Note

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Kanade Kirita, and Seijiro Hosokawa

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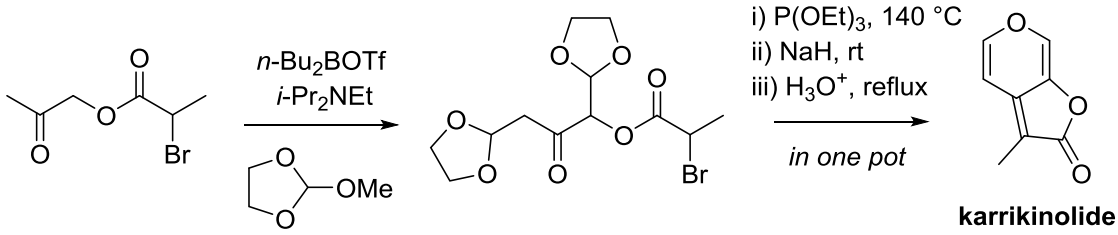
Synthesis of Karrikinolide Using the Aldol Type Acetal Addition Reaction

Kanade Kirita and Seijiro Hosokawa*

Department of Applied Chemistry, Faculty of Advanced Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan..

Supporting Information Placeholder



ABSTRACT: A short step total synthesis of karrikinolide has been achieved. The both α and α' positions of *O*-acylated acetol were alkylated by the boron-mediated aldol type acetal addition reaction. One pot sequence including the Arbuzov reaction, intramolecular Horner-Wadsworth-Emmons reaction, acidic hydrolysis of acetals, and pyran formation provided karrikinolide. This procedure was applicable to gram-scale synthesis of karrikinolide.

Karrikinolide (**1**, Figure 1) has been isolated from plant-derived smoke and indicated to have potent seed-germination activity against a wide range plant species.[1] Since smoke contains very small amount of karrikinolide, the attractive bioactivity and less availability have embarked chemists to synthesize this compound. Heretofore, six total syntheses of karrikinolide (**1**) have been reported.[2-7] All of them include construction of the five or six membered ring in the early stage of the total synthesis.

Recently, we developed the wide range stereocontrol strategy, the strategy to synthesize acyclic polyketides in short step, which is based on the initial construction of the central part of the molecule and a subsequent functionalization of the surroundings.[8] This strategy might be applicable to synthesize cyclic compounds. Based on our background, we planned the synthesis of karrikinolide (**1**) including cyclization reactions for both rings in the late stage. Herein, we present a concise synthesis of karrikinolide (**1**) by the boron-mediated aldol type acetal addition.

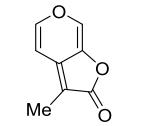
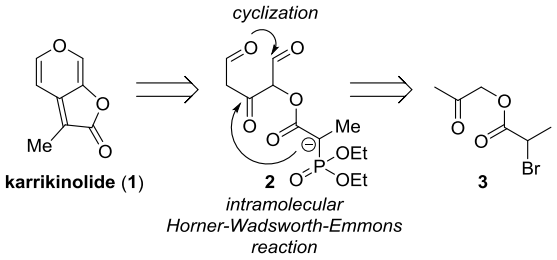


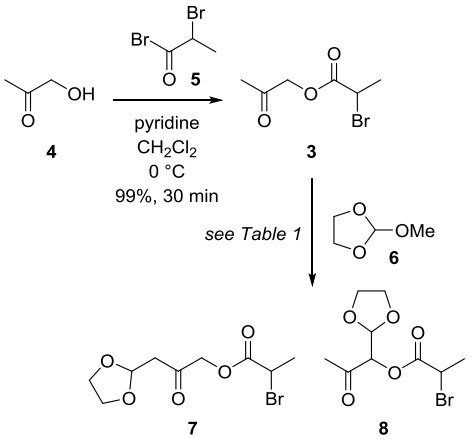
Figure 1. Structure of karrikinolide (**1**).

Our synthetic plan is disclosed in Scheme 1. Karrikinolide (**1**) would be synthesized by the intramolecular Horner-Wadsworth-Emmons reaction to construct the γ-lactone and cyclization of dialdehyde **2** to form the pyran ring. Dialdehyde **2** could be derived from acylated acetol **3**.

Scheme 1. Retrosynthesis of karrikinolide (1).



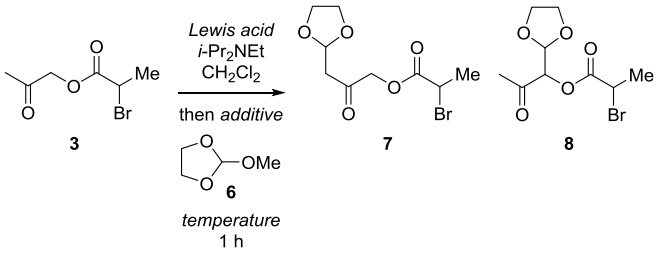
Scheme 2. Acylation and the sequential formylation.



