ORGANIC LETTERS

1999
Vol. 1, No. 9
1447−1450

Highly Stereoselective 1,4-Conjugate Addition of Organocopper Reagents to Methyl α-D-Glucopyranoside Derivatives Tethering an Unsaturated Ester Moiety at C-4 or C-6[1]

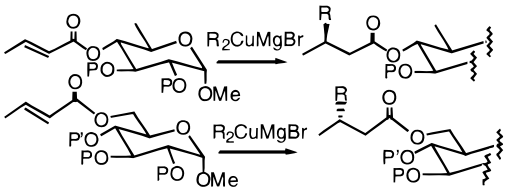
Kiichiro Totani,[†] Takayuki Nagatsuka,[†] Ken-ichi Takao,[†] Shigeru Ohba,[‡] and Kin-ichi Tadano*,[†]

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

tadano@applc.keio.ac.jp

Received August 31, 1999

ABSTRACT



The 1,4-conjugate additions of a variety of organocopper reagents to some 4-*O*-crotonyl derivatives of methyl α-D-glucopyranoside proceeded with a high level of diastereochemical induction to provide the adducts carrying a *β*-substituted butanoic ester at C-4. The 1,4-conjugate addition to a 6-*O*-crotonyl derivative afforded the adduct with reverse configuration at the *β*-carbon to that obtained from the 4-*O*-crotonyl derivatives.

The development of chiral auxiliaries based on readily available natural products is an ongoing subject in the field of asymmetric synthesis for obtaining useful levels of stereoinduction.[2] It has been widely recognized that a number of carbohydrate-based templates existing in pentofuranose or hexopyranose form can serve as good chiral auxiliaries since they provide a stereochemically biased environment.[3,4]

We have investigated the utility of hexopyranose derivatives with the expectation that they are synthetically useful chiral auxiliaries in stereoseletive carbon−carbon-bond forming reactions. In this paper, we provide recent results on the 1,4-conjugate additions[5] of a variety of organocopper reagents to the 4-*O*- or 6-*O*-crotonyl derivatives of methyl α-D-glucopyranoside.[6]

[†] Department of Applied Chemistry.
[‡] Department of Chemistry.

(1) This paper is dedicated with respect and admiration to Professor Kenneth L. Rinehart on the occasion of his 70th birthday.

(2) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3−12.

(3) Cintas, P. *Tetrahedron* **1991**, *47*, 6079−6111. Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336−358. Kunz, H. *Pure Appl. Chem.* **1995**, *67*, 1627−1635. Hultin, P. G.; Earle, M. A.; Sudharshan, M. *Tetrahedron* **1997**, *53*, 14823−14870.

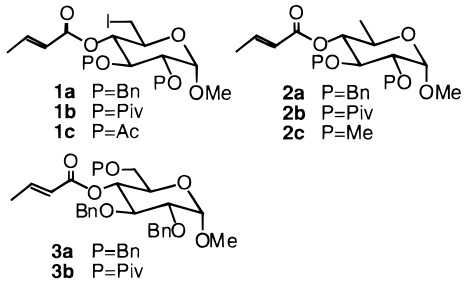
(4) For recent relevant reports on this subject, see: Ko, K.-Y.; Park, J.-Y. *Tetrahedron Lett.* **1997**, *38*, 407−410. Follmann, M.; Kunz, H. *Synlett* **1998**, 989−990. Weymann, M.; Schultz-Kukula, M.; Kunz, H. *Tetrahedron Lett.* **1998**, *39*, 7835−7838.

(5) For leading reviews on asymmetric 1,4-conjugate addition, see: Rossiter, B. E.; Swingle, N. M. *Chem Rev.* **1992**, *92*, 771−806. Noyori, R. *Asymmetric Catalysts in Organic Synthesis*; John Wiley and Sons: New York, 1994; pp 207−212. Alexakis, A. In *Organocopper Reagents, a Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, U.K., 1994; pp 159−183. Feringa, B. L.; de Vries, A. H. M. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press Inc: Greenwich, CT, 1995; Vol. 1, pp 151−192.

10.1021/ol9909942 CCC: $18.00 © 1999 American Chemical Society
Published on Web 09/30/1999

The substrates we designed were methyl 2,3-di-*O*-protected 6-iodo- (**1a**−**1c**), 6-deoxy- (**2a**−**2c**), and 2,3,6-tri-*O*-protected (**3a**, **3b**) α-D-glucopyranosides (Scheme 1).

