Tetrahedron Letters 50 (2009) 1139–1142

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Stereoselective α-alkylation of methyl 6-deoxy-3,4-di-*O*-(*tert*-butyldimethylsilyl)-2-*O*-(2-methyl-3-oxobutanoyl)-α-D-glucopyranoside

Yoko Akashi, Ken-ichi Takao, Kin-ichi Tadano *

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

ARTICLE INFO

*Article history:*
Received 28 October 2008
Revised 16 December 2008
Accepted 18 December 2008
Available online 25 December 2008

*Keywords:*
α-Alkylation
Asymmetric synthesis
Carbohydrates
Chiral auxiliary
Stereoselective synthesis

ABSTRACT

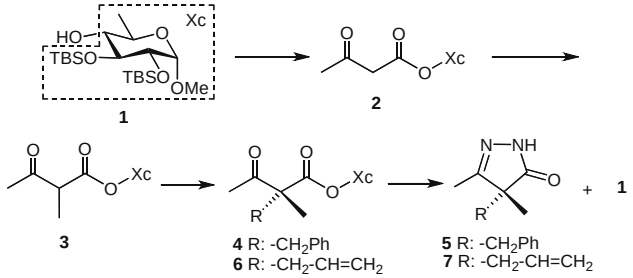
Allylation and benzylation at the α-carbon of α-methylated acetoacetyl (2-methyl-3-oxobutanoyl) group incorporated into the 2-OH of methyl 6-deoxy-3,4-O-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside provided the respective α,α-differentially alkylated acetoacetyl derivatives, both with high diastereoselectivity. Thus-obtained doubly alkylated products possess an all-carbon quaternary stereogenic center with an absolute stereochemistry opposite to that introduced by using the 4-*O*-acetoacetyl regioisomer as the alkylation substrate.



Stereoselective access to enantiomerically enriched building blocks with an all-carbon stereogenic center is one of actively investigated subjects in the field of current synthetic organic chemistry. For this subject, a number of sophisticated asymmetric approaches have been realized by using transition-metal-based chiral catalysts,[1] chiral auxiliaries,[2] or organocatalysts.[3] Especially, the building blocks with a stereochemically defined all-carbon quaternary center can be used as structural elements in the synthesis of biologically intriguing compounds.

During the past several years, we had demonstrated the synthetic utility of methyl 6-deoxy-2,3-di-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside **1** (Scheme 1), readily prepared from methyl α-D-glucopyranoside, as a chiral template for stereoselective carbon–carbon bond-forming reactions.[4] In a recent paper,[5] we reported stereoselective sequential alkylation at the α-carbon of the 4-*O*-acetoacetyl (3-oxobutanoyl) derivative **2**, which was prepared by the acylation of **1**. The base-mediated sequential α-alkylation of **2** with different carbon electrophiles such as MeI, then benzyl bromide or allyl bromide eventually provided **4** or **6** via the initially formed mono-C-methylated diastereomeric mixture **3**. The second alkylation proceeded with remarkable diastereoselectivity in both cases.[6] The stereochemical assignment of the thus-introduced all-carbon quaternary center in the alkylated product **4** or **6** was ascertained after converting **4** or **6** into the known stereochemically defined pyrazoline derivative **5** or **7**, respectively.

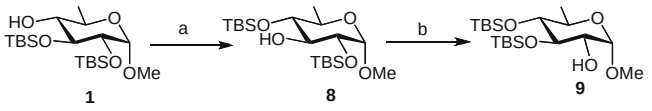
To further demonstrate the utility of our sugar-based chiral template approach for access to enantiomerically enriched building blocks, we have sought other sugar-based templates, which can realize highly stereoselective carbon–carbon bond-forming reactions. The results revealed another D-glucose-based template **9** (Scheme 2). Herein, we describe the synthetic utility of **9**, exemplified by the α-alkylation of the 2-methyl-3-oxobutanoyl ester derived from **9**. The template **9** was prepared efficiently via stepwise migration of the two *tert*-butyldimethylsilyl (TBS) groups attached on *O*-3 and *O*-2 in **1** to the *O*-4 and *O*-3 positions by sequential treatment of two kinds of bases, namely, the TBS group on *O*-3 migrated to the 4-OH group by the treatment of **1** with NaOMe,