The synthesis started from commercially available materials, acetol (**4**) and 2-bromopropionyl bromide (**5**) (Scheme 2). The acylation reaction proceeded smoothly to afford ester **3** in quantitative yield. Next, the aldol type acetal addition reaction to give monoacetals **7** and **8** was examined (Table 1).

Boron trifluoride diethyl etherate in the presence of Hünig base[9] did not work to afford any adduct (entry 1). When TMSOTf or TBSOTf with $BF_3 \cdot OEt_2$ was employed,[10] the Mukaiyama aldol type acetal addition proceeded to afford adducts **7** and **8** in good yield in a non-selective manner (entries 2 and 3). Although the reaction with TIPSOTf proceeded slowly (in 18 h) even at the elevated temperature (40 ºC), it gave adducts in high yield with moderate regioselectivity (**7**:**8** = 2.7:1), in which the *exo* adduct **7** was the major isomer (entry 4). When TMSCl and *i*-Pr_2NEt in the presence of $BF_3 \cdot OEt_2$ were employed, no adduct was obtained even at the elevated temperature (entries 5 and 6). Changing Lewis acid to $SnCl_4$ or $TiCl_4$ did not afford the desired adducts (entries 7 and 8). However, *n*-Bu_2BOTf[11] gave adducts in high yield with high regioselectivity being the *endo* adduct **8** as the major product (entry 9).

Table 1. Aldol type acetal addition of ketone 3.



entry	Lewis acid	additive	temp. (°C)	yield (%)	**7**:**8** [a]
1	$BF_3 \cdot OEt_2$	-	–78	0	-
2	TMSOTf	-	25	72	1.2:1
3	TBSOTf	$BF_3 \cdot OEt_2$	25	76	1:1
4[b]	TIPSOTf	$BF_3 \cdot OEt_2$	40	82	2.7:1
5	TMSCl	$BF_3 \cdot OEt_2$	25	0	-
6[c]	TMSCl	$BF_3 \cdot OEt_2$	60	0	-
7	$SnCl_4$	-	–78 to –10	0	-
8	$TiCl_4$	-	–78 to –10	0	-
9	*n*-Bu_2BOTf	-	–78 to –10	90	1:8

[a] The ratio was determined by 400 MHz ^1H NMR.

[b] The reaction time was 18 h.

[c] $ClCH_2CH_2Cl$ was employed as solvent and the reaction time was 17 h.

Since both regioisomers **7** and **8** were produced in the aldol type acetal addition reaction of ketone **3** (Table 1), the second aldol type acetal addition of each regioisomer was examined to obtain α,α'-adduct **9** (Scheme 3).

At first, the aldol type acetal addition of **7** was examined (Table 2). Employing TBSOTf with $BF_3 \cdot OEt_2$ gave α,α'-adduct **9** in low yield (entry 1). Although $SnCl_4$ did not provide **9**, $TiCl_4$ produced the target molecule in low yield (entries 2 and 3). The best result was obtained with *n*-Bu_2BOTf, but the yield was moderate (entry 4).

Scheme 3. Aldol type acetal addition of ketones 7 and 8.

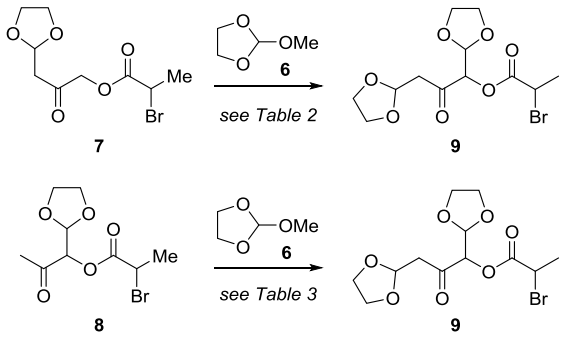
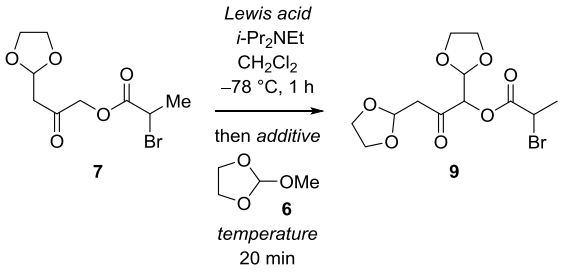
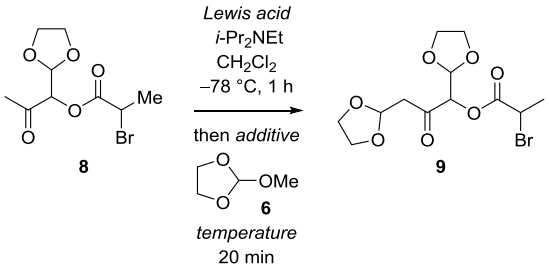


