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Tetrahedron Letters 49 (2008) 1203–1207
Tetrahedron Letters

Stereoselective synthesis of highly enantioenriched 3-methyl-2-cyclohexen-1-ones possessing an asymmetric quaternary carbon as C-4 or C-6: a sugar template approach

Hiroto Kubo, Ikuko Kozawa, Ken-ichi Takao, Kin-ichi Tadano *

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received 1 November 2007; revised 5 December 2007; accepted 7 December 2007
Available online 14 December 2007

Abstract

The 1,4-addition of the enolate generated from α-methylated acetoacetate incorporated at C-4 of methyl 6-deoxy-2,3-di-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside to methyl vinyl ketone, followed by aldol condensation of the resulting 1,4-addition product under two base-mediated conditions, provided 4-O-functionalized D-glucose derivatives with high diastereoselectivity. These products install a 3-methyl-2-cyclohexen-1-one-4- (or -6-) carboxylic acid as the *O*-4 ester, in which C-4 or C-6 is an asymmetric quaternary carbon. Removal of the sugar template from those aldol condensation products provided synthetically useful 3,6-dimethyl-2-cyclohexen-1-one-6-carboxylic acid and 3,4-dimethyl-2-cyclohexen-1-one-4-carboxylic acid derivatives both in high enantioenriched forms.

Keywords: Sugar template; 1,4-Addition; Aldol condensation; Intramolecular cyclization

We have studied on the diastereoselective carbon–carbon bond-forming reactions using sugar templates as stereocontrolling elements.[1] Through these studies, we found that a D-glucose derivative, that is, methyl 6-deoxy-2,3-di-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside (**1**),[2] prepared from methyl α-D-glucopyranoside in six steps, served as an effective chiral template for a variety of carbon–carbon bond-forming reactions using its 4-*O*-propionyl (**2**),[3] 4-*O*-acryloyl-(**3**),[4] and 4-*O*-crotonyl esters (**4**)[2,3a] (Fig. 1).

One of the highlights in current organic synthesis is the enantioselective construction of an all-carbon asymmetric quaternary carbon. The highly stereoselective induction of an all-carbon quaternary center has been investigated in a number of groups, mostly using transition-metal-catalysts,[5] organocatalysts,[6] or chiral auxiliaries.[7] Recently, we reported the highly diastereoselective quaternization of the α-carbon in the 4-acetoacetate **5** of **1** by a double C-alkylation strategy (**5** to **7** or **8**) and the transformation of the resulting differentially α,α-dialkylated acetoacetate **8** into a 2-cyclohexen-1-one-6-carboxylic acid ester **11**, installing an asymmetric quaternary carbon at C-6 via **9** and **10** by an aldol condensation strategy (Scheme 1).[8]

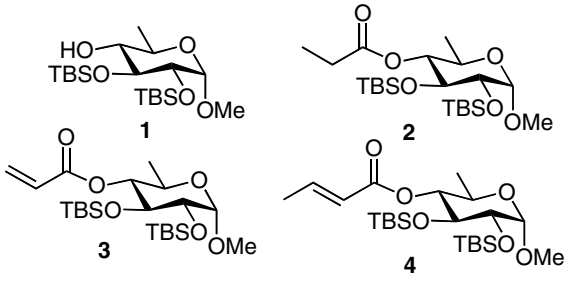

Fig. 1. Sugar template **1** and substrates **2**–**4** for stereoselective carbon–carbon bond-forming reactions.

As a further development of this sugar template strategy for asymmetric access to synthetically useful chiral carbocycles possessing an asymmetric quaternary carbon, we explored the 1,4-addition of the enolate generated from

* Corresponding author. Tel./fax: +81 45 566 1571.
E-mail address: tadano@applc.keio.ac.jp (K. Tadano).

