B, mono- or bis-imidomethylation was preferentially achieved with other alkylidenemalonates (Table 4). The reactions of benzylidenemalonate **1b** bearing an electron-withdrawing group with 1.2 or 3 equiv of **4b** proceeded smoothly and mainly gave **5bb** and **7bb** in 83% and 74% yield, respectively (entries 3 and 4). With **1c** bearing an electron-donating group, the product distribution also switched, and **5cb** and **7cb** were obtained in 77% and 70% yield by Methods C and B, respectively (entries 5 and 6). In the reaction with sterically hindered **1d**, the increased amount of **4b** (6 equiv) was required to gain **7db** in good yield (62%), but **5db** was obtained in 61% yield with 1.2 equiv of **4b** (entries 7 and 8). In these reactions, 14% and 10% of **1d** was recovered, respectively. Mono-imidomethylation of aliphatic substrate **1e** with Method C produced **5eb** in 84% yield (entry 9). Interestingly, even with 3 equiv of **4b**, the reaction of **1e** gave mainly **5eb** in 68% yield, and **7eb** was obtained as a minor product in 18% yield (entry 10).

Table 4. Mono- and Bis-imidomethylation of Alkylidenemalonates with Methods C and B.[a]



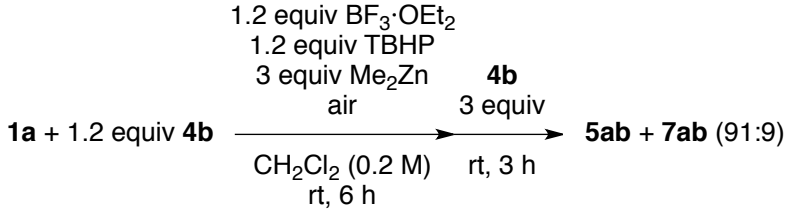
entry	**1**	R	**4b** equiv	**5** % yield	**7** % yield

1[b]	**1a**	Ph	1.2	**5ab**/81	**7ab**/6
2[c]	**1a**	Ph	3	**5ab**/14	**7ab**/76
3[d]	**1b**	4-ClC_6H_4	1.2	**5bb**/83	**7bb**/10
4	**1b**	4-ClC_6H_4	3	**5bb**/22	**7bb**/74
5	**1c**	4-$MeOC_6H_4$	1.2	**5cb**/77	**7cb**/7
6	**1c**	4-$MeOC_6H_4$	3	**5cb**/17	**7cb**/70
7[e]	**1d**	2-MeC_6H_4	1.2	**5db**/61	**7db**/10
8[f]	**1d**	2-MeC_6H_4	6	**5db**/16	**7db**/62
9[d]	**1e**	*i*-Bu	1.2	**5eb**/84	**7eb**/7
10	**1e**	*i*-Bu	3	**5eb**/68	**7eb**/18

[a] The reaction was conducted using **1** (0.5 mmol) with $BF_3{\cdot}OEt_2$ (1.2 equiv), TBHP (1.2 equiv), and Me_2Zn (3 equiv) in CH_2Cl_2 (2.5 mL) unless otherwise mentioned. Phth = phthaloyl [b] Data from Table 3, entry 1 for comparison. [c] Data from Table 3, entry 4 for comparison. [d] With **1** (2 mmol) in CH_2Cl_2 (10 mL). [e] With 14% recovery of **1d**. [f] With 10% recovery of **1d**.

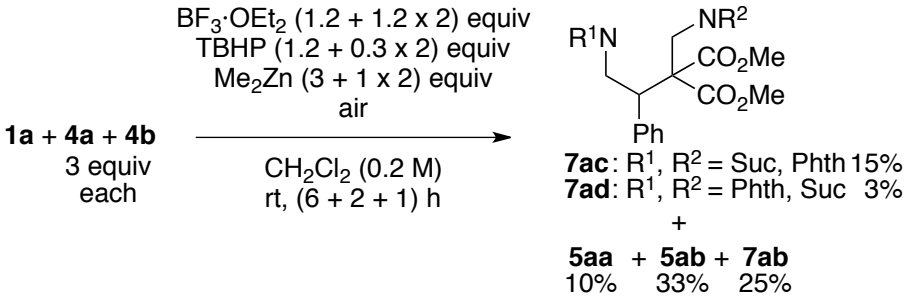
The following experiment excluded the possibility that **7** was formed by an S_N2 reaction of the zinc enolate, such as **C**, with imidomethyl iodide **4**: The reaction of **1a** was conducted under the conditions of Method C for 6 h, and then 3 equiv of **4b** was added to the reaction mixture, in which the zinc enolate intermediate, corresponding to **C**, should have formed as a major product (Scheme 4). After additional stirring for 3 h, the crude product was analyzed by ^1H NMR and was found to contain mono-imidomethyl adduct **5ab** and bis-imidomethylated product **7ab** as a 91:9 mixture. This result clearly indicates that the zinc enolate is not an intermediate to give **7ab**.

Scheme 4. Attempted Reaction of the Zinc Enolate Intermediate with **4b**.



The competition reaction with **4a** and **4b** provided more information about the difference between the succinimidomethyl and phthalimidomethyl radicals. Boron trifluoride diethyl etherate (1.2 equiv), TBHP (1.2 equiv), and dimethylzinc (3 equiv) were added to the mixture of **1a** (0.5 mmol), **4a**, and **4b** (3 equiv each) in dichloromethane (2.5 mL). After 6 and 8 h, additional boron trifluoride diethyl etherate, TBHP, and dimethylzinc (1.2, 0.4, and 1 equiv each) were added to the mixture. After 9 h in total, **1a** was completely consumed, and **5aa**, **5ab**, **7ab**, **7ac**, and **7ad** were produced in 10%, 33%, 25%, 15%, and 3% yield, respectively (Scheme 5). Because most of radicals, including the *tert*-butyl radical, undergo radical–radical coupling at the diffusion-controlled limit,[15] the reactions of a radical intermediate such as **B** with succinimidomethyl and phthalimidomethyl radicals are likely also diffusion-controlled, and thus, the rate constants should be almost the same for both radicals. This means that the product distribution of bis-imidomethylation should be proportional to the concentration of the radical species in the reaction mixture. In the above reaction, although 43% of **1a** was bis-imidomethylated in total, α-phthalimidomethylation mainly occurred, giving **7ab** and **7ac**, and α-succinimidomethylated adduct **7ad** was produced in only 3% yield. This result indicates that the amount of the phthalimidomethyl radical was approximately 10-fold higher than that of the succinimidomethyl radical in the reaction mixture, which is in good agreement with the calculated relative stability of the phthalimidomethyl and succinimidomethyl radicals, corresponding to a ratio of 90:10 at 25 °C (Scheme 3).

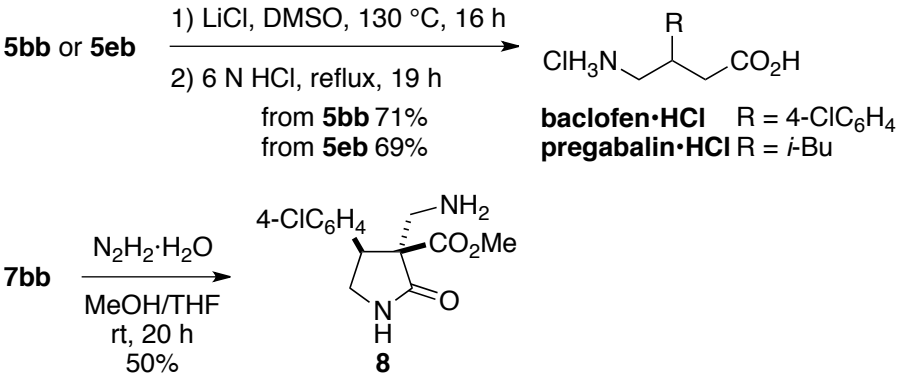
Scheme 5. Competition Experiment between **4a** and **4b** (Phth = phthaloyl, Suc = succinoyl).



