Studies on the Model Synthesis of the Brassinolide and Dolicholide's Side Chains†

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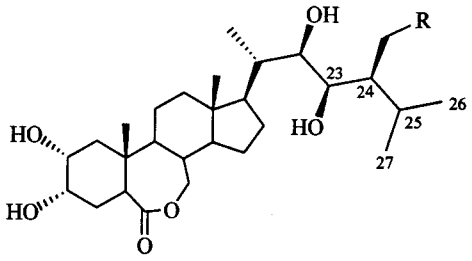
A highly stereoselective synthesis of the side chain enantiomers of brassinolide and dolicholide through an aldol reaction of 2-(4-methoxy benzyloxyl) propionylaldehyde (5) with the anion of 1-(*tert*-butyldimethylsiloxy)-3-methyl-2-butanone (6) is described.

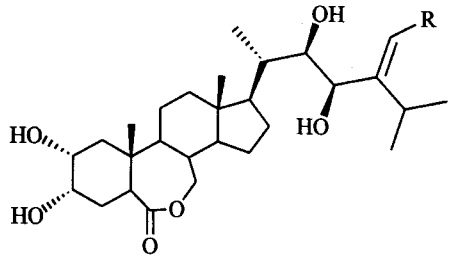
Keywords brassinolide, dolicholide, side chain, aldol reaction

Brassinolide **1** as well as its analogues **2**, **3**, **4** (Fig. 1) is a new type of promoting material for plant growth.[1,2] Owing to their novel structural features and their remarkable physiological activity, much effort has been expanded on the development of methods for their syntheses and biosynthesis.[3] So far the work on the steroidal nuclei of **1** is rather successful. The main differences of various synthetic routes of **1** are the syntheses of the side chains.[3] In our previous work,[4] we found methyl isopropyl ketone and its derivatives have high regioselectivety at −78 ℃. This can also serve as a good way to conduce C-23 to C-27 fragment of the side chain of steroids. Now we report here a new stereoselective method for constructing the side chain of **1** and related compounds with high yields.

On the basis of the structure characteristic of brassinolide **1** and dolicholide **3**, we synthesized **11** and **10**, which are the side chain enantiomers of **1** and **3** using 2-(4-methoxybenzyloxyl) propionylaldehyde (**5**) as starting material. Aldehyde **5** was prepared in two steps from ethyl (*S*)-(−)-lactate by *p*-methoxybenzylation[5] and the DIBAL-H reduction. This aldehyde was then used in an aldol reaction with the lithium enolate of 1-(*tert*-butyldimethylsiloxy)-3-methyl-2-butanone (**6**).[4] The anion was generated in THF from the α-silyloxy ketone **6** and LDA and was cooled to −78 ℃ before addition of the aldehyde. The temperature was maintained for 0.5 h and was allowed to warm up to 0 ℃, and then the reaction was quenched with dilute hydrochloric acid. Without isolation of the products, treatment of the resulting mixture with *n*-Bu_4NF, the 3*R*,4*R* diol **7**[6] was obtained along with its *syn* isomer **12** in 75% yield in a ratio of 19:1 as determined by TLC and ^1H NMR (Scheme 1). When the aldol reaction mixture was maintained below −78 ℃ for 3 h and the reaction was quenched with dilute hydrochloric acid at this temperature under these conditions (kinetic), the 3*R*,4*S* intermediate **12**[6] was obtained along with its *anti* isomer **7** in 70% yield in a ratio of 19:1 (Scheme 2). Mukaiyama-type aldol reaction[7] of silyl enol ethers **13**[8] and aldehyde **5** turned out to be more efficient than the direct reaction of the lithium enolate of **6**. Reaction of **13** and aldehyde **5** mediated by $TiCl_4$ afforded aldol products with silylated aldol products. Without isolation of the products, treatment of the resulting mixture with *n*-Bu_4NF afforded desilylated



R = H, brassinolide **1**
R = CH_3, homobrassinolide **2**



R = H, dolicholide **3**
R = CH_3, homodolicholide **4**

Fig. 1 Structure of Brassinolide **1** and its analogues **2**, **3**, **4**.