Table 2. Aldol type acetal addition of ketone 7.



entry	Lewis acid	additive	temperature (°C)	yield (%)
1	TBSOTf	$BF_3 \cdot OEt_2$	25	32
2	$SnCl_4$	-	–78 to –10	0
3	$TiCl_4$	-	–78 to –10	30
4	*n*-Bu_2BOTf	-	–78 to –10	47

Table 3. Aldol type acetal addition of ketone 8.



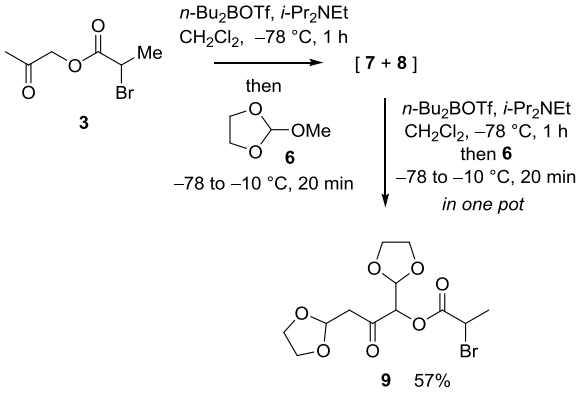
entry	Lewis acid	additive	temperature (°C)	yield (%)
1	TBSOTf	$BF_3 \cdot OEt_2$	25	8
2	$SnCl_4$	-	–78 to –10	30
3	$TiCl_4$	-	–78 to –10	77
4	*n*-Bu_2BOTf	-	–78 to –10	83

Next, the aldol type acetal addition of **8** was examined (Table 3). Employing TBSOTf with $BF_3 \cdot OEt_2$ gave α,α'-adduct **9** in very low yield (entry 1). $SnCl_4$ provided **9** in low

yield (entry 2), while $TiCl_4$ produced the target molecule in good yield (entry 3). The best results was obtained by treatment with *n*-Bu_2BOTf, which gave adduct **9** in 83% yield.

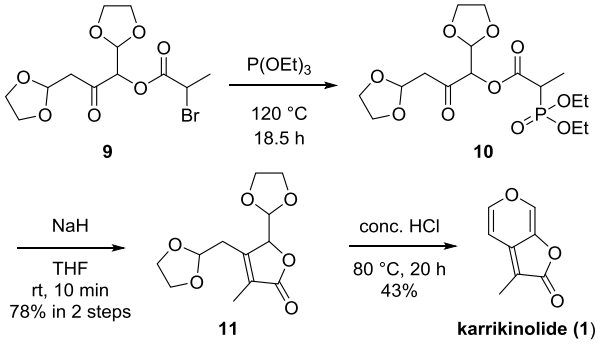
Since both the first and second acetal addition reactions proceeded well by employing *n*-Bu_2BOTf, the one pot procedure to obtain **9** from **3** was examined (Scheme 4). After generation of mono-acetals 7 and **8**, additional Hünig base, *n*-Bu_2BOTf, and orthoester **6** were introduced to the reaction mixture. This procedure worked to promote the double aldol type acetal addition to give **9** directly from **3**.

Scheme 4. Double aldol type acetal addition of ketone 3.



With α,α'-adduct **9** in hand, the total synthesis of karrikinolide (**1**) was completed (Scheme 5). The Arbuzov reaction of **9** proceeded to give phosphate **10**, which was subjected to the intramolecular Horner-Wadsworth-Emmons reaction to construct γ-lactone **11**. Each reaction proceeded well to give **11** in good yield. Finally, treatment of diacetal **11** with concentrated hydrochloric acid at the elevated temperature promoted the hydrolysis of acetals followed by cyclization to construct the pyran ring, affording karrikinolide (**1**).

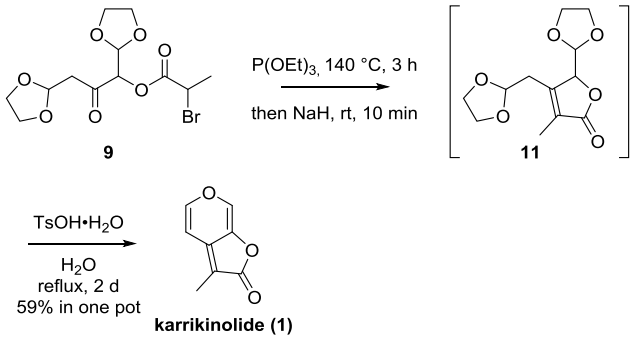
Scheme 5. Stepwise conversion of ketone 9 into karrikinolide (1).



