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Unprecedented Highly Stereoselective α- and β-C-Glycosidation with Chiral Titanium Enolates

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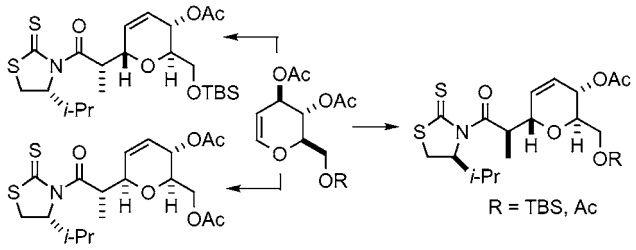
ABSTRACT



Lewis acid mediated addition of chiral titanium enolates to glycals provides either α- or β-1′-methyl-substituted *C*-glycosides. This highly stereoselective methodology permits the modular preparation of three of the four possible diastereomers.

C-Glycosides are regarded as mimics of biologically relevant *O*-glycosides[1] in which the replacement of the exo-anomeric oxygen by a methylene group confers upon them resistance to both acid and enzymatic hydrolysis.[2] Furthermore, they can be considered from a structural point of view as oxygenated heterocyclic moieties, which are found in a vast array of natural products with important pharmacological properties.[3] Thus, a large number of strategies directed toward the stereoselective synthesis of *C*-glycosides have already been devised.[4] However, there is still a lack of methods that enable one to predictably generate α- or β-*C*-glycosides from a single glycosyl donor,[5] and moreover, only a few allow the stereoselective generation of both new stereocenters (C-1 and C-1′ in Scheme 1) associated with the forming carbon−carbon bond.[6] Herein we disclose a highly stereoselective approach to provide enantiomerically pure *C*-glycosides, based on the Lewis acid mediated cross-coupling reaction of glycals to chiral titanium enolates derived from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione ((*S*)-**1**) and its enantiomer ((*R*)-**1**).

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(1) (a) Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. *Biochemistry* **1996**, *35*, 3619−3624. (b) Ravishankar, R.; Surolia, A.; Vijayan, M.; Lim, S.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 11297−11303. (c) García-Herrero, A.; Montero, E.; Muñoz, J. L.; Espinosa, J. F.; Vián, A.; García, J. L.; Asensio, J. L.; Cañada, F. J.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **2002**, *124*, 4804−4810.

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(3) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2473.

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(5) For a recent report on α- and β-*C*-glycoside formation from a single glycal through an oxidation-nucleophilic addition sequence, see: Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997−2009.

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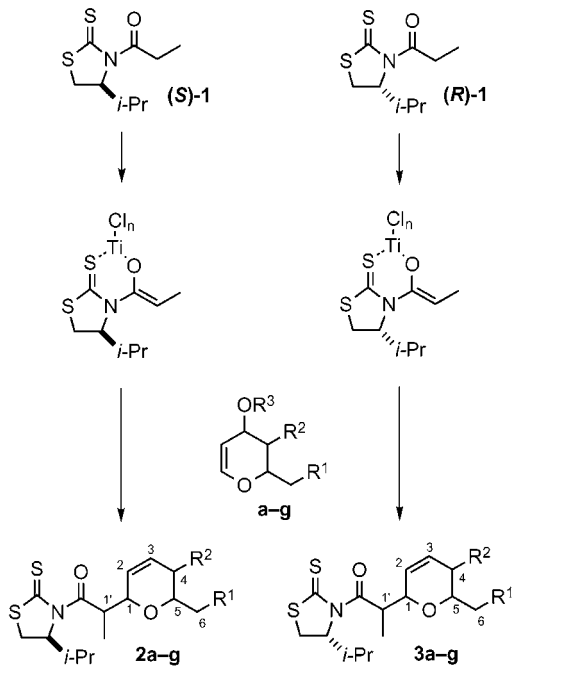
Scheme 1. Lewis Acid Mediated Cross-Coupling Reaction of Glycals to Chiral Titanium Enolates Derived from (*S*)- and (*R*)-**1**