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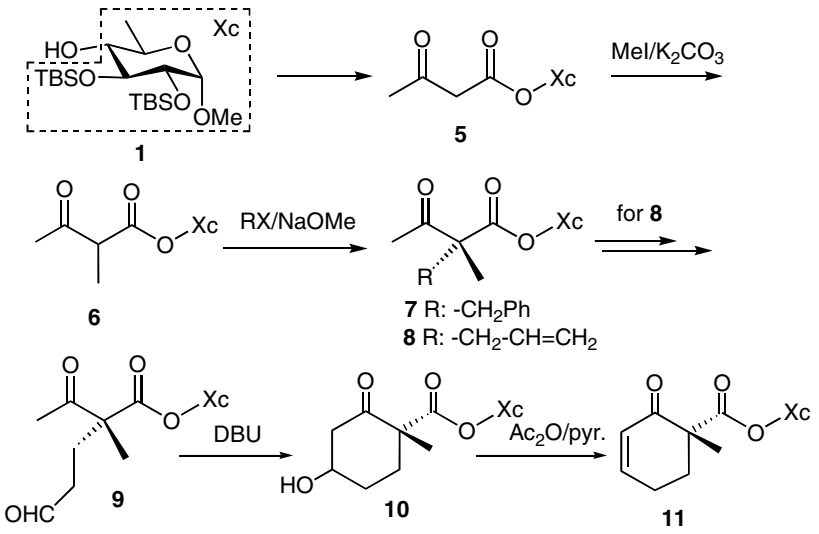
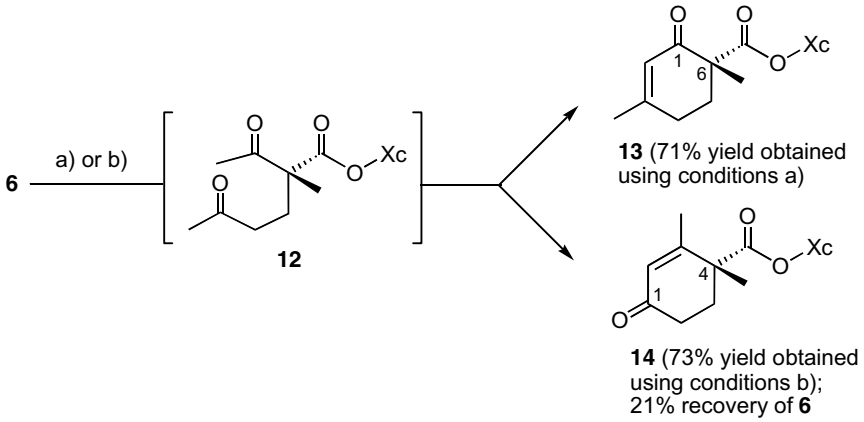
doi:10.1016/j.tetlet.2007.12.031



Scheme 1. Highly stereoselective formation of enantioenriched 2-cyclohexen-1-one with an asymmetric quaternary carbon from **5**.

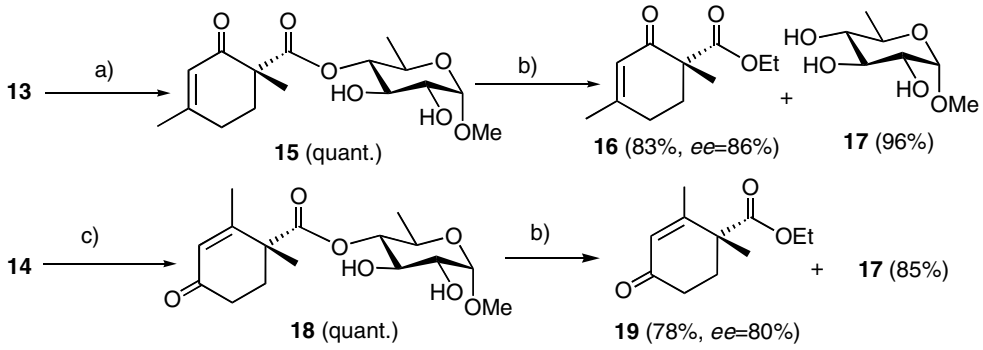


Scheme 2. 1,4-Addition and successive intramolecular cyclization in the reaction of **6** and methyl vinyl ketone. Reagents and conditions: (a) methyl vinyl ketone, MeONa in MeOH, −78 °C (3 h), −18 °C (0.5 h), 0 °C (0.5 h) then rt (3 h); (b) methyl vinyl ketone, pyrrolidine/AcOH, Et_2O, rt (5 d).

