

Highly 1,2-*trans* Stereoselective Allylations of 1,2-O-Isopropylidene Protected Glycofuranosides. A Remarkable Bicyclic Acetal Template Effect***

Fernando García-Tellado, Pedro de Armas, José Juan Marrero-Tellado

The Lewis acid-mediated cleavage of chiral cyclic acetals is a useful synthetic tool for the asymmetric synthesis of C-C bonds.^[1] Specifically, one of the most widely used methods for the formation of C-glycosides involves a glycosidic acetal, a Lewis acid and a carbon nucleophile.^[2] The reaction goes through an cyclic oxocarbenium ion which undergoes the nucleophile attack in a stereoelectronically controlled mode to provide the product with a high stereoselectivity.^[3-5] Conformational effects have been invoked to explain the stereoselective reactions of substituted five-membered-ring oxocarbenium ions (Figure 1a).^[4]

Because of the biological and chemical importance of the C-glycofuranosides^[2,6] we undertook the study of the Lewis acid-promoted cleavage of 1,2-O-isopropylidene-protected glycofuranosides by allyltrimethylsilane as a feasible and stereoselective route to these structures.^[7] This procedure was introduced by us in the formal synthesis of the antibiotic (+)-preusin to install the C-5 nonyl chain with the required *R* configuration (Scheme 1).^[8] We hypothesized that the high

diastereoselectivity obtained in this experiment was due to the own bicyclic nature of these acetals which confers an intrinsic and general *exo*-facial bias to the incoming nucleophile regardless of the remainder of the substituents on the heterocyclic ring (Figure 1b). If this was the case, then this template effect of the bicyclic acetal should be general for any 1,2-O-isopropylidene-protected glycofuranoside providing an invariable 1,2-*trans* stereoselectivity in the nucleophilic substitution at the anomeric center. In this communication we present experimental evidence to confirm our initial hypothesis and establish the generality of this remarkable *exo*-facial template effect exercised by the 1,2-O-isopropylidene protective group.

To this end, we prepare the structurally related 1,2-O-isopropylidene-protected furanosides **1a-h**^[9] and carried out a systematic study of their allylation reactions (table 1). Remarkably, an uniform 1,2-*trans* selectivity was achieved in all of the experiments ran with boron trifluoroetherate or titanium tetrachloride as the Lewis acids and allyltrimethylsilane as the nucleophile (Scheme 2).^[10] In general, the yields ranged from modest to good and the reaction conditions were sufficiently mild to be supported by other acid-sensitive groups present in the molecule. The diminished reactivity of these acetals with regard to other anomeric activating groups^[2c,6a] called for room

temperature in the case of the boron trifluoro etherate and 0°C for titanium tetrachloride.

Examination of the results depicted in table 1 reveals the following features: Firstly, the nucleophile always adds to the *exo*-face of the bicyclic acetal; secondly, the stereochemical outcome of the reaction neither depends of the size nor configuration of the substituents on the ring; thirdly, the yield of the reaction decreases with the bulkiness of the C-4 alkyl group (compare **1a** and **1e** with **1d**) and increases with the enlargement of the alkyl chain (compare **1a**, **1b** and **1c**). Finally, the C-3 alkoxy group behaves like a mere spectator in sharp contrast with the well-established influence of this group in the 1,3-*syn* stereoselectivity found in the C-glycosidation of ribose derivatives.^[4]

The effect of the C-4 alkyl substituents on the yield of the reaction can be interpreted in terms of the destabilizing 1,3-diaxial interaction between the nucleophile and the alkyl group. From the model illustrated in figure 1b, it is clear that an increase in the size of the alkyl group at C-4 produces greater steric congestion on the *exo*-face of the bicyclic molecule whilst a enlargement of the alkyl chain places to the bulky pivaloyloxy group more far from the anomeric position reducing the steric congestion around this centre.

