

# Stereocontrolled spirocyclization of *exo*-glucal derivatives for stereodivergent synthesis of spiro[5.5]ketals

Sho Matsuda,<sup>a,b</sup> Akihiro Yoshida,<sup>a</sup> Junki Nakagawa,<sup>b</sup> Mikio Watanabe,<sup>b</sup> Yoshiki Oda,<sup>a</sup> and Takashi Yamanoi<sup>c,\*</sup>

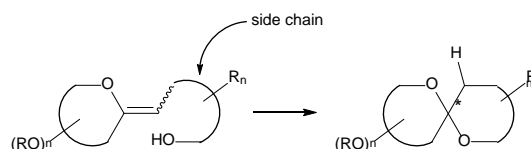
<sup>a</sup>The Noguchi Institute, 1-8-1 Kaga, Itabashi-ku, Tokyo 173-0003, Japan

<sup>b</sup>Department of Chemistry, School of Science, Tokai University, 4-1-1 Kitakaname, Hiratsuka, Kanagawa 259-1292, Japan

<sup>c</sup>Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan

**ABSTRACT**- This paper describes a stereoselective synthetic approach to spiro[5.5]ketals from the *exo*-glucals, constructed from 1-(4-hydroxyalkylidene)-1,5-anhydro-D-glucitol, by spirocyclization based on intramolecular  $\alpha$ - and  $\beta$ -selective glycosylation. Stereodivergent synthesis of both  $\alpha$ - and  $\beta$ -glucoside of spiro[5.5]ketals was attained by combination of chiral D-glucopyranose environment and C-4' chiral center on the side chain.

*exo*-Glycals are enol ether derivatives of sugars and useful intermediates for preparing more elaborate compounds in carbohydrate chemistry.<sup>1</sup> They are susceptible to nucleophilic attack by an alcohol in the presence of an acid catalyst to readily form *O*-ketosides.<sup>2</sup> Recent attention has been focused on the formation of spiro-fused *O*-ketosides, *i.e.* spiroketals, from glycals with an appropriate side chain by spirocyclization based on intramolecular glycosylation (Scheme 1).<sup>3</sup>

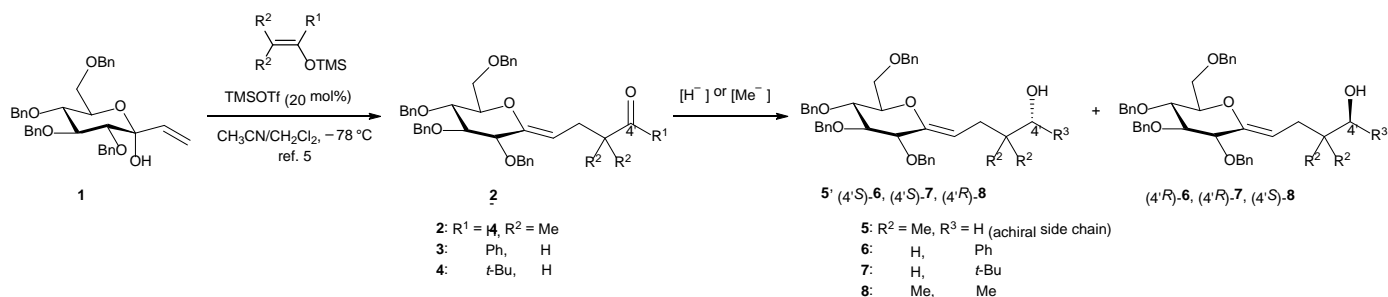


**Scheme 1.** Lewis acid-promoted cyclization of *exo*-glucal to yield spiro[5.5]ketal.

The glycals can be changed into various optically active spiroketals with original carbohydrate skeletons. Some of them are useful building blocks for synthesizing spiroketal fragments in naturally occurring products of marine, insect and bacterial origins.<sup>4</sup> One of the major problems in synthetic approaches to spiroketals from glycals is the synthetic difficulty in creating the appropriate glycals for spirocyclization.<sup>3</sup> It is also necessary to clarify the spirocyclization properties of the glycals.

