Synthesis of functionalized Morita–Baylis–Hillman adducts by a conjugate addition–elimination sequence†

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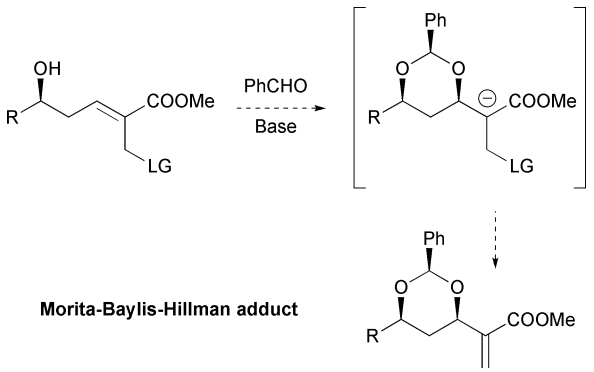
We have developed a new conjugate addition–elimination sequence for the diastereoselective synthesis of protected allylic *syn* 1,3-diols which are Morita–Baylis–Hillman adducts. The synthesis of the substrates involves a challenging cross-metathesis reaction that leads to hindered trisubstituted olefins.

Introduction

The coupling of electrophiles with activated alkenes in the presence of tertiary amines or phosphines, known as the Morita–Baylis–Hillman reaction, has received wide attention from organic chemists.[1,2] In this paper, we wish to report the synthesis of functionalized Morita–Baylis–Hillman adducts, encompassing a *syn* 1,3-diol protected as a benzylidene acetal, by a new method (Scheme 1).



Scheme 1 Addition–elimination sequence.

Results

We envisioned to install the protected *syn* 1,3-diol motif by a stereoselective intramolecular conjugate addition of a hemiacetal anion formed *in situ* from a homoallylic alcohol and benzaldehyde in the presence of base,[3] followed in the same pot by elimination of a suitable leaving group (Scheme 1). We have recently reported such a one-pot conjugate addition–elimination sequence on vinyl sulfones.[4]

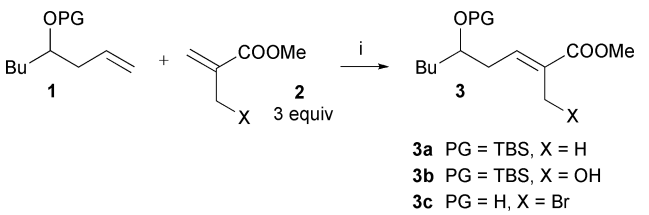
We planned to synthesize the conjugate addition precursor **3** by a challenging cross-metathesis (CM) between protected homoallylic alcohol **1** and methacrylate derivative **2** (Scheme 2). There are very few examples of CM reactions for the formation of trisubstituted double-bonds, and even fewer when one of the substituents is not a methyl group.[5] As cross-metatheses between methyl methacrylate and unhindered terminal olefins proceed in good yields and excellent *E*/*Z* selectivity with **Grubbs 2** catalyst,[6] we first tested the metathesis of compounds **1** with **2** (X = H). CM of unprotected homoallylic alcohol **1** (PG = H) with **2** (X = H) only led to the dimer of the former substrate (Table 1, entry 1). Protection of the alcohol of **1** as a *tert*-butyldimethylsilyl ether slowed the dimerization, and compound **3a** was obtained in quantitative yield after heating **1** with methyl methacrylate (3 equiv) in dichloromethane for 2 days in the presence of 5 mol% of **Grubbs 2** (entry 2).