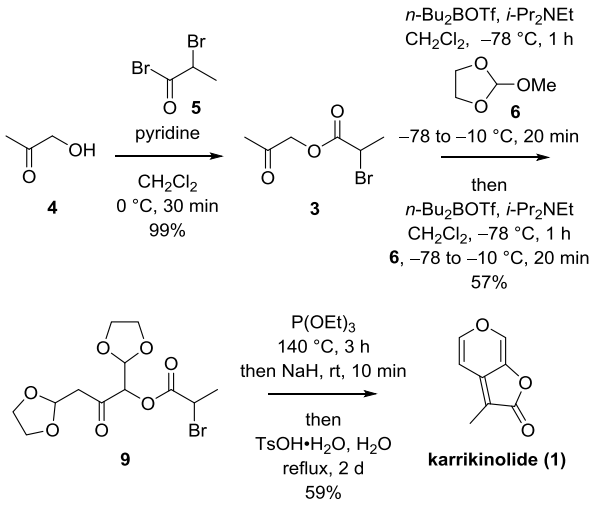
Based on the stepwise synthesis of karrikinolide (**1**) in Scheme 5, the sequence was shortened into the one pot procedure (Scheme 6). Treatment of **9** in triethyl phosphite at 140 ºC for 3 hours gave the corresponding phosphate **10**, and after cooling to room temperature NaH was added to the reaction mixture to provide lactone **11**. After TLC showed disappearance of phosphate **10**, water and *p*-toluenesulfonic acid were added into the reaction mixture and the reaction temperature was raised to reflux. After 2 days, karrikinolide (**1**) was obtained in 59% yield from diacetal **9**.

Therefore, the three steps synthesis of karrikinolide (**1**) has been established (Scheme 7). This procedure worked reproductively to synthesize **1** (three steps, 33% overall yield) in 100 mg scale.

Scheme 6. One pot conversion of ketone 9 into karrikinolide (1).



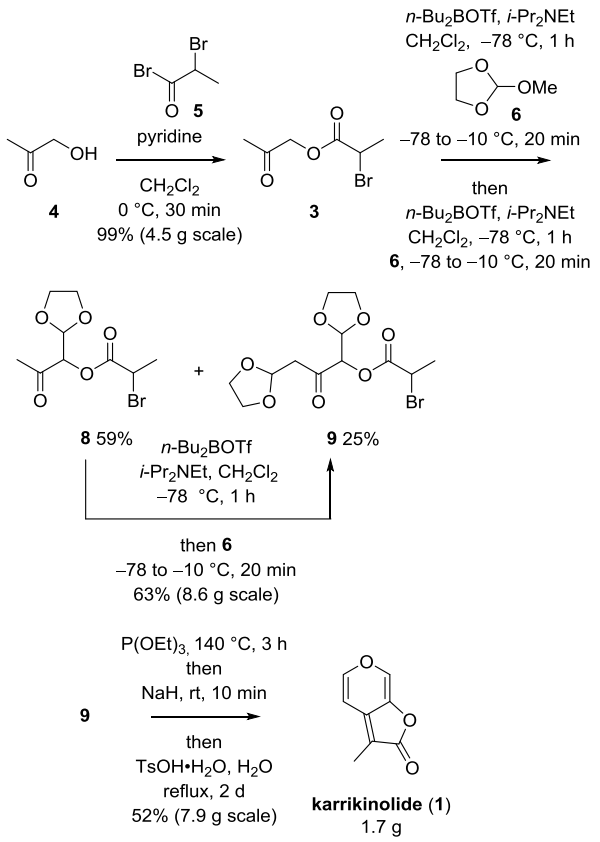
Scheme 7. Three-pot synthesis of karrikinolide (1) in 100 mg scale.



Additionally, the gram scale synthesis of karrikinolide was performed (Scheme 8). Acylation of acetol (**4**) proceeded quantitatively to give bromoester **3**. One pot sequential acetal addition in multi gram scale afforded monoaetal **8** and diacetal **9**, in which monoacetal **8** was the major product. Monoacetal **8** was converted into diacetal **9** under the conditions as mentioned in Table 3. Finally, the one pot sequence including the Arbuzov reaction, the intramolecular Horner-Wadsworth-Emmons reaction, acidic hydrolysis, and cyclization gave karrikinolide (**1**). This procedure gave karrikinolide (**1**) in gram scale.