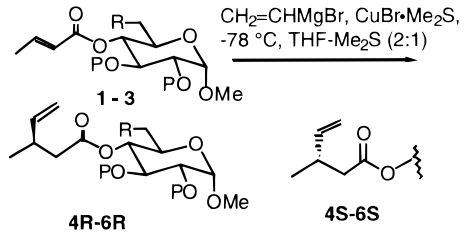
Scheme 1



These substrates were prepared from known 2,3-di-*O*-protected[7] or 2,3,6-tri-*O*-protected derivatives[8] of methyl α-D-glucopyranoside.[9]

First, we investigated the conjugate addition of a vinyl group to the 4-*O*-crotonyl derivatives **1a**−**1c**, **2a**−**2c**, **3a**, and **3b** (Scheme 2). The carbon nucleophile was prepared

Scheme 2



by mixing vinylmagnesium bromide (10 molar equiv to the substrate) and cuprous bromide−dimethyl sulfide complex (5 molar equiv). In every case, the additions took place rapidly to provide the respective 1,4-adducts in good to high yields, and with exceptionally high diastereoselectivity in specified cases. The results are summarized in Table 1.[10]

Table 1

substrate	P	R	products	yield[a]	d.r.
1a	Bn	I	**4aR**	75	> 99:1[b]
1b	Piv	I	**4bR**	56(33)	> 99:1[b]
1c	Ac	I	**4cR/S**	51	55:45[c,d]
2a	Bn	H	**5aR**	90	> 99:1[b]
2b	Piv	H	**5bR**	61(36)	> 99:1[b]
2c	Me	H	**5cR/S**	72(16)	56:44[c,d]
3a	Bn	OBn	**6aR/S**	84	88:12[e]
3b	Bn	OPiv	**6bR/S**	81	86:14[e]

[a] Isolated yields; yields in parentheses are for the recovered starting material. [b] Determined by HPLC (TOSOH TSK-GEL SILICA-60, EtOAc/hexane = 1:30 for **4bR** and **5bR**, EtOAc/hexane = 1:20 for **4aR** and **5aR**). [c] Determined by ^{1}H NMR. [d] The stereochemistry of each diastereomer was not determined. [e] Determined by ^{13}C NMR.

The 6-iodo derivatives **1a** and **1b** afforded the adducts **4aR** and **4bR**, respectively, both virtually as a single diastereomer.[11] In addition, the adduct **4bR** was isolated as crystals suitable for single-crystal analysis[12] to unambiguously determine the stereochemical assignment of the newly introduced stereogenic carbon as depicted in Scheme 2. Furthermore, the stereochemistry of **4aR** was confirmed to be that assigned by chemical correlation to the stereochemistry of **4bR**. In the case of **1c**, an inseparable mixture of two isomers **4cR** and **4cS** was obtained with virtually no stereoselectivity. The 6-deoxy derivatives **2a** and **2b** provided almost exclusively **5aR** and **5bR**, respectively.[13] Stereochemical assignment of the newly introduced stereogenic center in **5aR** or **5bR** was conducted by chemical transformation and comparison with derivatives prepared from the adducts **4aR** or **4bR**. Consequently, the 1,4-additions to **1a**, **1b**, **2a**, and **2b**, in all cases, provided the respective *R*-isomer with complete stereoinduction. The same stereochemical outcome was observed when the 6-*O*-protected substrates **3a** and **3b** were subjected to 1,4-addition under the same reaction conditions as those used for **1** and **2**. The levels of diastereoselection were lower in the 1,4-additions to **3a** and **3b** (dr = 88:12 or

(6) Some of the results described herein have been presented at the 19th International Carbohydrate Symposium (University of California, San Diego, August 9−14, 1998) and at the 36th National Organic Chemistry Symposium (University of Wisconsin−Madison, June 13−17, 1999).

(7) Compounds **1a**, **1b**, **1c**, **2a**, **2b**, and **2c** were prepared in the conventional manner from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (for **1a** and **2a**) (Yoshimoto, K.; Itatani, Y.; Shibata, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1980**, *28*, 208−219); from methyl 2,3-di-*O*-pivaloyl-α-D-glucopyranoside (for **1b** and **2b**) (Tomic-Kulenovic, S.; Keglevic, D. *Carbohydr. Res.* **1980**, *85*, 302−306); from methyl 2,3-di-*O*-acetyl-α-D-glucopyranoside (for **1c**) (Whistler, R. L.; Kazenjac, S. J. *J. Am. Chem. Soc.* **1954**, *76*, 3044−3045); and from methyl 6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (for **2c**) (Shono, T.; Matsumura, Y.; Hamaguchi, H.; Naitoh, S. *J. Org. Chem.* **1983**, *48*, 5126−5128).

(8) Compound **3a** was prepared from methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside: Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10−C11. Compound **3b** was prepared from the above methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside.

