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Radical One-Pot α,β-Dual and β-Mono-Oxymethylation of Alkylidenemalonate

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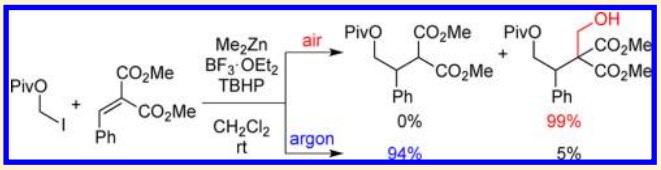
Supporting Information

ABSTRACT: Dimethylzinc-mediated radical conjugate addition reaction of dimethyl alkylidenemalonates with iodomethyl pivalate gave a high yield of the α,β-dual oxymethylation product in one pot under air and the β-pivaloyloxymethylation product under argon.



INTRODUCTION

The conjugate addition reaction of nucleophiles to activated olefins is a versatile tool in synthetic organic chemistry.[1,2] We previously reported the conjugate addition of α-oxy carbon-centered radicals[3] to α,β-unsaturated imines[4] and alkylidenemalonates,[5] giving the corresponding adducts in high yield. We also reported the tin-free generation of acyloxymethyl radicals from the corresponding iodomethyl esters and their 1,2-addition reaction to imines.[6] During our continued studies to develop a conjugate addition reaction of an acyloxymethyl radical with alkylidenemalonates, we unexpectedly observed an intriguing one-pot α,β-dual functionalization of alkylidenemalonates and found that the reaction requires the presence of air. Although dimethylzinc-mediated conjugate addition of the acyloxymethyl radical to fumarate and the following intramolecular addition of the resulting zinc enolate intermediate to the acyloxy moiety were reported during this study,[7] the reaction of alkylidenemalonates proceeded more rapidly without the subsequent intramolecular reaction, providing γ-pivaloyloxy butanoic acid derivatives with a β-aryl or a β-alkyl substituent. Herein, we report dimethylzinc-mediated conjugate addition[8] of a pivaloyloxymethyl radical to alkylidenemalonate, realizing one-pot α,β-dual or β-mono-oxymethylation by controlling the atmosphere in which the reaction is performed.

RESULTS AND DISCUSSION

We began our studies with the reaction of pivaloyloxymethyl iodide **1** with dimethyl benzylidenemalonate **2a** under orthodox radical-generating conditions using triethylborane. A 1.0 M hexane solution of triethylborane (3 mmol) was added to a solution of **1** (3 mmol) and **2a** (1 mmol) in dichloromethane (1 mL) at room temperature. The mixture was then stirred at room temperature under an ordinary atmosphere, and a solution of triethylborane (1 mmol) was added every 2 h. After the addition of a total of 6 mmol of triethylborane, another portion of triethylborane (3 mmol) was added, and the mixture was allowed to stand under stirring at room temperature for another 15 h. Workup and silica gel column chromatography revealed the expected β-adduct **3a** in 29% yield along with the α,β-bispivaloyloxymethylated adduct **4a** in 22% yield (Table 1, entry 1). The addition of boron trifluoride diethyl etherate[5] (3 equiv) as a Lewis acid improved the yield of **3a** to 41%, and **4a** was also isolated in 8% yield (entry 2). The formation of **4a** is likely due to radical−radical coupling of pivaloyloxymethyl and the radical intermediate corresponding to **3a**,[9,10] implying slow conversion of the initially formed radical intermediate to a boron enolate with triethylborane.

When dimethylzinc was used as a radical initiator in place of triethylborane, α-hydroxymethylated β-pivaloyloxymethyl adduct **5a** was unexpectedly obtained in 59% yield as a major product along with **3a** and **4a** in 21% and 1% yields, respectively (Table 1, entry 3). The addition of boron trifluoride diethyl etherate (3 equiv) improved the yield of **5a** to 77%, while **3a** and **4a** were still obtained in 19% and 3% yields, respectively (entry 4). Interestingly, migration of the pivaloyl group to the α-position was not observed in these reactions, despite the reported migration in the reaction with fumarate.[7] The use of diethylzinc instead of dimethylzinc resulted in the production of the ethyl conjugate adduct in 78% yield, without the production of pivaloyloxymethyl adducts **3a**−**5a** (entry 5).

The reaction of **2a** was remarkably accelerated by adding 1.2 equiv of *tert*-butyl hydroperoxide (TBHP),[11] leading to the complete consumption of **2a** within 15 min, and affording both **3a** as a major product in 82% yield and **5a** in 18% yield (Table 1, entry 7). The amount of TBHP significantly affected the reaction; the yield of **3a** was decreased to 68% with 1.5 equiv of TBHP (entry 8), whereas the reaction slowed with 1.0 equiv of TBHP to give **3a** and **5a** after 0.5 h in 44% and 56% yields, respectively (entry 6). A prolonged 4 h reaction enabled complete conversion, giving **5a** in 97% yield (entry 9).

