Stereoselective Double Alkylation of the Acetoacetate Ester α-Carbon on a D-Glucose-Derived Template: Application to the Synthesis of Enantiopure Cycloalkenones Bearing an Asymmetric Quaternary Carbon

Ikuko Kozawa, Yoko Akashi, Kumiko Takiguchi, Daisuke Sasaki, Daisuke Sawamoto, Ken-ichi Takao, Kin-ichi Tadano*

Department of Applied Chemistry, Keio University, Hiyoshi, Yokohama 223-8522, Japan
Fax +81(45)5661571; E-mail: tadano@applc.keio.ac.jp

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Abstract: The previously developed D-glucose derivative, i.e., methyl 6-deoxy-2,3-di-*O*-(*tert*-butyldimethylsilyl)-α-D-glucopyranoside, served as a significant stereocontrolling element for the diastereoselective alkylation of the α-carbon in its acetoacetate at C-4 with two types of alkyl halides. The thus obtained doubly alkylated acetoacetate moiety bearing both methyl and allyl groups was efficiently converted into functionalized cycloalk-2-en-1-one derivatives by means of an intramolecular aldol strategy. Furthermore, the synthetic utility of the cycloalkenones was exemplified through the 1,4-addition to the thus obtained cyclopentenone derivative.

Key words: D-glucose derivatives, chiral auxiliary, double alkylation, asymmetric quaternization, intramolecular aldol reactions

In relation to the development of stereoselective carbon–carbon bond-forming reactions realized in a chiral environment, we have been using sugar-based templates as effective chiral auxiliaries.[1] As a result, we have found that a D-glucose derivative, i.e., 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 by using its 4-*O*-propionyl ester (**2**),[3] 4-*O*-acryloyl ester (**3**),[4] and 4-*O*-crotonyl ester (**4**)[2,3a] (Figure 1).

One of the highlights in current organic synthesis is the development of the enantioselective construction of an all-carbon asymmetric quaternary carbon center. For this subject, the asymmetric induction of a quaternary carbon has been extensively investigated by the use of a transition-metal catalyst,[5] an organocatalyst[6] or chiral auxiliaries.[7]

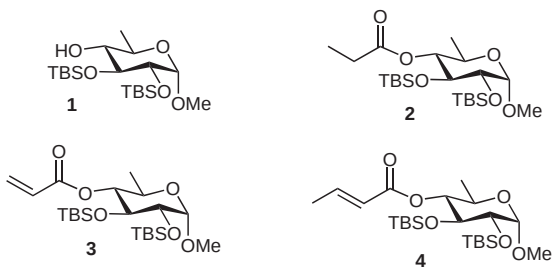

Figure 1 Previously used substrates for stereoselective carbon–carbon bond-forming reactions

We are interested in the use of the D-glucose-derived chiral template **1** for the stereoselective construction of an asymmetric quaternary carbon. We herein report the highly stereoselective quaternization of the α-carbon in the 4-*O*-acetoacetyl derivative of **1** by a double C-alkylation strategy and the utilization of the resulting differentially α-dialkylated acetoacetate for the synthesis of two cycloalk-2-en-1-ones, both incorporating an asymmetric quaternary carbon, connecting with **1**. The starting 4-acetoacetate **5**[8] was prepared by the acylation of **1** with 2,2,6-trimethyl-1,3-dioxin-4-one in refluxing *o*-xylene (Scheme 1). The acetoacetate **5** exists as a 3:1 mixture of 1,3-diketo and keto–enol forms. The C-methylation at the α-carbon of this mixture **5** occurred by using K_2CO_3 as a base with methyl iodide at 40 °C. The C-methylated product **6** exists as a 5:2:2 mixture of three tautomeric forms, as detected on the basis of ^{1}H NMR analysis. We did not characterize each form in this mixture but, rather, used the second alkylation directly. We explored the second alkylation with benzyl bromide as an electrophile. After the examination of several bases, we found that sodium methoxide was the most effective base for this reaction.[9] As a result, the benzylated product **7** was obtained as a single diastereomer (based on ^{1}H NMR analysis) in 75% yield. We recognized that the order of this sequential alkylation is essential for the observed high diastereoselectivity. When the two alkylations were carried out in the order of benzylation and methylation, the diastereomeric ratio for the doubly alkylated product **7** was significantly changed, with a decrease in the formation of **7**.[10] The absolute stereochemistry of the newly introduced stereogenic carbon in **7**, i.e., the *R*-configuration as depicted, was established by the following experiment. Treatment of **7** with hydrazine hydrate in EtOH at 140 °C provided a known pyrazoline derivative **8**[11] in 88% yield.[12] The sugar template **1** was also recovered in 87% yield. We then explored the allylation of **6** for the second alkylation. The allylation proceeded with complete diastereoselectivity by using allyl bromide as an electrophile, providing **9** in 80% yield as a single diastereomer. The configuration of the new quaternary carbon in **9** was confirmed to be *R*, as depicted, on the basis of converting **9** into a pyrazoline derivative **10** by treatment of **9** with hydrazine hydrate as in the case of **7**.[13]