We then applied these reaction conditions to the metathesis of **1** (PG = TBS) with the acetoxy derivative of **2** (X = OAc),[7] which would lead to the compound with the leaving group already in place for the cascade reaction. Unfortunately, no trace of the desired product was observed, and even conversion to the dimer of the protected homoallylic alcohol was very low (entry 3). This lack of reactivity of allylic acetates towards CM had already been observed by Cossy and co-workers,[8] and could be due to the formation of a non-reactive complex where the acetate

Table 1 Olefin cross-metathesis between **1** and **2**

	PG	X	Conversion Dimer of **1**	Conversion Product **3**	Yield of **3**
1	H	H	85%	—	—
2	**TBS**	**H**	**0%**	**100%**	**Quant. (3a)**
3	TBS	OAc	7%	—	—
4	TBS	OH	80%	20%	18% (**3b**)
5	TBS	Br	85%	15%	15%[a] (**3c**)
6	**TBS**	**OTES**	**35%**	**65%**	**58%**[b] (**3b**)

[a] After hydrolysis of the TBS ether with HF–CH_3CN (PG = H). [b] After hydrolysis of the TES ether with PPTS–MeOH–THF (X = OH).



Scheme 2 *Reagents and conditions:* (i) 5 mol% **Grubbs 2**, CH_2Cl_2, 0.5 M, reflux, 2 days.

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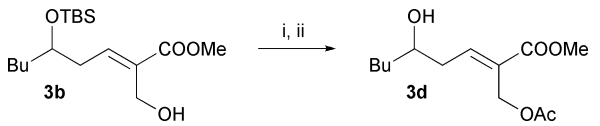
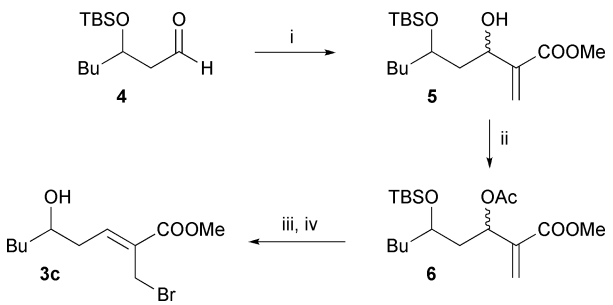
complexes the metallacyclobutane intermediate derived from **2**. Cross-metathesis of **1** (PG = TBS) with allylic alcohol **2** (X = OH) furnished compound **3b** in 18% yield (entry 4). This reaction is plagued by the formation of a large amount of the dimer of **1**. A similar result was observed with the bromo derivative of **2** (X = Br),[9] and allylic bromide **3c** was obtained in 15% yield after hydrolysis of the TBS ether with HF in acetonitrile (entry 5).‡ Finally, the best result was obtained with triethylsilyl ether **2** (X = OTES).§ A significant amount of the dimer of **1** was still observed, but alcohol **3b** was produced in 58% yield after subsequent hydrolysis of the TES ether under acidic conditions (entry 6).‡ Compound **3b** was then transformed into the suitable precursor **3d** for the cascade reaction by acetylation of the primary alcohol and hydrolysis of the TBS ether in good overall yield (Scheme 3).



Scheme 3 *Reagents and conditions:* (i) AcCl, Py, CH_2Cl_2; (ii) 5 : 95 HF–CH_3CN, 84% (2 steps).

We also explored an alternative way to prepare the substrates for the conjugate addition–elimination cascade. Morita–Baylis–Hillman reaction of β-siloxy aldehyde **4** with methyl acrylate afforded alcohol **5** as a 1 : 1 mixture of diastereomers (Scheme 4). This compound was converted to acetate **6** in good yield. This acetate was treated with magnesium bromide etherate to lead to the corresponding allylic bromide,[10] and removal of the silyl ether with HF in acetonitrile then furnished **3c** in quantitative yield.



Scheme 4 *Reagents and conditions:* (i) methyl acrylate, DABCO, MeOH, 7 days, 71%; (ii) AcCl, Py, CH_2Cl_2, 89%; (iii) $MgBr_2{\cdot}OEt_2$, THF, reflux; (iv) 5 : 95 HF–CH_3CN, 98% (2 steps).