The amount of boron trifluoride diethyl etherate also affected the reaction; with 1.2 equiv of boron trifluoride, the reaction

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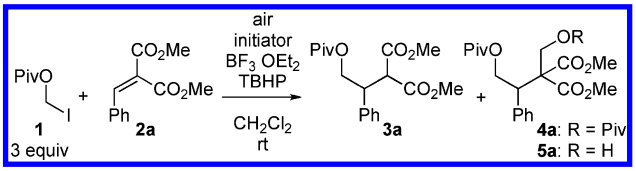
Table 1. Radical Conjugate Addition of 1 to 2a



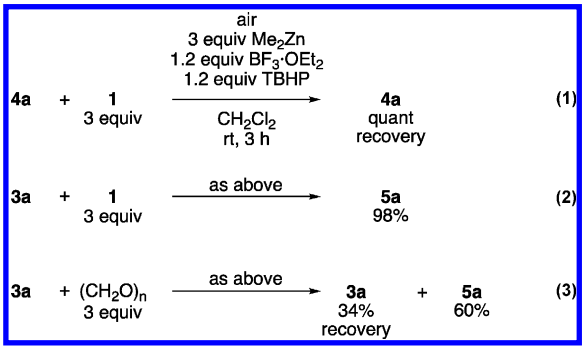
entry	initiator/equiv	$BF_3{\cdot}OEt_2$ (equiv)	TBHP (equiv)	time (h)	**3a** (% yield)	**4a** (% yield)	**5a** (% yield)
1	Et_3B/9	0	0	24	29	22	0
2	Et_3B/9	3	0	24	41	8	0
3	Me_2Zn/9	0	0	24	21	1	59
4	Me_2Zn/9	3	0	24	19	3	77
5	Et_2Zn/3	1	0	3	0[a]	0	0
6	Me_2Zn/3	1	1	0.5	44	0	56
7	Me_2Zn/3	1	1.2	0.25	82	0	18
8	Me_2Zn/3	1	1.5	0.25	68	0	20
9	Me_2Zn/3	1	1.2	4	0	0	97
10	Me_2Zn/3	1.2	1.2	3	0	0	99
11	Me_2Zn/3	1.5	1.2	3	10	0	76

[a]Ethyl conjugate adduct was obtained in 78% yield.

completed after 3 h to give **5a** quantitatively (Table 1, entry 10), although α-hydroxymethylation proceeded slower with 1.5 equiv of the boron reagent to give **5a** in 76% yield and **3a** in 10% yield (entry 11).

We excluded the possibility that **4a** was selectively hydrolyzed to **5a** based on the fact that treatment of **4a** under the reaction conditions failed to produce **5a**, and **4a** was quantitatively recovered unchanged (Scheme 1, eq 1). TLC

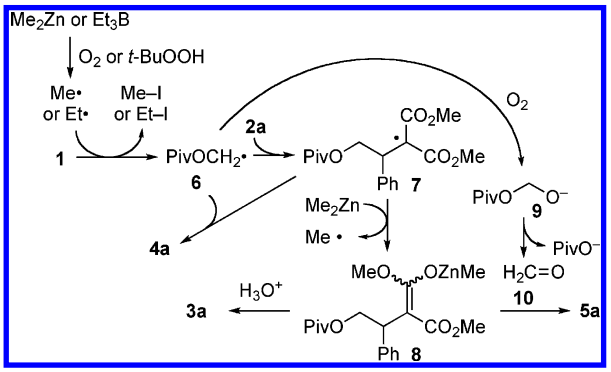
Scheme 1. Reaction of 3a and 4a



monitoring of the reaction clearly revealed the disappearance of **3a** with simultaneous production of **5a** (Table 1, entries 6–11). Indeed, treatment of **3a** under the reaction conditions gave **5a** in 98% yield (eq 2). A critical experiment was the reaction of **3a** with paraformaldehyde in the absence of **1** under the reaction conditions to give **5a** in 60% yield (Scheme 1, eq 3).

The reactions shown in Scheme 1 suggest that **5a** results from the reaction of zinc enolate **8** with a formaldehyde equivalent (Scheme 2). The methyl radical, generated by the reaction of dimethylzinc with molecular oxygen and/or TBHP, abstracts an iodine atom from **1** to form pivaloyloxymethyl radical **6**, which undergoes a conjugate addition reaction with **2a** to give **7**. The resulting radical **7** is then trapped by dimethylzinc and converted into zinc enolate **8**. Formaldehyde **10** is probably generated by the oxidation of **6** with oxygen and reacts with **8** to afford **5a**. In the reactions in eqs 2 and 3 (Scheme 1), dimethylzinc probably deprotonated **3a** to generate **8**. Interestingly, iodomethyl pivalate (**1**) seemed to

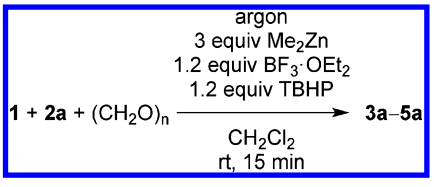
Scheme 2. Radical Pathway to 3a, 4a, and 5a from 1 and 2a



function as a better formaldehyde donor than paraformaldehyde (eq 2 vs eq 3, Scheme 1).