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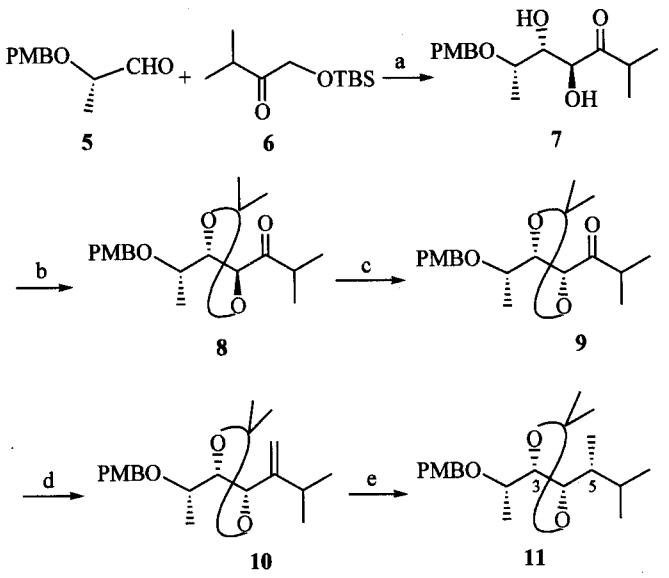
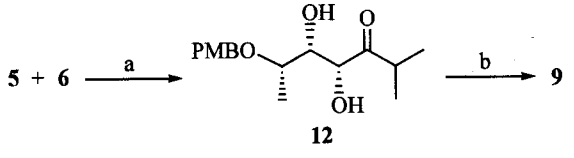
aldol products. Under these conditions, the 3*S*, 4*S* intermediate **12**[6] was obtained in 85% yield (Scheme 3).

Scheme 1



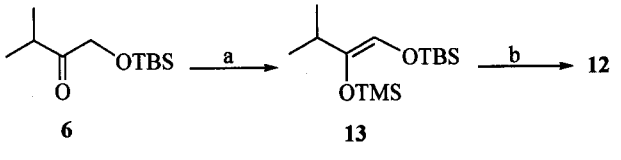
Reagents and conditions: a) 1. LDA, THF, −78 ℃—0 ℃, 0.5 h; 2. TBAF, THF, r.t., 5 min, 75%; b) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 84%; c) K_2CO_3, MeOH, reflux, 0.5 h, 93%; d) Ph_3PCH_3I, *n*-BuLi, THF, r.t., 8 h, 85%; e) PtO_2, MeOH, H_2, r.t., 6 h, 98%. PMB = *p*-methoxy-benzyl.

Scheme 2



Reagents and conditions: a) 1. LDA, THF, −78 ℃, 3 h; 2. TBAF, THF, r.t., 5 min, 70%; b) $(CH_3)_2C(OCH_3)_2$, DMF, *p*-TsOH, 2 h, 88%.

Scheme 3



Reagents and conditions: a) $NaN(SiMe_3)_2$, −78 ℃, 30 min, then TMSCl, −78 ℃—0 ℃, 2.5 h, 88%; b) 1. **5**, $TiCl_4$, CH_2Cl_2, −78 ℃, 5 h; 2. TBAF, THF, r.t., 10 min, 85%.

Diol **7** was transformed into *erythro* acetonide **8**. Treatment of **8** with potassium carbonate[9] in methanol under reflux for 0.5 h led to the epimerization of C-4 center of the acetonide to give the desired *threo* acetonide **9**,[9] which showed identical spectral data with that obtained from the diol **12**. After Witting olefination, the product **10** was hydrogenated by treating with PtO_2 in MeOH to give an 85:15 (400 MHz ^{1}H NMR) mixture of isomers of the desired product **11** in virtually quantitative yield. The coupling constant for H-4 to H-5 (J = 3.2 Hz) in the major product was smaller than that for H-4 to H-5 (J = 6.8 Hz) in the minor product and the stereochemistry at C-5 was therefore tentatively assigned as 5*R*. The observed stereochemistry in favor of the 5*R* isomer may be a result of the directing influence from the chiral acetonide group at C-3 and C-4 on the addition of hydrogen.

Conclusion

We have developed an efficient method for the stereoselective synthesis of the C-22—C-28 segment of brassinolide and dolicholide. The work on the addition of ketone **6** with the steroidal-aldehyde is in progress.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-80 or Bruker AM-400 Bruker Advance DXR-200 spectrometer in $CDCl_3$ solution using TMS as an internal reference. IR spectra were obtained using a FT-170SX spectrophoto-meter. LRMS were measured on a VG ZAB-HS spectrometer by direct inlet at 70 eV, and signals are given in *m/z* with relative intensity (%) in brackets. HRMS were determined on a Bruker Daltonics APEXII 47e Fourier Transfer spectrometer with each of EI, CI, FAB, SIMS ionization methods. All anhydrous solvents were freshly purified by standard techniques. All reactions were conducted under an argon atmosphere unless otherwise noted, and monitored by TLC. Organic extractive phases were dried over anhydrous $MgSO_4$. Purification of products was performed by flash column chromatography (FCC) on silica gel (200—300 mesh) purchased from Qing Dao Marine Chemical Co. (Qingdao, China).