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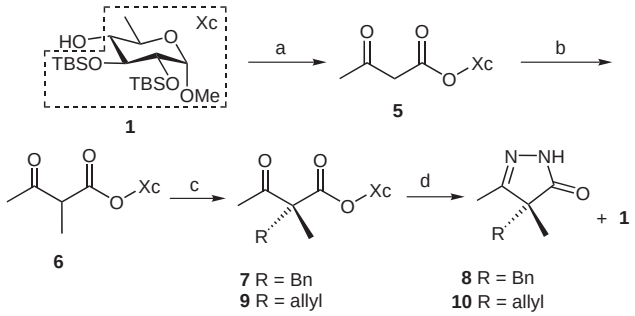
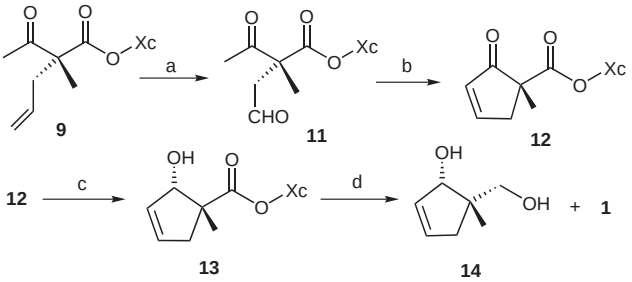
We had experienced analogous high diastereoselectivities, which were realized using the 4-*O*-acyl substrates **2**–**4** for a variety of carbon–carbon bond-forming reactions. We had also explained that these stereoselectivities were effectively brought by the existence of a bulky OTBS group installed at C-3 of **2**–**4**, which disturbs the approach of reactive species to the reaction site installed at C-4 from the front side, i.e., the side shielded by the OTBS group. In the present case, base-mediated deprotonation from **6** is likely to result in the exclusive formation of *Z*-enolate, as shown in Scheme 2.[3] In this transition state, the 3-*O*-TBS group hinders the approach of the electrophile from the front side. Consequently, the alkyl halides predominantly approached from the rear side of the enolate as depicted. Although we could not determine the geometry of the intermediary enolate by spectroscopic means, the aforementioned argument is most likely to explain the observed diastereoselectivity in the second alkylation step.



Scheme 1 Asymmetric quaternization of the α-carbon of acetoacetate **5**. *Reagents and conditions*: (a) 2,2,6-trimethyl-1,3-dioxin-4-one, *o*-xylene, reflux, 93%; (b) MeI, K_2CO_3, acetone, 40 °C, quantitatively; (c) for **7**: BnBr, MeONa, THF, –78 °C to r.t., 75%; for **9**: allyl bromide, MeONa, THF, 80%; (d) $N_2H_4{\cdot}H_2O$, EtOH, 140 °C (sealed tube); 88% for **8** (87% for **1**); quantitative yield for **10** (60% for **1**).