The above speculation of the formaldehyde formation suggested that, in the absence of air, that is, under an argon atmosphere, enolate **8** should survive to be protonated at the workup, affording **3a**. This speculation was confirmed by the reaction under an argon atmosphere for 15 min, giving **3a** in 94% yield and **5a** in 5% yield (Table 2, entry 1). Under an argon atmosphere, the reaction proceeded with almost the

Table 2. Radical Reaction of 1 and 2a under Argon



entry	**1** (equiv)	$(CH_2O)_n$ (equiv)	**3a** (% yield)	**4a** (% yield)	**5a** (% yield)
1	3	0	94	0	5
2	2	0	94	0	5
3[a]	1.2	0	91	0	2
4[b]	3	3	5	0	73

[a]The reaction for 30 min. Recovery of **2a** in 4% yield. [b]Recovery of **2a** in 5% yield.

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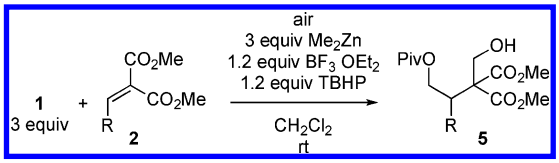
same efficiency, even with a reduced amount of **1** (2 equiv), to afford **3a** in 94% yield, probably because the reaction of **6** with molecular oxygen was avoided (entry 2). Although the reaction was slightly slower, **3a** was obtained in comparable yield (91%) with 1.2 equiv of **1** (entry 3). Even under an argon atmosphere, α-hydroxymethylation product **5a** was obtained in 73% yield after 15 min when the reaction was conducted in the presence of 3 equiv of paraformaldehyde (entry 4). Probably due to the low nucleophilicity of **8** and/or a favored retro-aldol process, however, the reaction of **1** and **2a** with Me_2Zn in the presence of other aldehydes, such as benzaldehyde and acetaldehyde, failed to provide products corresponding to **5a**.

The established conditions (Table 1, entry 10) were successfully applied to one-pot α,β-dual oxymethylation of other alkylidenemalonates **2** (Table 3). 4-Chlorobenzylidenemalonate **2b** gave **5b** in quantitative yield (entry 2). 4-Methoxybenzylidenemalonate **2c** also gave **5c** in quantitative yield (entry 3). Ethylidenemalonate **2d** was also a good radical acceptor to give **5d** in 83% yield (entry 4). Notably, this radical polar crossover reaction with alkylidenemalonate occurred intermolecularly, which is unprecedented.[12]

Table 3. One-Pot Dual Oxymethylation of 2 with 1 Giving 5[a]

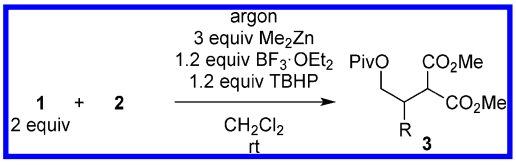


entry	2	R	time (h)	5	% yield
1	**2a**	Ph	3	**5a**	99
2	**2b**	4-ClC_6H_4	4	**5b**	99
3	**2c**	4-$MeOC_6H_4$	4	**5c**	99
4	**2d**	Me	3	**5d**	83

[a]With **2** (1 mmol) in CH_2Cl_2 (1 mL) under an ordinary atmosphere.

The conditions for the conjugate β-pivaloyloxymethylation (Table 2, entry 2) were applied to the reactions of other alkylidenemalonates **2** (Table 4). Although the reaction was somewhat slower with **2b** and **2c**, bearing an electron-withdrawing 4-chloro and an electron-donating 4-methoxy substituent on the phenyl group, conjugate adducts **3b** and **3c** were obtained in reasonably high yield, 95% and 92%, after 1 and 1.5 h, respectively (entries 2 and 3). The reaction with ethylidenemalonate **2d** was very rapid, giving **3d** in 84% yield after 5 min (entry 4).

Table 4. Conjugate Pivaloyloxymethylation of 2 with 1 Giving 3

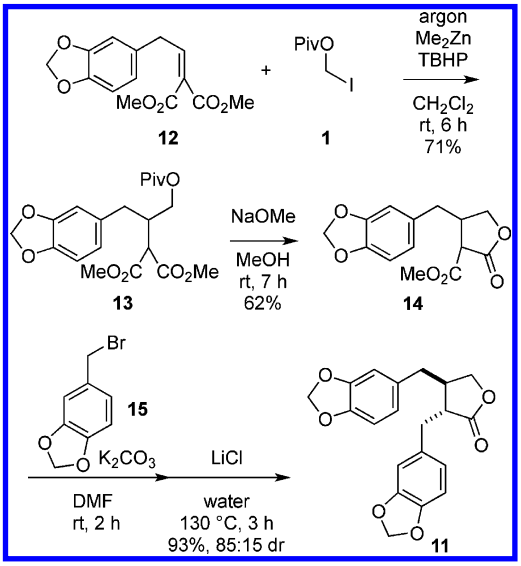


entry	2	R	time (min)	3	% yield[a]
1	**2a**	Ph	15	**3a**	94
2	**2b**	4-ClC_6H_4	60	**3b**	95
3	**2c**	4-$MeOC_6H_4$	90	**3c**	92
4	**2d**	Me	5	**3d**	84

[a]With **2** (1 mmol) in CH_2Cl_2 (2 mL). A 3–5% yield of **5** was produced.