Our recent study showed a novel synthetic approach to *exo*-glucals **2-4** by reactions of 1-*C*-vinylated D-glucopyranose **1** with silyl enolates in the presence of trimethylsilyl trifluoromethanesulfonate.<sup>5</sup> We investigated the preparation of the *exo*-glucals **5-8** from **2-4** for spirocyclization (Scheme 2). The C-4' carbonyl groups of the *exo*-glucals **2-4** were converted into the corresponding alcohol derivatives using NaBH<sub>4</sub> in THF/MeOH (v/v = 5/1) at 0 °C, K-Selectride® in THF at -78 °C and methyllithium in THF at -78 °C. Table 1 shows the results. The desired *exo*-glycals **5-8** were produced in yields of 67-86%, and the diastereomer ratios (*R/S* at C-4') of **6-8** ranged from 47/53 to 59/41. We conveniently produced all the both C-4' isomers by chromatography separation. The absolute configurations at C-4' of **6-8** were determined by the modified Mosher's method.<sup>6</sup>

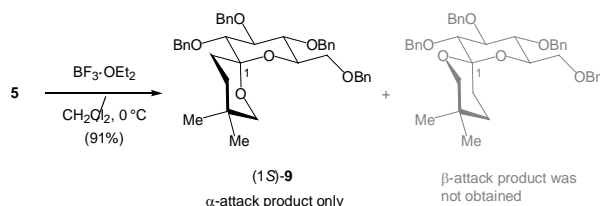
First, we investigated the synthesis of the spiro[5.5]ketals by spirocyclization of **5** with achiral alcohol on the side chain based on intramolecular glycosylation (Schemes 3). We carried out the spirocyclizations using BF<sub>3</sub>·OEt<sub>2</sub> (1 equiv.) as an activator in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C for 1 h. Compound **5** was smoothly spirocyclized through intramolecular  $\alpha$ -attack to give a spiroketal (1*S*)-**9** in 91% yield as a single isomer. Thus, we found that the chiral glucopyranose environment made C-4' alcohol differentiate between both diastereofaces of oxocarbenium and attack from the  $\alpha$ -face. The  $\alpha$ -attack product (1*S*)-**9** was stable due to the “double” anomeric effects. Considering the reaction mechanism,  $\alpha$ -attack is also more favorable than  $\beta$ -attack because of the unstable twist boat/chair intermediate just after  $\beta$ -attack (Figure 1).



**Scheme 2.** Synthesis of *exo*-glucals for spirocyclization.

**Table 1.** Synthesis of *exo*-glucals for spirocyclization.

Entr y	Starting <i>exo</i> -glucal		Reagents and conditions	Produced <i>exo</i> -glucal				
	R <sup>1</sup>	R <sup>2</sup>			R <sup>2</sup>	R <sup>3</sup>	Yield/% (ratio)	
1	<b>2</b>	H	Me	NaBH <sub>4</sub> , THF/MeOH (5/1), 0 °C	<b>5</b>	Me	H	79
2	<b>3</b>	Ph	H	NaBH <sub>4</sub> , THF/MeOH (5/1), 0 °C	(4′ <i>S</i> )- & (4′ <i>R</i> )- <b>6</b>	H	Ph	73 (47/53)
3	<b>3</b>	Ph	H	K-selectride®, THF, −78 °C	(4′ <i>S</i> )- & (4′ <i>R</i> )- <b>6</b>	H	Ph	74 (59/41)
4	<b>4</b>	<i>t</i> Bu	H	NaBH <sub>4</sub> , THF/MeOH (5/1), 0 °C	(4′ <i>S</i> )- & (4′ <i>R</i> )- <b>7</b>	H	<i>t</i> Bu	86 (54/46)
5	<b>2</b>	H	Me	MeLi, THF, −78 °C	(4′ <i>R</i> )- & (4′ <i>S</i> )- <b>8</b>	Me	Me	67 (48/52)