Taking into account the high performance displayed by **1** in preceding studies,[7] we envisioned that if their titanium enolates were able to react with glycals the stereocenter C-1′ would be completely dependent on the chirality of the auxiliary.[8] In turn, the configuration of the anomeric center (C-1) would arise from the well-known α-glycosidic bias exerted by these carbohydrate derivatives.[4,6a,c−e]

The reaction of commercially available tri-*O*-acetyl-D-glucal (**a**) with titanium enolates from (*S*)- and (*R*)-**1** was first examined. Contrary to our previous experience with related systems,[7,9] poor yields (<15%) were always obtained in both cases. Therefore, several Lewis acids were surveyed with the aim to activate the glycal, and finally it was found that $SnCl_4$[10,11] promoted the formation of the predicted α-*C*-glycoside **2a** from (*S*)-**1** and, surprisingly, the unexpected *β*-*C*-glycoside **3a** from (*R*)-**1** in good yields and diastereoselectivities (see entry 1 in Table 1).[12] At this point, some key issues deserve further comments: (1) throughout the overall optimization process no adducts arising from the nucleophilic attack at the C-3 position of the glucal were detected; (2) only two of the four possible diastereomers were observed; and (3) to the best of our knowledge, this is the first case in which either the α- or *β*-*C*-glycoside is obtained from a single glycosyl donor through a simple change of the stereochemistry of the nucleophile.

Encouraged by the obvious potentiality of these findings, glycals **b**−**d**[13] were submitted to the same reaction conditions in order to gain further insight into the influence of R^2 (see Scheme 1) on the stereochemical outcome of the process.[14] To our delight, stereoselectivity was greatly improved moving from glucal **a** to galactal **b** to the point that virtually only one diastereomer was detected in the reaction mixtures (see entry 2 in Table 1). In turn, addition of titanium enolate from (*S*)-**1** to **c** and **d** also proceeded with excellent diastereoselectivity, although it was slightly eroded when (*R*)-**1** was used instead (see entries 3 and 4 in Table 1). Importantly, the configuration of both new stereocenters, C-1 and C-1′, is defined by the chiral auxiliary, and α- or *β*-*C*-glycosides can be produced from a single glycosyl donor depending on the use of (*S*)- or (*R*)-**1**, in good to excellent yields and diastereomeric ratios (see entries 1−4 in Table 1).[15]

Finally, glycals **e**−**g**[13] were evaluated to look for adducts with different functionality at R^1 (see Scheme 1). Excellent yields and diastereomeric ratios were again attained, but contrary to what had been observed in the preceding cases, these glycals only provided access to the corresponding α-*C*-glycosides irrespective of the stereochemistry of the auxiliary, which only determined the configuration at C-1′.[16]

These results suggest that α- and *β*-*C*-glycosides can be prepared when R^1 = OOCR depending on the chirality of the auxiliary, whereas α-*C*-glycosides are always obtained when R^1 = H, OTBS (compare entries 1−4 with 5−7 in

(7) Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615−617.

(8) When chlorotitanium enolates derived from 1,3-oxazolidin-2-ones act as nucleophiles in S_N1-like processes, the configuration of C-1′ is also completely controlled by the auxiliary. For a related *C*-glycosidation example, see ref 6e. See also: Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.

(9) Titanium enolate from **1** reacts with $PhCH(OMe)_2$ to afford the corresponding *anti*-*β*-methoxy-α-methyl adduct in moderate yield without the need of an additional activation. Unpublished results from Cosp, A. Ph.D. Thesis, Universitat de Barcelona, Barcelona, 2002.

(10) Other Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt_2$, and $ZrCl_4$) were also investigated but turned out to be less suitable.

(11) A careful optimization of other variables including stoichiometry, temperature, and time was carried out.

(12) For the stereochemical proof of **2a** and **3a**, see Supporting Information.