The radical conjugate addition reaction was applicable for the synthesis of hinokinin (**11**), a representative lignin[13] with antiviral, antifungal, and pesticidal activities.[14] The reaction of arylethylidenemalonate **12**[15] with **1** under an argon atmosphere gave conjugate pivaloyloxymethylation adduct **13** in 71% yield (Scheme 3).[16] Treatment of **13** with sodium methoxide in methanol afforded lactone **14**, which was then subjected to alkylation with **15**,[17] followed by decarboxylation[18] to give **11** in 93% yield as an 85:15 mixture with isohinokinin. Spectral data, including ^1H and ^{13}C NMR and IR, were consistent with those reported in the literature.[19]

Scheme 3. Short-Step Total Synthesis of Hinokinin 11 via Conjugate Pivaloyloxymethylation of 12



CONCLUSION

We successfully developed a dimethylzinc-mediated radical one-pot dual oxymethylation and β-pivaloyloxymethylation of alkylidenemalonate with pivaloyloxymethyl iodide by controlling the atmosphere in which the reaction is performed. The synthetic utility of the reaction was clearly demonstrated by the synthesis of bioactive hinokinin.

EXPERIMENTAL SECTION

General Methods. Alkylidenemalonates **2a–2c**[20] and bromide **15**[17] were prepared according to the literature. Iodomethyl pivalate (**1**) was prepared by the reported procedure[21] and decolorized by being passed through Al_2O_3 prior to use. Anhydrous solvents, CH_2Cl_2, DMF, and THF, and hexane solutions of Me_2Zn and Et_3B were purchased and used as received. $BF_3{\cdot}OEt_2$ was distilled prior to use. MeOH was distilled from sodium prior to use. Reactions were performed using dried glassware in dry solvent, unless otherwise mentioned. Column chromatography was performed using silica gel. All melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shifts and coupling constants are presented in parts per million (ppm δ) relative to Me_4Si and hertz (Hz), respectively. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, and m = multiplet), coupling constants, integration. ^{13}C peak multiplicity assignments were made on the basis of DEPT spectra. IR spectroscopy of oil and solid samples were measured as neat liquid films and KBr pellets, respectively. The wave numbers of

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maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. A double-focusing magnetic sector mass spectrometer was used for both low- and high-resolution FABMS, while low-resolution EIMS was measured with a quadrupole mass spectrometer.

Typical Procedure for Table 4. Dimethyl 2-(1-Phenyl-2-pivaloyloxyethyl)malonate (3a) (Entry 1). A magnetic stir bar and **2a** (220 mg, 1.0 mmol) were placed in a dried 20 mL round-bottom flask that was capped with an argon balloon. To the flask were added CH_2Cl_2 (2.0 mL), **1** (0.5 mL, 3.0 mmol), and a 5.3 M decane solution of TBHP (0.23 mL, 1.2 mmol) at rt. The solution was degassed by freeze−pump−thaw three times and then cooled in an ice−water bath. To the solution were added $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) and a 1.0 M hexane solution of Me_2Zn (3.0 mL, 3.0 mmol). The cooling bath was removed, and the mixture was stirred at rt under an argon atmosphere for 15 min. The reaction was quenched by the addition of sat. NH_4Cl, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with 10% $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then concentrated. The purification of the resulting residue by column chromatography (hexane/EtOAc 9/1 to 4/1) gave the title compound (316 mg, 94%) as a colorless oil: ^{1}H NMR: 1.09 (s, 9H), 3.48 (s, 3H), 3.78 (s, 3H), 3.79 (ddd, J = 4.5, 6.5, 10.5, 1H), 3.90 (d, J = 10.5, 1H), 4.20 (dd, J = 4.5, 11.5, 1H), 4.41 (dd, J = 6.5, 11.5, 1H), 7.22−7.31 (m, 5H). ^{13}C NMR: 27.0 (CH_3), 38.7 (C), 44.4 (CH), 52.4 (CH_3), 52.8 (CH_3), 54.4 (CH), 65.6 (CH_2), 127.5 (CH), 128.3 (CH), 128.5 (CH), 138.4 (C), 167.8 (C), 168.3 (C), 178.1 (C). IR: 2963, 1736, 1458, 1435, 1281, 1157, 1026, 764, 702. FABMS m/z: 337 (M + H), 235 (M − t-BuCO_2), 221 (M − t-BuCO_2CH_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{18}H_{25}O_6$, 337.1646; found, 337.1649.

*Dimethyl 2-(1-(4-Chlorophenyl)-2-pivaloyloxyethyl)malonate (**3b**):* Purified by column chromatography (hexane/EtOAc 9/1). Colorless oil (352 mg, 95%): ^{1}H NMR: 1.10 (s, 9H), 3.51 (s, 3H), 3.75−3.81 (m, 4H), 3.86 (d, 1H, J = 11.0), 4.17 (dd, 1H, J = 11.5, 4.5), 4.38 (dd, 1H, J = 11.5, 7.0), 7.20 (dt, 2H, J = 8.5, 2.0), 7.25−7.30 (m, 2H). ^{13}C NMR: 27.0 (CH_3), 38.7 (C), 43.7 (CH), 52.6 (CH_3), 52.9 (CH_3), 54.1 (CH), 65.3 (CH_2), 128.6 (CH), 129.7 (CH), 133.3 (C), 137.0 (C), 167.5 (C), 167.9 (C), 177.8 (C). IR: 2963, 1736, 1489, 1281, 1150. FABMS m/z: 373 (M + 2 + H), 371 (M + H), 271 (M + 2 + H − t-BuCO_2), 269 (M + H − t-BuCO_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{18}H_{24}ClO_6$, 371.1261; found, 371.1264.