The combination of trimethylsilyl triflate and boron trifluoride etherate as the Lewis acid deserves a comment. The strongest Lewis acid character of this mixture benefits the reaction (the yield increases \sim 20%), but diminishes the diastereoselectivity in a 25%. If the starting bicyclic acetal is cleaved in the medium before the nucleophilic attack, no template effect can be exercised and the stereochemical outcome of the reaction should be directed by the conformation of the 2-trimethylsilyloxy five-membered-ring oxocarbenium ion. We believe this is the case being the stereoselection level in good accordance with the low stereoselectivities reported by some C-2 substituted furanosides^[11] and γ -lactols.^[4b]

To the best of our knowledge, this is the first case in which a 1,2-O-isopropylidene group is used to activate the carbohydrate anomeric position and to direct the stereochemical outcome of the reaction on this centre.^[12] From a synthetic point of view, the easy access to these 1,2-O-isopropylidene-protected glycofuranosides and the intrinsic and complete 1,2-*trans* stereoselectivity of the reaction makes this strategy a very interesting and solid alternative to the established C-glycosidation methods. Despite of the moderate reactivity of these bicyclic acetals we believe that they are still enough reactive to allow the use of other π nucleophiles.

Experimental section

Method A: Under a nitrogen atmosphere, the 1,2-O-isopropylidene glycofuranoside (0.1 mmol) dissolved in dry dichloromethane (1 ml) was cooled to 0°C and allyltrimethylsilane (0.4 mmol) was added. The homogeneous solution was stirred for 10 min and the boron trifluoro etherate was added (0.2 mmol). The resulting solution was stirred at 0°C for 15 min, warmed to room temperature and stirred for 3 h. After quenching with aqueous saturated sodium bicarbonate solution (0.1 ml) the reaction mixture was poured into more aqueous saturated sodium bicarbonate solution and extracted with dichloromethane. The organic phases were combined, washed with aqueous saturated sodium chloride dried over sodium sulfate, filtered and concentrated to give an oily residue which was flash chromatographed.

Method B: Under a nitrogen atmosphere, the 1,2-O-isopropylidene glycofuranoside (0.1 mmol) dissolved in dry dichloromethane (1 ml) was cooled to 0°C and allyltrimethylsilane (0.1 mmol) was added. The homogeneous solution was stirred for 10 min and the boron trifluoro etherate in dry dichloromethane (0.5 M) (0.1 ml) was added. The resulting solution was stirred at 0°C for 15 min, warmed to room temperature and stirred for 0.5 h. More allyltrimethylsilane (0.1 mmol) and boron trifluoride etherate in dichloromethane (0.1 ml) were added every 0.5 h for three times and the solution was stirred at room temperature for a

2 h further. More allyltrimethylsilane (4 x 0.1 mmol) and boron trifluoride etherate in dichloromethane (4 x 0.1 ml) were again sequentially added every 0.5 h and the reaction mixture was stirred overnight. The reaction was quenched and worked up as in method A.

Method C: Under a nitrogen atmosphere, the 1,2-O-isopropylidene glycofuranoside (0.1 mmol) dissolved in dry dichloromethane (1 ml) was cooled to 0°C and allyltrimethylsilane (0.4 mmol) was added. The homogeneous solution was stirred for 10 min and titanium tetrachloride (0.2 mmol) in dichloromethane (1 ml) was added via a cannule. The reaction mixture was stirred for 10 min at this temperature and quenched and worked up as in method A.

Method D: Under a nitrogen atmosphere, the 1,2-O-isopropylidene glycofuranoside (0.1 mmol) dissolved in dry dichloromethane (1 ml) was cooled to 0°C and allyltrimethylsilane (0.4 mmol) was added. The homogeneous solution was stirred for 10 min and the boron trifluoro etherate in dry dichloromethane (0.5 M) (0.1 ml) was added. The resulting solution was stirred at 0°C for 15 min, warmed to room temperature and stirred for 0.5 h. More boron trifluoride etherate in dichloromethane (0.1 ml) was added every 0.5 h three times and the solution was stirred at room temperature for 1 h further. The reaction mixture was quenched and worked up as in method A.