(9) The substrates were prepared as follows: for **1a**−**1c**, transformation of the 6-OH to an iodo group via the respective tosylate and then esterification of the 4-OH with crotonic anhydride; for **2a**−**2c**, hydride attack or hydrogenolysis of the 6-*O*-tosyl or the 6-iodo derivatives followed by esterification of the 4-OH; and for **3a** and **3b**, regioselective protection of the 6-OH and then esterification of the 4-OH.

(10) All of the purified new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, and either HRMS or combustion analysis.

(11) We selected the 6-iodo derivatives **1a** and **1b**, with the expectation that a tandem intramolecular carbon−carbon bond formation could occur through the enolate, which would be generated as a result of the 1,4-addition. The enolate could then attack the C-6 carbon with removal of the iodo group. This would have entailed the introduction of a second and consecutive stereogenic center. However, the second carbon−carbon bond formation did not occur in case of either **1a** or **1b**.

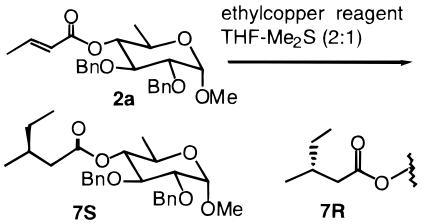
(12) **X-ray Crystallographic Data for 4bR.** Crystal data for **4bR** (crystals were grown from a methanol solution): $C_{23}H_{37}IO_8$; $M_r = 3568.45$; monoclinic $P2_1$; $a = 14.982(6)$ Å, $b = 6.147(4)$ Å, $c = 15.473(8)$ Å; $V = 1421.7(14)$ Å^3; $Z = 2$; $D_x = 1.328$ mg m^{-3}; Mo Kα radiation $\lambda = 0.710\,73$ Å; 3070 independent reflections, $R = 0.052$, wR = 0.052, $S = 1.403$, 2445 reflections, 288 parameters.

(13) We also examined the conjugate addition to **2a** using a catalytic amount of CuBr·Me$_2$S (0.1 molar equiv to **2a**) and a reduced amount (4.0 molar equiv) of vinylmagnesium bromide. In this case, **5aR** was isolated in 72% yield as virtually a single diastereomer (d.r. >99:1) (19% of **2a** was recovered). However, the amount of Grignard reagent was critical for the progression of the reaction. Thus, the use of 1.0 or 2.0 molar equiv of the reagent resulted in the recovery of **2a** in 93% or 91% yield, respectively.

86:14) than in the 1,4-additions to **1a**, **1b**, **2a**, or **2b**, although the 1,4-additions to **3a** and **3b** proceeded smoothly at −78 °C.

We also examined the use of various organocopper reagents on the diastereoselectivity, exemplified by the addition to **2a** using three types of ethylcopper reagents, i.e., magnesium diethylcuprate, ethylcopper boron trifluoride complex, or lithium diethylcuprate (Scheme 3, Table 2). The

Scheme 3



first and second reagents provided predominantly the adduct **7S**. These results are similar to the cases shown in Table 1. However, the last reagent (the so-called Gilman-type cuprate) preferentially provided **7R**. This product incorporated a reverse stereochemistry to that observed in the two cases described above. From these results, we concluded that it is essential to use the organocopper reagents prepared from the corresponding Grignard reagent to realize the observed high level of diastereoselective 1,4-addition.

Table 2

ethyl copper	temp (°C)	yield[a]	**7S:7R**[b]
$Et_2CuMgBr$	-78 to -18	88	86:14
$EtCu{\cdot}BF_3$	-78 to rt	72(11)	73:27
Et_2CuLi	-78	76(10)	34:66

[a] Isolated yields; yields in parentheses are for the recovered starting material. [b] Determined by ^{1}H NMR.

To confirm the generality of the reaction, we examined the conjugate addition to cinnamoyl ester derivative **8** (Scheme 4, Table 3). Two organocopper reagents prepared from the corresponding Grignard reagent each attacked the same face (*si*-face) of the *β*-carbon, preferentially providing

Scheme 4

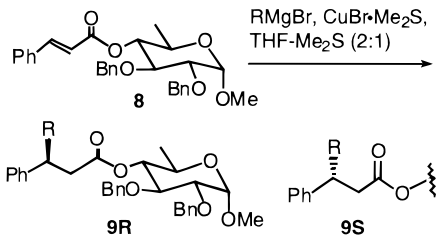


Table 3

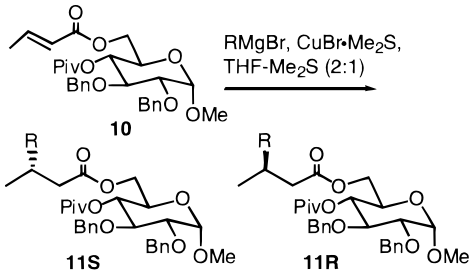
R	temp (°C)	yield[a]	**9R:9S**
CH_2=CH	-78	60(33)	89:11[c]
Me	-78 to 0	72(15)	90:10[b]

[a] Isolated yields; yields in parentheses are for the recovered starting material. [b] Determined by HPLC (TOSOH TSK-GEL SILICA-60, EtOAc/hexane=1:12). [c] Determined by ^{1}H NMR.