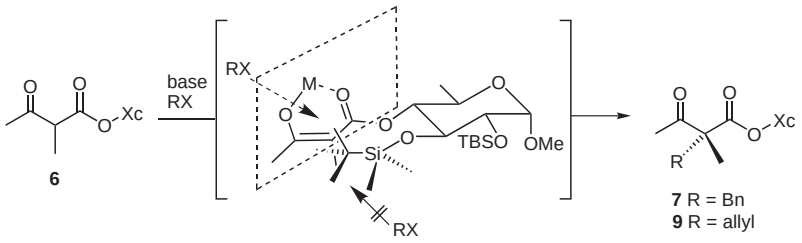
We next investigated the synthetic utility of the differentially α-disubstituted acetoacetate moiety in **9** as an enantiopure building block. As one example for this aim, we explored the transformation of **9** into a differentially 5,5-disubstituted cyclopent-2-en-1-one **12** (Scheme 3). Ozonolysis of the double bond in **9** followed by work-up with PPh_3 provided aldehyde **11**, which was subjected to a DBU-mediated intramolecular aldol condensation. The desired cyclopentenone **12**[14] was obtained in 65% yield over two steps. Then, the DIBAL-H reduction of **12** was carried out at –78 °C, producing allylic alcohol **13** with a >20:1 diastereomeric ratio. The newly introduced stereogenic center at the allylic position was established after removal of the sugar template from **13**. The hydride reduction of **13** using excess DIBAL-H eventually removed the sugar template, providing a 2-cyclopentenol derivative **14**[15,16] in a virtually enantiopure form, and the sugar template **1** was recovered.[17]



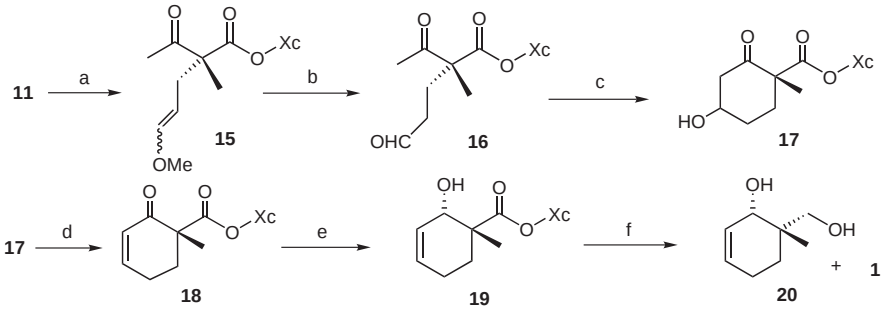
Scheme 3 Synthesis of a cyclopent-2-en-1-one derivative **12** and removal of the sugar template. *Reagents and conditions*: (a) O_3 (3% O_3 in O_2), CH_2Cl_2, –78 °C, then PPh_3, 95%; (b) DBU, DMF, 50 °C, 69%:(c) DIBAL-H, CH_2Cl_2, –78 °C, 79%, dr > 20:1; (d) DIBAL-H (3 equiv, then 2 equiv), CH_2Cl_2, –78 °C to 0 °C, 61% for **14** and 59% for **1** (recovery of **13**, 20%).

We also explored the synthesis of the cyclohexenone homologue of **12**, i.e. compound **18**. This task was accomplished uneventfully by the analogous intramolecular aldol condensation strategy used for the synthesis of **12** (Scheme 4). The Wittig carbon-elongation reaction of aldehyde **11** with the ylide prepared from $Ph_3PCH_2OCH_3Cl$ provided an *E*/*Z*-mixture of methyl vinyl ether **15**. Acid hydrolysis of this mixture **15** afforded the one-carbon-elongated aldehyde **16**. When **16** was treated with DBU in toluene at room temperature, the expected intramolecular aldol reaction proceeded smoothly to afford the β-hydroxylated cyclohexanone **17**. Acetylation of **17** followed by treatment of the resulting acetate with triethylamine provided **18** in 74% from **16**. 1,2-Hydride reduction of the cyclohexenone **18** under Luche conditions[18] provided allylic alcohol **19**[19] virtually as a single product.[20] Treatment of **19** with excess DIBAL-H (two additions of a 5.0 equiv of DIBAL-H at –18 °C) resulted in the removal of the sugar template, providing cyclohexenol bearing an asymmetric quaternary carbon center **20**[21] in 83% yield.[22]

To demonstrate the synthetic utility of the enantiopure cycloalkenones **12** and **18**, we explored the diastereoselectivity in the 1,4-additions of carbon nucleophiles to