**Scheme 1.** Stereoselective α,α-dialkylation of 4-*O*-acetoacetate **2** derived from **1**.[5]

* Corresponding author.
*E-mail address:* tadano@applc.keio.ac.jp (K. Tadano).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.091



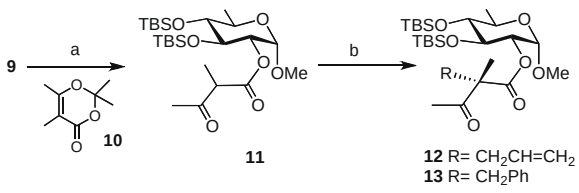
**Scheme 2.** Synthesis of **9**. Reagents and conditions: (a) NaOMe, MeOH, rt, 70% (91% after one recycle); (b) LiHMDS, THF, rt, 85%.

providing **8**[7] in 70% yield and 30% of **1** was recovered. The recovered **1** was subjected to the same NaOMe treatment to obtain additional **8**. Finally, the 2,4-di-*O*-TBS derivative **8** was obtained in an overall yield of 91% after one recycle. Then the treatment of **8** with lithium hexamethyldisilazide (LiHMDS) solely provided the 3,4-di-*O*-TBS derivative **9** in a good yield of 85%.[8] None of the 2,3-di-*O*-TBS derivative **1** was found in the reaction mixture.[9] Therefore, in the case of **8**, the silyl migration from *O*-2 to *O*-3 occurs exclusively under the basic conditions employed. Although we have no firm evidence for these facile silyl-group migrations from *O*-3 to *O*-4, then from *O*-2 to *O*-3, we presume that the 3,4-di-*O*-TBS derivative **9** is the least spatially congested regioisomer, compared with **1** or **8**.

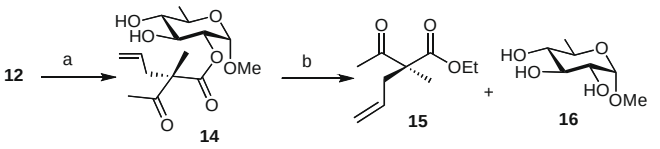
We explored the potential of **9** as a chiral template, exemplified by the α-alkylation of its 2-*O*-(2-methyl-3-oxobutanoyl) derivative **11**. The preparation of **11** and its α-alkylation with two electrophiles are summarized in Scheme 3.[10] Heating **9** with 2,2,5,6-tetramethyl-1,3-dioxin-4-one[11] **10** in refluxing *o*-xylene provided **11** as a diastereomeric mixture.[12] This mixture **11** was subjected to α-alkylation with allyl bromide using *tert*-BuOK as the base, providing the α,α-differentially alkylated acetoacetate **12** in 93% yield with almost complete diastereoselectivity.[13,14] Analogously, the benzylation of **11** provided the α-benzylated product **13** in 79% yield as an apparently single diastereomer.[15]

Then, we determined the stereochemistry of the newly introduced quaternary stereogenic center incorporated into the allylated product **12** by detachment of the optically active α-methyl-α-allyl-3-oxobutanoyl moiety from the sugar template. For this purpose, two TBS-protecting groups in **12** were first removed by acid hydrolysis, providing **14** (Scheme 4). The sugar template was smoothly removed by alcoholysis of **14** with NaOEt in EtOH, providing ethyl (*S*)-2-allyl-2-methyl-3-oxobutanoate (**15**) and methyl 6-deoxy-α-D-glucopyranoside (**16**), both in excellent yields.[16] The levorotatory sign for **15** [$[\alpha]_D^{20}$ −25.4 (*c* 1.18, $CHCl_3$)] confirmed its absolute stereochemistry to be (*S*) by comparison with the reported $[\alpha]_D$ for the (*S*)-enantiomer.[17] Consequently, the chirality of the asymmetric all-carbon quaternary center in **12** was opposite to that introduced in the allylation executed for the substrate **3** during our previous study.[5]