The conjugate addition of the succinimidomethyl radical produced **5aa** and **7ac**, while the conjugate addition of the phthalimidomethyl radical led to the formation of **5ab**, **7ab**, or **7ad**. The ratio of the combined yields of **5aa** and **7ac** (25%) to that of **5ab**, **7ab**, and **7ad** (61%) was 3:7 and clearly higher than the relative concentration of these imidomethyl radicals (approximately 1:10, *vide supra*). Therefore, the succinimidomethyl radical seems to have undergone addition to **1a** approximately four times faster than the phthalimidomethyl radical, indicating higher nucleophilicity of the succinimidomethyl radical. The observed lower nucleophilicity of the phthalimidomethyl radical suggests that its higher stability is due to the electron-withdrawing ability of the benzene ring, which delocalizes the spin density of the radical. Actually, the DFT calculations indicated lower spin density at the reaction center of the phthlimidomethyl radical than that of the succinimidomethyl radical (0.833 and 0.858 at the B3LYP/6-311++G(3df,3pd)//B3LYP/6-31+G* level of theory, respectively).[13] It is interesting that **4a** was a superior imidomethyl radical source than **4b** in the addition reaction with *N*-Boc imine to give the corresponding adduct in better yield.[11c] This could be attributable to the inferior electrophilicity of the imine[16] in the reaction in which the nucleophilicity of the radical could be a more important factor than its concentration.

Adducts **5bb** and **5eb** were readily converted into GABA analogs for medical use (Scheme 6). Decarboxylation and subsequent hydrolysis of **5bb** and **5eb** provided baclofen hydrochloride (R = 4-ClC_6H_4)[8a] and pregabalin hydrochloride (R = *i*-Bu)[8b] in 71% and 69% yield in 2 steps, respectively. The treatment of bis-imidomethylated product **7bb** with N_2H_4•H_2O afforded α-aminomethyl γ-lactam **8** in 50% yield as a sole diastereomer.

Scheme 6. Conversion of **5bb** and **5eb** into GABA Analogs, and **7bb** into γ-Lactam **8**



CONCLUSION

We developed a mono- and bis-imidomethylation reaction of alkylidenemalonate with dimethylzinc-mediated conjugate addition of imidomethyl radicals. The nucleophilicity of the phthalimidomethyl radical was inferior to that of the succinimidomethyl radical, but exhibited better performance in the conjugate addition because of its higher concentration in the reaction mixture as a result of its superior stability. This is a striking contrast to the reaction of imine, in which the nucleophilicity of the radicals was a dominant factor, and the addition of the succinimidomethyl radical proceeded more smoothly. Importantly, bis-imidomethylation occurred via highly selective radical–radical cross-coupling, probably due to the steric protection of the adduct radical intermediate toward the self-coupling. This provides a rare example of a highly selective and efficient radical–radical cross-coupling reaction. Facile conversion of the products into clinically useful GABA analogs highlights the utility of this reaction.

EXPERIMENTAL SECTION

General. All melting points were measured after recrystallization from hexane–EtOAc and are reported without correction. Silica gel was used for column chromatography. NMR (500 and 125 MHz for ^{1}H and ^{13}C, respectively) was measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts (δ)

and coupling constants (*J*) are presented in parts per million relative to tetramethylsilane and hertz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.^{13}C peak multiplicity assignments were made on the basis of DEPT data. IR spectroscopy was recorded using an attenuated total reflectance FTIR unless otherwise noted, and the wave numbers of maximum absorption peaks are reported in cm^{-1}. Quadrupole, double-focusing magnetic sector, and TOF mass spectrometers were used for EI-, FAB-, and HRMS-ESI, respectively. Solvents, including anhydrous dichloromethane and THF, hexane solutions of dimethylzinc, diethylzinc and triethylborane, were purchased and used as received.

Starting Materials. Alkylidenemalonates **1a** and **1c**,[17] **1b**,[18] **1d**,[19] and **1e**;[20] iodides **4a** and **4b**[11c] were prepared according to literature procedures.

Method A (Table 2, entry 1). Dimethyl 2-(1-Phenyl-2-succinimidoethyl)malonate (5aa), Dimethyl 2-Hydroxymethyl-2-(1-phenyl-2-succinimidoethyl)malonate (6aa), Dimethyl 2-(1-Phenyl-2-succinimidoethyl)-2-succinimidomethylmalonate (7aa): A magnetic stir bar and **1a** (220 mg, 1.00 mmol) were placed in a dried 20 mL two-neck round-bottom flask that was capped with an argon balloon. To the flask, were added CH_2Cl_2 (10 mL), **4a** (0.72 mg, 3.0 mmol), and a 6.6 M decane solution of TBHP (60 μL, 0.40 mmol) at rt. To the stirred solution cooled in an ice–water bath, were added $BF_3{\cdot}OEt_2$ (0.16 mL, 1.2 mmol), and a 1.0 M hexane solution of Me_2Zn (1.0 mL, 1.0 mmol). The argon balloon was replaced with a NaOH drying tube, and the cooling bath was removed. The solution of TBHP (60 μL, 0.40 mmol each) and the solution of Me_2Zn (1.0 mL, 1.0 mmol each) were added to the mixture every two hours. After addition of 3.0 mmol Me_2Zn in total, the mixture was stirred for further 2 h, and the reaction was quenched by the addition of aq saturated NH_4Cl. The whole was extracted three times with EtOAc, and the combined organic layers were washed with sat. $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then evaporated. The purification of the resulting residue by column chromatography (hexane/EtOAc 9:1 to 1:1) gave **5aa** (306 mg, 92%) as a colorless solid of mp 70–71 °C, **6aa** (13 mg, 4%) as a white solid of mp 111–112 °C, and **7aa** (12 mg, 3%) as a white solid of

mp 230–231 °C.

5aa: ^{1}H NMR: 2.47–2.52 (m, 4H), 3.43 (s, 3H), 3.78 (s, 3H), 3.81 (dd, *J* = 13.5, 7.0, 1H), 3.85 (d, *J* = 10.5, 1H), 3.90 (dd, *J* = 13.5, 8.5, 1H), 4.00 (ddd, *J* = 10.5, 8.5, 7.0, 1H), 7.18–7.30 (m, 5H). ^{13}C NMR 27.9 (CH_2), 41.9 (CH_2), 42.4 (CH), 52.4 (CH_3), 52.8 (CH_3), 56.2 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 137.4 (C), 167.6 (C), 168.3 (C), 176.8 (C). IR: 3020, 1736, 1701, 1435, 1404, 1215, 1165, 752. ESIMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{20}NO_6$, 334.1285; found, 334.1285.

6aa: ^{1}H NMR: 2.35–2.50 (m, 4H), 2.58 (br s, 1H), 3.78 (dd, *J* = 13.5, 4.5, 1H), 3.78-3.82 (br m, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 3.94 (dd, *J* = 11.0, 4.5, 1H), 4.60 (dd, *J* = 13.5, 11.0, 1H), 7.14–7.16 (m, 2H), 7.23-7.25 (m, 3H). ^{13}C NMR: 27.8 (CH_2), 40.4 (CH_2), 45.7 (CH), 52.7 (CH_3), 52.9 (CH_3), 63.0 (C), 65.8 (CH_2), 128.1 (CH), 128.4 (CH), 129.3 (CH), 135.5 (C), 170.0 (C), 170.4 (C), 176.7 (C). IR: 3017, 1732, 1701, 1404, 1215, 1169, 760. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{18}H_{22}NO_7$, 364.1391; found, 364.1389.