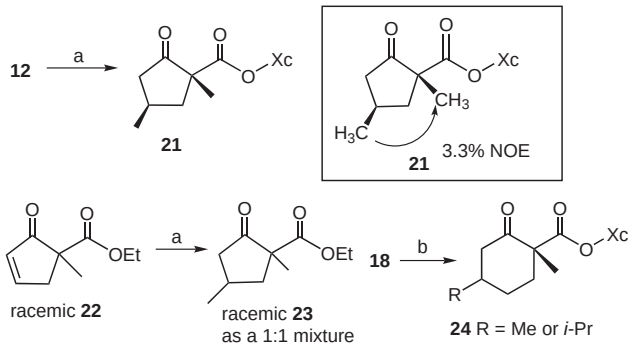


Scheme 2 A plausible transition state for the second alkylation of **6**



Scheme 4 Synthesis of a cyclohex-2-en-1-one derivative **18** and removal of the sugar template from **18**. *Reagents and conditions*: (a) Ph_3PCH_2OMeCl, NaHMDS, THF, r.t., 84%; (b) CF_3CO_2H–H_2O–CH_2Cl_2 (1:1:5), 0 °C, 96%; (c) DBU, toluene, r.t., dr = 1.3:1; (d) 1) Ac_2O–pyridine (1:1), r.t.; 2) Et_3N, CH_2Cl_2, r.t., 74% from **16**; (e) $NaBH_4$, $CeCl_3·7H_2O$, MeOH–CH_2Cl_2 (1:1), –78 °C, 81%; (f) DIBAL-H (total 10 equiv), –18 °C to r.t., 83% for **20**.

12 and **18** (Scheme 5). In the case of the cyclopentenone derivative **12**, Me_2CuLi as a carbon nucleophile attacked in a 1,4-addition fashion with remarkable diastereoselectivity, providing **21** as a single adduct. The configuration at newly introduced β-carbon in **21** was confirmed to be depicted by ^{1}H NMR analysis, including a NOE experiment, which revealed that two methyl groups on the cyclopentanone **21** are in a *cis* relationship.[23] To evaluate the role of the sugar template for effecting the stereoselectivity in the 1,4-addition to **12**, we explored the 1,4-addition of racemic 5-carboethoxy-5-methyl-2-cyclopenten-1-one (racemic **22**). The racemic **22** was prepared according to a previous report.[24] The 1,4-addition of a methyl nucleophile to the racemic **22** under the same conditions used for **12** quantitatively provided the 1,4-adduct, racemic **23**, as an approximately 1:1 diastereomeric mixture. These results suggested the remarkable role of the sugar template part in **12** as a stereocontrolling element for the exclusive diastereoselectivity observed in the 1,4-addition of carbon nucleophiles to **12**. Although we cannot propose a distinct transition-state model to account for these high stereoselectivities, further utilization of **12**, such as the elaboration of the enone part, is to be expected. On the other hand, the 1,4-addition of two alkylcuprates (R = Me or *i*-Pr) to the cyclohexenone derivative **18** provided the corresponding 1,4-adducts **24**. In contrast to the case of **12**, the diastereoselectivities observed in **24** were low to modest [R = Me, dr = 1.6:1 on the basis of the ^{1}H NMR analysis of the inseparable mixture (82% combined yield); R = *i*-Pr, dr = 5.3:1 (48% combined yield); the configurations of the newly created stereogenic centers for these adducts were not determined]. Therefore, the superiority of **12** to **18** as the substrate for the 1,4-addition of carbon nucleophiles is obvious.



Scheme 5 1,4-Additions of alkylcuprates to **12** and **18**. *Reagents and conditions*: (a) MeLi (6 equiv), CuI (3 equiv), Et_2O, –78 °C, 74% for **21**; quantitatively for racemic **23**; (b) for R = Me same as (a); for R = *i*-Pr, *i*-PrMgBr (6 equiv), CuBr·SMe_2 (3 equiv), Et_2O, –78 °C.

In conclusion, we have demonstrated the highly stereoselective quaternization of the α-carbon of acetoacetate ester installed at C-4 of the sugar template **1**. One of the doubly alkylated products (**9**) thus obtained serves as a versatile building block. For example, compound **9** was transformed into cycloalk-2-en-1-ones **12** and **18**, both bearing a methyl and an alkoxycarbonyl group at C-5 and C-6, respectively, by means of an intramolecular aldol strategy. The synthetic utility of **12** was enhanced by the highly stereoselective 1,4-addition of carbon nucleophiles to **12**. The further synthetic utilization of **12** and **18** for stereoselective carbon–carbon bond-forming reactions is our current concern.