In conclusion, an efficient synthesis of karrikinolide (**1**) has been established. The both α and α' positions of *O*-acylated acetol were alkylated by the boron-mediated aldol type acetal addition reaction. One pot sequence including the Arbuzov reaction, intramolecular Horner-Wadsworth-Emmons reaction, acidic hydrolysis of acetals, and pyran formation provided karrikinolide. The synthesis was achieved in three steps with 33% overall yield in 100 mg scale. This procedure was applicable to gram-scale synthesis of karrikinolide.

Scheme 8. Gram scale synthesis of karrikinolide (1).



EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were recorded at 400 MHz with JEOL ECS-400 instruments. Coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were recorded at 101 MHz with JEOL ECS-400 instruments. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak. FT-IR spectra were recorded with Thermo Fisher SCIENTIFIC NICOLET 6700 FT-IR. HR-MS were obtained with Thermo Fisher SCIENTIFIC EXACTIVE PLUS (ESI/Orbitrap MS). All reactions were monitored by TLC (silica gel 60 F_{254}, Merck). CH_2Cl_2 was distilled from P_2O_5 immediately before use. *i*-Pr_2NEt was distilled from CaH_2 before use. Di-*n*-butylboron trifluoromethanesulfonate, and 2-methoxy-1,3-dioxolane were prepared by general method[1)2)3)]. All reactions were performed under a static nitrogen atmosphere in glassware with magnetic stirring.

Experimental Procedure. *2-Bromopropionic acid 2-oxopropyl ester (**3**).* To a solution of hydroxyacetone **4** (4.20 mL, 61.2 mmol) in CH_2Cl_2 (84.0 mL) were added pyridine (7.41 mL, 91.8 mmol) and 2-bromopropionyl bromide **5** (9.62 mL, 91.8 mmol) at 0 °C. After stirring for 30 min, a saturated aqueous solution of $NaHCO_3$ (84.0 mL) was added. The aqueous layer was extracted with ethyl acetate (84.0 mL×5) and the combined organic layer was concentrated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane : CH_2Cl_2 = 1 : 1) to give the compound 3 as a colorless oil (12.70 g, 60.8 mmol, 99%). : R_f value : 0.73 (*n*-hexane : ethyl acetate = 1 : 1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.76 (1H, d, *J* = 16.4 Hz), 4.70 (1H, d, *J* = 16.4 Hz), 4.49 (1H, q, *J* = 7.0 Hz), 2.19 (3H, s), 1.89 (3H, d, *J* = 7.0 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$ 101 MHz): δ (ppm) 200.7, 169.6, 69.1, 39.2, 26.1, 21.6. IR (thin film, KBr): 2985, 2934, 1755, 1732, 1373, 1224, 1152, 963 cm^{-1}. HRMS(ESI) m/z calcd for $C_6H_9O_3BrNa$ [M + Na]$^+$, 230.9627; found 230.9627.

*Procedure of the aldol type acetal addition of acetol ester **3**.* To a solution of compound **3** (28.7 mg, 137 μmol) in dry CH_2Cl_2 (580 μL) was added *i*-Pr_2NEt (26.9 μL, 158 μmol) at room temperature. After stirring 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethanesulfonate in dry CH_2Cl_2 (178 μL, 178 μmol) was dropwise added at -78 °C. After stirring for 1 h, 2-methoxy-1,3-dioxolane **6** (15.9 μL, 168 μmol) was dropwise added. After warming up to -10 °C over 20 min, a saturated aqueous solution of $NaHCO_3$ (580 μL) was added. The aqueous layer was extracted with CH_2Cl_2 (580 μL×5). The combined organic layer was concentrated in *vacuo*. The residue (91.7 mg) was analyzed by ^{1}H NMR spectroscopy (**7**:**8**:**3** = 10:80:10). *2-Bromopropionic acid 3-(1,3-dioxolan-2-yl)-2-oxopropyl ester (**7**)*: R_f value : 0.31 (*n*-hexane : ethyl acetate = 2 : 1) : ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) : 5.21 (1H, t, *J* = 4.5 Hz), 4.86 (1H, d, 17.0 Hz), 4.77 (1H, d, 17.0 Hz), 4.49 (1H, q, 7.0 Hz), 4.03-3.87 (4H, m), 2.83 (2H, d, *J* = 4.5 Hz), 1.89 (3H, d, *J* = 7.0 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) 199.2, 169.5, 100.3, 69.5, 65.1, 44.0, 39.2, 21.7. IR (thin film, KBr): 2961, 2927, 2894, 1747, 1732, 1260, 1133, 1075, 1031, 945, 801. HRMS(ESI) m/z calcd for $C_9H_{13}O_5BrNa$ [M + Na]$^+$, 302.9839; found 302.9838. *2-Bromopropionic acid 1-(1,3-dioxolan-2-yl)-2-oxopropyl ester (**8**)*: R_f value : 0.42 (*n*-hexane : ethyl acetate = 2 : 1) : ^{1}H NMR ($CDCl_3$, 400 MHz): Peaks of the diastereomer are indicated in bracket. δ (ppm) 5.34 (1H, d, *J* = 3.0 Hz), [5.31 (1H, d, *J* = 3.0 Hz)], 5.21 (1H, d, *J* = 3.0 Hz), [5.17 (1H, d, *J* = 3.0 Hz)], 4.51 (1H, q, *J* = 7.0 Hz), [4.48 (1H, q, *J* = 7.0 Hz)], 4.12-4.03 (2H, m), [4.12-4.03 (2H, m)], 3.99-3.90 (2H, m), [3.99-3.90] (2H, m)], 2.26 (3H, s), [2.26 (3H, s)], 1.89 (3H, d, *J* = 7.0 Hz), [1.88 (3H, d, *J* = 7.0 Hz)]. ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ (ppm) [202.2], 201.6, 169.3, [169.2], [101.8], 101.7, 79.2, [79.2], 65.8, [65.6], 39.1, [39.1], 27.8, [27.8], 21.6, [21.6]. IR (thin film, KBr): 2981, 2987, 1747, 1732, 1359, 1222, 1159, 948 cm^{-1}. HRMS(ESI) m/z calcd for $C_9H_{13}O_5BrNa$ [M + Na]$^+$, 302.9839; found 302.9836.