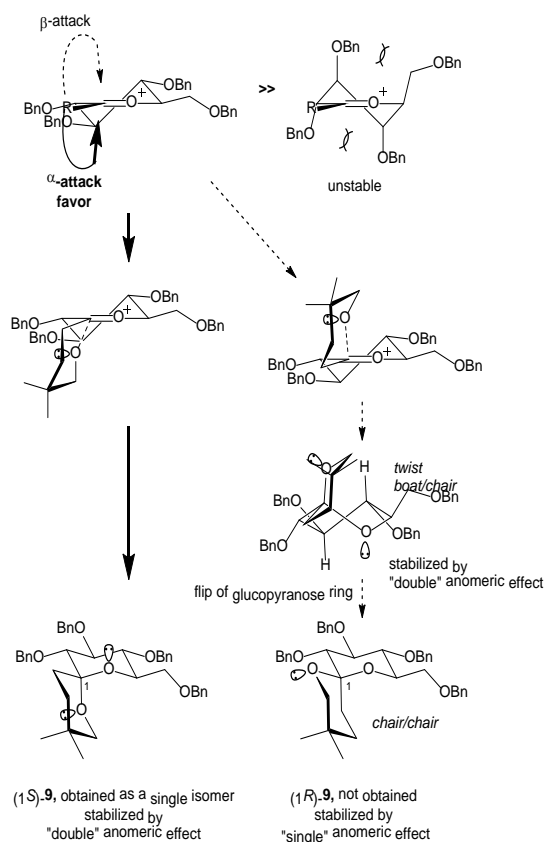


**Scheme 3.** Spirocyclization of the substrate **5** with achiral side chain

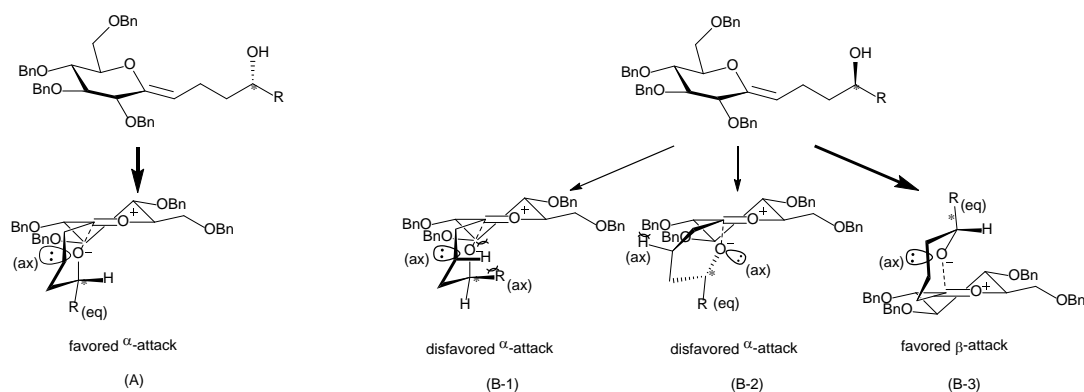
It is difficult to attack from  $\beta$ -side particularly in the case of ketopyranose.<sup>7</sup> We think that  $\beta$ -attack product can be obtained when a suit combination of the chiral glucopyranose and chiral alcohol on the side chain is used. The chiral glucopyranose gave  $\alpha$ -attack product in the previous experiment using the substrate **5**. When the chiral alcohol environment on the side chain gives  $\alpha$ -attack product, it is expected to obtain  $\alpha$ -attack product only. This case corresponds to the matched pair in the double asymmetric induction.<sup>8</sup> In order to obtain  $\beta$ -attack product, the chiral alcohol environment on the side chain must have a strong force for  $\beta$ -attack. This case corresponds to the mismatched pair in the double asymmetric induction.<sup>8</sup> Thus, we planned the spirocyclization of the substrate (4'*S*)-**6**, (4'*S*)-**7**, (4'*R*)-**8**, (4'*R*)-**6**, (4'*R*)-**7**, and (4'*S*)-**8**.

We predicted the stereoselectivity of the spirocyclization before the experiments. Considering the reaction mechanism, it appears that BF<sub>3</sub> is preferentially coordinated to the oxygen of hydroxyl than those of benzyloxy groups. Thus, BF<sub>3</sub> accelerates the protonation to the vinyl ether moiety to form the oxocarbenium ion, which was the key intermediate for spirocyclization. One epimer, which corresponds to (*R*)-alcohol as described above, can be cyclized through a six-membered ring transition state (A) in which the C-4' R-substituent possesses an equatorial orientation to afford the  $\alpha$ -attack product (Figure 2).<sup>9</sup> Stereoelectronic effect of the interaction between  $n_O$  at the axial position of the six-membered ring transition state and  $\sigma^*_{C=O+}$  also stabilizes the transition state (A). When  $\beta$ -attack occurs, the C-4' R-substituent is at a disfavored axial position. In contrast, spirocyclization of the other epimer, which corresponds to (*S*)-alcohol as described above, can be unfavorable through a similar transition state (B-1) that includes the C-4' R-substituent at the axial position because of 1,3-diaxial repulsion. In the case of the transition state (B-2), the  $\alpha$ -attack occurs with difficulty because of severe steric hindrance due to the existence of the C-2 benzyloxy function despite the presence of C-4' R-substituent at the

equatorial position. In addition, the transition state (B-2) is not stabilized by interaction between axial  $n_O$  and  $\sigma^*_{C=O+}$ . Thus, we predicted that the  $\beta$ -attack, which is essentially unfavorable (in the case of spirocyclization of **5**), may preferentially occur *via* the transition state (B-3). It would appear that the reaction proceeds through the similar route as drawn on the right side of Figure 2 to afford the  $\beta$ -attack product.