(2S,3R,4R)-2-(4-Methoxybenzyloxy)-3,4-dihydroxy-5-oxo-6-methyl-heptane (**7**)

To a stirred solution of *i*-Pr_2NH (1.0 mL, 7.0 mmol) in 6 mL of dry THF was added dropwise a hexane solution of *n*-butyl lithium (1.60 mol/L, 4.0 mL, 6.4 mmol) at 0 ℃ over 5 min. After being stirred for an additional 0.5 h at r.t., the resulting mixture was cooled to −78 ℃ and syringed dropwise into a solution of α-silyloxy ketone **6** (1.30 g, 6.0 mmol) in dry THF (3.0 mL). The reaction mixture was stirred for a further 45 min after which a solution of **5** (390 mg, 2.0 mmol) in 3.0 mL of THF was added dropwise to it at −78 ℃. The resulting mixture was stirred for 0.5 h at −78 ℃ and allowed to warm gradually to 0 ℃, when it was quenched with saturated aqueous ammonium chloride (2 mL). The resulting mixture was diluted with water (6 mL) and diethyl ether (20 mL). After the organic phase was separated, the aqueous layer was then extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed with water and brine, dried, and evaporated under reduced pressure.

To a stirred solution of crude silyl ether in 15 mL of THF was added a solution of TBAF in THF (1.0 mol·dm^{-3}, 2.0 mL, 2.0 mmol) at r.t.. The resulting mixture was then stirred for 5 min and concentrated under reduced pressure to give a residue that was taken in diethyl ether (50 mL) and the solution was washed with water and brine and dried. Removal of the solvent by rotary evaporation gave a crude oil, which was then subjected to purification by FCC (light petroleum-ethyl acetate, 4:1, *V*:*V*) to afford the diols **7** (444 mg, 75%) as gum. $[\alpha]_D^{20}$ + 48 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.18 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.43—4.40 (m, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.17 (d, *J* = 11.6 Hz, 1H), 3.86—3.84 (m, 1H), 3.80 (s, 3 H), 3.56—3.53 (m, 1H), 2.89—2.86 (m, 1 H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 212.6, 159.2, 129.9, 113.6, 75.7, 75.5, 73.4, 70.3, 55.2, 37.0, 19.8, 16.8, 15.6; IR (film) ν: 1648 cm^{-1}; EIMS *m/z* (%): 296 (M^+, 19). Anal. calcd for $C_{16}H_{24}O_5$: C 64.84, H 8.16; found C 64.74, H 8.14.

(2*S*,3*R*,4*S*)-2-(4-*Methoxybenzyloxy*)-3,4-*isopropylidenedioxy*-5-*oxo*-6-*methyl-heptane* (**8**)

p-TsOH was added to a solution of **7** (340 mg, 1.15 mmol) in $Me_2C(OMe)_2$(3 mL) and DMF (3 mL). After stirring for 2 h at room temp., the mixture was poured into $NaHCO_3$ aq. and extracted with diethyl ether. The diethyl ether solution was washed with water, dried ($NaSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 to give 325 mg (84%) of **8** as gum. $[\alpha]_D^{20}$ + 3.7 (*c* 3.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.20 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.81 (d, *J* = 6.4 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.20 (t, *J* = 6.4 Hz, 1H), 4.15 (d, *J* = 11.6 Hz, 1H), 3.78 (s, 3H), 3.56—3.53 (m, 1H), 2.71—2.68 (m, 1H), 1.54 (s, 3H), 1.37 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 209.5, 159.0, 130.3, 129.1, 113.6, 109.5, 81.2, 78.6, 72.8, 69.7, 55.1, 39.6, 27.2, 25.3, 18.3, 17.7, 16.0; IR (film) ν: 1656 cm^{-1}; EIMS *m/z* (%): 336 (M^+, 6). Anal. calcd for $C_{19}H_{28}O_5$: C 67.83, H 8.39; found C 67.89, H 8.44.