References and Notes

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(6) Some recent prominent papers on this subject: (a) Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672. (b) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.

(7) A recent review on this subject: Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917.
(8) All new compounds were fully characterized by spectral means (^{1}H NMR and ^{13}C NMR, IR, and HRMS). Yields refer to isolated products after purification by column chromatography on silica gel.
(9) We examined the following bases for the second benzylation, which was carried out in THF. The yield of **7** using NaHMDS (–78 °C to r.t.), 18%; using LiHMDS (–18 °C to r.t.), 35%; and using NaH (–78 °C to r.t.), 74%.
(10) The yield of the first benzylation (BnBr, EtONa, THF, 0 °C to r.t.) was 97%. The conditions and yields of the second methylation for the two diastereomers, i.e., **7** and its epimer at the α-carbon, were as follows: a) MeI and KHMDS in THF at –18 °C to r.t., 46% and 10%; b) EtONa as the base at –78 °C to r.t., 64% and 16%; c) MeONa as the base at –78 °C to r.t., 63% and 14%. In all cases, the major product was **7**.
(11) (a) (4*R*)-4-Benzyl-3,4-dimethyl-2-pyrazolin-5-one (**8**): $[\alpha]_D^{22}$ –186 (*c* 1.24, $CHCl_3$). For the reported $[\alpha]_D$ for **8** $[\alpha]_D^{15}$ –186 (*c* 1.24, $CHCl_3$) see ref. 11b. In this paper, the Vallribera group reported the asymmetric construction of a quaternary carbon using D-ribolactone acetonide or its cyclohexanone ketal as a sugar-based chiral template. Their sugar templates also served as good stereocontrolling elements, which provided the doubly α-alkylated (both Me and Bn) acetoacetates installed at C-5 in the sugar templates in 56–69% yield with 80:20 to 75:25 diastereomeric ratios in favor of the respective *R*-isomer. Thus, the diastereoselectivities observed in their cases were lower than those in ours with the use of the pyranose-type template **1**. (b) Moreno-Mañas, M.; Trepat, E.; Sebastián, R. M.; Vallribera, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4211.
(12) We also synthesized the *S*-antipode of **8** from the minor α-dialkylated acetoacetate obtained by the reverse double alkylation of **5** with the same alkyl halides followed by the analogous pyrazoline formation used for the case of **7**. The synthesized *S*-isomer possessed the following optical rotation: $[\alpha]_D^{21}$ +180 (*c* 0.30, $CHCl_3$).
(13) (a) We synthesized the antipode of **10**, i.e., (*S*)-**10**, as follows. As a substrate for the pyrazoline formation, enantioenriched ethyl (*S*)-2-acetyl-2-methyl-4-pentenoate was prepared at first by the α-allylation of racemic ethyl 2-methyl-acetoacetate using L-valine *tert*-butyl ester as a chirality inducer, according to a known procedure reported by Koga and co-workers, see ref. 13b. The thus obtained α-disubstituted acetoacetate ester was then treated with $N_2H_4{\cdot}H_2O$, providing enantioenriched (*S*)-**10**. The comparison of the sign and magnitude of the optical rotatory property for (*S*)-**10** {$[\alpha]_D^{27}$ +128 (*c* 0.49, $CHCl_3$)} with our (*R*)-**10** {$[\alpha]_D^{26}$ –123 (*c* 0.78, $CHCl_3$)} clearly established the *R*-configuration for the new stereogenic carbon center in **9**. (b) Ando, K.; Takemasa, Y.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 1579.