*Dimethyl 2-(1-(4-Methoxyphenyl)-2-pivaloyloxyethyl)malonate (**3c**):* Purified by column chromatography (hexane/EtOAc 9/1). Colorless oil (338 mg, 92%): ^{1}H NMR: 1.11 (s, 9H), 3.50 (s, 3H), 3.74 (ddd, 1H, J = 11.0, 6.5, 4.5), 3.77 (s, 3H), 3.78 (s, 3H), 3.85 (d, 1H, J = 11.0), 4.16 (dd, 1H, J = 11.5, 4.5), 4.37 (dd, 1H, J = 11.0, 6.5), 6.82 (dt, 2H, J = 8.5, 3.0), 7.17 (dt, 2H, J = 8.5, 3.0). ^{13}C NMR: 27.0 (CH_3), 38.7 (C), 43.6 (CH), 52.5 (CH_3), 52.8 (CH_3), 54.5 (CH), 55.2 (CH_3), 65.8 (CH_2), 113.8 (CH), 129.4 (CH), 130.3 (C), 158.8 (C), 167.8 (C), 168.2 (C), 178.0 (C). IR: 2963, 1736, 1512, 1250, 1150. FABMS m/z: 367 (M + H), 265 (M − t-BuCO_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{19}H_{27}O_7$, 367.1757; found, 367.1757.

*Dimethyl 2-(1-Methyl-2-pivaloyloxyethyl)malonate (**3d**):* Purified by column chromatography (hexane/EtOAc 9/1). Colorless oil (231 mg, 84%): ^{1}H NMR: 1.07 (d, 3H, J = 7.0), 1.21 (s, 9H), 2.63 (m, 1H), 3.45 (d, 1H, J = 8.0), 3.74 (s, 3H), 3.75 (s, 3H), 4.02 (dd, 1H, J = 11.0, 5.5), 4.05 (dd, 1H, J = 11.0, 5.5). ^{13}C NMR: 14.6 (CH_3), 27.0 (CH_3), 32.9 (CH), 38.7 (C), 52.2 (CH_3), 52.3 (CH_3), 53.7 (CH), 66.1 (CH_2), 168.4 (C), 168.5 (C), 177.9 (C). IR: 2970, 1736, 1435, 1281, 1157. FABMS m/z: 275 (M + H), 173 (M − t-BuCO_2), 57 (t-Bu). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{13}H_{23}O_6$, 275.1489; found, 275.1496.

*Dimethyl 2-(1-Phenyl-2-pivaloyloxyethyl)-2-(pivaloyloxymethyl)-malonate (**4a**):* Purified by column chromatography (hexane/EtOAc 9/1 to 3/1). Colorless oil (98 mg, 22%): ^{1}H NMR: 0.92 (s, 9H), 1.21 (s, 9H), 3.68 (s, 3H), 3.79 (s, 3H), 3.93 (dd, J = 4.0, 11.0, 1H), 4.14 (d, J = 11.5, 1H), 4.49 (d, J = 11.5, 1H), 4.52 (dd, J = 4.0, 11.0, 1H), 4.74 (dd, J = 11.0, 11.0, 1H), 7.12 (d, J = 7.0, 2H), 7.23−7.29 (m, 3H). ^{13}C NMR: 26.7 (CH_3), 27.0 (CH_3), 38.5 (C), 38.7 (C), 47.0 (CH), 52.6 (CH_3), 52.8 (CH_3), 59.9 (C), 63.9 (CH_2), 64.4 (CH_2), 127.9 (CH), 128.5 (CH), 129.0 (CH), 136.4 (C), 168.5 (C), 168.7 (C), 177.4 (C), 178.1 (C). IR: 2970, 1736, 1481, 1396, 1281, 1227, 1150, 1034, 995, 918, 733. FABMS m/z: 451 (M + H), 349 (M − t-BuCO_2), 335 (M − t-BuCO_2CH_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{24}H_{35}O_8$, 451.2326; found, 451.2332.