(2*S*,3*R*,4*R*)-2-(4-*Methoxybenzyloxy*)-3,4-*isopropylidenedioxy*-5-*oxo*-6-*methyl-heptane* (**9**)

To a solution of *erythro* acetonide **8** (270 mg, 0.8 mmol) in 10 mL of MeOH was added K_2CO_3(550 mg, 4 mmol) at r.t.. After being stirred for 0.5 h under reflux, the resulting mixture was cooled to r.t., and then diluted with water (5 mL) and diethyl ether (20 mL). After the organic phase was separated, the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic phase was washed with water and brine, dried, and evaporated under reduced pressure. Purification of the residue by FCC (light petroleum-ethyl acetate, 8:1, *V*/*V*) gave the *thero* acetonide **9** (250 mg, 93%) as colorless oil. $[\alpha]_D^{20}$ + 2.6 (*c* 6.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.24 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.43—4.41 (m, 1H), 4.16—4.14 (m, 1H), 3.75 (s, 3H), 3.66—3.64 (m, 1H), 3.00—2.98 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.07 (t, *J* = 6.8 Hz, 6H); IR (film) ν: 1644 cm^{-1}; EIMS *m/z* (%): 336 (M^+, 16). Anal. calcd for $C_{19}H_{28}O_5$: C 67.83, H 8.39; found C 67.94, H 8.34.

(2*S*,3*R*,4*S*)-2-(4-*Methoxybenzyloxy*)-3,4-*isopropylidenedioxy*-5-*methylene*-6-*methyl-heptane* (**10**)

To a stirred mixture of Ph_3PCH_3I (404 mg, 1.0 mmol) in 10 mL of dry THF was added dropwise a hexane solution of *n*-butyl lithium (1.40 mol·dm^{-3}, 0.71 mL, 1.0 mmol) at 0 ℃ over 5 min under N_2. After being stirred for an additional 0.5 h at r.t., the resulting mixture was syringed dropwise into a solution of *thero* acetonide **9** (200 mg, 0.6 mmol) in THF (3.0 mL). The reaction mixture was stirred for a further 16 h before it was quenched with saturated aqueous ammonium chloride (3 mL). The resulting mixture was diluted with water (10 mL) and diethyl ether (20 mL). After the organic phase was separated, the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic phase was washed with water and brine, dried, and evaporated under reduced pressure. Purification of the residue by FCC (light petroleum-ethyl acetate, 8:1, *V*/*V*) gave **10** (170 mg, 85%) as gum. $[\alpha]_D^{20}$ + 15.6 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.28 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.01 (s, 1H), 5.00 (s, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.78 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.54—3.52 (m, 1H), 2.30—2.28 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.1, 153.3, 130.7, 129.4, 113.7, 111.3, 108.7, 83.3, 80.5, 72.8, 70.6, 55.3, 29.2, 27.2, 26.9, 23.5, 23.2, 16.4, 16.2; IR (film) ν: 2957, 2927, 1601, 1472, 1072, 1016 cm^{-1}; EIMS *m/z* (%): 334 (M^+, 9); HRMS (ESI) calcd. for $C_{20}H_{34}O_2$ + H 335.2217, found 335.2215.

(2*S*,3*R*,4*S*,5*R*)-2-(4-*Methoxybenzyloxy*)-3,4-*isopropylidenedioxy*-5,6-*dimethylheptane* (**11**)

Compound **10** (34 mg, 0.1 mmol) in ethyl acetate (3 mL) was hydrogenated over PtO_2(1 mg) at 30 ℃ for 40 h. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel to give **11** (33

mg, 98%) in quantitative yield. $[\alpha]_D^{20}$ + 13.0 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.28 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.04 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.81 (s, 3H), 3.75 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.54—3.52 (m, 1H), 1.62—1.59 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 131.0, 129.3, 113.7, 108.5, 82.1, 78.3, 73.9, 70.7, 55.3, 40.5, 31.1, 29.7, 27.4, 27.1, 21.0, 19.2, 16.0, 9.8, 16.2; IR (film) ν: 2954, 2933, 1611, 1466, 1085, 1006 cm^{-1}; EIMS *m/z* (%): 336 (M^+, 12); HRMS (ESI) calcd for $C_{20}H_{34}O_2$ + H 337.2373, found 337.2379.

(2S,3R,4S)-2-(4-Methoxybenzyloxy)-3,4-dihydroxy-5-oxo-6-methyl-heptane (**12**)

To a stirred solution of *i*-Pr_2NH (0.45 mL, 3.4 mmol) in 6 mL of dry THF was added dropwise a hexane solution of *n*-butyl lithium (1.60 mol/L, 2.0 mL, 3.2 mmol) at 0 ℃ over 5 min. After being stirred for an additional 0.5 h at r.t., the resulting mixture was cooled to − 78 ℃ and syringed dropwise into a solution of α-silyloxy ketone **6** (650 mg, 3.0 mmol) in dry THF (3.0 mL). The reaction mixture was stirred for a further 45 min after which a solution of **5** (194 mg, 1.0 mmol) in 3.0 mL of THF was added dropwise to it at − 78 ℃. The resultant mixture was stirred for 3.0 h at − 78 ℃ and was quenched with saturated aqueous ammonium chloride (2 mL). The resulting mixture was diluted with water (6 mL) and diethyl ether (20 mL). After the organic phase was separated, the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phase was washed with water and brine, dried, and evaporated under reduced pressure.