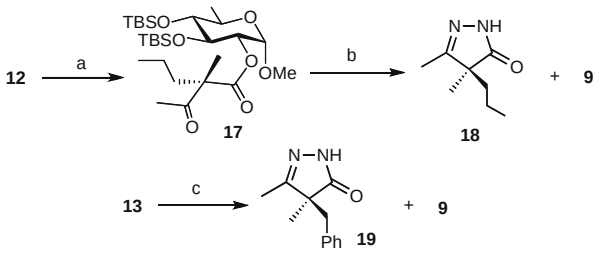
Next, we determined the enantiomeric excess (ee) of the newly introduced stereogenic center in **12** accurately by chiral HPLC analysis. The allyl group in **12** was first hydrogenated to a propyl group, providing **17** (Scheme 5).[18] The hydrazinolysis of **17** at 140 °C[19] provided a pyrazolone derivative **18**,[20] and the sugar template **9** was recovered efficiently. Based on the chiral HPLC measurement



**Scheme 3.** Synthesis of 2-*O*-(2-methyl-3-oxobutanoyl) derivative **11** and its α-alkylation with two electrophiles. Reagents and conditions: (a) **10**, *o*-xylene, reflux, 92%; (b) for **12**: allyl bromide, *tert*-BuOK, THF, −78 to 5 °C, 93%; for **13**: benzyl bromide, *tert*-BuOK, THF, −78 to 0 °C, 79%.



**Scheme 4.** Removal of the sugar template from **12**. Reagents and conditions: (a) 6 M aq HCl/THF = 1:1, rt; (b) NaOEt, EtOH, rt, 90% for **15** and 97% for **16** for 2 steps.

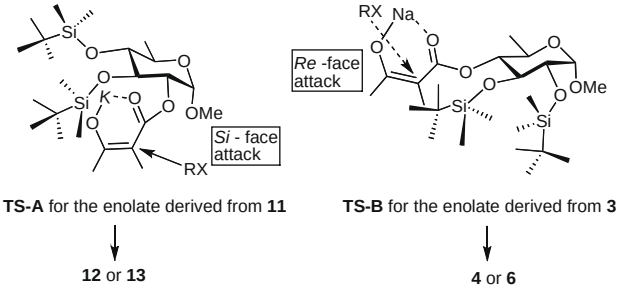


**Scheme 5.** Conversion of **12** or **13** into **18** or **19**, respectively, for determination of the enantiomeric excess of the quaternary stereogenic center. Reagents and conditions: (a) $H_2$, Pd/C, MeOH; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, 140 °C in a sealed tube, 82% of **18** and 83% of **9** for 2 steps; (c) $NH_2NH_2{\cdot}H_2O$, EtOH, 140 °C in a sealed tube, quantitative yield.

of **18**, the ee of the quaternary carbon center in **18**, and thus that in **12**, was determined to be 95%.[21]

Analogously, the hydrazinolysis of **13** provided a pyrazolone derivative **19**, accompanied by isolation of **9**. The absolute stereochemistry of the quaternary carbon was determined to be (*S*) by comparison with the reported $[\alpha]_D$ value.[22] The ee of **19** was determined by chiral HPLC analysis to be 89%.[23] As in the case of the formation of **12**, the α-benzylation of **11** provided **13** with an all-carbon quaternary center, the absolute stereochemistry of which was opposite to that obtained through our previous approach using **3**.[5]

We propose the transition state **TS-A** depicted in Scheme 6 for the excellent stereoselectivity observed in the α-alkylation of **11**, together with the transition state **TS-B** for our previous results.[5] In the transition state **TS-A**, it is most likely that the (*Z*)-potassium-chelated enolate formed by the *tert*-BuOK-treatment of **11** was attacked by alkyl halide to provide **12** or **13**. Furthermore, the attack of the electrophile to the enolate predominantly occurred from the less-congested front side as shown (*Si*-face of the α-carbon to the carbonyl in the enolate form), because the rear side was well shielded by the bulky TBSO group attached at C-3. This phenomenon was the complete reverse of what we observed using substrate **3** via transition state **TS-B**.[5] At the present time, however, we do not have any reasonable explanation for the higher diastereoselectivity observed in the attack of sterically less-congested allyl bromide, compared with that observed in the attack of benzyl bromide.[24]