Typical Procedure for Table 3. Dimethyl 2-Hydroxymethyl-2-(1-phenyl-2-pivaloyloxyethyl)malonate (5a) (Entry 1). A magnetic stir bar and **2a** (220 mg, 1.0 mmol) were placed in a dried 20 mL round-bottom flask that was capped with an argon balloon. To the flask were added CH_2Cl_2 (1.0 mL), **1** (0.33 mL, 2.0 mmol), and a 5.3 M decane solution of TBHP (0.23 mL, 1.2 mmol) at rt. To the stirred solution cooled in an ice−water bath were added $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) and a 1.0 M hexane solution of Me_2Zn (3.0 mL, 3.0 mmol). The cooling bath was removed, and the mixture was stirred at rt under an ordinary atmosphere for 3 h. The reaction was quenched by the addition of sat. NH_4Cl, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with 10% $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then concentrated. Purification of the resulting residue by column chromatography (hexane/EtOAc 9/1 to 4/1) gave the title compound (361 mg, 99%) as colorless prisms of mp 70−71 °C (Et_2O−hexane): ^{1}H NMR: 0.96 (s, 9H), 2.51 (dd, J = 5.0, 9.0, 1H), 3.73−3.78 (m, 2H), 3.79 (s, 3H), 3.84 (m, 1H), 3.84 (s, 3H), 4.40 (dd, J = 4.5, 11.0, 1H), 4.78 (dd, J = 11.0, 11.0, 1H), 7.17 (d, J = 6.5, 2H), 7.23−7.30 (m, 3H). ^{13}C NMR: 26.8 (CH_3), 38.5 (C), 47.7 (CH), 52.7 (CH_3), 52.9 (CH_3), 62.3 (C), 65.0 (CH_2), 65.7 (CH_2), 127.8 (CH), 128.6 (CH), 129.0 (CH), 136.6 (C), 170.3 (C), 170.5 (C), 178.1 (C). IR: 3518, 2963, 1728, 1458, 1281, 1218, 1165, 1042, 910, 733, 702. EIMS m/z: 335 (M − $HOCH_2$), 251 (M − t-BuCO_2CH_2). FABMS m/z: 367 (M + H), 265 (M − t-BuCO_2), 251 (M − t-BuCO_2CH_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{19}H_{27}O_7$, 367.1757; found, 367.1766. Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.20; H, 7.04.

*Dimethyl 2-(1-(4-Chlorophenyl)-2-pivaloyloxyethyl)-2-hydroxymethylmalonate (**5b**):* Purified by column chromatography (hexane/EtOAc 4/1 to 2/1). Colorless oil (399 mg, 99%): ^{1}H NMR: 0.97 (s, 9H), 2.58 (brs, 1H), 3.76−3.79 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 3.85 (d, J = 11.5, 1H), 4.40 (dd, J = 4.5, 11.0, 1H), 4.75 (dd, J = 11.0, 11.0, 1H), 7.16 (d, J = 8.5, 2H), 7.27 (d, J = 8.5, 2H). ^{13}C NMR: 26.8 (CH_3), 38.5 (C), 46.8 (CH), 52.7 (CH_3), 53.0 (CH_3), 62.2 (C), 64.6 (CH_2), 65.1 (CH_2), 128.7 (CH), 130.5 (CH), 133.7 (C), 135.3 (C), 170.0 (C), 170.1 (C), 178.1 (C). IR: 3510, 2963, 1728, 1489, 1435, 1281, 1220, 1165, 1096, 1042, 972, 756. FABMS m/z: 403 (M + 2 + H), 401 (M + H), 385 (M + 2 − OH), 383 (M − OH), 301 (M + 2 − t-BuCO_2), 299 (M − t-BuCO_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{19}H_{26}O_7Cl$, 401.1367; found, 401.1369.

*Dimethyl 2-Hydroxymethyl-2-(1-(4-methoxyphenyl)-2-pivaloyloxyethyl)malonate (**5c**):* Purified by column chromatography (hexane/EtOAc 4/1 to 2/1). Colorless oil (396 mg, 99%): ^{1}H NMR: 0.98 (s, 9H), 2.55 (dd, J = 4.5, 9.0, 1H), 3.70 (dd, J = 4.5, 10.5, 1H), 3.75−3.85 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 4.37 (dd, J = 4.5, 11.0, 1H), 4.74 (dd, J = 10.5, 11.0, 1H), 6.81 (d, J = 8.5, 2H), 7.09 (d, J = 8.5, 2H). ^{13}C NMR: 26.8 (CH_3), 38.5 (C), 46.8 (CH), 52.6 (CH_3), 52.9 (CH_3), 55.1 (CH_3), 62.5 (C), 65.0 (CH_2), 65.6 (CH_2), 113.9 (CH), 128.5 (C), 130.0 (CH), 159.1 (C), 170.3 (C), 170.5 (C), 178.2 (C). IR: 3510, 2962, 1728, 1612, 1512, 1458, 1288, 1250, 1180, 1034, 841, 756. FABMS m/z: 397 (M + H), 295 (M − t-BuCO_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{20}H_{29}O_8$, 397.1862; found, 397.1871.

*Dimethyl 2-Hydroxymethyl-2-(1-methyl-2-pivaloyloxyethyl)-malonate (**5d**):* Purified by column chromatography (hexane/EtOAc 4/1 to 2/1). Colorless oil (253 mg, 83%): ^{1}H NMR: 1.07 (d, J = 7.0, 3H), 1.20 (s, 9H), 2.55 (m, 1H), 2.81 (dd, J = 6.5, 7.5, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.01 (dd, J = 7.5, 11.5, 1H), 4.05 (dd, J = 8.0, 11.5, 1H), 4.07 (dd, J = 6.5, 11.5, 1H), 4.19 (dd, J = 4.5, 11.5, 1H). ^{13}C NMR: 13.8 (CH_3), 27.1 (CH_3), 35.9 (CH), 38.7 (C), 52.60 (CH_3), 52.62 (CH_3), 62.4 (C), 64.8 (CH_2), 66.3 (CH_2), 170.7 (C), 178.4 (C). IR: 3518, 2970, 1728, 1458, 1404, 1288, 1234, 1165, 1057, 980, 771. FABMS m/z: 305 (M + H), 203 (M − t-BuCO_2). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{14}H_{25}O_7$, 305.1600; found, 305.1599.