(14) Compound **12**: TLC: R_f = 0.50 (EtOAc–hexane, 1:3); $[\alpha]_D^{25}$ +64.1 (*c* 1.49, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09, 0.10 (2 s, each 6 H), 0.84, 0.91 (2 s, each 9 H), 1.05 (d, 3 H, *J* = 6.3 Hz), 1.42 (s, 3 H), 2.53, 3.45 (2 ddd, each 1 H, *J* = 19.2, 2.2, 2.2 Hz), 3.33 (s, 3 H), 3.56–3.64 (m, 1 H), 3.66 (dd, 1 H, *J* = 8.7, 3.5 Hz), 3.87 (t, 1 H, *J* = 8.7 Hz), 4.60 (d, 1 H, *J* = 3.5 Hz), 4.72 (dd, 1 H, *J* = 9.8, 8.7 Hz), 6.17 (ddd, 1 H, *J* = 5.6, 2.2, 2.2 Hz), 7.74 (ddd, 1 H, *J* = 5.6, 2.2, 2.2 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): δ = –4.2 × 2, –3.2, –2.6, 17.5, 17.9, 18.5, 21.9, 26.0 × 3, 26.2 × 3, 42.1, 53.7, 54.8, 65.3, 72.0, 74.6, 78.2, 99.8, 131.5, 163.0, 170.3, 205.8. IR (neat): 2950, 2850, 2750, 2710, 1730, 1715, 1590, 1450, 1360 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{22}H_{39}O_7Si_2$ [M^+ – *t*-Bu]: 471.2234; found: 471.2233.
(15) (1*S*,5*S*)-5-Hydroxymethyl-5-methyl-2-cyclopenten-1-ol (**14**): TLC: R_f = 0.44 (EtOAc); $[\alpha]_D^{23}$ +65.6 (*c* 0.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 3 H), 1.98 (d, 1 H, *J* = 17.1 Hz), 2.48 (dd, 1 H, *J* = 17.1, 2.1 Hz), 3.63, 3.70 (2 d, each 1 H, *J* = 11.1 Hz), 4.44 (br s, 1 H), 5.74–5.76 (m, 1 H), 5.95–5.97 (m, 1 H). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 24.0, 41.9, 45.2, 68.3, 85.4, 131.6, 134.9. IR (neat): 3250, 3060, 2930, 1730, 1460 cm^{-1}. HRMS (EI): *m/z* calcd for $C_7H_{12}O_2$ [M^+]: 128.0837; found: 128.0841
(16) (a) (1*S*,5*R*)-5-Hydroxymethyl-5-methyl-2-cyclopenten-1-ol, the 5-epimer of **14**, is a known compound that was synthesized by Kato and co-workers using a chiral acetal-mediated asymmetric alkylation, see ref. 16b. The ^{1}H NMR and ^{13}C NMR spectra of the 5-epimer were distinctly different from those of **14**. Furthermore, the NOE experiment of the 5-epimer revealed a 2.9% signal enhancement for the methylene of the hydroxymethyl group at C-5 when the proton at C-1 (H-1) was irradiated. On the other hand, the irradiation of H-1 in **14** resulted in a 1.3% signal enhancement of the methyl protons at C-5. (b) Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T.; Baba, M.; Yamaguchi, K.; Akita, H. *Chem. Pharm. Bull.* **1999**, *47*, 1256.
(17) We explored the removal of the sugar template from **12** directly by methanolysis (MeONa in MeOH). In this case, compound **12** was quantitatively recovered. The removal of the sugar template from the protected forms of the allylic alcohol **13** as its TBS or MOM ethers was also fruitless. For these ethers, saponification or hydride attack resulted in the recovery of the starting material.
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(19) The configuration of newly introduced allylic carbinol carbon in **19** as depicted was confirmed by the NOE experiment in which a significant (7.3%) signal enhancement of the proton at the allylic carbinol carbon was observed when the adjacent methyl group was irradiated.
(20) The DIBAL-H reduction of **18** (1.5 equiv, CH_2Cl_2, –78 °C) also provided **19** as a single product in a less effective yield of 63%.
(21) The observed dextrorotatory property for **20** {$[\alpha]_D^{21}$ +138,7 (*c* 0.355, $CHCl_3$)} confirmed the absolute stereochemistry of **20**. For the reported enantioenriched **20** (94% ee), $[\alpha]_D$ +104.1 (*c* 0.95, $CHCl_3$) was reported, see: Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812.
(22) In this case, the sugar template **1** was recovered in 19% yield. Under the harsh DIBAL-H reduction of **19**, the silyl group at C-2 in **1** was unexpectedly deprotected to a large extent. Thus, the 3-*O*-TBS derivative was obtained in a significant yield of 75%.
(23) We also examined the 1,4-addition using *n*-Bu_2CuLi under analogous conditions as those used for the Me_2CuLi addition. The 1,4-addition proceeded with complete stereoselectivity to provide a single 1,4-adduct in 75% yield. Unfortunately, we could not establish the configuration at the β-carbon of this adduct unambiguously from ^{1}H NMR spectral analysis.
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