7aa: ^{1}H NMR: 2.28–2.43 (m, 4H), 2.69 (s, 4H), 3.775 (s, 3H), 3.783 (s, 3H), 3.86 (d, *J* = 14.5, 1H), 3.88 (dd, *J* = 13.0, 4.5, 1H), 3.98 (dd, *J* = 11.5, 4.5, 1H), 4.18 (d, *J* = 14.5, 1H), 4.44 (dd, *J* = 13.0, 11.5, 1H), 7.20–7.24 (m, 5H). ^{13}C NMR: 27.7 (CH_2), 28.0 (CH_2), 40.3 (CH_2), 41.7 (CH_2), 45.6 (CH), 52.7 (CH_3), 53.1 (CH_3), 59.9 (C), 128.08 (CH), 128.11 (CH), 130.0 (CH), 135.2 (C), 168.96 (C), 169.04 (C), 176.5 (C), 176.9 (C). IR: 3017, 1732, 1705, 1400, 1215, 1165, 760. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_8$, 445.1605; found, 445.1606.

Dimethyl 2-(1-(4-Chlorophenyl)-2-succinimidoethyl)malonate (5ba): Method A, using **1b** (255 mg, 1.00 mmol) in place of **1a**, gave **5ba** (243 mg, 66%) as a colorless solid of mp 147–148 °C: ^{1}H NMR: 2.52 (s, 4H), 3.47 (s, 3H), 3.75–3.80 (m, 2H), 3.77 (s, 3H), 3.90 (dd, *J* = 13.5, 8.5, 1H), 4.00 (ddd, *J* = 10.5, 8.5, 7.5, 1H), 7.15 (d, *J* = 8.5, 2H), 7.24 (d, *J* = 8.5, 2H). ^{13}C NMR: 27.9 (CH_2), 41.6 (CH_2), 41.9 (CH), 52.6 (CH_3), 52.9 (CH_3), 56.0 (CH), 128.7 (CH), 129.8 (CH), 133.6 (C), 136.0 (C), 167.4 (C), 168.0 (C), 176.7 (C). IR: 3021, 1736, 1701, 1404, 1215, 1161, 752. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{19}ClNO_6$, 368.0895; found, 368.0895.

Dimethyl 2-(1-(4-Methoxyphenyl)-2-succinimidoethyl)malonate (5ca): Method A, using **1c** (250 mg, 1.00 mmol) in place of **1a**, gave **5ca** (308 mg, 85%) as a colorless solid of mp 105–106 °C: ^{1}H NMR: 2.50 (s, 4H), 3.45 (s, 3H), 3.76–3.80 (m, 2H), 3.77 (s, 6H), 3.88 (dd, *J* = 13.5, 8.5, 1H), 3.96 (ddd, *J* = 10.5, 8.5, 7.5, 1H), 6.79 (d, *J* = 8.5, 2H), 7.11 (d, *J* = 8.5, 2H). ^{13}C NMR: 27.9 (CH_2), 41.7 (CH), 41.9 (CH_2), 52.4 (CH_3), 52.8 (CH_3), 55.1 (CH_3), 56.4 (CH), 113.8 (CH), 129.2 (C), 129.4 (CH), 158.9 (C), 167.6 (C), 168.3 (C), 176.8 (C). IR: 3021, 1736, 1701, 1516, 1404, 1215, 1165, 752. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{22}NO_7$, 364.1391; found, 364.1390.

Dimethyl 2-(2-Succinimido-1-*o*-tolylethyl)malonate (5da): Method A, using **1d** (234 mg, 1.00 mmol) in place of **1a**, gave **5da** (244 mg, 70%) as a colorless solid of mp 105–106 °C: ^{1}H NMR: 2.41 (s, 3H), 2.56 (s, 4H), 3.37 (s, 3H), 3.72–3.79 (m, 1H), 3.76 (s, 3H), 3.82, (dd, *J* = 13.5, 8.0, 1H), 3.94 (d, *J* = 10.5, 1H), 4.28 (m, 1H), 7.12–7.14 (m, 4H). ^{13}C NMR: 19.5 (CH_3), 27.9 (CH_2), 37.3 (CH), 42.0 (CH_2), 52.3 (CH_3), 52.8 (CH_3), 56.3 (CH), 125.9 (CH), 126.6 (CH), 127.3 (CH), 130.6 (CH), 136.1 (C), 137.0 (C), 167.7 (C), 168.6 (C), 177.0 (C). IR: 3021, 1732, 1701, 1404, 1215, 1165, 818, 752. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{22}NO_6$, 348.1442; found, 348.1441.

Dimethyl 2-(3-Methyl-1-(succinimidomethyl)butyl)malonate (5ea): Method A, using **1e** (200 mg, 1.00 mmol) in place of **1a**, gave **5ea** (263 mg, 84%) as a colorless solid of mp 70–71 °C: ^{1}H NMR: 0.89 (d, *J* = 6.5, 3H), 0.91 (d, *J* = 6.5, 3H), 1.14 (ddd, *J* = 14.0, 8.5, 4.5, 1H), 1.35 (ddd, *J* = 14.0, 9.0, 5.5, 1H), 1.71 (m, 1H), 2.51 (ddtd, *J* = 8.5, 7.0, 5.5, 5.0, 1H), 2.69 (d, *J* = 9.5, 2H), 2.71 (d, *J* = 9.5, 2H), 3.42 (d, *J* = 5.5, 1H), 3.64 (dd, *J* = 14.0, 5.0, 1H), 3.69 (dd, *J* = 14.0, 7.0, 1H), 3.74 (s, 3H), 3.76 (s, 3H). ^{13}C NMR: 21.8 (CH_3), 23.1 (CH_3), 25.5 (CH), 28.1 (CH_2), 35.3 (CH), 39.0 (CH_2), 40.5 (CH_2), 52.41 (CH_3), 52.43 (CH_3), 53.7 (CH), 168.8 (C), 168.9 (C), 177.5 (C). IR: 2955, 1732, 1701, 1404, 1215, 1172, 763. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{24}NO_6$, 314.1598; found, 314.1599.

Method C (Table 4, entry 1). Dimethyl 2-(1-Phenyl-2-phthalimidoethyl)malonate (5ab): A magnetic stir bar and **1a** (110 mg, 0.500 mmol) were placed in a dried 10 mL two-neck round-bottom flask that was capped with an argon balloon. To the flask, were added CH_2Cl_2 (2.5 mL), **4b** (0.17 g, 0.60

mmol), and a 5.8 M decane solution of TBHP (0.10 mL, 0.60 mmol) at rt. To the stirred solution cooled in an ice–water bath, were added $BF_3{\cdot}OEt_2$ (80 μL, 0.60 mmol) and a 1.0 M hexane solution of Me_2Zn (1.5 mL, 1.5 mmol). The argon balloon was replaced with a NaOH drying tube, and the cooling bath was removed. After 6 h, the reaction was quenched by the addition of aq saturated NH_4Cl, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with aq saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then evaporated. The purification of the residue by column chromatography (hexane/EtOAc 9:1 to 1:1) gave **5ab** (157 mg including 3 mg of unidentified phthalimide derivatives), which was characterized after further purification by preparative TLC to give a colorless solid of mp 109–110 °C: ^{1}H NMR: 3.44 (s, 3H), 3.69 (s, 3H), 3.89 (d, *J* = 10.0, 1H), 4.00 (m, 1H), 4.06–4.12 (m, 2H), 7.16–7.23 (m, 5H), 7.66 (dd, *J* = 5.5, 3.0, 2H), 7.76 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 41.3 (CH_2), 43.6 (CH), 52.4 (CH_3), 52.8 (CH_3), 56.0 (CH), 123.2 (CH), 127.6 (CH), 128.35 (CH), 128.44 (CH), 131.7 (C), 133.9 (CH), 137.5 (C), 167.6 (C), 167.9 (C), 168.2 (C). IR: 3021, 1736, 1712, 1396, 1215, 752. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{20}NO_6$, 382.1285; found, 382.1280. The yields (**5ab**: 81%, **7ab**: 6%) were determined by ^{1}H NMR on the basis of the integration area of the signals at 3.44 and 3.81 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard

Dimethyl 2-(1-(4-Chlorophenyl)-2-Phthalimidoethyl)malonate (5bb): Method C, using **1b** (509 mg, 2.00 mmol) in place of **1a** in CH_2Cl_2 (10 mL) with **4b** (0.69 g, 2.4 mmol), the solution of TBHP (0.40 mL, 2.4 mmol), $BF_3{\cdot}OEt_2$ (0.32 mL, 2.4 mmol), and the solution of Me_2Zn (6.0 mL, 6.0 mmol), gave **5bb** (688 mg, 83%) as a colorless oil: ^{1}H NMR: 3.49 (s, 3H), 3.71 (s, 3H), 3.83 (d, *J* = 10.0, 1H), 3.96 (m, 1H), 4.05–4.12 (m, 2H), 7.18 (d, *J* = 9.0, 2H), 7.20 (d, *J* = 9.0, 2H), 7.68 (dd, *J* = 5.5, 3.0, 2H), 7.77 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 41.0 (CH_2), 43.0 (CH), 52.6 (CH_3), 52.9 (CH_3), 55.9 (CH), 123.3 (CH), 128.7 (CH), 129.8 (CH), 131.6 (C), 133.5 (C), 134.0 (CH), 151.6 (C), 167.4 (C), 167.8 (C), 168.0 (C). IR (neat): 2954, 1735, 1716, 1435, 1396, 721. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{19}ClNO_6$, 416.0895; found, 416.0897. The yield of **7bb** (10%) was determined by ^{1}H NMR of the crude mixture on the basis of the integration area of the signal at 3.49 ppm, using Ph_3CH (5.55 ppm) as an internal

standard.

Dimethyl 2-(1-(4-Methoxyphenyl)-2-phthalimidoethyl)malonate (5cb): Method C, using **1c** (125 mg, 0.500 mmol) in place of **1a**, gave **5cb** (167 mg including 9 mg of unidentified phthalimide derivatives), which was characterized after further purification by preparative TLC: a colorless oil. ^{1}H NMR: 3.47 (s, 3H), 3.69 (s, 3H), 3.73 (s, 3H), 3.83 (d, *J* = 10.0, 1H), 3.96 (m, 1H), 4.02–4.10 (m, 2H), 6.75 (d, *J* = 8.5, 2H), 7.15 (d, *J* = 8.5, 2H), 7.66 (dd, *J* = 5.5, 3.0, 2H), 7.76 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 41.3 (CH_2), 42.8 (CH), 52.4 (CH_3), 52.7 (CH_3), 55.1 (CH_3), 56.3 (CH), 113.8 (CH), 123.2 (CH), 129.35 (C), 129.44 (CH), 131.7 (C), 133.9 (CH), 158.8 (C), 167.7 (C), 167.9 (C), 168.3 (C). IR (neat): 2954, 1736, 1713, 1516, 1250, 725. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{22}NO_7$, 412.1391; found, 412.1394. The yields (**5cb**: 77%, **7cb**: 7%) were determined by ^{1}H NMR on the basis of the integration area of the signals at 3.47 and 3.71 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Dimethyl 2-(2-Phthalimido-1-*o*-tolylethyl)malonate (5db): Method C, using **1d** (117 mg, 0.500 mmol) in place of **1a**, gave **5db** (135 mg including 15 mg of unidentified phthalimide derivatives), which was characterized after further purification by preparative TLC to give a colorless oil: ^{1}H NMR: 2.42 (s, 3H), 3.39 (s, 3H), 3.62 (s, 3H), 3.93–4.02 (m, 3H), 4.41 (dt, *J* = 10.5, 7.0, 1H), 7.05–7.14 (m, 3H), 7.20 (d, *J* = 7.5, 1H), 7.68 (dd, *J* = 5.5, 3.0, 2H), 7.79 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 19.6 (CH_3), 41.2 (CH_2), 52.4 (CH_3), 52.7 (CH_3), 56.0 (CH), 123.2 (CH), 126.0 (CH), 127.3 (CH), 130.6 (CH), 131.8 (C), 133.9 (CH), 136.2 (C), 137.1 (C), 167.8 (C), 168.0 (C), 168.4 (C). IR (neat): 2990, 1736, 1713, 1215, 903, 756, 725. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{22}NO_6$, 396.1442; found, 396.1441. The yields (**5db**: 61%, **7db**: 10%) were determined by ^{1}H NMR on the basis of the integration area of the signals at 3.39 and 3.77 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Dimethyl 2-(3-Methyl-1-(phthalimidomethyl)butyl)malonate (5eb): Method C, using **1e** (400 mg, 2.00 mmol) in place of **1a** in CH_2Cl_2 (10 mL) with **4b** (0.69 g, 2.4 mmol), the solution of TBHP (0.40 mL, 2.4 mmol), $BF_3{\cdot}OEt_2$ (0.32 mL, 2.4 mmol), and the solution of Me_2Zn (6.0 mL, 6.0 mmol), gave **5eb** (607 mg, 84%) as a colorless oil: ^{1}H NMR: 0.90 (d, *J* = 6.5, 3H), 0.93 (d, *J* = 6.5, 3H), 1.19 (ddd, *J*

= 14.5, 8.5, 4.5, 1H), 1.42 (ddd, *J* = 14.5, 8.5, 5.5, 1H), 1.77 (m, 1H), 2.63 (ddddd, *J* = 8.5, 7.0, 6.0, 5.5, 4.5, 1H), 3.49 (d, *J* = 6.0, 1H), 3.71 (s, 3H), 3.76 (s, 3H), 3.83 (dd, *J* = 14.0, 5.5, 1H), 3.87 (dd, *J* = 14.0, 7.0, 1H), 7.73 (dd, *J* = 5.5, 3.0, 2H), 7.85 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 21.9 (CH_3), 23.1 (CH_3), 25.6 (CH), 36.2 (CH), 38.8 (CH_2), 39.7 (CH_2), 52.4 (CH_3), 53.4 (CH), 123.3 (CH), 131.9 (C), 134.0 (CH), 168.6 (C), 168.9 (C), 169.0 (C). IR (KBr): 2954, 1713, 1435, 1396, 1157, 725. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{24}NO_6$, 362.1598; found, 362.1598. The yield of **7eb** (7%) was determined by ^{1}H NMR of the crude mixture on the basis of the integration area of the signal at 4.47 ppm, using Ph_3CH (5.55 ppm) as an internal standard.