α-methylated acetoacetate **6** to methyl vinyl ketone (Scheme 2). This intermediate **6** exists as a 5:2:2 mixture of three tautomeric forms. We did not determine the structure of each tautomer. If the 1,4-addition could provide an adduct **12** stereoselectively, as in the case of the formation of **7** and **8**, the base-mediated intramolecular aldol cyclization of the resulting 1,5-diketone **12** would be expected to simultaneously proceed to aldol-like cyclization, providing highly enantioenriched 3,6-dimethyl-2-cyclohexen-1-one-6-carboxylic ester **13** and/or 3,4-dimethyl-2-cyclohexen-1-one-4-carboxylic ester **14**, both attached to C-4 of **1**.

We explored the 1,4-addition of the enolate generated from **6** to vinyl methyl ketone under two conditions. As shown in Scheme 2, we first examined MeONa as the base. As a result, a diastereomer **13** was obtained in 71% yield in one-pot with high stereoselectivity.[9] The structure of **13** was determined by ^1H NMR analysis. Previously, we observed that the second alkylation of **6** occurred exclusively from the side opposite to the bulky (*tert*-butyldimethyl)silyl (TBS) group located at C-3.[8] This result was explainable on the basis of the steric hindrance caused by the TBS group. Similarly, the 1,4-addition in the present case proceeded with high diastereoselectivity to provide the intermediary 1,4-addition product **12**. The structure of **13** having an (*R*)-configuration for the newly introduced quaternary carbon was confirmed later. On the other hand, this sequential 1,4-addition/intramolecular condensation of **6** was carried out using pyrrolidine/acetic acid. After stirring a solution of **6** in Et_2O in the presence of pyrrolidine and acetic acid at rt for 5 days, another cyclohexenone **14** was obtained in 89% yield based on recovered **6**.[10] The structure of **14** was confirmed as depicted through experiments described later. Some previous papers demonstrated a similar difference of regioselectivity in the second aldol condensation realized by switching the activator.[11]

Next, we examined the detachment of the sugar moiety from the cyclization products **13** and **14**. After several attempts, we could not find efficient procedures to remove the sugar moiety directly from **13** and **14**.[12] However, this was smoothly achieved by the ethanolysis of de-O-silylated

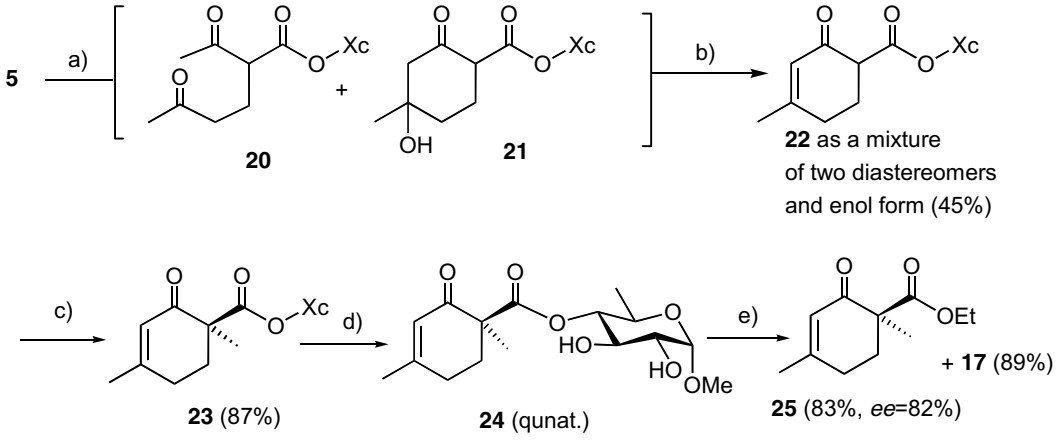


Scheme 3. Removal of the sugar template from **13** and **14**. Reagents and conditions: (a) 6 M aq HCl/THF (1:1), rt; (b) EtONa/EtOH, rt; (c) 4 M aq HCl/THF (1:1), rt.