**Scheme 6.** Plausible transition states for the formation of **4** (or **6**) and **12** (or **13**).

These α,α-differentially alkylated 3-oxobutanoic acid ester **15** and pyrazolone derivatives **18** and **19** are expected to serve as versatile building blocks for the synthesis of enantiomerically enriched carbocyclic and heterocyclic compounds with a stereochemically defined all-carbon quaternary stereogenic center. We had demonstrated the synthetic utility of similar building blocks in our previous papers.[4k,5]

In summary, we have further developed our sugar-based chiral template approach for the stereoselective carbon–carbon bond-forming reaction, exemplified by the design of a new and effective template, that is, methyl 6-deoxy-3,4-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside. The α-allylation and α-benzylation of the 2-*O*-(2-methyl-3-oxo-butanoyl) derivative of the sugar template provided the respective α,α-differentially dialkylated products in remarkably high diastereoselectivity. The direction of the electrophile attack is highly controlled by the bulky silyl ether located at C-3 of the sugar template. These facts complement our previous results on the stereoselective introduction of the α,α-differentially alkylated quaternary center achieved using the 4-*O*-acetoacetate regioisomer.[25]

## References and notes


1. Some recent prominent papers on this subject: (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480–4481; (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847; (c) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927.
2. A recent review on this subject: Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947.
3. Some recent prominent papers on this subject: (a) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672–5673; (b) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616–11617.
4. An account on our sugar-based chiral template approach for stereoselective carbon–carbon bond-forming reactions: (a) Totani, K.; Takao, K.; Tadano, K. *Synlett* **2004**, 2066–2080; Our previous publications on this topic: (b) Totani, K.; Nagatsuka, T.; Takao, K.; Ohba, S.; Tadano, K. *Org. Lett.* **1999**, *1*, 1447–1450; (c) Munakata, R.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2000**, 979–982; (d) Totani, K.; Nagatsuka, T.; Yamaguchi, S.; Takao, K.; Ohba, S.; Tadano, K. *J. Org. Chem.* **2001**, *66*, 5965–5975; (e) Nagatsuka, T.; Yamaguchi, S.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2001**, 481–484; (f) Totani, K.; Asano, S.; Takao, K.; Tadano, K. *Synlett* **2001**, 1772–1776; (g) Nagatsuka, T.; Yamaguchi, S.; Totani, K.; Takao, K.; Tadano, K. *J. Carbohydr. Chem.* **2001**, *20*, 519–535; (h) Tamai, T.; Asano, S.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2003**, 1865–1867; (i) Asano, S.; Tamai, T.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2003**, 2252–2254; (j) Sasaki, D.; Sawamoto, D.; Takao, K.; Tadano, K.; Okue, M.; Ajito, K. *Heterocycles* **2007**, *72*, 103–110; (k) Kubo, H.; Kozawa, I.; Takao, K.; Tadano, K. *Tetrahedron Lett.* **2008**, *49*, 1203–1207.