Dimethyl 2-(2-(3,4-Methylenedioxyphenyl)ethylidene)-malonate (12). Although the title compound could be prepared

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according to the reported modified conditions for Knoevenagel condensation,[15] the following procedure was utilized, for we were unable to reproduce the results reported with phenylacetaldehyde: A mixture of 5-(1-iodoethyl)-3,4-methylenedioxybenzene[22] (1.9 g, 6.9 mmol), K_2CO_3 (4.8 g, 35 mmol), and dimethyl malonate (0.8 mL, 6.9 mmol) in acetone (140 mL) was heated under reflux for 21 h. After the mixture was cooled to rt, water was added, and the whole was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated. Purification of the resulting residue by column chromatography (hexane/EtOAc 9/1) gave a pale yellow oil (1.7 g), which was dissolved in anhydrous THF (5 mL). To the solution cooled in an ice−water bath was added a 1.0 M THF solution of LiHMDS (7.0 mL, 7.0 mmol), and the mixture was stirred for 10 min. To the solution was added PhSeBr (2.8 g, 12 mmol) as a solution in THF (8 mL), and the cooling bath was removed. After 20 h, the mixture was diluted with Et_2O; washed with 10% HCl twice, water, sat $NaHCO_3$, and brine; dried over Na_2SO_4; and then concentrated. Purification of the resulting residue by column chromatography (hexane/EtOAc 19/1) gave a pale yellow oil (2.2 g). To a solution of the oil in THF (40 mL) was added 30% H_2O_2 (21 mL, 200 mmol). The mixture was stirred for 12 h and diluted with Et_2O. The organic layer was separated, washed with water three times and brine, dried over Na_2SO_4, and then concentrated. Purification of the resulting residue by column chromatography (neutral silica gel, hexane/EtOAc 9/1) gave the title compound as a pale yellow oil (1.0 g, 54%). ^{1}H NMR: 3.53 (d, J = 8.0, 2H), 3.78 (s, 3H), 3.88 (s, 3H), 5.94 (s, 2H), 6.66 (dd, J = 8.0, 1.5, 1H), 6.71 (d, J = 1.5, 1H), 6.75 (d, J = 8.0, 1H), 7.08 (t, J = 8.0, 1H). ^{13}C NMR: 35.6 (CH_2), 52.4 (CH_3), 101.0 (CH_2), 108.5 (CH), 109.2 (CH), 121.7 (CH), 127.8 (C), 130.6 (C), 146.5 (C), 147.9 (C), 164.2 (C), 165.6 (C). IR: 3024, 1724, 1489, 1438, 1219, 1037. FABMS m/z: 279 (M + H), 246 (M − MeOH). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{14}H_{15}O_6$, 279.0863; found, 279.0859.

Dimethyl 2-(2-(3,4-Methylenedioxypheny)-1-pivaloyloxymethylethyl)malonate (13). A magnetic stir bar and **12** (139 mg, 0.50 mmol) were placed in a dried 20 mL round-bottom flask that was capped with an argon balloon. To the flask were added CH_2Cl_2 (1.0 mL), **1** (0.42 mL, 2.5 mmol), and a 5.3 M decane solution of TBHP (0.10 mL, 0.53 mmol). To the stirred solution cooled in an ice−water bath was added a 1.0 M hexane solution of Me_2Zn (1.5 mL, 1.5 mmol). The cooling bath was removed, and the mixture was stirred at rt under an argon atmosphere while additional portions of Me_2Zn (0.50 mL, 0.50 mmol each) and TBHP (0.03 mL, 0.2 mmol each) were added every 1 h. After total addition of 8 equiv of Me_2Zn and 3.2 equiv of TBHP, the mixture was stirred for another 1 h, and the reaction was quenched by the addition of sat. NH_4Cl. The mixture was extracted three times with EtOAc, and the combined organic layers were washed with 10% $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and then concentrated. The resulting residue was purified by column chromatography (hexane/EtOAc 9/1) to give the title compound (140 mg, 71%) as a colorless oil: ^{1}H NMR: 1.22 (s, 9H), 2.60 (m, 1H), 2.65−2.78 (m, 2H), 3.56 (d, 1H, J = 7.5), 3.75 (s, 3H), 3.76 (s, 3H), 3.96 (dd, 1H, J = 11.5, 5.0), 4.03 (dd, 1H, J = 11.5, 4.5), 5.93 (s, 2H), 6.62 (dd, 1H, J = 7.5, 1.5), 6.68 (d, 1H, J = 1.5), 6.73 (d, 1H, J = 7.5). ^{13}C NMR: 27.1 (CH_3), 34.9 (CH_2), 38.8 (C), 40.2 (CH), 52.5 (CH), 52.6 (CH_3), 62.9 (CH_2), 100.8 (CH_2), 108.2 (CH), 109.3 (CH), 122.1 (CH), 132.3 (C), 146.2 (C), 147.7 (C), 168.5 (C), 168.7 (C), 178.0 (C). IR: 2963, 1736, 1489, 1443, 1157, 1042. FABMS m/z: 395 (M + H), 394 (M), 393 (M − H), 293 (M − t-BuCO_2), 292 (M − H − t-BuCO_2), 262 (M − H − CH(CO_2Me)$_2$). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{20}H_{27}O_8$, 395.1700; found, 395.1707.