When the conjugate addition–elimination sequence was performed under the conditions that had been optimized for the vinyl sulfones,[4a] benzylidene acetal **7** was obtained in 85% yield, but with a disappointing *syn*/*anti* selectivity (Scheme 5, Table 2, entry 1).¶ We reasoned that the elimination reaction was taking

‡ The silyl ether was hydrolyzed for separation purposes.

§ Compound **2** (X = OTES) was prepared by protection (TESCl, Et_3N, DMAP, CH_2Cl_2, quant.) of the known corresponding alcohol (described in ref. 7).

¶ Only one of the two possible protected *anti* diols was formed, and the configuration of its acetal stereocenter was not determined. The relative configuration of the newly formed stereocenters of the *syn* diastereomer was determined by NOE experiments.

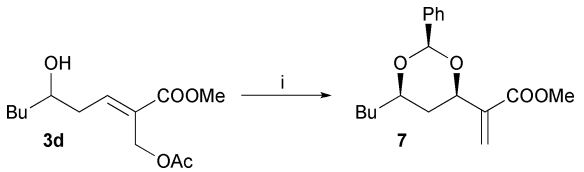
Table 2 Cascade reaction of **3d**

	T	*t*	Yield of **7**	*syn*/*anti*
1	0 °C	10 min	85%	80 : 20
2	–40 °C to 20 °C	15 min	71%	90 : 10
3	**–78 °C to 20 °C**	**15 min**	**92%**	**90 : 10**[a]

[a] Reaction performed with 2 equiv of *t*-BuOK.

Table 3 Cascade reaction of **3c**

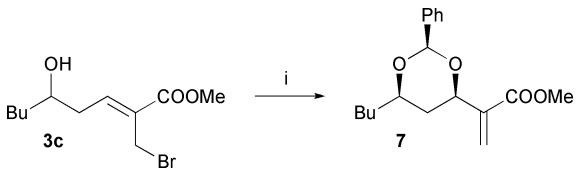
	Equiv of *t*-BuOK	*t*	Yield of **7**	*syn*/*anti*
1	3 equiv	10 min	41%	>98 : 2
2	**1.5 equiv**	**10 min**	**50%**	**>98 : 2**
3	3 × 0.4 equiv	3 × 15 min	50%	89 : 11



Scheme 5 *Reagents and conditions:* (i) 3 equiv PhCHO, 3 equiv *t*-BuOK.

place before the thermodynamic equilibrium of the conjugate addition leading to the most stable *syn* benzylidene acetal was reached. Since this equilibrium can be attained at lower temperatures for the conjugate addition on simple unsaturated esters,[3] the cascade reaction was performed from –40 °C to 20 °C (entry 2). The *syn*/*anti* ratio improved to 90 : 10, but the yield was lower. Finally, when running the reaction from –78 °C to 20 °C, compound **7** was produced in 92% yield with a 90 : 10 *syn*/*anti* selectivity (entry 3).

This cascade reaction was also tested on bromide **3c**. In this case, the diastereoselectivity was excellent, but the yield only moderate (Scheme 6, Table 3, entry 1) due to partial degradation of the starting material. Since only one equivalent of base is needed in theory for a complete reaction, we decreased the amount of potassium *tert*-butoxide employed.‖ The best yield was obtained with 1.5 equivalent of base added in one portion (entry 2). We do not have any explanation for the better selectivity observed with the bromide derivative.



Scheme 6 *Reagents and conditions:* (i) 3 equiv PhCHO, *t*-BuOK, THF, –78 °C to 20 °C.

Conclusion

We have developed a new conjugate addition–elimination sequence that leads to protected allylic *syn* 1,3-diols which are Morita–Baylis–Hillman adducts. In addition, we have optimized

‖ No other base was tested for this reaction.

a highly demanding cross-metathesis reaction for the synthesis of hindered trisubstituted olefins.