Keywords: Carbohydrates * C-glycosides * C-C-coupling * asymmetric synthesis * synthetic methods

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- [7] Many stereocontrolled approaches to these structures have been reported. Among them, the nucleophilic substitution at the anomeric centre of a furanoid glycal or a furanosyl halide appears as an general strategy to prepare the corresponding 2-substituted tetrahydrofuran (See ref. [2]).
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- [9] The 1,2-O-Isopropylidene group is easily introduced in the carbohydrate either by direct treatment of the free sugar with acetone (or a suitable derivative) and acid^[4a] or by using the Suarez's protocol which entails the rearrangement of a suitable 2,3-O-isopropylidene-protected furanoside to the required 1,2-protected one.^[12]
- [10] After work up and chromatography no other diastereomers could be isolated or detected. The stereochemistry assigned to each newly created stereogenic centre was confirmed by nOe spectroscopic analysis.

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- [13] A serie of 3-alkoxymethyl-5-alkoxy-2,7dioxabicyclo[2.2.1]heptane acetals derived from 6-O-protected D-galactal have been used as electrophilic substrates for the C-glycosidation.^[14] In this case, the bicycle does not seem to play in special role in the stereochemical outcome of these reactions and the 1,3-*syn* stereoselectivity observed is in total accordance with the stereoelectronic model proposed by Woerpel et al.^[4b]
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- [15] Selected physical data for **2d** (diacetate): $[\alpha]_{D20} = -27.8$ (c = 0.56 in chloroform); $^1\text{H NMR}$ (500 MHz, CDCl_3) $\delta = 0.05$ (s, 3H; MeSi), 0.10 (s, 3H; MeSi), 0.90 (s, 9H; t-BuSi), 1.21(d, J = 6.2 Hz, 3H; Me), 2.04 (s, 3H; AcO), 2.44 (m, 2H; CH₂-CH=CH₂), 3.80 (td, J = 6.9 and 2.2 Hz, 1H; H-1), 3.88 (dd, J = 3.2 and 0.9, 1H; H-3), 4.00 (qd, J = 6.2 and 3.2 Hz, 1H; H-4), 4.77 (dd, J = 2.2 and 0.9 Hz, 1H; H-2), 5.07 (m, 2H; CH₂=CH-), 5.81 (m, 1H; -CH=CH₂); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = -5.4, -4.9, 14.3, 18.0, 21.0, 25.7, 38.4, 77.5, 77.6, 82.5, 83.1, 117.1, 134.4, 170.0$; IR (chloroform): $\nu = 3080,$

1735 1643 cm^{-1} ; MS870 eV): m/z (%): 299 (M^+-15)(0.5), 273 (9.3), 257 (52.8), 197 (15.4), 123 (18.4), 117 (100), 75 (41.4), 73 (31.6), 57 (8); elemental analysis calcd. for $\text{C}_{16}\text{H}_{30}\text{O}_4\text{Si}$: C 61.11, H 9.61; found: C 61.40, H 9.78. The stereochemistry assigned at C-1 was confirmed by a NOESY experiment which showed nOes between H-2 and allylic protons, and between H-1 and H-3, H-4 and AcO.