9R isomers.[14] These results imply that the reaction of each cuprate occurred from the same direction on all of the substrates irrespective of the bulkiness of the *β*-substituent.

Next, we investigated conjugate addition to 6-*O*-crotonylated glucopyranoside derivative **10** (Scheme 5).[15] As shown

Scheme 5



in Table 4, remarkable diastereoselection was observed in the 1,4-addition of vinyl and ethyl groups to 6-*O*-crotonylated derivative **10** of methyl α-D-glucopyranoside. Quite interestingly, the stereochemistry of the newly introduced stereogenic carbon in the predominant products **11S** (R = vinyl or Et)[16] was opposite of that in the predominant products obtained from the 4-*O*-crotonyl derivatives **1a**, **1b**, **2a**, and **2b**. The precise mechanism that is responsible for the stereochemical preference may remain uncertain until we have accumulated sufficient experimental results. However, it is apparent that the pivaloyloxy group at C-4 is necessary because the C-6 crotonyl derivative bearing a benzyloxy group at C-4 led to a lower level of diastereoselectivity (at most 1.7 to 1) for the addition of a vinyl group.

Table 4

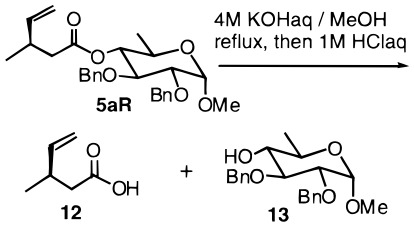
R	temp (°C)	yield[a]	**11S:11R**[b]
CH_2=CH	-78	58(21)	86:14
Et	-78 to -18	86	93:7

[a] Isolated yields; yields in parentheses are for the recovered starting material. [b] Determined by ^{1}H NMR.

Finally, removal of the carbohydrate moiety is readily accomplished as shown for the adduct **5aR** (Scheme 6).

(14) The stereochemistry of the introduced stereogenic center in the major adduct **9R** was determined by comparing the optical rotation of the acid, which was obtained by cleavage of the carbohydrate auxiliary, to that of known 3-vinyl-(or methyl-)3-phenylpropanoic acid.

Scheme 6



Alkaline hydrolysis followed by extractive workup of the reaction solution with chloroform afforded methyl 6-deoxy-2,3-di-*O*-benzyl-α-D-glucopyranoside **13** (94%) in spectroscopically pure form. The aqueous layer was acidified, and extraction with chloroform provided (−)-3-methyl-4-pentenoic acid **12** (96%).[17]

In summary, our novel asymmetric 1,4-conjugate addition approach based on the carbohydrate auxiliary concept can be used to synthesize a variety of β-alkylated butanoic acid derivatives in an efficient manner. Although the precise transition states in the conjugate additions presented in this study could not be elucidated, further utilization of the substrates such as **2a** and **2b** in other types of carbon−carbon bond-forming reactions is expected. Furthermore, we are currently investigating the feasibility of using other hexopyranosides as effective chiral auxiliaries.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research (No.10073038) from the Ministry of Education, Science, Sports and Culture, Japan, and in part by the Sasakawa Scientific Research Grant from the Japan Science Society (K. Totani, 11-120).

Supporting Information Available: Detailed experimental procedure for the synthesis of **5aR** and its hydrolysis to obtain **12**, characterization of the products, and ORTEP plot for **4bR**. This material available free of charge via the Internet at http://pubs.acs.org.

OL9909942

(15) Compound **10** was prepared from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[7] by preferential crotonylation of 6-OH followed by pivaloylation of 4-OH.

(16) The stereochemical assignment of **11S** (R = vinyl or Et) was confirmed by comparison with the known optical sign of the butanoic acid, which was obtained by removal of the carbohydrate auxiliary.

(17) Compound **12**: $[\alpha]^{30.0}_{D}$ −17.4 (*c* 0.58, $CHCl_3$); lit. $[\alpha]^{24}_{D}$ −17.42 (*c* 2.06, $CHCl_3$) [Uematsu, T.; Umemura, T.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 597−601.].