Methyl 4-(3,4-Methylenedioxyphenylmethyl)-2-oxotetrahydrofuran-3-carboxylate (14). To a solution of **13** (152 mg, 0.39 mmol) in MeOH (1.0 mL) was added a 1.0 M methanolic solution of NaOMe (1.9 mL, 1.9 mmol) at rt. The mixture was stirred for 5 h, and then another portion of the NaOMe solution (1.9 mL, 1.9 mmol) was added again. After 2 h, the reaction was quenched by the addition of sat. NH_4Cl, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated. Purification of the resulting residue by column chromatography (hexane/EtOAc 9/1) gave a 92:8 diastereomeric mixture of the title compound as a colorless oil (67 mg, 62%). The diastereomeric ratio was determined by the integration area of ^{1}H NMR signals at 3.74 and 3.81 ppm. ^{1}H NMR: 2.54 (dd, J = 14.0, 10.0, 0.08H), 2.72 (dd, J = 14.0, 8.0, 0.92H), 2.78 (dd, J = 14.0, 7.0, 0.92H), 2.88 (dd, J = 14.0, 6.0, 0.08H), 3.06 (m, 0.08H), 3.23 (m, 0.92H), 3.32 (d, J = 8.5, 0.92H), 3.59 (d, J = 9.0, 0.08H), 3.74 (s, 2.76H), 3.81 (s, 0.24H), 3.99 (dd, J = 9.0, 8.0, 0.92H), 4.23 (dd, J = 9.0, 9.0, 0.08H), 4.28 (dd, J = 9.0, 7.5, 0.08H), 4.42 (dd, J = 9.0, 7.5, 0.92H), 5.95 (s, 2H), 6.55−6.62 (m, 1H), 6.63−6.68 (m, 1H), 6.70−6.80 (m, 1H). ^{13}C NMR: 37.5 (CH_2), 41.7 (CH), 51.7 (CH), 53.0 (CH_3), 71.3 (CH_2), 101.1 (CH_2), 108.5 (CH), 109.0 (CH), 121.8 (CH), 130.6 (C), 146.6 (C), 148.0 (C), 167.6 (C), 171.6 (C). IR: 2916, 1782, 1736, 1497, 1442, 1250, 1150, 1034. FABMS m/z: 279 (M + H), 278 (M), 277 (M − H), 247 (M − OMe). HRMS−FAB (m/z): $[M + H]^+$ calcd for $C_{14}H_{15}O_6$, 279.0863; found, 279.0859.

Hinokinin (11) and Isohinokinin. A solution of **14** (67 mg, 0.24 mmol), K_2CO_3 (57 mg, 0.41 mmol), and **15**[17] (58 mg) in anhydrous DMF (1.3 mL) was stirred for 2 h at rt. To the solution were added LiCl (52 mg, 1.2 mmol) and water (8.4 μL, 0.47 mmol), and the resulting solution was heated at 130 °C for 3 h. After cooling the solution to rt, EtOAc and water were added, and the separated aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with 0.1 N HCl and brine, dried over $MgSO_4$, and concentrated. Purification of the resulting residue by column chromatography (hexane/EtOAc 19/1) gave an 85:15 mixture of hinokinin (**11**) and isohinokinin (79 mg, 93%) as a colorless oil: ^{1}H NMR: 2.30 (t, J = 13.5, 0.15H), 2.41−2.64 (m, 3.55H), 2.74 (dd, J = 15.0, 11.0, 0.15H), 2.84 (dd, J = 14.0, 7.5, 0.85H), 2.89 (dd, J = 13.0, 3.0, 0.15H), 2.99 (dd, J = 14.0, 5.0, 0.85H), 3.05 (m, 0.15H), 3.23 (dd, J = 15.0, 5.0, 0.15H), 3.86 (dd, J = 9.5, 7.5, 0.85H), 3.97−4.10 (m, 0.3H), 4.13 (dd, J = 9.5, 7.0, 0.85H), 5.92−5.96 (m, 3.7H), 5.97 (s, 0.3H), 6.44−6.49 (m, 1.7H), 6.49−6.55 (m, 0.3H), 6.58−6.65 (m, 1.7H), 6.69−6.81 (m, 2.3H). The diastereomeric ratio was determined by the integration area of ^{1}H NMR signals at 2.99 and 3.05 ppm. ^{1}H and ^{13}C NMR, IR, and MS of hinokinin (**11**) and ^{1}H NMR of isohinokinin were identical to those reported.[19b]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR charts of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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