Dr F. García-Tellado, Dr. P. Armas

CSIC-Instituto de Productos Naturales y Agrobiología

ASTROFÍSICO Francisco Sánchez 3

38206 La Laguna-Tenerife-Spain

FAX: (+34)922260135

E-mail: fgarcia@ipna.csic.es; parmas@ipna.csic.es

Dr J. J. Marrero-Tellado

Instituto Universitario de Bioorgánica Antonio González

Universidad de La Laguna

Astrofísico Francisco Sánchez 2

38206 La Laguna-Tenerife-Spain.

E-mail: jtellado@ull.es

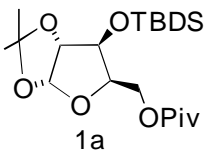
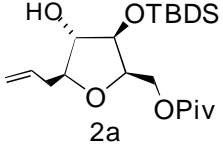
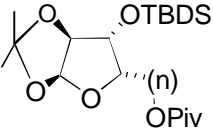
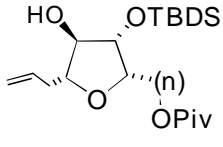
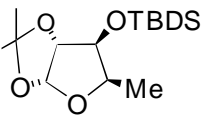
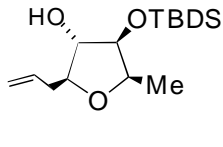
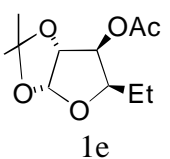
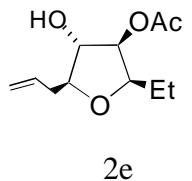
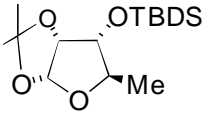
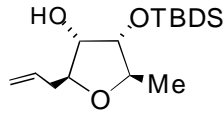
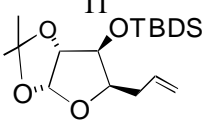
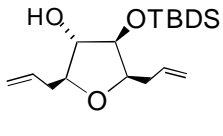
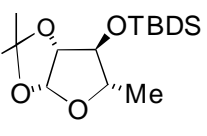
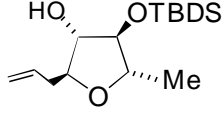
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Figure 1. [a] Postulated stereoelectronic model. Nucleophilic attack occurs by a stereoelectronically controlled “inside attack” on the lower energy conformer of the cation to provide the product in its lower energy. [b] The *exo*-facial template effect exercised by the 1,2-O-isopropylidene protective group. The nucleophile attack is directed by the acetal onto the *exo*-face of the molecule to give the 1,2-*trans* product.

Scheme 1. Stereoselective formal synthesis of (+)-preusin. The alkyl chain at C-5 is introduced with the required R configuration by diastereoselective allylation of the bicyclic 1,2-O-isopropylidene protected dihydroxy pyrrolidine intermediate.

Scheme 2. Stereoselective Lewis acid catalyzed C-glycosidation of the D-xylofuranoside derivative **1d** using the 1,2-O-isopropylidene acetal group as the anomeric activator and stereochemical controller and allyltrimethylsilane as the nucleophile.

Table 1. Lewis acid promoted allylation of the 1,2-O-isopropylidene protected glycofuranosides **1a-h** with allyltrimethylsilane .

Substrate	Lewis acid	Method ^[a]	Yield [%] ^[b]	Product ^[c]
 1a	BF ₃ .Et ₂ O	A	40 ^[d]	 2a
	BF ₃ .Et ₂ O-TMSOTf (8-2)	A	59 (α/β= 1/3)	
 1b n = 2 1c n = 3	BF ₃ .Et ₂ O	A	42 ^[d]	 2b n = 2 2c n = 3
	"	B	62	
	"	A	89	
 1d	"	A	74	 2d
	TiCl ₄	C	83	
 1e	BF ₃ .Et ₂ O	A	39 ^[e]	 2e
	"	D	39 ^[f]	
 1f	"	A	47	 2f
	"	A	55	
 1g	"	A	55	 2g
 1h	"	A	68	 2h

[a] See experimental section. [b] Yields of isolated compounds. [c] All the new compounds gave physical and spectroscopic data coherent with the proposed structures. [d] Starting material was recovered (38%). [e] Starting material was recovered (25%). [f] Starting material was recovered (56%). TBDS = t-Butyldimethylsilyl, Piv = Trimethylacetyl, TMSOTf = Trimethylsilyl trifluoromethanesulphonate

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An impressively entire 1,2-trans stereoselectivity is achieved in the Lewis acid promoted allylations of 1,2-O-isopropylidene protected furanosides regardless of the other substituents on the tetrahydrofurane ring. The bicyclic acetal acts as a basic stable anomeric protecting group, which under acid conditions and in the presence of a carbon nucleophile, activates the carbohydrate anomeric position and directs the stereochemical outcome of the substitution reaction at this centre.