derivatives **15** and **18**, which were prepared quantitatively from **13** and **14**, respectively, by acid hydrolysis (Scheme 3).[13] The ethanolysis of **15** provided **16**[14] and methyl 6-deoxy-α-D-glucopyranoside **17**[15] both in good yields. By the analogous ethanolysis of **18**, another cyclohexenone **19**[16] was obtained together with **17**. The enantiomeric excess (ee) of **16**[17] and **19**[18] was measured by chiral HPLC analysis to be 86% and 80%, respectively. The (*R*)-configuration for **16** was confirmed by the comparison of its levorotatory property [$[\alpha]_D^{26}$ −50.0 (*c* 0.87, $CHCl_3$)] to that of a known (+)-(*S*)-enantiomer.[11c] Moreover, the (*R*)-configuration of **19** [$[\alpha]_D^{24}$ +93.5 (*c* 0.23, $CHCl_3$)] was confirmed by the comparison of the sign of $[\alpha]_D$ to that of a known (−)-(*S*)-isomer.[11c]

Finally, we explored the 1,4-addition of the enolate generated from **5** to methyl vinyl ketone in the presence of MeONa/MeOH (Scheme 4). This 1,4-addition followed a partial intramolecular aldol cyclization to provide a mixture of 1,4-adduct **20** and the cyclized aldol product **21**. Without the determination of their stereostructures, the mixture was further treated with MeONa in MeOH at rt. This treatment provided the aldol condensation product **22** as a ca. 7:2:1 mixture of two diastereomers and an enol form in 45% yield from **5**. Then the methylation of the α′-carbon of cyclohexenone **22** with iodomethane in the presence of MeONa occurred with high diastereoselectivity to provide **23**.[19] Removal of the TBS groups in the sugar moiety of **23** and ethanolysis of the resulting **24**[20] provided **25**,[21] the (*S*)-antipode of the aforementioned (*R*)-enantiomer, that is, **16**. The planar and absolute configurations of **25** were confirmed by spectral and $[\alpha]_D$ comparisons with those of **16**. The enantiomeric excess of **25** was measured to be 82% by chiral HPLC analysis. The useful level of the diastereoselectivity observed in the methylation at the α′-position of the α,β-unsaturated cyclohexenone **22** should be emphasized in comparison to the fact that the second methylation of other linear-chain-substituted acetoacetates did not reveal such a high diastereoselectivity as that observed in the case of **22**.[22]

In summary, highly enantioenriched ethyl (*R*)-3,6-dimethyl-2-cyclohexen-1-one-6-carboxylate and ethyl (*R*)-3,4-dimethyl-2-cyclohexen-1-one-4-carboxylate were efficiently synthesized via diastereoselective 1,4-addition reaction at the methyl-branched α-carbon of the 4-*O*-acetoacetyl derivative of methyl 6-deoxy-2,3-di-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside with methyl vinyl



Scheme 4. Synthesis of **25**, the antipode of **16**. Reagents and conditons: (a) methyl vinyl ketone, MeONa/MeOH, −78 °C (1 h), −18 °C (1 h), 0 °C (1 h), rt (24 h); (b) MaONa/MeOH, rt (24 h); (c) MeI, MeONa/MeOH, −78 °C (0.5 h), −18 °C (0.5 h), 0 °C (0.5 h), rt (24 h); (d) 6 M aq HCl/THF (1:1), rt (32 h); (e) EtONa/EtOH, rt (0.5 h).

ketone, followed by intramolecular aldol condensation. Furthermore, it should be emphasized that the single sugar template used in this study, that is, methyl 6-deoxy-2, 3-di-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside, works remarkably well as enantiodiscriminating element in the 1,4-addition step, resulting in the formation of both enantiomers of ethyl 3,6-dimethyl-2-cyclohexen-1-one-6-carboxylates.