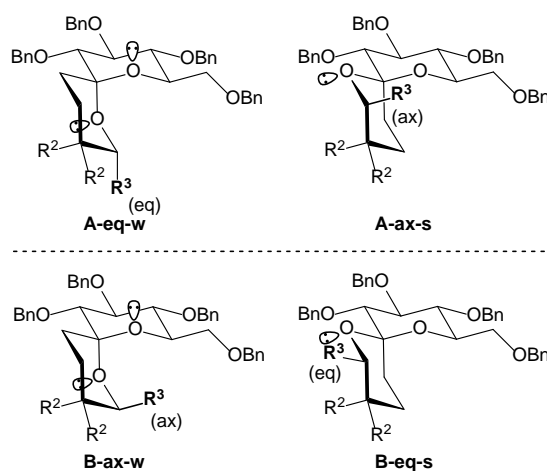
**Figure 1.** Proposed reaction mechanism of spirocyclization of the substrate **5** to yield (1S)-**9**.



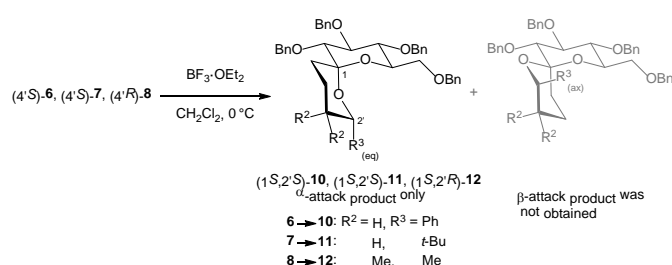
**Figure 2.** Proposed transition state of spirocyclization of *exo*-glucals

Considering stability of the spirocyclized products, the product **A-eq-w** from the transition state **A** is much more stable than the product **A-ax-s** due to the  $R^3$ -substituent at the equatorial position and the double anomeric effects (Figure 3). On the other hand, it appears that the product **B-ax-s** ( $R^3$ -substituent at the axial position and double anomeric effects) from the transition state **B-1** or **B-2** is almost as stable as the product **B-eq-s** ( $R^3$ -substituent at the equatorial position and single anomeric effect) from the transition state **B-3**. Deslongchamps and coworkers have reported the spirocyclization to 2-methyl-1,7-dioxaspiro[5.5]undecane.<sup>10</sup> This report can be the model study for our spirocyclization. According to this report, the relative stability of the four isomers is as follows: **A-eq-w** type (0 kcal/mol), **A-ax-s** type (2.4 kcal/mol), **B-ax-w**

type (2.9 kcal/mol), and **B-eq-s** (2.4 kcal/mol). In this experimental study, spirocyclized products were **A-eq-w** and the enantiomer of **A-eq-w**. We are interested how stereoselectivity changes when *exo*-glucal is used.



**Figure 3.** Spirocyclized products.



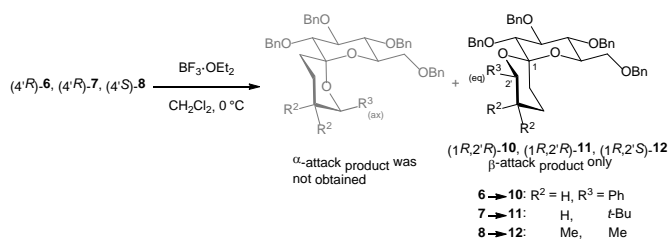
**Scheme 4.** Spirocyclization of *exo*-glucals (matched pair).