Experimental

General

^{1}H NMR spectra were recorded on a BRUKER AM 400 (400 MHz) instrument, and ^{13}C NMR spectra on the same instrument at 100 MHz, as $CDCl_3$ solutions. Infrared spectra (IR) were obtained on a PERKIN-ELMER FT 1600 instrument using NaCl salt plates (thin film) and are reported in terms of frequency of absorption (ν, cm^{-1}). Mass spectra (MS) were obtained on a HEWLETT-PACKARD HP 5989B spectrometer *via* either direct introduction or GC/MS coupling with a HEWLETT-PACKARD HP 5890 chromatograph. Ionization was obtained by chemical ionisation with ammonia (CI, NH_3). Mass spectral data are reported as m/z. High resolution mass spectra (HRMS) were obtained on a JEOL JMS-Gcmate II, GC/MS system spectrometer. Flash chromatography was performed on silica gel 60, 230–400 mesh.

Methyl (*E*)-5-*tert*-butyldimethylsiloxy-2-methyl-non-2-enoate 3a

To a degassed solution of 119 mg of **1** (PG = TBS) (0.49 mmol) and 125 mg of methyl methacrylate (1.2 mmol, 3.0 equiv) in 5 mL of CH_2Cl_2 under nitrogen were added 23 mg of [1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]-[benzylidene] ruthenium (IV) dichloride (second-generation Grubbs' catalyst) (0.02 mmol, 5 mol%). The reaction mixture was heated at reflux for 2 days. The mixture was then cooled to 20 °C, concentrated *in vacuo*, and directly purified by flash chromatography on silica gel (diethyl ether–petroleum ether 2 : 98) to yield 152 mg (quant.) of **3a** as a colorless oil. IR (CH_2Cl_2) 2956, 2933, 2858, 2361, 1708, 1650, 1462, 1434, 1366, 1264, 1254, 1083 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dt, J = 7.5, 1.4 Hz, 1H), 3.77 (s, 1H), 3.77 (m, 3H), 2.33 (t, J = 6.7 Hz, 2H), 1.85 (s, 3H), 1.45 (m, 2H), 1.29 (m, 4H), 0.90 (m, 12H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 139.5, 128.7, 71.7, 51.8, 37.2, 36.8, 27.7, 26.0, 22.9, 18.2, 14.2, 12.8, –4.5. HRMS calcd for $C_{17}H_{34}O_3$ 314.2277, found 314.2285.

Methyl (*E*)-5-(*tert*-butyldimethylsiloxy)-2-(hydroxymethyl)non-2-enoate 3b

From **2** (X = OH): to a degassed solution of 64 mg of **1** (PG = TBS) (0.26 mmol) and 88 mg of **2** (X = OH) (0.76 mmol, 3.0 equiv) in 0.4 mL of CH_2Cl_2 under nitrogen were added 10 mg of second-generation Grubbs' catalyst (0.01 mmol, 5 mol%). The reaction mixture was heated at reflux for 2 days. The mixture was then cooled to 20 °C, concentrated *in vacuo*, and directly purified by flash chromatography on silica gel (diethyl ether–petroleum ether 20 : 80 then 30 : 70) to obtain 12 mg (18%) of **3b** as a colorless oil.