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9. For the synthesis of **13**, the following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **6** (135 mg, 267 μmol) in MeOH (2.7 mL) was added NaOMe (1.0 M solution in MeOH, 320 μL, 320 μmol). The mixture was stirred at −78 °C for 30 min, and methyl vinyl ketone (45 μL, 560 μmol) was added. After being stirred at −78 °C for 3 h, at −18 °C for 0.5 h, at 0 °C for 0.5 h, and at rt for 3 h, the mixture was quenched with saturated aqueous NH_4Cl (1 mL). The mixture was diluted with AcOEt (10 mL), and washed with saturated aqueous NH_4Cl (5 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated in vacuo.The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:80) to provide 105 mg (71%) of **13** as a colorless oil: TLC, R_f 0.54 (AcOEt/hexane, 1:3); $[\alpha]_D^{23}$ +68.2 (*c* 0.82, $CHCl_3$); IR ν_{max} (neat) 2930, 2860, 1730, 1680 cm^{-1}; ^1H NMR (300 MHz) δ 0.00, 0.07, 0.09, 0.09 (4s, each 3H), 0.82, 0.91 (2s, each 9H), 1.14 (d, 3H, *J* = 6.3 Hz), 1.39 (s, 3H), 1.85–2.58 (m, 4H), 1.92 (s, 3H), 3.37 (s, 3H), 3.66 (dd, 1H, *J* = 8.4, 3.3 Hz), 3.68 (m, 1H), 3.90 (t, 1H, *J* = 8.4 Hz), 4.59 (d, 1H, *J* = 3.3 Hz), 4.73 (t, 1H, *J* = 8.4 Hz), 5.86 (s, 1H); ^{13}C NMR (68 MHz) δ −4.3, −4.2, −3.2, −2.6, 17.8, 17.9, 18.5, 20.7, 24.2, 25.9 × 3, 26.2 × 3, 28.2, 32.5, 52.5, 54.9, 65.6, 72.0, 74.5, 78.4, 99.6, 125.6, 161.7, 171.3, 195.7; HRMS calcd for $C_{27}H_{49}O_6Si_2$ (M^+–OCH_3) *m*/*z* 525.3068, found 525.3070.
10. For the synthesis of **14**, the following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **6** (118 mg, 234 μmol) in Et_2O (2.4 mL) were added methyl vinyl ketone (40 μL, 490 μmol), pyrrolidine (20 μL, 250 μmol), and AcOH (15 μL, 200 μmol). After being stirred at rt for 5 days, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with AcOEt (10 mL) and washed with saturated aqueous NH_4Cl (5 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:20) to provide 94.7 mg (73%) of **14** as a colorless oil and 24.5 mg (21%) of recovered **6**. Compound **14**: TLC, R_f 0.49 (AcOEt/ hexane, 1:3); IR ν_{max} (neat) 2930, 2860, 1730, 1680 cm^{-1}; $[\alpha]_D^{26}$ +147 (*c* 1.21, $CHCl_3$); ^1H NMR (300 MHz) δ 0.03 (s, 3H), 0.11 (s, 9H), 0.84, 0.93 (2s, each 9H), 1.06 (d, 3H, *J* = 6.3 Hz), 1.48 (s, 3H), 1.90–2.69 (m, 4H), 2.04 (s, 3H), 3.37 (s, 3H), 3.69 (dd, 1H, *J* = 8.2, 3.3 Hz), 3.71 (m, 1H), 3.93 (t, 1H, *J* = 8.2 Hz), 4.62 (d, 1H, *J* = 3.3 Hz), 4.77 (t, 1H, *J* = 8.2 Hz), 5.94 (s, 1H); ^{13}C NMR (68 MHz) δ −4.3, −4.2, −3.2, −2.7, 17.9, 18.1, 18.5, 21.3, 24.1, 25.9 × 3, 26.2 × 3, 33.7, 34.5, 47.1, 55.0, 65.3, 72.1, 74.3, 78.6, 99.6, 129.1, 160.7, 172.5, 198.2; HRMS calcd for $C_{27}H_{49}O_6Si_2$ (M^+–OCH_3) *m*/*z* 525.3068, found 525.3069.
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12. We examined the following reaction conditions for the removal of the sugar moiety from **13** and **14**. For **13**: NaOEt in EtOH, rt to 50 °C, 8 h [recovery of **13** (51%), **16** (17%), **1** (9%), C-3 to C-4 silyl migrated sugar (28%)]. For **14**: NaOEt in EtOH, rt to reflux, 5 h [recovery of **14** (39%), **19** (19%); **1** (23%), C-3 to C-4 silyl migrated sugar (37%). For **13**: hydrazine hydrate in EtOH, 140 °C (sealed tube), 24 h[8] [the hydrazine adduct = a pyrazoline derivative (19%), **1** (77%), C-3 to C-4 silyl migrated sugar (17%)].