*Procedure of the aldol type acetal addition of ester **7**.*To a solution of compound **7** (63.7 mg, 227 μmol) in dry CH_2Cl_2 (1.27 mL) was added *i*-Pr_2NEt (40.5 μL, 238 μmol) at room temperature. After stirring 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethanesulfonate in dry CH_2Cl_2 (272 μL, 272 μmol) was dropwise added at -78 °C. The resulting mixture was stirred for 1 h, and 2-methoxy-1,3-dioxolane **6** (24.0 μL, 249 μmol) was dropwise added at -78 °C. The reaction mixture was warmed up to -10 °C over 20 min and a saturated aqueous solution of $NaHCO_3$ (1.5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (1.5 mL×5). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 4 : 1) to give the compound **9** as a yellow oil (37.6 mg, 107 μmol, 47%). *2-Bromopropionic acid bis-1,3-(1,3-dioxolan-2-yl)-2-oxopropyl ester (**9**)*: R_f value : 0.40 (*n*-hexane : ethyl acetate = 1 : 1) : ^{1}H NMR (C_6D_6, 400 MHz): Peaks of the diastereomer are indicated in brackets. δ (ppm) 5.42 (1H, d, *J* = 2.5 Hz), [5.39 (1H, d, *J* = 2.5 Hz)], 5.30 (1H, t, *J* = 5.0 Hz), 5.26 (1H, d, *J* = 2.5 Hz), [5.25 (1H, d, *J* = 2.5 Hz)], [5.25 (1H, t, *J* = 5.0 Hz)], 4.06 (1H, q, *J* = 7.0 Hz), [4.00 (1H, q, *J* = 7.0 Hz)], 3.53-3.38 (4H, m), [3.53-3.38 (4H, m)], 3.15-3.26 (4H, m), [3.15-3.26 (4H, m)], 3.08-2.95 (2H, m), [3.08-2.95 (2H, m)], 1.47 (3H, d, *J* = 6.5Hz), [1.46 (3H, d, *J* = 6.5Hz)]. ^{13}C {^{1}H} NMR (C_6D_6, 101 MHz): δ (ppm) 199.3, [199.0], 169.1, [168.8], 102.1, [102.1], 100.7, [100.6], 79.6, [79.4], 65.5, [65.5], 65.2, [65.2], 64.8, [64.7], 45.4, [45.4], 39.8, [39.5], 21.5, [21.4]. IR (thin film, KBr): 2962, 2895, 1748, 1732, 1220, 1146, 946 cm^{-1}. HRMS(ESI) m/z calcd for $C_{12}H_{17}O_7BrNa$ [M + Na]$^+$, 375.0050; found 375.0047.

*Procedure of the aldol type acetal addition of ester **8***. To a solution of compound **8** (54.5 mg, 194 μmol) in dry CH_2Cl_2 (1.09 mL) was added *i*-Pr_2NEt (34.6 μL, 204 μmol) at room temperature. After stirring 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethanesulfonate in dry CH_2Cl_2 (233 μL, 233 μmol) was dropwise added at -78 °C. The resulting mixture was stirred for 1 h, and 2-methoxy-1,3-dioxolane **6** (20.6 μL, 213 μmol) was dropwise added at -78 °C. The reaction mixture was warmed up to -10 °C over 20 min and a saturated aqueous solution of $NaHCO_3$ (1.3 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (1.3 mL × 5). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 4 : 1) to give the compound **9** as a yellow oil (56.7 mg, 160 mmol, 83%, diastereomer mixture).