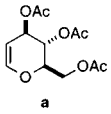
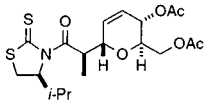
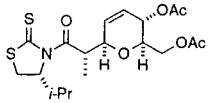
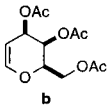
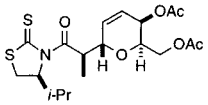
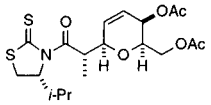
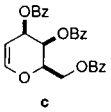
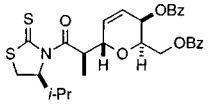
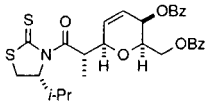
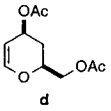
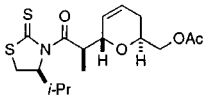
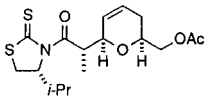
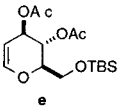
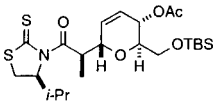
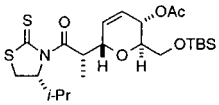
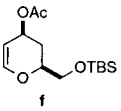
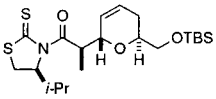
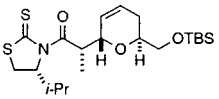
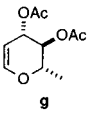
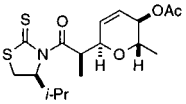
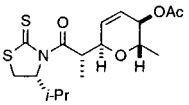
(13) Glycals **b**, **c**, and **g** are commercially available. Glycals **d**, **e**, and **f** have been prepared from glucal **a** following standard procedures.

(14) **Typical Experimental Procedure.** To a solution of **1** (217 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) under N_2 at 0 °C was added $TiCl_4$ (0.12 mL, 1.1 mmol) dropwise. The resulting yellow suspension was stirred for 5 min and cooled to −78 °C, and a solution of *i*-Pr_2NEt (0.18 mL, 1.1 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise. The dark red solution was stirred for 30 min, then warmed to −50 °C and stirred for 2 h. It was cooled to −78 °C and $SnCl_4$, 1 M in CH_2Cl_2 (1.1 mL, 1.1 mmol), was added, followed by glycal (0.5 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred for 30 min and kept at −20 °C for 16 h. It was quenched at −78 °C with saturated aqueous NH_4Cl (6 mL) and allowed to reach room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (25 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The reaction mixture was analyzed by HPLC and purified by column chromatography on silica gel.

(15) The stereochemistry of *β*-*C*-glycoside **3c** was established by X-ray diffraction analysis. CCDC-186242 contains the crystallographic data for **3c**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). In the other cases, configuration of C-1 was established by NMR studies including difference NOE and COSY experiments. The configuration at C-1′ was assumed to be *R* when (*S*)-**1** was used and *S* when (*R*)-**1** was used on the basis of the known stereochemical outcome of the reaction of chiral titanium enolates derived from **1** (see ref 7) and related chiral titanium enolates (see ref 8) with substrates able to react via a S_N1 pathway, which affords complete enolate facial control in that position. Furthermore, the chemical shifts and coupling constants are consistent in the α- and *β*-series.

(16) The stereochemistry of **2g** was established by X-ray diffraction analysis. CCDC-186243 contains the crystallographic data for **2g**. In the other cases, configuration of C-1 and C-1′ was assigned as has been stated in ref 15.

Table 1. Addition of Titanium Enolates from (*S*)-**1** and (*R*)-**1** to Glycals **a**−**g**[14]

Entry	Glycal	Major diastereomer from (*S*)-**1** Yield[a] (dr)[b]	Major diastereomer from (*R*)-**1** Yield[a] (dr)[b]
1	 **a**	 **2a** 79%[c] (92:8)	 **3a** 94%[c] (82:18)
2[d]	 **b**	 **2b** 70% (99:1)	 **3b** 71% (99:1)
3	 **c**	 **2c** 62% (98:2)	 **3c** 82%[c] (92:8)
4	 **d**	 **2d** 78% (99:1)	 **3d** 67% (82:18)
5	 **e**	 **2e** 94% (>98:2)	 **3e** 97% (99:1)
6	 **f**	 **2f** 82% (99:1)	 **3f** 66% (99:1)
7	 **g**	 **2g** 94% (95:5)	 **3g** 84% (86:14)

[a] Yield of isolated chromatographically pure compound, except where stated. [b] Determined by HPLC in the reaction mixtures. [c] Overall yield. [d] Reaction time 72 h.