To a stirred solution of crude silyl ether in 15 mL of THF was added a solution of TBAF in THF (1.0 mol·dm^{-3}, 1.0 mL, 1.0 mmol) at r.t.. The resulting mixture was then stirred for 5 min and concentrated under reduced pressure to give a residue that was taken in diethyl ether (50 mL) and the solution was washed with water and brine and dried. Removal of the solvent by rotary evaporation gave a crude oil, which was then subjected to purification by FCC (light petroleum-ethyl acetate, 4:1, *V*:*V*) to afford the diols **12** (200 mg, 70%) as gum. $[\alpha]_D^{20}$ − 17.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.27 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.67 (brs, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 3.81 (s, 3H), 3.76—3.74 (m, 1H), 3.64—3.62 (m, 1H), 2.95—2.93 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 215.3, 159.2, 130.3, 129.4, 113.8, 75.4, 74.6, 74.5, 71.1, 55.2, 35.5, 19.0, 17.6, 16.6; IR (film) ν: 1660 cm^{-1}; EIMS *m/z* (%): 296 (M^+, 9). Anal. calcd for $C_{16}H_{24}O_5$: C 64.84, H 8.16; found C 64.90, H 8.22.

Z-1-(tert-Butyldimethylsiloxy)-2-(trimethylsiloxy)-3-methyl-1-butylene (**13**)

To a stirred mixture of α-silyloxy ketone **6** (2.16 g, 10.0 mmol) in 15 mL of dry THF was added dropwise a hexane solution of NaN(TMS) (2.0 mol/L, 5.5 mL, 11.0 mmol) at − 78 ℃ over 15 min under N_2. After being stirred for an additional 0.5 h at − 78 ℃, the resulting mixture was syringed dropwise into a solution of TMSCl (1.52 mL, 12 mmol) in THF (3.0 mL). The resulting mixture was stirred for 2.5 h at − 78 ℃ and allowed to warm gradually to 0 ℃, when it was quenched with saturated aqueous ammonium chloride (3 mL). The resulting mixture was diluted with water (6 mL) and diethyl ether (20 mL). After the organic phase was separated, the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic phase was washed with water and brine, dried, and evaporated under reduced pressure. Purification of the residue by flash column chromatography (light petroleum-ethyl acetate, 80:1, *V*/*V*) gave the silyl enol ethers **13** (2.53 g, 88%) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.60 (s, 1H, = CH), 2.34—2.30 (m, 1H, C**H**$(CH_3)_2$), 1.04 (d, *J* = 6.8 Hz, 6H, 2× CH_3), 0.97 (s, 9H, C$(CH_3)_3$), 0.19 (s, 3H, CH_3), 0.16 (s, 3H, CH_3), 0.03 (s, 9H, Si$(CH_3)_3$); IR (film) ν: 1640 (s, C = C) cm^{-1}; EIMS *m/z* (%): 288 (M^+, 24). Anal. calcd for $C_{14}H_{32}O_2Si_2$: C 58.27, H 11.18; found C 58.40, H 11.22.

Representative procedure for Mukaiyama aldol reaction

A solution of aldehyde **5** (194 mg, 1.0 mmol) and $TiCl_4$(190 mg, 1.0 mmol) in 5 mL of CH_2Cl_2 was stirred at 0 ℃ for 30 min. After the solution was cooled to − 78 ℃, a solution of silyl enol ether **13** (320 mg, 1.1 mmol) in CH_2Cl_2 was added slowly to this solution. After 5 h of stirring at − 78 ℃, the reaction was quenched with 10 mL of 1 mol/L $NaHCO_3$ and extracted with CH_2Cl_2. After evapouration of the dried CH_2Cl_2 solution, the residue was dissolved in 2 mL of THF. To this solution was added *n*-Bu_4NF (1.15 mL of 1 mol/L solution in THF) at room temperature. After being stirred for an additional 10 min, the reaction mixture was diluted with 30 mL of diethyl ether and washed with water and brine, dried, and evaporated under reduced pressure. Purification of the residue by FCC (light petroleum-ethyl acetate, 8:1) gave the diols **12** (250 mg, 85%) and the diols **7** (6 mg, 2%) as gum.

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