From **2** (X = OTES): to a degassed solution of 100 mg of **1** (PG = TBS) (0.4 mmol) and of 300 mg of **2** (X = OTES) (1.3 mmol, 3.2 equiv) in 0.3 mL of CH_2Cl_2 under nitrogen were added 10 mg of second-generation Grubbs' catalyst (0.01 mmol, 5 mol%). The reaction mixture was heated at reflux for 2 days, and the solvent was removed *in vacuo*. The resulting mixture was then diluted with 12 mL of methanol and 1.2 mL of THF, and a catalytic amount of pyridinium *p*-toluenesulfonate was added. The resulting solution was stirred for 20 min, quenched with solid $NaHCO_3$, and diluted with water. The aqueous phase was then extracted with diethyl ether, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 30 : 70) to obtain 76 mg (58%) of **3b** as a colorless oil. IR (CH_2Cl_2) 3597, 3052, 2956, 2860, 1704, 1462, 1376, 1291, 1268, 1222, 1065, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (t, J = 7.8 Hz, 1H), 4.35 (s, 2H), 3.80 (s, 1H), 3.80 (m, 3H), 2.44 (dd, J = 7.8, 5.9 Hz, 2H), 1.45 (m, 2H), 1.29 (m, 4H), 0.89 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 142.9, 132.4, 71.5, 57.5, 52.0, 37.3, 36.1, 27.5, 26.0, 22.9, 18.2, 14.2, –4.4. HRMS calcd for $C_{13}H_{25}O_4Si$ (M^+ – *t*Bu) 273.1522, found 273.1522.

Methyl (*E*)-5-hydroxy-2-(bromomethyl)non-2-enoate 3c

From **2** (X = Br): to a degassed solution of 1.0 g of **1** (4.1 mmol) and of 2.2 g of **2** (X = Br) (12.4 mmol, 3.0 equiv) in 8 mL of CH_2Cl_2 under nitrogen were added 200 mg of second-generation Grubbs' catalyst (0.2 mmol, 5 mol%). The reaction mixture was heated at reflux for 2 days. The mixture was then cooled to 20 °C, concentrated *in vacuo*, and directly purified by flash chromatography on silica gel (diethyl ether–petroleum ether 1 : 99) to obtain 1.27 g of a pale yellow oil. Half of this oil was treated with 50 mL of a solution of 5 : 95 HF–acetonitrile, and the solution was stirred at room temperature for 3 days. The resulting mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 50 : 50) to obtain 84 mg (15%) of **3c** as a colorless oil.

From **6**: To a solution of 4.03 g of **6** (10.8 mmol) in 60 mL of THF was added 6.1 g of magnesium bromide etherate (23.7 mmol, 2.2 equiv). The resulting solution was stirred overnight at reflux. The mixture was then quenched with water, and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 1 : 9) to give 4.17 g (98%) of siloxy **3c** as a pale yellow oil. The deprotection step was performed as described above and furnished **3c** in quantitative yield. IR ($CDCl_3$) 3054, 2958, 2932, 2864, 1718, 1425, 1383, 1276, 1224, 1160, 1113, 1075, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 7.6 Hz, 1H), 4.26 (s, 2H), 3.82 (s, 1H), 3.82 (m, 3H), 2.48 (m, 2H), 1.59 (s, 1H), 1.53 (m, 2H), 1.35 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 144.4, 131.1, 70.6, 523, 37.2, 36.8, 27.8, 24.3, 22.6, 14.2. HRMS calcd for $C_{11}H_{19}O_3$ (M^+ – Br) 199.1334, found 199.1330.

Methyl (*E*)-2-(acetoxymethyl)-5-hydroxynon-2-enoate 3d

To a solution of 36 mg of **3b** (0.1 mmol) and of 10 μL of pyridine (0.11 mmol, 1.1 equiv) in 0.5 mL of CH_2Cl_2 were added 10 μL of acetyl chloride (0.13 mmol, 1.3 equiv) at 0 °C. The solution was allowed to warm to 20 °C and was stirred for 3 h. The mixture was then quenched by saturated aqueous NH_4Cl,

and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous NH_4Cl and with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 20 : 80) to give 34 mg (84%) of methyl (*E*)-5-*tert*-butyldimethylsiloxy-2-(acetoxymethyl)non-2-enoate as a colorless oil.