*The double aldol type acetal addition reaction of ester **3***: To a solution of compound **3** (108.1 mg, 517 μmol) in dry CH_2Cl_2 (2.2 mL) was added *i*-Pr_2NEt (92 μL, 569 μmol) at room temperature. After stirring for 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethanesulfonate in dry CH_2Cl_2 (620 μL, 620 μmol) was dropwise added at -78 °C. After stirring for 1 h at -78 °C, 2-methoxy-1,3-dioxolane **6** (54.8 μL, 569 μmol) was dropwise added. The reaction mixture was warmed up to -10 °C over 20 min and *i*-Pr_2NEt (92 μL, 569 μmol) was added at -78 °C. After stirring for 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethane sulfonate in dry CH_2Cl_2 (620 μL, 620 μmol) was dropwise added at -78 °C. The resulting mixture was stirred for 1 h, and 2-methoxy-1,3-dioxolane **6** (54.8 μL, 569 μmol) was dropwised added. The reaction mixture was warmed up to -10 °C over 20 min, a saturated aqueous solution of $NaHCO_3$ (3.5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3.5 mL × 5). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) to give the compound **9** as a yellow oil (102.9 mg, 29.1 μmol, 57%).

*The double aldol type acetal addition reaction in 9.35 g scale of ester **3***: To a solution of compound **3** (9.35 g, 44.7 mmol) in dry CH_2Cl_2 (187 mL) in 1 L one-neck flask was added *i*-Pr_2NEt (7.99 mL, 47.0 mmol) at room temperature. After stirring 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethanesulfonate in dry CH_2Cl_2 (53.7 mL, 53.7 mmol) was dropwise added at -78 °C. The resulting mixture was stirred for 1 h at -78 °C, and 2-methoxy-1,3-dioxolane **6** (4.74 mL, 49.2 mmol) was dropwise added. The reaction mixture was warmed up to -10 °C over 20 min and *i*-Pr_2NEt (7.99 mL, 47.0 mmol) was added at -78 °C. After stirring for 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethanesulfonate in dry CH_2Cl_2 (53.7 mL, 53.7 mmol) was dropwise added at -78 °C. After stirring for 1 h, 2-methoxy-1,3-dioxolane **6** (4.74 mL, 49.2 mmol) was dropwised added. The reaction mixture was warmed up to -10 °C over 20 min, a saturated aqueous solution of $NaHCO_3$ (187 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (187 mL × 5). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 4 : 1) to give the compound **8** as a yellow oil (7.44 g, 26.5 mmol, 59%) and the compound **9** as a yellow oil (2.39 g, 11.0 mmol, 25%).

*The aldol type acetal addition reaction in 8.56 g scale of **8*** : To a solution of compound **8** (8.56 g, 30.5 mmol) in dry CH_2Cl_2 (127 mL) in 500 mL one-neck flask was added *i*-Pr_2NEt (5.44 mL, 32.0 mmol) at room temperature. After stirring 10 min at -78 °C, a solution of 1.0 M di-*n*-butylboron trifluoromethanesulfonate in dry CH_2Cl_2 (36.5 mL, 36.5 mmol) was dropwise added at -78 °C. The resulting mixture was stirred for 1 h, and 2-methoxy-1,3-dioxolane **6** (3.23 mL, 33.5 mmol) was dropwise added. The reaction mixture was warmed up to -10 °C over 20 min and a saturated aqueous solution of $NaHCO_3$ (170 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (170 mL × 5). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1) to give the compound **9** as a yellow oil (6.71 g, 19.0 mmol, 63%, diastereomer mixture).