Method B (Table 4, entry 2). Dimethyl 2-(1-Phenyl-2-phthalimidoethyl)-2-phthalimidomethylmalonate (5ab). A magnetic stir bar and **1a** (110 mg, 0.500 mmol) were placed in a dried 10 mL two-neck round-bottom flask that was capped with an argon balloon. To the flask, were added CH_2Cl_2 (2.5 mL), **4b** (0.43 g, 1.5 mmol), and a 5.8 M decane solution of TBHP (0.10 mL, 0.60 mmol) at rt. To the stirred solution cooled in an ice–water bath, were added $BF_3{\cdot}OEt_2$ (80 μL, 0.60 mmol) and a 1.0 M hexane solution of $M_{e2}Zn$ (1.5 mL, 1.5 mmol). The argon balloon was replaced with a NaOH drying tube, and the cooling bath was removed. After 6 h, the reaction was quenched by the addition of aq saturated NH_4Cl, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with aq saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then evaporated. The purification of the residue by column chromatography (hexane/EtOAc 9:1 to 1:1) gave **7ab** (625 mg including 417 mg of unidentified phthalimide derivatives), which was characterized after further purification by preparative TLC to give a white solid of mp 174–175 °C: ^{1}H NMR: 3.81 (s, 3H), 3.84 (s, 3H), 4.03 (d, *J* = 14.5, 1H), 4.12–4.19 (m, 2H), 4.32 (d, *J* = 14.5, 1H), 4.63 (m, 1H), 7.17–7.30 (m, 5H), 7.60 (dd, *J* = 5.5, 3.0, 2H), 7.68 (dd, *J* = 5.5, 3.0, 2H), 7.71 (dd, *J* = 5.5, 3.0, 2H), 7.83 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 40.2 (CH_2), 41.4 (CH_2), 47.2 (CH), 52.7 (CH_3), 53.1 (CH_3), 60.6 (C), 123.0 (CH), 123.4 (CH), 128.1 (CH), 128.2 (CH), 129.9 (CH), 131.6 (C), 131.8 (C), 133.7 (CH), 134.0 (CH), 135.3 (C), 167.7 (C), 167.9 (C), 169.1 (C), 169.2 (C). IR: 3021, 1775, 1717, 1396, 1215, 752. HRMS-ESI (*m/z*):

$[M + H]^+$ calcd for $C_{30}H_{25}N_2O_8$, 541.1605; found, 541.1605. The yields (**5ab**: 14%, **7ab**: 76%) were determined by ^1H NMR on the basis of the integration area of the signals at 3.44 and 3.81 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Dimethyl 2-(1-(4-Chlorophenyl)-2-phthalimidoethyl)-2-phthalimidomethylmalonate (7bb): Method B, using **1b** (127 mg, 0.500 mmol) in place of **1a**, gave **7bb** as (521 mg including 308 mg of unidentified phthalimide derivatives, 74%), which was characterized after further purification by preparative TLC to give a colorless solids of mp 84–85 °C: ^1H NMR: 3.80 (s, 3H), 3.83 (s, 3H), 4.02 (d, J = 14.5, 1H), 4.14 (dd, J = 13.5, 4.0, 1H), 4.19 (dd, J = 11.5, 4.0, 1H), 4.35 (d, J = 14.5, 1H), 4.61 (dd, J = 13.5, 11.5, 1H), 7.17 (d, J = 8.5, 2H), 7.29 (d, J = 8.5, 2H), 7.63 (dd, J = 5.5, 3.0, 2H), 7.69 (dd, J = 5.5, 3.0, 2H), 7.73 (dd, J = 5.5, 3.0, 2H), 7.85 (dd, J = 5.5, 3.0, 2H). ^{13}C NMR: 39.8 (CH_2), 41.1 (CH_2), 46.3 (CH), 52.8 (CH_3), 53.2 (CH_3), 60.6 (C), 123.1 (CH), 123.5 (CH), 128.4 (CH), 131.46 (CH), 131.54 (C), 131.8 (C), 133.8 (CH), 133.9 (C), 134.0 (C), 134.2 (CH), 167.7 (C), 168.0 (C), 168.9 (C × 2). IR: 3021, 1775, 1717, 1396, 1215, 748. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{30}H_{24}ClN_2O_8$, 575.1216; found, 575.1221. The yields (**5bb**: 22%, **7bb**: 74%) were determined by quantitative ^1H NMR on the basis of the integration area of the signals at 3.49 and 3.80 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Dimethyl 2-(1-(4-Methoxyphenyl)-2-phthalimidoethyl)-2-phthalimidomethylmalonate (7cb): Method C, using **1c** (125 mg, 0.500 mmol) in place of **1a**, gave **7cb** (321 mg including 121 mg of unidentified phthalimide derivatives), which was characterized after further purification by preparative TLC to give a white solids of mp 166–167 °C. Method C using **1c** (125 mg, 0.500 mmol) in place of **1a**, gave **7cb** (321 mg including 121 mg of unidentified phthalimide derivatives), which was characterized after further purification by preparative TLC to give a white solids of mp 166–167 °C: ^1H NMR: 3.71 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.01 (d, J = 14.5, 1H), 4.10 (dd, J = 13.5, 4.0, 1H), 4.15 (dd, J = 11.0, 4.0, 1H), 4.32 (d, J = 14.5, 1H), 4.62 (dd, J = 13.5, 11.0, 1H), 6.73 (d, J = 9.0, 2H), 7.22 (d, J = 9.0, 2H), 7.61 (dd, J = 5.5, 3.0, 2H), 7.69 (dd, J = 5.5, 3.0, 2H), 7.72 (dd, J = 5.5, 3.0, 2H), 7.84 (dd, J = 5.5, 3.0,

2H). ^{13}C NMR: 40.0 (CH_2), 41.3 (CH_2), 46.3 (CH), 52.6 (CH_3), 53.1 (CH_3), 55.0 (CH_3), 60.7 (C), 113.6 (CH), 123.0 (CH), 123.4 (CH), 126.9 (C), 131.0 (CH), 131.7 (C), 131.8 (C), 133.6 (CH), 134.0 (CH), 159.1 (C), 167.8 (C), 168.0 (C), 169.1 (C), 169.2 (C). IR: 3021, 1721, 1501, 1215, 745. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_9$, 571.1711; found, 571.1716. The yields (**5cb**: 17%, **7cb**: 70%) were determined by ^{1}H NMR on the basis of the integration area of the signals at 3.47 and 3.71 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Dimethyl 2-(2-Phthalimido-1-*o*-tolylethyl)-2-phthalimidomethylmalonate (7db): Method C, using **1d** (117 mg, 0.500 mmol) and **4b** (0.86 g, 3.0 mmol) in place of **1a** and **4b** (1.5 mmol), gave **7db** (239 mg including 68 mg of unidentified phthalimide derivatives, 62%), which was characterized after further purification by preparative TLC to give a colorless solid of mp 214–215 °C: ^{1}H NMR: 2.15 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 4.07 (d, *J* = 14.5, 1H), 4.15 (dd, *J* = 13.5, 3.5, 1H), 4.23 (d, *J* = 14.5, 1H), 4.47 (dd, *J* = 11.0, 3.5, 1H), 4.55 (dd, *J* = 13.5, 11.0, 1H), 6.95 (d, *J* = 7.5, 1H), 7.08 (t, *J* = 7.5, 1H), 7.21 (t, *J* = 7.5, 1H), 7.35 (d, *J* = 7.5, 1H), 7.63 (dd, *J* = 5.5, 3.0, 2H), 7.69 (dd, *J* = 5.5, 3.0, 2H), 7.71 (dd, *J* = 5.5, 3.0, 2H), 7.81 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 20.1 (CH_3), 41.0 (CH_2), 41.4 (CH_2), 42.1 (CH), 52.6 (CH_3), 53.2 (CH_3), 61.0 (C), 123.1 (CH), 123.3 (CH), 126.5 (CH), 127.7 (CH), 128.2 (CH), 130.5 (CH), 131.7 (C), 131.9 (C), 133.8 (CH), 134.0 (CH), 134.4 (C), 137.7 (C), 167.8 (C × 2), 169.1 (C), 169.7 (C). IR: 2955, 1717, 1396, 1246, 910, 725. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_8$, 555.1762; found, 555.1763. The yields (**5db**: 16%, **7db**: 62%) were determined by ^{1}H NMR on the basis of the integration area of the signals at 3.39 and 3.77 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Dimethyl 2-(3-Methyl-1-phthalimidomethylbutyl)-2-phthalimidomethylmalonate (7eb): Method C, using **1e** (117 mg, 0.500 mmol) in place of **1a**, gave **7eb** (256 mg including 209 mg of unidentified phthalimide derivatives, 18%), which was characterized after further purification by preparative TLC to give a colorless oil: ^{1}H NMR: 0.81 (d, *J* = 6.5, 3H), 0.86 (d, *J* = 6.5, 3H), 1.34 (ddd, *J* = 14.0, 9.5, 2.0, 1H), 1.54 (ddd, *J* = 14.0, 9.0, 4.5, 1H), 1.63 (m, 1 H), 2.65 (dddd, *J* = 9.0, 7.0, 5.5, 2.0, 1H), 3.69 (s, 3H),