To 142 mg (0.38 mmol) of this ester were added 20 mL of a solution of HF–acetonitrile 5 : 95. The solution was stirred for 24 h, and was quenched by saturated aqueous $NaHCO_3$. The aqueous phase was extracted with diethyl ether, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 50 : 50) to give 103 mg (quant.) of **3d** as a colorless oil. IR ($CDCl_3$) 3054, 3056, 2960, 2932, 2865, 1723, 1425, 1372, 1295, 1265, 1237, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, $J = 7.8$ Hz, 1H), 4.86 (s, 2H), 3.77 (s, 4H), 3.77 (m, 3H), 2.49 (m, 2H), 2.04 (s, 3H), 1.87 (s, 1H), 1.34 (m, 2H), 1.10–1.30 (m, 4H), 0.90 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 166.8, 145.9, 128.8, 70.8, 58.2, 52.1, 37.2, 36.7, 27.9, 22.7, 21.0, 14.1. HRMS calcd for $C_{19}H_{36}O_5Si$ 372.2332, found 372.2349.

3-(*tert*-Butyldimethylsiloxy)heptanal 4

Through a solution of 3.0 g (12 mmol) of (1-allylpentyloxy)-*tert*-butyldimethylsilane in 140 mL of CH_2Cl_2 and 40 mL of methanol in the presence of a few drops of pyridine at −78 °C was bubbled ozone for 30 min. Then 5 mL of dimethyl sulfide were added at −78 °C and the reaction was stirred overnight at 20 °C. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (ethyl acetate–petroleum ether 20 : 80) to give 2.7 g (89%) of aldehyde **4** as a colorless oil. IR (CH_2Cl_2) 3123, 2929, 2731, 1722, 1463, 1369, 1273, 1254, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, $J = 2.5$ Hz, 1H), 4.19 (quint, $J = 5.6$ Hz, 1H), 2.52 (dd, $J = 5.7$, 2.5 Hz, 2H), 1.54 (m, 2H), 1.31 (m, 4H), 0.91 (t, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 68.4, 50.9, 37.6, 27.4, 25.9, 22.8, 18.1, 14.1, −4.3, −4.6; HRMS calcd for $C_9H_{19}O_2Si$ ($M^+ - t$Bu) 187.1154, found 187.1153.

Methyl 3-hydroxy-5-*tert*-butyldimethylsiloxy-2-methylenenonanoate 5

To a solution of 2.0 g of **4** (8.2 mmol) in 5 mL of methanol were added 17 mL of methyl acrylate (190 mmol, 23 equiv) and 4.7 g of DABCO (42 mmol, 5.1 equiv). The resulting mixture was stirred at 20 °C for 7 days. Saturated aqueous NH_4Cl was then added. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a colorless oil that was purified by flash chromatography on silica gel (diethyl ether–petroleum ether 10 : 90) to furnish 1.96 g (71%) of **5** as a colorless oil. IR (CH_2Cl_2) 3465, 2956, 2860, 1716, 1630, 1462, 1437, 1368, 1307, 1265, 1196, 1156, 1087, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.27 (m, 1H), 5.99 (m, 1H), 4.82 (d, $J = 9.9$ Hz, 0.5H), 4.62 (d, $J = 9.0$ Hz, 0.5H), 4.00 (m, 1H), 3.77 (s, 1.5H), 3.76 (s, 1.5H), 1.88 (m, 1H), 1.64 (m, 1H), 1.57 (m, 1H), 1.51 (m, 1H), 1.31 (m, 4H), 0.91 (m, 12H), 0.15 (s, 1.5H), 0.13 (s, 1.5H), 0.11 (s, 1.5H), 0.10 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 143.1, 142.6, 124.9, 124.8, 73.6, 71.8, 70.1, 67.6, 51.9, 51.8, 43.0, 41.4, 37.7, 35.9, 27.8, 26.8, 26.0, 25.9, 25.8, 23.0, 22.9, 18.1, 18.1, 14.2, −3.9, −4.4, −4.6, −4.7; HRMS calcd for $C_{17}H_{34}O_4Si$ 330.2226, found 330.2226.