5. Kozawa, I.; Akashi, Y.; Takiguchi, K.; Sasaki, D.; Sawamoto, D.; Takao, K.; Tadano, K. *Synlett* **2007**, 399–402.
6. When the two alkylations were carried out in the order of benzylation and methylation, the diastereomeric ratio for **4** significantly changed with a decrease in the formation of **4** (4.5:1 to 4:1 in favor of the formation of **4**).[4k,5]
7. All new compounds were fully characterized by spectral means [$^1$H and $^{13}$C NMR, IR, and HRMS]. Yields refer to isolated products after purification by column chromatography on silica gel.
8. The preparation of **9** from **1** via **8**. To a cooled (0 °C) stirred solution of **1** (500 mg, 1.23 mmol) in MeOH (10 mL) was added NaOMe (1.0 M solution in MeOH, 1.8 mL, 1.8 mmol). The mixture was stirred at rt for 15 h, quenched with satd aq $NH_4Cl$ (5.0 mL), diluted with EtOAc (40 mL), and then washed with satd aq $NH_4Cl$ (20 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:25 then 1:10) to provide 349 mg (70%) of **8** and 153 mg (30%) of **1**. The same procedure was repeated for the recovered **1** (153 mg, 0.376 mmol) to provide 105 mg of additional **8** (46 mg of **1** was recovered). Thus, 454 mg (91%) of **8** was obtained as a colorless oil: TLC $R_f$ 0.52 (EtOAc/hexane = 1:5); $[\alpha]_D^{20}$ +76.7 (*c* 1.19, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.09, 0.10 (2s, each 3H), 0.11, 0.14 (2s, each 3H), 0.89, 0.91 (2s, each 9H), 1.23 (d, 3H, *J* = 6.2 Hz), 2.08 (d, 1H, *J* = 2.1 Hz), 3.18 (t, 1H, *J* = 9.0 Hz), 3.38 (s, 3H), 3.52 (dd, 1H, *J* = 3.6, 9.0 Hz), 3.61–3.70 (m, 2H), 4.55 (d, 1H, *J* = 3.6 Hz); $^{13}$C NMR (75 MHz) δ −4.6, −4.5, −3.8 (2C), 18.2 (2C), 18.3, 25.8 (2C), 25.9 (3C), 55.1, 67.7, 74.1, 76.5, 77.5, 99.7; HRMS calcd for $C_{18}H_{39}O_4Si_2$ ($M^+$−OMe) *m/z* 375.2387, found 375.2389. The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **8** (544 mg, 1.34 mmol) in THF (10 mL) was added LiHMDS (1.0 M solution in THF, 2.0 mL, 2.0 mmol). The mixture was stirred at rt for 1 h, quenched with satd aq $NH_4Cl$ (5.0 mL), diluted with EtOAc (40 mL), and then washed with satd aq $NH_4Cl$ (20 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene = 1:80) to provide 462 mg (85%) of **9** as a colorless oil: TLC $R_f$ 0.38 (EtOAc/toluene = 1:10); $[\alpha]_D^{20}$ +73.4 (*c* 2.52, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.09, 0.11 (2s, each 3H), 0.12, 0.13 (2s, each 3H), 0.91, 0.93 (2s, each 9H), 1.28 (d, 3H, *J* = 6.8 Hz), 2.31 (d, 1H, *J* = 10.5 Hz), 3.25 (t, 1H, *J* = 7.1 Hz) 3.43 (s, 3H), 3.44 (ddd, *J* = 3.2, 7.9, 10.5 Hz), 3.74–3.80 (m, 2H), 4.69 (d, 1H, *J* = 3.2 Hz); $^{13}$C NMR (75 MHz) δ −3.8, −3.6, −3.1, −2.9, 18.1 (2C), 18.4, 26.1 (2C), 26.3 (3C), 55.5, 70.3, 72.7, 75.7, 77.2, 98.0; HRMS calcd for $C_{18}H_{39}O_4Si_2$ ($M^+$−OMe) *m/z* 375.2387, found 375.2382.
9. We examined this silyl-group migration using other bases. For example, 2,4-di-*O*-TBS derivative **8** (44%), 3,4-di-*O*-TBS derivative **9** (16%), and **1** (32% recovery) were obtained when LiHMDS (1.0 mol equiv) was used in THF at −78 to −20 °C. For convenient purification and high-yield of **9**, we adopted the stepwise migration via the isolation of **8**.