3.70 (s, 3H), 4.04 (dd, J = 14.5, 5.5, 1H), 4.08 (dd, J = 14.5, 7.0, 1H), 4.43 (d, J = 14.5, 1H), 4.52 (d, J = 14.5, 1H), 7.719 (dd, J = 5.5, 3.0, 2H), 7.724 (dd, J = 5.5, 3.0, 2H), 7.85 (dd, J = 5.5, 3.0, 2H), 7.86 (dd, J = 5.5, 3.0, 2H). ^{13}C NMR: 21.5 (CH_3), 23.7 (CH_3), 27.2 (CH), 38.5 (CH), 39.5 (CH_2), 39.8 (CH_2), 40.4 (CH_2), 52.7 (CH_3), 52.8 (CH_3), 60.8 (C), 123.3 (CH), 123.5 (CH), 131.9 (C), 132.0 (C), 134.0 (CH), 134.1 (CH), 168.3 (C), 168.6 (C), 169.4 (C), 169.5 (C). IR: 2958, 1774, 1716, 1465, 1431, 1396, 1261, 1215. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_8$, 521.1918; found, 521.1921. The yields (**5eb**: 68%, **7eb**: 18%) were determined by ^{1}H NMR on the basis of the integration area of the signals at 3.71 and 4.47 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Competition Experiment of 4a and 4b (Scheme 5): A magnetic stir bar and **1a** (110 mg, 0.500 mmol) were placed in a dried 20 mL two-neck round-bottom flask that was capped with an argon balloon. To the flask, were added CH_2Cl_2 (2.5 mL), **4a** (0.36 g, 1.50 mmol), **4b** (0.43 g, 1.50 mmol), and a 5.8 M decane solution of TBHP (0.10 mL, 0.60 mmol) at rt. To the stirred solution cooled in an ice–water bath, were added $BF_3{\cdot}OEt_2$ (80 μL, 0.60 mmol) and a 1.0 M hexane solution of Me_2Zn (1.5 mL, 1.5 mmol). The argon balloon was replaced with a NaOH drying tube, and the cooling bath was removed. After 6 and 8 h, to the stirred solution were added a 5.8 M decane solution of TBHP (0.10 mL, 0.60 mmol), $BF_3{\cdot}OEt_2$ (80 μL, 0.60 mmol) and a 1.0 M hexane solution of Me_2Zn (1.5 mL, 1.5 mmol) respectively. After 10 h in total, the reaction was quenched by the addition of aq saturated NH_4Cl, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with aq saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then evaporated. The yields (**5aa**: 10%, **5ab**: 33%, **7aa**: 0%, **7ab**: 25%, **7ac**: 15%, **7ad**: 3%) were determined by quantitative ^{1}H NMR on the basis of the integration area of the signals at 2.49, 3.44, 3.78, 3.84, 4.30 and 2.70 ppm, respectively, using Ph_3CH (5.55 ppm) as an internal standard.

Preparation of Authentic Samples of 7ac and 7ad. **Dimethyl 2-(1-Phenyl-2-succinimidoethyl)-2-phthalimidomethylmalonate (7ac)**: A mixture of **5aa** (33.0 mg, 0.100 mmol) and NaH (44 mg, 0.11 mmol) in DMSO (1 mL) were stirred for 1 h. Then, **4b** (34 mg, 0.12 mmol) was added to the mixture,

and the mixture was heated at 50 °C for 22 h. After addition of water, the mixture was extracted three times with Et_2O. The combined organic layers were washed with water three times and brine, dried over Na_2SO_4, and then evaporated. The purification of the residue by column chromatography (hexane/EtOAc 2:1) gave **7ac** (4.9 mg, 10%) as a pale yellow solid of mp 179–180 °C: ^{1}H NMR: 2.27–2.44 (m, 4H), 3.77 (s, 3H), 3.81 (s, 3H), 3.96 (dd, *J* = 13.5, 4.0, 1H), 4.00 (d, *J* = 14.5, 1H), 4.13 (dd, *J* = 11.5, 4.0 1H), 4.30 (d, *J* = 14.5, 1H), 4.49 (dd, *J* = 13.5, 11.5, 1H), 7.23–7.28 (m, 5H), 7.71 (dd, *J* = 5.5, 3.0, 2H), 7.83 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 27.7 (CH_2), 40.3 (CH_2), 41.3 (CH_2), 45.8 (CH), 52.7 (CH_3), 53.1 (CH_3), 60.4 (C), 123.4 (CH), 128.15 (CH), 128.19 (CH), 130.1 (CH), 131.8 (C), 134.1 (CH), 135.1 (C), 168.0 (C), 169.0 (C), 176.6 (C × 2). IR: 2920, 2845, 1367, 1775, 1719, 1383, 1248, 1084, 721. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_8$, 493.1605; found, 493.1604.

Dimethyl 2-(1-Phenyl-2-phthalimidoethyl)-2-succinimidomethylmalonate (7ad): The above procedure using **5ab** (38.1 mg, 0.100 mmol) and **4a** (29 mg, 0.12 mmol) in place of **5aa** and **4b** gave **7ad** (15 mg, 28%) as a white solid of mp 182–183 °C: ^{1}H NMR: 2.70 (s, 4H), 3.81 (s, 3H), 3.82 (s, 3H), 3.88 (d, *J* = 14.0, 1H), 4.04 (dd, *J* = 11.5, 4.0, 1H), 4.07 (dd, *J* = 13.5, 4.0, 1H), 4.19 (d, *J* = 14.0, 1H), 4.58 (dd, *J* = 13.5, 11.5, 1H), 7.16–7.20 (m, 3H), 7.24–7.26 (m, 2H), 7.61 (dd, *J* = 5.5, 3.0, 2H), 7.68 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 28.0 (CH_2), 40.2 (CH_2), 41.7 (CH_2), 46.9 (CH), 52.7 (CH_3), 53.1 (CH_3), 60.1 (C), 123.0 (CH), 128.1 (CH), 128.2 (CH), 129.9 (CH), 131.6 (C), 133.7 (CH), 135.3 (C), 169.0 (C), 169.2 (C), 176.9 (C × 2). IR: 2955, 1932, 2252, 1775, 1713, 1396, 1250, 910, 733. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_8$, 493.1605; found, 493.1607.

Scheme 6. **Baclofen Hydrochloride**: A mixture of **5bb** (703 mg, 1.66 mmol) and LiCl (141 mg, 3.32 mmol) in DMSO (2.5 mL) was heated at 130 °C for 19 h. After addition of water, the mixture was extracted with $CHCl_3$ five times. The combined organic layers were washed with brine, dried over Na_2SO_4, and then evaporated. The purification of the residue by column chromatography (hexane/EtOAc 9:1 to 5:2) gave methyl 3-(4-chlorophenyl)-4-phthalimidobutanoate (247 mg, 42%) as a brown oil and 3-(4-chlorophenyl)-4-phthalimidobutanoic acid (203 mg, 36%) as a yellow solid of mp

49.0–50.0 °C.