Methyl 3-acetoxy-5-*tert*-butyldimethylsiloxy-2-methylenenonanoate 6

To a solution of 1.01 g of **5** (3.0 mmol) and 0.3 mL of dry pyridine (4.5 mmol, 1.5 equiv) in 15 mL of CH_2Cl_2 at 0 °C was added 0.3 mL of acetyl chloride (3.6 mmol, 1.2 equiv). The solution was allowed to warm to 20 °C and was stirred overnight. The mixture was then quenched by saturated aqueous NH_4Cl, and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous NH_4Cl and with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 10 : 90) to give 820 mg (74%) of **6** as a colorless oil. IR (CH_2Cl_2) 2956, 2859, 1735, 1633, 1462, 1437, 1371, 1280, 1262, 1239, 1156, 1111, 1063, 1036, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.28 (m, 0.5H), 6.26 (m, 0.5H), 5.76 (m, 0.5H), 5.71 (m, 0.5H), 5.64 (m, 1H), 3.78 (m, 4H), 2.08 (s, 1.5H), 2.08 (s, 1.5H), 1.89 (ddd, $J = 13.4$, 8.5, 4.2 Hz, 1H), 1.78 (dd, $J = 6.7$, 5.7 Hz, 1H), 1.47 (m, 2H), 1.29 (m, 4H), 0.91 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 165.7, 141.2, 140.4, 125.3, 124.9, 70.0, 70.0, 69.4, 68.8, 52.1, 42.2, 42.1, 37.6, 36.2, 27.2, 26.9, 26.0, 23.0, 22.9, 21.2, 21.2, 18.2, 18.1, 14.2, 14.2, −4.0, −4.4, −4.9; HRMS calcd for $C_{19}H_{36}O_5Si$ ($M^+ - t$Bu) 315.1628, found 315.1626.

Methyl (2*R**,4*R**,6*S**)-2-(6-butyl-2-phenyl-1,3-dioxan-4-yl)acrylate 7

From **3d**: to 36 mg of **3d** (130 μmol) in 1.4 mL of THF were added 100 μL of freshly distilled benzaldehyde (0.4 mmol, 3.0 equiv) and 30 mg of potassium *tert*-butoxide (0.26 mmol, 2.0 equiv) at −78 °C. The mixture was allowed to warm to 20 °C and was stirred for 15 min. The mixture was then quenched by saturated aqueous NH_4Cl, and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 20 : 80) to give 37 mg (92%) of **7** (*syn*/*anti* = 90 : 10) as a colorless oil.

From **3c**: to 10 mg of **3c** (36 μmol) in 0.5 mL of THF were added 20 μL of freshly distilled benzaldehyde (80 μmol, 3.0 equiv) and 10 mg of potassium *tert*-butoxide (90 μmol, 3.0 equiv) at −78 °C. The mixture was allowed to warm to room temperature and was stirred for 10 min. The mixture was then quenched by saturated aqueous NH_4Cl, and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (diethyl ether–petroleum ether 20 : 80) to give 37 mg (50%) of **7** (*syn*/*anti* > 98 : 2) as a colorless oil. IR ($CDCl_3$) 3054, 2959, 2931, 2861, 1718, 1426, 1276, 1106, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H),

7.34–7.40 (m, 3H), 6.34 (m, 1H), 6.08 (m, 1H), 5.67 (s, 1H), 4.76 (1H), 3.91 (m, 1H), 3.80 (s, 3H), 2.02 (dt, $J = 13.0$, 2.2 Hz, 1H), 1.67 (m, 1H), 1.50–1.60 (m, 2H), 1.35–1.40 (m, 4H), 0.92 (t, $J =$ 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 140.6, 138.8, 128.8, 128.3, 126.3, 125.6, 100.9, 77.3, 74.6, 52.0, 37.7, 35.6, 27.3, 22.8, 14.2. HRMS calcd for $C_{12}H_{19}O_4$ (M^+ – Ph) 227.1283, found 227.1291.

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Notes and references

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