13. For the acid hydrolysis of **13**: To a cooled (0 °C) stirred solution of **13** (302 mg, 542 μmol) in THF (3.0 mL) was added 6 M aqueous HCl (3.0 mL). The mixture was stirred at rt for 32 h and neutralized with saturated aqueous $NaHCO_3$ (20 mL). This was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:10) to provide 178 mg (quant.) of **15** as a colorless oil: TLC, R_f 0.27 (AcOEt); IR ν_{max} (neat) 3450, 2940, 1730, 1680 cm^{-1}; $[\alpha]_D^{28}$ +110 (*c* 1.47, $CHCl_3$); ^1H NMR (300 MHz) δ 1.18 (d, 3H, *J* = 6.3 Hz), 1.41 (s, 3H), 1.86–2.60 (m, 4H), 1.97 (s, 3H), 2.42 (br s, 1H), 3.22 (br s, 1H), 3.42 (s, 3H), 3.60 (dd, 1H, *J* = 9.2, 3.8 Hz), 3.77 (t, 1H, *J* = 9.2 Hz), 3.77 (m, 1H), 4.65 (t, 1H, *J* = 9.2 Hz), 4.74 (d, 1H, *J* = 3.8 Hz), 5.89 (s, 1H); ^{13}C NMR (68 MHz) δ 17.2, 19.5, 24.2, 28.2, 32.2, 52.6, 55.3, 65.1, 72.5, 72.7, 77.0, 99.0, 124.9, 162.6, 172.5, 197.3; HRMS calcd for $C_{16}H_{24}O_7$ (M^+) *m*/*z* 328.1522, found 328.1532.
Using 4 M aqueous HCl, compound **18** was obtained from **14** analogously as above: **18** as a colorless oil: TLC, R_f 0.25 (AcOEt); IR ν_{max} (neat) 3400, 2950,1730, 1680 cm^{-1}; $[\alpha]_D^{27}$ +159 (*c* 1.46, $CHCl_3$); ^1H NMR (300 MHz) δ 1.17 (d, 3H, *J* = 6.3 Hz), 1.46 (s, 3H), 1.95–2.67 (m, 4H), 1.99 (s, 3H), 2.67 (br, 1H), 3.11 (br, 1H), 3.43 (s, 3H), 3.55 (dd, 1H, *J* = 9.6, 3.6 Hz), 3.73 (t, 1H, *J* = 9.6 Hz), 3.76 (m, 1H), 4.70 (t, 1H, *J* = 9.6 Hz), 4.73 (d, 1H, *J* = 3.6 Hz), 5.94 (s, 1H); ^{13}C NMR (68 MHz) δ 17.4, 21.2, 22.7, 34.2, 34.6, 47.5, 55.5, 65.0, 72.5, 73.0, 76.2, 99.0, 128.5,161.0, 173.6,198.8; HRMS calcd for $C_{16}H_{24}O_7$ (M^+) *m*/*z* 328.1522, found 328.1527.
14. For the ethanolysis of **15**: To a cooled (0 °C) stirred solution of **15** (27.9 mg, 75.8 μmol) in EtOH (1.0 mL) was added EtONa (1.0 M solution in EtOH, 80 μL, 80 μmol). The mixture was stirred at rt for 30 min and Amberlite IR 120 [H^+] was added for neutralization. The resin was filtered off and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:10 then AcOEt) to provide 12.4 mg (83%) of **16** and 12.9 mg (96%) of **17**. Compound **16** was obtained as a colorless oil: TLC, R_f 0.80 (AcOEt); IR ν_{max} (neat) 2980, 2940, 1730, 1680 cm^{-1}; $[\alpha]_D^{26}$ −50.0 (*c* 0.87, $CHCl_3$); ^1H NMR (300 MHz) δ 1.23 (t, 3H, *J* = 7.1 Hz), 1.37 (s, 3H), 1.82–2.52 (m, 4H), 1.95 (s, 3H), 4.16 (q, 2H *J* = 7.1 Hz), 5.90 (s, 1H); ^{13}C NMR (68 MHz) δ 14.1, 20.3, 24.2, 28.6, 33.1, 52.2, 61.2, 125.6, 161.4, 172.8, 196.8; HRMS calcd for $C_{11}H_{16}O_3$ (M^+) *m*/*z* 196.1099, found 196.1104. Compound **17** was obtained as white crystals: TLC, R_f 0.09 (AcOEt); mp 93–96 °C; IR ν_{max} (KBr) 3400, 2940 cm^{-1}; $[\alpha]_D^{22}$ +147 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz) δ 1.29 (d, 3H, *J* = 6.3 Hz), 2.18 (br s, 1H), 3.15 (t, 1H, *J* = 9.2 Hz), 3.42 (s, 3H), 3.53–3.72 (m, 3H), 4.01 (br s, 1H), 4.70 (d, 1H, *J* = 3.3 Hz), 4.71 (br s,