*5-(1,3-dioxolan-2-yl)4-((1,3-dioxolan-2-yl)methyl-3-methyl-2(5H)-furanone **(11)***: To a solution of compound **9** (56.0 mg, 160 μmol) in triethyl phosphite (500 μL) was stirring for 18.5 h at 120 °C. The reaction mixture was cooled to room temperature and the solvent was removed by toluene azeotrope. The crude product was dissolved in THF (1.0 mL) and sodium hydride (55% in mineral oil suspension, 9.4 mg, 215 μmol) was added at 0 °C. After stirring for 10 min at room temperature, AcOH (13.6 μL) and a saturated aqueous solution of $NaHCO_3$ (1.0 mL) was added. The aqueous layer was extracted with ethyl acetate (1.0 mL × 3). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 4 : 1) to give the compound **11** as yellow oil (50.8 mg, 125 μmol, 78% in 2 steps). : R_f value : 0.48 (*n*-hexane : ethyl acetate = 1 : 1) : ^1H NMR ($CDCl_3$, 400 MHz): 5.23 (1H, d, *J* = 2.5 Hz), 5.03 (1H, dd, *J* = 5.0, 3.5 Hz), 5.02-4.99 (1H, m), 4.13-4.08 (1H, m), 4.02-3.84 (7H, m), 2.97 (1H, dd, *J* = 14.5, 3.5 Hz), 2.70 (1H, ddq, *J* = 14.5, 5.0, 1.0 Hz), 1.88 (3H, dd, *J* = 1.5, 1.0 Hz). ^{13}C {^1H} NMR ($CDCl_3$, 101 MHz), δ (ppm): 174.0, 153.2, 127.9, 101.9, 101.7, 82.8, 65.8, 65.6, 65.1, 65.0, 31.6, 8.9. IR (thin film, KBr): 2897, 1755, 1677, 1131, 1094, 1054, 947, 762. (HRMS(ESI) m/z calcd for $C_{12}H_{17}O_6$ $[M + H]^+$, 257.1020, found 257.1021.

*Karrikinolide **(1)***: To a solution of compound **11** (21.5 mg 85.0 μmol) in concentrated hydrochloric acid (600 μL) was stirred for 20 h in 80 °C. The mixture was cooled to room temperature and Et_2O (600 μL) was added. The aqueous layer was extracted with Et_2O (600 μL × 20). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 4 : 1) to give the karrikinolide (**1**) as light yellow crystal (5.4 mg, 36.6 μmol, 43%) : R_f value : 0.64 (*n*-hexane : ethyl acetate = 1 : 1): mp 118-119 °C: ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.44 (1H, s), 7.32 (1H, d, *J* = 5.5 Hz), 6.51 (1H, d, *J* = 5.5 Hz), 1.94 (3H, s). ^{13}C {^1H} NMR ($CDCl_3$, 101 MHz), δ (ppm): 171.3, 148.0, 142.3, 139.7, 126.8, 103.4, 100.3, 7.7. IR (thin film, KBr): 3087, 2923, 1743, 1669, 1624, 1557, 1314, 1286, 1229, 1115, 1075, 991, 881, 867, 809 cm^{-1}. HRMS(ESI) m/z calcd for $C_8H_7O_3$ $[M + H]^+$, 151.0390; found 151.0389.

*One pot procedure from ester **9** to karrikinolide **(1)***: To a solution of compound **9** (2.35 g, 6.65 mmol) in triethyl phosphite (47.0 mL) was stirring for 3 h at 140 °C. The reaction mixture was cooled to room temperature and sodium hydride (436 mg, 9.98 mmol) was added to the mixture. The mixture was stirred for 10 min, and H_2O (23.5 mL) and *p*-toluenesulfonic acid monohydrate (31.6 g, 16.6 mmol) was added at 0 °C. After stirring for 1 h at room temperature, H_2O (212 mL) was added. After stirring for 2 d in reflux, then the reaction mixture was cooled to room temperature and Et_2O (280 mL) was added. The aqueous layer was extracted with Et_2O (280 mL × 10). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 1 : 1) to give karrikinolide (**1**) as light yellow crystal (584 mg, 3.89 mmol, 59%).

*One pot procedure from ester **9** to karrikinolide **(1)** in 7.87 g scale of ester **9***: To a solution of compound **9** (7.87 g, 22.3 mmol) in triethyl phosphite (157 mL) in 2 L one-neck flask with reflux condenser (φ = 3.5 cm, h = 30 cm) was stirring for 3 h at 140 °C. The reaction mixture was cooled to room temperature and sodium hydride (1.46 g, 33.4 mmol) was added to the mixture. The mix-

ture was stirred for 10 min, and H_2O (78.7 mL) and *p*-toluenesulfonic acid monohydrate (106.0 g, 55.7 mmol) was added at 0 °C. After stirring for 1 h at room temperature, H_2O (708.3 mL) was added. After stirring for 2 d in reflux, then the reaction mixture was cooled to room temperature and Et_2O (800 mL) was added. The aqueous layer was extracted with Et_2O (800 mL × 10). The combined organic layer was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane : ethyl acetate = 1 : 1) to give karrikinolide (**1**) as light yellow crystal (1.72 g, 11.4 mmol, 52%).

ASSOCIATED CONTENT

Supporting Information

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

The Supporting information includes comparison of spectroscopic data and the melting points of the synthesized karrikinolide with reported literature values, and ^1H and ^{13}C NMR spectra of compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

* seijiro@waseda.jp

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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