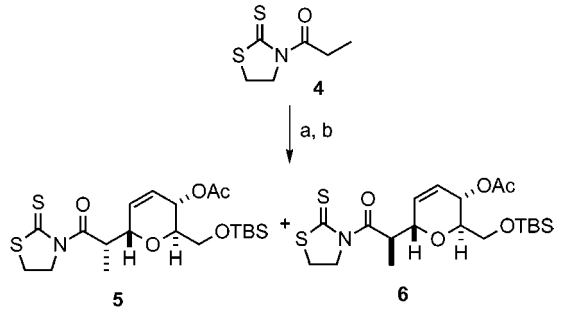
Table 1). The impact of R^2 is also noteworthy (compare entries 1−4) but does not reverse the stereochemical outcome of the process.

The crucial role played by R^1 was confirmed through the study of related reactions involving achiral *N*-propanoyl-1,3-thiazolidine-2-thione (**4**). As shown in Scheme 2, addition of the titanium enolate derived from **4** to glycal **e** (R^1 = OTBS) afforded only two adducts whose stereochemistry corresponds to α-*C*-glycosides **5** and **6** (95% overall yield, dr 62:38). In contrast, four diastereomers (95% overall yield, dr 49:24:22:5) were obtained in the case of glycal **a** (R^1 = OAc). Therefore, it can be stated that when R^1 = OTBS the glycal overrides any trend induced by the auxiliary on the configuration of C-1 and mainly the corresponding α-*C*-glycosides are obtained in any case. Alternatively, when R^1 = OAc the configuration of C-1 arises from a compromise between the induction exerted by the auxiliary and the glycal. Thus, substituent R^1 deserves paramount attention in order to predict the stereochemical outcome of the process.[17] Further investigations into the mechanism of this process are currently underway and results will be reported in due course.

Finally, removal of the auxiliary was carried out under very mild conditions. Taking **2e** as a model, enantiopure alcohol **7**, methyl ester **8**, and Weinreb's amide **9** were

(17) Although Woerpel has pointed out the dramatic influence of the substituents in the stereoselective reactions of tetrahydropyran acetals with nucleophiles, the aforementioned effects are unparalleled. See: Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.

Scheme 2[a]



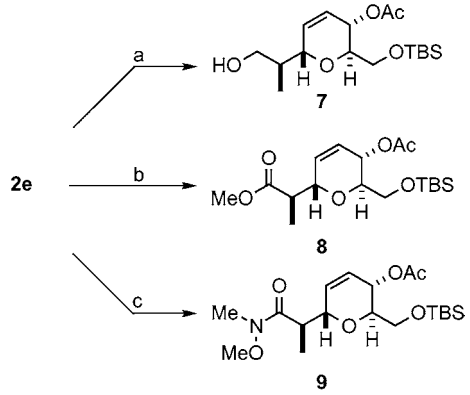
[a] (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 to −50 °C, 2 h; (b) $SnCl_4$, **e**, −78 to −20 °C, 16 h, 95%.

isolated in very good yields as shown in Scheme 3. Notably, the end point is reached when the initial yellow solution becomes almost colorless.[18]

In conclusion, we have developed a new, highly regio- and stereoselective *C*-glycosidation procedure based on the Lewis acid cross-coupling reaction between chiral titanium enolates and glycals. The judicious combination of glycals and titanium enolates gives high levels of selectivity as a result of the stereochemical control elements within each reaction component and permits enantiopure 1′-methyl-substituted *C*-glycosides to be obtained. These can then be

(18) The chiral auxiliary was recovered by flash column chromatography in ≥90% yield.

Scheme 3[a]



[a] (a) $NaBH_4$, THF−H_2O, rt, 1.5 h, 75%; (b) MeOH, DMAP cat., rt, 16 h, 82%; (c) MeONHMe·HCl, Et_3N, DMAP cat., CH_2Cl_2, rt, 16 h, 86%.

easily transformed into complex, densely functionalized building blocks.

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Supporting Information Available: Full characterization data for adducts **2** and **3**; stereochemical proof of **2a** and **3a**; ^1H NMR spectra of **2e**, **7**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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