Methyl 3-(4-Chlorophenyl)-4-phthalimidobutanoate: ^{1}H NMR: 2.69 (dd, *J* = 16.0, 8.5, 1H), 2.74 (dd, *J* = 16.0, 6.0, 1H), 3.51 (s, 3H), 3.74 (dtd, *J* = 8.5, 7.5, 6.0, 1H), 3.86 (dd, *J* = 13.5, 7.5, 1H), 3.90 (dd, *J* = 13.5, 7.5, 1H), 7.21 (d, *J* = 8.5, 2H), 7.25 (d, *J* = 8.5, 2H), 7.71 (dd, *J* = 5.5, 3.0, 2H), 7.80 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 38.2 (CH_2), 40.1 (CH), 42.8 (CH_2), 51.7 (CH_3), 123.3 (CH), 128.8 (CH), 129.0 (CH), 131.7 (C), 133.0 (C), 134.0 (CH), 138.8 (C), 168.0 (C), 171.6 (C). IR (neat): 2949, 1736, 1713, 1396, 719, 530. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{17}ClNO_4$, 358.0841; found, 358.0843.

3-(4-Chlorophenyl)-4-phthalimidobutanoic Acid: ^{1}H NMR: 2.70 (dd, *J* = 16.5, 8.5, 1H), 2.75 (dd, *J* = 16.5, 6.5, 1H), 3.70 (tdd, *J* = 8.5, 7.0, 6.5, 1H), 3.85 (dd, *J* = 13.5, 8.5, 1H), 3.88 (dd, *J* = 13.5, 7.0, 1H), 7.20 (d, *J* = 8.5, 2H), 7.25 (d, *J* = 8.5, 2H), 7.70 (dd, *J* = 5.5, 3.0, 2H), 7.80 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 37.9 (CH_2), 39.8 (CH), 42.7 (CH_2), 123.4 (CH), 128.8 (CH), 129.0 (CH), 131.6 (C), 133.1 (C), 134.1 (CH), 138.4 (C), 168.1 (C), 176.7 (C). IR: 3013, 1736, 1713, 1396, 910, 737. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{15}ClNO_4$, 344.0684; found, 344.0689. ^{1}H and ^{13}C NMR were consistent with those reported.[21]

A mixture of the methyl ester (150 mg, 0.42 mmol), the carboxylic acid (124 mg, 0.36 mmol), and 6 N HCl (14 mL) was heated under reflux for 13 h and cooled in an ice–water bath. The precipitated phthalic acid was filtered off, and the filtrate was evaporated to dryness. The resulting solids were suspended in cold water (10 mL) and filtered to remove insoluble materials. The filtrate was evaporated to dryness under reduced pressure to afford baclofen hydrochloride (139 mg, 71%) as a yellow solids of mp 145–146 °C, lit 183–184 °C[22a] and 198–200 °C:[22b] ^{1}H NMR (D_2O): 2.68 (dd, *J* = 16.0, 9.0, 1H), 2.79 (dd, *J* = 16.0, 6.0, 1H), 3.18 (dd, *J* = 13.0, 10.0, 1H), 3.31 (dd, *J* = 13.0, 5.0, 1H), 3.36 (dddd, *J* = 10.0, 9.0, 6.0, 5.0, 1H), 7.27 (d, *J* = 8.5, 2H), 7.37 (d, *J* = 8.5, 2H). The ^{1}H NMR data were identical to those reported previously.[23]

Pregabain Hydrocholide: A mixture of **5eb** (607 mg, 1.68 mmol) and LiCl (156 mg, 3.68 mmol) in DMSO (2.5 mL) was heated at 130 °C for 19 h. After addition of water, the mixture was extracted with

$CHCl_3$ five times. The combined organic layers were washed with brine, dried over Na_2SO_4, and then evaporated. The purification of the residue by column chromatography (hexane/EtOAc 9:1 to 5:2) gave methyl 5-methyl-3-(phthalimidomethyl)hexanoate (255 mg, 50%) as a brown oil and 5-methyl-3-(phthalimidomethyl)hexanoic acid (91 mg, 19%) as a pale yellow solid of mp 113.0–114.0 °C.

Methyl 5-Methyl-3-(phthalimidomethyl)hexanoate: ^{1}H NMR: 0.90 (d, *J* = 6.5, 3H), 0.96 (d, *J* = 6.5, 3H), 1.16-1.28 (m, 2H), 1.74 (m, 1H), 2.28 (dd, *J* = 16.0, 6.5, 1H), 2.34 (dd, *J* = 16.0, 6.5, 1H), 2.47 (m, 1H), 3.55 (s, 3H), 3.62 (dd, *J* = 13.5, 8.5, 1H), 3.70 (dd, *J* = 13.5, 5.0, 1H), 7.72 (dd, *J* = 5.5, 3.0, 2H), 7.85 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 22.5 (CH_3), 22.7 (CH_3), 25.3 (CH), 32.7 (CH), 37.5 (CH_2), 41.8 (CH_2), 41.9 (CH_2), 51.4 (CH_3), 123.2 (CH), 132.0 (C), 133.9 (CH), 168.6 (C), 172.9 (C). IR: 2957, 1713, 1398, 1384, 1084, 912, 733. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{17}H_{22}NO_4$, 304.1543; found, 304.1542.

5-Methyl-3-(phthalimidomethyl)hexanoic Acid: ^{1}H NMR: 0.90 (d, *J* = 6.5, 3H), 0.95 (d, *J* = 6.5, 3H), 1.18–1.28 (m, 2H), 1.75 (m, 1H), 2.28 (dd, *J* = 16.0, 6.5, 1H), 2.35 (dd, *J* = 16.0, 6.5, 1H), 2.43 (m, 1H), 3.63 (dd, *J* = 13.5, 8.5, 1H), 3.71 (dd, *J* = 13.5, 5.0, 1H), 7.71 (dd, *J* = 5.5, 3.0, 2H), 7.85 (dd, *J* = 5.5, 3.0, 2H). ^{13}C NMR: 22.5 (CH_3), 22.7 (CH_3), 25.2 (CH), 32.6 (CH), 37.2 (CH_2), 41.7 (CH_2), 123.3 (CH), 131.9 (C), 134.0 (CH), 168.7 (C), 177.3 (C). IR (KBr): 2955, 1709, 1396, 910, 729. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{20}NO_4$, 290.1387; found, 290.1387.

A mixture of the methyl ester (152 mg, 0.502 mmol), the carboxylic acid (57.8 mg, 0.200 mmol), and 6 N HCl (14 mL) was heated under reflux for 13 h, and cooled in an ice–water bath. The precipitated phthalic acid was filtered off, and the filtrate was evaporated to dryness. The resulting solids were suspended in cold water (10 mL) and filtered to remove insoluble materials. The filtrate was evaporated to dryness under reduced pressure to afford pregabain hydrocholide (139 mg, quant) as a pale yellow solid of mp 113–114 °C: ^{1}H NMR (D_2O): 0.80 (d, *J* = 6.5, 3H), 0.82 (d, *J* = 6.5, 3H), 1.17 (dd, *J* = 7.5, 7.0, 2H), 1.57 (t septet, *J* = 7.5, 6.5, 1H), 2.17 (ttd, *J* = 7.0, 6.5, 6.0, 1H), 2.36 (dd, *J* = 16.5, 7.0, 1H), 2.43 (dd, *J* = 16.5, 6.0, 1H), 2.95 (d, *J* = 6.5, 2H). ^{1}H and ^{13}C NMR data were identical to those reported

previously.[24]

Methyl (*RS*,*RS*)-3-Aminomethyl-4-(4-chlorophenyl)-2-oxopyrrolidine-3-carboxylate (8): A mixure of **7bb** (115 mg, 0.200 mmol) and $N_2H_4 \cdot H_2O$ (0.10 mL, 2.0 mmol) in MeOH/THF (1.5 mL + 2.5 mL) was stirred at rt for 17 h. The resulting solids were removed by filtration, and the filtrate was evaporated. To the residue, was added 2N HCl, and the whole was washed with $CHCl_3$ three times. The aqueous layer was basified by 1N NaOH, and extracted with $CHCl_3$ three times. The combined organic layers were dried over Na_2SO_4 and evaporated to give **8** (28 mg, 50%) as a white solid of mp 138–139 °C: ^{1}H NMR: 2.94 (d, *J* = 13.5, 1H), 3.43 (d, *J* = 13.5, 1H), 3.50 (s, 3H), 3.63 (dd, *J* = 9.5, 8.0, 1H), 3.85 (t, *J* = 9.5, 1H), 4.03 (dd, *J* = 9.5, 8.0, 1H), 6.77 (br s, 1H), 7.15 (d, *J* = 8.5, 2H), 7.31 (d, *J* = 8.5, 2H). ^{13}C NMR: 42.6 (CH_2), 44.4 (CH_2), 45.4 (CH), 52.1 (CH_3), 62.0 (C), 128.8 (CH), 129.4 (CH), 133.8 (C), 134.8 (C), 169.4 (C), 174.6 (C). IR: 3341, 3021, 1728, 1697, 1215, 748. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{16}ClN_2O_3$, 283.0844; found, 283.0840. Recrystallization from hexane–ethyl acetate gave colorless platelets suitable for X-ray crystal structural analysis, which confirmed the relative configuration. The CIF file is available as a separate file in the supporting information.