10. We also explored the α-methylation of the 2-*O*-(3-oxo-butanoyl) derivative, prepared from **9** by the acylation with 2,2,6-trimethyl-1,3-dioxin-4-one, with methyl iodide using $K_2CO_3$ as base. As a result, 2-*O*-(2-methyl-3-oxobutanoyl) derivative **11** was obtained in less satisfactory yield with concomitant production of the 2-*O*-(2,2-dimethyl-3-oxobutanoyl) derivative. For this reason, we prepared **11** by direct introduction of the 2-methyl-3-oxobutanoyl group at *O*-2 of **9** under the neutral retro-Diels–Alder strategy shown in Scheme 3.
11. Sato, M.; Ogasawara, M.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896–1901.
12. Based on the $^{13}$C NMR analysis, the diastereomeric ratio of **11** was estimated to be ca. 2:1 to 3:1. As separation of the diastereomers was fruitless, we did not determine the stereochemistry of the respective diastereomers.
13. *Synthesis of* **12**. The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **11** (94 mg, 0.185 mmol) in THF (1.9 mL) was added *tert*-BuOK (27 mg, 0.204 mmol). The mixture was stirred at −78 °C for 5 min, and allyl bromide (32 μL, 0.37 mmol) was added. After being stirred at −78 °C for 30 min and 5 °C for 18.5 h, the mixture was quenched with satd aq $NH_4Cl$ (5 mL), diluted with EtOAc (10 mL), and washed with satd aq $NH_4Cl$ (5 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:80) to provide 94 mg (93%) of **12** as a colorless oil: TLC $R_f$ 0.45 (EtOAc/hexane = 1:7); $[\alpha]_D^{23}$ +59.1 (*c* 1.14, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.11, 0.12 (2s, each 6H), 0.87, 0.91 (2s, each 9H), 1.35 (d, 3H, *J* = 6.4 Hz), 1.54 (s, 3H), 2.20 (s, 3H), 2.58 (dd, 1H, *J* = 7.6, 14.0 Hz), 2.65 (dd, 1H, *J* = 6.9, 14.0 Hz), 3.34 (s, 3H), 3.37 (dd, 1H, *J* = 5.1, 9.0 Hz), 3.72 (m, 1H), 3.91 (dd, 1H, *J* = 5.1, 6.8 Hz), 4.82 (d, 1H, *J* = 3.8 Hz), 4.91 (dd, *J* = 3.8, 6.8 Hz), 5.10–5.16 (m, 2H), 5.60–5.71 (m, 1H); $^{13}$C NMR (75 MHz) δ −3.9, −3.6, −3.3, −2.7, 18.0, 18.2, 18.9, 19.0, 26.0 (3C), 26.1(3C), 26.5, 39.6, 54.9, 59.5, 69.0, 73.1, 73.3, 77.9, 95.7, 118.9, 132.8, 172.3, 204.7; HRMS calcd for $C_{27}H_{52}O_7Si_2$ ($M^+$) *m/z* 544.3252, found 544.3258.
14. We also explored the sequential α-alkylation in the order of allylation and methylation of 2-*O*-(3-oxobutanoyl) derivative. The initial allylation (allyl bromide, NaOMe, THF, −78 °C to rt) provided mono-allylated product (44%). The second methylation (MeI, NaOMe, THF, rt) of the α-allylated product provided the α,α-dialkylated product in 44% yield. Unfortunately, the diastereomeric ratio of the products was approximately 1:1 based on $^1$H NMR analysis.
15. Compound **13** as a colorless oil: TLC $R_f$ 0.42 (EtOAc/hexane = 1:7); $[\alpha]_D^{21}$ +51.9 (*c* 0.91, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.10, 0.11 (2s, each 3H), 0.13 (s, 6H), 0.88, 0.89 (2s, each 9H), 1.26 (d, 3H, *J* = 6.4 Hz), 1.29 (s, 3H), 2.24 (s, 3H), 3.10 (d, 1H, *J* = 13.8 Hz), 3.21 (s, 3H), 3.31 (d, 1H, *J* = 13.8 Hz), 3.37 (dd, 1H, *J* = 5.3, 8.4 Hz), 3.70 (m, 1H), 3.96 (dd, 1H, *J* = 5.3, 7.1 Hz), 4.73 (d, 1H, *J* = 3.8 Hz), 4.93 (dd, 1H, *J* = 3.8, 7.1 Hz), 7.11–7.14 (m, 2H), 7.22–7.28 (m, 3H); $^{13}$C NMR (75 MHz) δ −3.9, −3.7, −3.2, −2.6, 18.0, 18.1, 18.8 (2C), 26.0 (3C), 26.1(3C), 26.7, 40.8, 54.9, 60.9, 69.1, 73.0, 73.3, 77.8, 95.8, 126.8, 128.1 (2C), 130.4 (2C), 136.3, 172.1, 204.8; HRMS calcd for $C_{30}H_{51}O_6Si_2$ ($M^+$−OMe) *m/z* 563.3224, found 563.3242.