**Table 2.** Spirocyclization of *exo*-glucals (matched pair).

Entry	<i>exo</i> -Glucal	R <sup>2</sup>	R <sup>3</sup>	Spiroketal	Yield/%
<i>cf.</i>	<b>5</b>	Me	H	(1 <i>S</i> )- <b>9</b>	91
1	(4' <i>S</i> )- <b>6</b>	H	Ph	(1 <i>S</i> ,2' <i>S</i> )- <b>10</b>	99
2	(4' <i>S</i> )- <b>7</b>	H	<i>t</i> -Bu	(1 <i>S</i> ,2' <i>S</i> )- <b>11</b>	94
3	(4' <i>R</i> )- <b>8</b>	Me	Me	(1 <i>S</i> ,2' <i>R</i> )- <b>12</b>	95

We accomplished spirocyclizations using (4'*S*)-**6** and (4'*R*)-**6** under similar reaction conditions in order to clarify how C-4' chirality influences the stereoselectivity of spiro quaternary carbon of the cyclized product. According to our hypothesis, it is predicted that (4'*S*)-**6** can be converted into (1*S*,2'*S*)-**10** exclusively *via* an  $\alpha$ -attack to the oxocarbenium faces, since the pair of the chiral D-glucopyranose environment and the C-4' *S* chirality is matched for an  $\alpha$ -attack.<sup>8</sup> On the other hand, it is suspected that (4'*R*)-**6** can be converted into a mixture of (1*R*,2'*R*)- and (1*S*,2'*R*)-**10** because of a mismatched chiral pair of D-glucopyranose (favored for  $\alpha$ -attack) and C-4' *R* chirality (favored for  $\beta$ -attack).<sup>8</sup> As a result, (4'*S*)-**6** was converted into (1*S*,2'*S*)-**10** as a single isomer in 99% yield. Surprisingly, (4'*R*)-**6** was also converted into (1*R*,2'*R*)-**10** as a single isomer in 88% yield.<sup>10</sup> Thus, the spirocyclizations from both epimers of **6** proceeded stereoselectively with high efficiency to produce different spiroketal isomers. The structures of the produced spiroketal isomers (1*S*,2'*S*)- and (1*R*,2'*R*)-**10** supported our hypothesis on the cyclization mechanism; the stereochemistry of the spiro quaternary carbon of the product **10** could be induced by the C-4' chirality despite the existence of chiral D-glucopyranose. It should be noted that the stereocontrolling ability of C-4' *R* chirality ( $\beta$ -attack  $\rightarrow$  (1*R*)-isomer) overcomes that of a chiral D-glucopyranose environment ( $\alpha$ -attack  $\rightarrow$  (1*S*)-isomer).<sup>11</sup> We also attempted spirocyclizations using (4'*S*)- and (4'*R*)-**7**

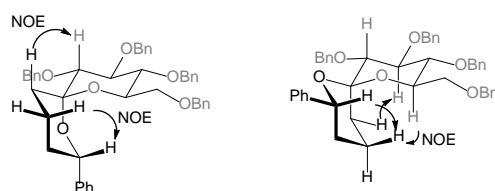
and (4'*R*)- and (4'*S*)-**8**. The substrates (4'*S*)-**7** and (4'*R*)-**8** were converted into (1*S*,2'*S*)-**11** and (1*S*,2'*R*)-**12** as single isomers in 94% and 95% yields, respectively, while (4'*R*)-**7** and (4'*S*)-**8** were converted into (1*R*,2'*R*)-**11** and (1*R*,2'*S*)-**12** as single isomers in 99% and 97% yields, respectively. In complete agreement with our speculation, the produced spiroketal structures were similarly determined by the stereochemistry at C-4' of **6-8**. We confirmed the produced spiroketal structures by measurements of the NOE interactions shown in Figure 4.



**Scheme 5.** Spirocyclization of *exo*-glucals (mismatched pair).

**Table 3.** Spirocyclization of *exo*-glucals (mismatched pair).

Entry	<i>exo</i> -Glucal	R <sup>2</sup>	R <sup>3</sup>	Spiroketal	Yield/%
1	(4' <i>R</i> )- <b>6</b>	H	Ph	(1 <i>R</i> ,2' <i>R</i> )- <b>10</b>	88
2	(4' <i>R</i> )- <b>7</b>	H	<i>t</i> -Bu	(1 <i>R</i> ,2' <i>R</i> )- <b>11</b>	99
3	(4' <i>S</i> )- <b>8</b>	Me	Me	(1 <i>R</i> ,2' <i>S</i> )- <b>12</b>	97



**Figure 4.** NOE measurements of spirocyclization products

In summary, we investigated a synthetic approach to spiro[5.5]ketals from *exo*-glucal derivatives having a C-4' hydroxyl group in the side chain by spirocyclization based on intramolecular glycosylation. We achieved the facile synthesis of the *exo*-glucal derivatives for spirocyclization and elucidated the effect of the C-4' chirality on the spirocyclization properties using the both C-4' epimeric isomers. It can be concluded that the effect of the C-4' chirality of the *exo*-glucals enabled stereocontrolled cyclizations. We accomplished highly stereoselective synthesis of both  $\alpha$ - and  $\beta$ -glucoside spiroketals. It is noteworthy that the  $\beta$ -glucoside was obtained with high stereoselectivity from one epimer of *exo*-glucal, which was a ketopyranose equivalent.