Acknowledgement. We thank the Japan Society for the Promotion of Science [Grant-in-Aid for Scientific Research (C)] and the Japanese Ministry of Education, Culture, Sports, Science and Technology (a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” and a Grants-in-Aid for Scientific Research and Platform for Drug Design, Discovery, and Development).

Supporting Information Available. NMR spectra for new compounds and details of the DFT calculations and the X-ray crystallography of compound **8**. These are available free of charge on the World Wide Web at http://pubs.acs.org.

References and Notes

(1) Ionic conjugate addition: Tomioka, K.; Yamamoto, Y.; Yamada, K. in *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds; Elsevier, 2012; Vol. 4, Chapter 7 and references cited therein.

(2) Radical conjugate addition: (a) Vibert, F.; Maury, J.; Lingua, H.; Besson, E.; Siri, D.; Bertrand, M. P.; Feray, L. *Tetrahedron* **2015**, *71*, 8991–9002. (b) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672–675. (c) Lamas, M.-C.; Studer, A. *Org. Lett.* **2011**, *13*, 2236–2239 and references cited therein.

(3) Reviews of dimethylzinc mediated radical reactions: (a) Yamada, K.; Tomioka, K. *Chem. Rec.* **2015**, *15*, 854–871. (b) Chemla, F.; Dulong, F.; Ferreira, F.; Nüllen, M. P.; Pérez-Luna, A. *Synthesis* **2011**, 1347–1360. (c) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42,* 345–355. (d) Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60,* 260–265. (e) Yamada, K.; Yamamoto, Y.; Tomioka, K. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 1158–1165.

(4) Yamada, K.; Umeki, H.; Maekawa, M.; Yamamoto, Y.; Akindele, T.; Nakano, M.; Tomioka, K. *Tetrahedron* **2008**, *64*, 7258–7265.

(5) (a) Yamada, K.; Maekawa, M.; Akindele, T.; Nakano, M.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 9535–9538. (b) Yamada, K.; Maekawa, M.; Akindele, T.; Yamamoto, Y.; Nakano, M.; Tomioka, K. *Tetrahedron* **2009**, *65*, 903–908. (c) Yamada, K.; Konishi, T.; Nakano, M.; Fujii, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 5775–5780.

(6) Review: Renaud, P.; Giraud, L. *Synthesis* **1996**, 913–926.

(7) Conjugate addition of *N*-substituted aminomethyl radical: (a) Maury, J.; Mouysset, D.; Feray, L.; Marque, S. R. A.; Siri, D.; Bertrand, M. P. *Chem. Eur. J.* **2012**, *18*, 3241–3247. (b) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338–3341. (c) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889. (d) Nagatomo, M.; Nishiyama, H.; Fujino, H.; Inoue, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 1537–1541.

(8) (a) Xu, F.; Peng, G.; Phan, T.; Dilip, U.; Chen, J. L.; Chernov-Rogan, T.; Zhang, X.; Grindstaff, K.; Annamalai, T.; Koller, K.; Gallop, M. A.; Wustrow, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6582–6585. (b) *GABA-neurotransmitters. Pharmacochemical, Biochemical and Pharmacological Aspects*; Krogsgaard-Larsen, P., Scheel-Krueger, J., Kofod, H., Eds.; Munksgaard: Copenhagen, 1979.

(9) Recent examples of dialkylzinc-mediated radical conjugate addition: (a) Ueda, M.; Doi, N.; Miyagawa, H.; Sugita, S.; Takeda, N.; Shinada, T.; Miyata, O. *Chem. Commun.* **2015**, *51*, 4204– 4207. (b) Maury, J.; Feray, L.; Bertrand, M. P. *Org. Lett.* **2011**, *13*, 1884–1887. (c) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. *Org. Lett.* **2010**, *12*, 3590–3593. (d) Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Chem. Eur. J.* **2008**, *14*, 8784–8788. (e) Giboulot, S.; Pérez-Luna, A.; Botuha, C.; Ferreira, F.; Chemla, F. *Tetrahedron Lett.* **2008**, *49*, 3963–3966. (f) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77–85. (g) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261–4274. (h) Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 385–393. (i) Bazin, S.; Feray, L.; Siri, D.; Naubron, J.-V.; Bertrand, M. P. *Chem. Commun.* **2002**, 2506–2507.

(10) Indeed, *N*-(hydroxymethyl)imides were always detected by ^{1}H NMR of the crude mixtures (<1% and 10–20% based on **4a** and **4b** used in the reaction, respectively).

(11) (a) Yamada, K.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805–3808. (b) Yamada, K.; Konishi, T.; Nakano, M.; Fujii, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 1547–1553. (c) Fujii, S.; Konishi, T.; Matsumoto, Y.; Yamaoka, Y.; Takasu, K.; Yamada, K. *J. Org. Chem.* **2014**, *79*, 8128–8133.

(12) Indicated by the following p*K*a values in water; SucNH 9.51, PivOH 5.03: (a) Huffman, R. W. *J. Org. Chem.* **1982**, *47*, 3687–3691. (b) Lomas, J. S. *J. Phys. Org. Chem.* **2012**, *25*, 620–627.

(13) The DFT calculations were performed using Gaussian 09W program. See SI for details.

(14) (a) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581–3610. (b) Studer, A. *Chem. Eur. J.* **2001**, *7*, 1159–1164.

(15) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 193–200.

(16) Indicated by the following p*K*a values in DMSO; $EtOCONH_2$ 24.2, $(MeOCO)_2CH_2$ 15.9: (a) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223. (b) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.

(17) Goldberg, A. F. G.; O'Connor, N. R.; Craig, II, R. A.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314–5317.

(18) Zhang, S.; Cheng, K.; Wang, X.; Yin, H. *Bioorg. Med. Chem.* **2012**, *20*, 6073–6079.

(19) Dias, D. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3694–3697.

(20) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Syn. Commun.* **2003**, 33, 1587–1594.

(21) AbdeI-Hafez, A. A.-M. *Arch. Pharm. Res.* **2004**, *27*, 495–501.

(22) (a) Fryszkowska, A.; Fisher, K.; Gardiner, J. M.; Stephens, G. M. *Org. Biomol. Chem.* **2010**, *8*, 533–535. (b) Naciuk, F. F.; Vargas, D. Z.; D'oca, C. R. M.; Moro, C. C.; Russowsky, D. *New J. Chem.* **2015**, *39*, 1643–1653.

(23) Han, F.; Chen, J.; Zhang, X.; Liu, J.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *Tetrahedron Lett.* **2011**, *52*, 830–833.

(24) Yu, H.-J.; Shao, C.; Cui, Z.; Feng, C.-G.; Lin, G.-Q. *Chem. Eur. J.* **2012**, *18*, 13274–13278.