16. The detachment of the sugar template from **12** did not proceed under the ethanolytic conditions. We had encountered the same difficulty in the detachment of the sugar template from other α,α-dialkylated acetoacetate-derivatives; see Ref. 4k.
17. For the reported value of **15**: $[\alpha]_D^{22}$ −27.1 (*c* 1.17, $CHCl_3$), see: Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828.
18. The hydrazinolysis of **12** was accompanied by the hydrogenation of the allylic olefin to some extent. Thus, **12** was subjected to hydrogen addition prior to hydrazinolysis.
19. For the hydrazinolysis conditions, see: Moreno-Mañas, M.; Trepat, E.; Sebastián, R. M.; Vallribera, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4211–4224.
20. Compound **18** as colorless crystals: mp 61–62 °C; $[\alpha]_D^{19}$ +49.1 (*c* 0.265, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.1 Hz), 0.92–1.31 (m, 2H), 1.22 (s, 3H) 1.52 (ddd, 1H, *J* = 4.5, 4.7, 12.2 Hz), 1.75 (ddd, *J* = 4.5, 4.7, 12.2 Hz), 1.98 (s, 3H), 8.47 (br s, 1H); $^{13}$C NMR (75 MHz) δ 13.1, 14.0, 17.9, 20.3, 37.4, 51.9 164.6, 180.2; HRMS calcd for $C_8H_{14}N_2O$ ($M^+$) *m/z* 154.1106, found 154.1092.
21. The chiral HPLC conditions: CHIRALPAK AD-H column, hexane/2-propanol = 20:1. Racemic **18** was prepared from ethyl 2-methylacetoacetate as follows: (1) allyl bromide, *tert*-BuOK, THF, 0 °C; (2) $H_2$, Pd/C, MeOH; (3) $NH_2NH_2{\cdot}H_2O$, EtOH, 140 °C in a sealed tube.
22. Compound **19**, (4*S*)-4-benzyl-3,4-dimethyl-2-pyrazolin-5-one as colorless crystals: mp 90–91 °C; $[\alpha]_D^{22}$ +162 (*c* 0.73, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 2.04 (s, 3H), 2.83 (d, 1H, *J* = 13.6 Hz), 3.12 (d, 1H, *J* = 13.6 Hz), 7.07–7.11 (m, 2H), 7.12–7.23 (m, 3H), 8.28 (br s, 1H); $^{13}$C NMR (75 MHz) δ 14.3, 20.6, 41.2, 53.5, 127.2 (2C), 128.4 (2C), 128.9, 135.2, 163.4,

179.5; HRMS calcd for $C_{12}H_{14}N_2O$ ($M^+$) $m/z$ 202.1106, found 202.1106. For the reported $[\alpha]_D$ for **5**, the enantiomer of **19**: $[\alpha]_D^{15}$ −186 ($c$ 1.24, $CHCl_3$), see Ref. 19.

23. The conditions: CHIRALPAK OD column, hexane/2-propanol = 20:1.
24. A referee suggested the participation of anomeric OMe for the potassium-chelate formation. Although we have no evidence which rules out this possibility, we insist on the presence of the chelate structure depicted in Scheme 6 by the following reason. If the potassium-chelate forms between the OMe and enolate, the sterically less-congested space might turn out to be *Re*-face (not the *Si*-face) of the α-methylated enolate.
25. As described previously,[4k,5] the highly stereoselective introduction of the (*S*)-quaternary carbon center into the acetoacetate ester **2** could not be attained by changing the order of the addition of the electrophiles, that is, allylation (or benzylation) and then methylation.