1H); ^{13}C NMR (68 MHz) δ 17.5, 55.1, 67.3, 72.4, 74.4, 75.5, 99.3; HRMS calcd for $C_7H_{13}O_5$ (M^+–H) m/z 177.0763, found 177.0764.

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16. By the ethanolysis of **18** as described for the conversion of **15** to **16**, compound **19** was obtained as a colorless oil: TLC, R_f 0.81 (AcOEt/hexane, 1:1); $[\alpha]_D^{24}$ +93.5 (*c* 0.23, $CHCl_3$); IR ν_{max} (neat) 2980, 2940, 1730, 1680 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.27 (t, 3H, $J = 7.2$ Hz), 1.44 (s, 3H), 1.89–2.57 (m, 4H), 1.97 (s, 3H), 4.20 (q, 2H, $J = 7.2$ Hz), 5.92 (s, 1H); ^{13}C NMR (68 MHz) δ 14.1, 21.1, 22.3, 34.2, 34.3, 47.3, 61.4, 128.1, 161.5, 174.1, 198.3; HRMS calcd for $C_{11}H_{16}O_3$ (M^+) m/z 196.1099, found 196.1100.
17. HPLC analysis (column, Daicel Chiralpak AD-H, 2-propanol:hexane = 1:80, flow rate = 0.5 mL/min); t_R (min) = 38.1 for **16**, 34.2 for (***S***)-**16**. A racemic mixture of **16** was prepared from commercial ethyl 2-methylacetoacetate y treatment with methyl vinyl ketone in MeOH in the presence of MeONa, followed by ester exchange with EtONa in EtOH.
18. HPLC analysis (column, Daicel Chiralpak OJ-H, MeOH:hexane = 1:80, flow rate = 0.5 mL/min); t_R (min) = 24.2 for **19**, 21.5 for (***S***)-**19**. A racemic mixture of **19** was prepared from ethyl 2-methylacetoacetate by treatment with methyl vinyl ketone in the presence of pyrrolidine/AcOH.
19. For the synthesis of **23**, the following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **5** (309 mg, 630 μmol) in MeOH (6.2 mL) was added MeONa (1.0 M solution in MeOH, 760 μL, 760 μmol). The mixture was stirred at −78 °C for 30 min, and then methyl vinyl ketone (200 μL, 2.52 mmol) was added. The mixture was stirred at −78 °C for 1 h, at −18 °C for 1 h, at 0 °C for 1 h, and at rt for 24 h. The mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:10) to provide 318 mg of a mixture of **20** and **21**, which was used for the next step directly.

    The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of the mixture obtained above (318 mg) in MeOH (6.4 mL) was added MeONa (1.0 M solution in MeOH, 570 μL, 570 μmol). After being stirred at rt for 24 h, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:70) to provide 154 mg (45%) of **22** as a mixture (ca. 7:2:1) of diastereomers and an enol form. Mixture **22** was obtained as a colorless oil:TLC, R_f 0.68 (AcOEt/hexane, 1:3); IR ν_{max} (neat) 2930, 2860, 1730, 1680 cm^{-1}; ^{1}H NMR (300 MHz) for the major product δ 0.04, 0.08, 0.10, 0.11 (4s, each 3H), 0.85, 0.92 (2s, each 9H), 1.31 (d, 3H, $J = 6.0$ Hz), 1.92–2.51 (m, 4H), 1.98 (s, 3H), 3.32 (m, 1H), 3.36 (s, 3H), 3.66 (dd, 1H, $J = 9.2$, 3.6 Hz), 3.79 (m, 1H), 3.95 (t, 1H, $J = 9.2$ Hz), 4.62 (d, 1H, $J = 3.6$ Hz), 4.74 (t, 1H, $J = 9.2$ Hz), 5.89 (s, 1H); HRMS calcd for $C_{27}H_{50}O_7Si_2$ (M^+) m/z 542.3095, found 542.3103.