**General experimental procedure for spirocyclization is as follows:** To a solution of *exo*-glucal (0.26 mmol) in dichloromethane (3 mL) was added boron trifluoride etherate (0.26 mmol) at 0 °C under an argon atmosphere. After stirring for 1 h at that temperature, the reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate and extracted three times with ethyl acetate. Combined organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate = 4:1) afforded spiroketal product.

## References and notes

1. (a) Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Current Topics in Med. Chem.* **2005**, *5*, 1431-1457; (b) Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263-292.
2. (a) Namme, R.; Mitsugi, T.; Takahashi, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2006**, *62*, 9183-9192; (b) Hsu, S.-J.; Lin, H.-C.; Lin, C.-H.; *Carbohydr. Res.* **2006**, *341*, 1428-1437; (c) Lin, H.-C.; Du, W.-P.; Chang, C.-C.; Lin, C.-H. *Tetrahedron Lett.* **2005**, *46*, 5071-5076; (d) Namme, R.; Mitsugi, T.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2005**, *46*, 3033-3036; (e) Lin, H.-C.; Chang, C.-C.; Chen, J.-Y.; Lin, C.-H. *Tetrahedron: Asymmetry* **2005**, *16*, 297-301; (f) Lin, H.-C.; Yang, W.-B.; Gu, Y.-F.; Chen, C.-Y.; Wu, C.-Y.; Lin, C.-H. *Org. Lett.* **2003**, *5*, 1087-1089; (g) Sharma, G. V. M.; Rakesh; Chander, A. S.; Reddy, V. G.; Rao, M. H. V. R.; Kunwar, A. C. *Tetrahedron: Asymmetry* **2003**, *14*, 2991-3004; (h) Chang, C.-F.; Yang, W.-B.; Chang, C.-C.; Lin, C.-H. *Tetrahedron Lett.* **2002**, *43*, 6515-6519; (i) Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Synlett* **2001**, 1885-1888; (j) Li, X.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4283-4295.
3. Spirocyclization from *exo*-glycals to spiro[5.5]ketals: (a) Corbet, M.; Bourdon, B.; Gueyrard, D.; Goekjian, P. G. *Tetrahedron Lett.* **2008**, *49*, 750-754; Spirocyclization from *exo*-glycals to spiro[5.4]ketals: (b) Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323-1336; (c) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8183-8186; (d) Tomooka, K.; Nakamura, Y.; Nakai, T. *Synlett* **1995**, 321-322; Spirocyclization from *exo*-glycals to spiro[4.4]ketals: (e) Yang, W.-B.; Chang, C.-F.; Wang, S.-H.; Teo, C.-F.; Lin, C.-H. *Tetrahedron Lett.* **2001**, *42*, 4657-4660; Spirocyclization from *endo*-glycals to spiro[5.5]ketals: (f) Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2549-2552; (g) Conway, J. C.; Urch, C. J.; Quayle, P.; Xu, J. *Synlett* **2006**, 776-780.
4. (a) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406-4440; (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617-1661.
5. Yamanoi, T.; Nara, Y.; Matsuda, S.; Oda, Y.; Yoshida, A.; Katsuraya, K.; Watanabe, M. *Synlett* **2007**, 785-789.
6. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.
7. Toshima, K. In *Handbook of Chemical Glycosilation*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, 2008; pp 449-469.
8. For review: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1-30; For example, Mikami, K.; Yoshida, A. *Tetrahedron Lett.* **1994**, *35*, 7789-7792.
9. Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604-620.
10. (a) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauv  , G.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105-1121; (b) For review: Deslongchamps, P. *Stereoelectronic effects in organic chemistry*; Pergamon: Oxford, 1983. Fuwa *et al.* have recently reported a spirocyclization process to spiro[5.5]ketals from the *endo*-glucals having a C-4' stereocenter. The *endo*-glucals without a C-2 benzyloxy group indicated the cyclization stereospecificities different from those observed in our investigation. See ref. 3f.