    The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of the mixture obtained above **22** (111 mg, 204 μmol) in MeOH (2.2 mL) was added NaOMe (1.0 M solution in MeOH, 200 μL, 200 μmol). The mixture was stirred at −78 °C for 15 min, and then iodomethane (40 μL, 640 μmol) was added. After being stirred at −78 °C for 0.5 h, at −18 °C for 0.5 h, at 0 °C for 0.5 h, and at rt for 24 h, the mixture was quenched with saturated aqueous NH_4Cl (1 mL), diluted with saturated aqueous NH_4Cl (10 mL), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt/hexane, 1:80) to provide 99.2 mg (87%) of **23** as a colorless oil. TLC, R_f 0.54 (AcOEt/hexane, 1:3); IR ν_{max} (neat) 2930, 2860, 1730, 1680 cm^{-1}; $[\alpha]_D^{21}$ +71.7 (*c* 1.12, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.00, 0.06, 0.10, 0.10 (4s, each 3H), 0.85, 0.92 (2s, each 9H), 1.16 (d, 3H, $J = 6.3$ Hz), 1.41 (s, 3H), 1.84–2.59 (m, 4H), 1.95 (s, 3H), 3.36 (s, 3H), 3.66 (dd, 1H, $J = 8.4$, 3.3 Hz), 3.70 (m, 1H), 3.93 (t, 1H, $J = 8.4$ Hz), 4.60 (d, 1H, $J = 3.3$ Hz), 4.74 (t, 1H, $J = 8.4$ Hz), 5.87 (s, 1H); ^{13}C NMR (68 MHz) δ −4.3, −4.1, −3.2, −2.6, 17.6, 17.8, 18.5, 20.0, 24.2, 26.0 × 3, 26.2 × 3, 28.2, 32.9, 52.5, 54.9, 65.6, 71.7, 74.6, 78.2, 99.7, 125.3, 161.9, 171.8, 196.6; HRMS calcd for $C_{27}H_{49}O_6Si_2$ (M^+–OCH_3) m/z 525.3068, found 525.3073.
20. By the analogous acid hydrolysis used for the conversion of **13** into **15**, compound **23** was converted into **24** quantitatively. Compound **24** was obtained as a colorless oil.TLC, R_f 0.27 (AcOEt); IR ν_{max} (neat) 3180, 2880, 1730, 1680 cm^{-1}; $[\alpha]_D^{21}$ +54.4 (*c* 3.42, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.13 (d, 3H, $J = 6.0$ Hz), 1.40 (s, 3H), 1.89–2.65 (m, 4H), 1.98 (s, 3H), 2.64 (br s, 1H), 3.41 (s, 3H), 3.60 (br s, 1H), 3.60–3.80 (m, 3H), 4.66 (t, 1H, $J = 10.5$ Hz), 4.74 (d, 1H, $J = 4.1$ Hz) 5.90 (s, 1H); ^{13}C NMR (68 MHz) δ 17.1 19.1, 24.2, 28.0, 32.1, 52.9, 55.3, 64.9, 72.3 × 2, 76.8, 99.0, 125.0, 162.7, 172.4, 198.3; HRMS calcd for $C_{16}H_{24}O_7$ (M^+) m/z 328.1522, found 328.1525.
21. Compound **25** was obtained as a colorless oil: $[\alpha]_D^{21}$ +48.2 (*c* 1.17, $CHCl_3$).
22. In previous studies, we experienced that low diastereoselectivities were observed when the sequential alkylations at the α-carbon of **5** were executed in the order of benzylation then methylation (up to 4.5:1 in favor of the formation of **7**).[8] In the case of allylation and successive methylation, the diastereoselectivity was remarkably reduced to ca. 1:1.