[8] a) J.-E. Dubois, G. Axiotis, E. Bertounesque, *Tetrahedron Lett.* **1985**, *26*, 4371 – 4372; b) L. Wessjohann, T. Gabriel, *J. Org. Chem.* **1997**, *62*, 3772 – 3774.
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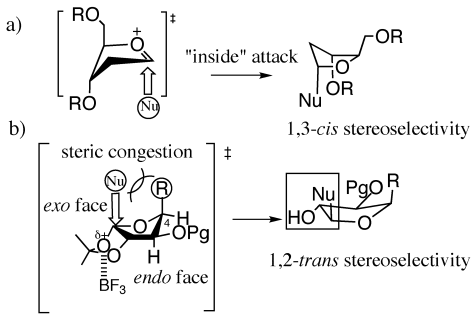
[10] For cyclopropanation of enones mediated by zinc and BF_3, see I. Elphimoff-Felkin, P. Sadra, *Tetrahedron* **1975**, *31*, 2781 – 2784.
[11] The following functional substrates were recovered under the standard reaction conditions (Table 1, entry 1) due to the mild nucleophilicity of the organochromium reagent: 1-dodecene (97 %), 1-dodecyne (93 %), 1-chlorododecane (91 %), ethyl octanoate (93 %), nonanenitrile (93 %), 3-phenylpropyl acrylate (95 %), nonanal ethylene acetal (94 %), 4-phenyl-2-butanone (96 %).
[12] Both diastereomers of **6** gave an *E* isomer of **12** as a major product. This is probably due to the stability of a carbocation adjacent to the cyclopropane ring; see H. Maeta, T. Nagasawa, Y. Handa, T. Takei, Y. Osamura, K. Suzuki, *Tetrahedron Lett.* **1995**, *36*, 899 – 902.
[13] The β,γ-unsaturated ketone **13** was obtained as a mixture of geometrical isomers.
[14] Chromium(II) chloride (99.9 % purity, anhydrous powder, <100 ppm H_2O) was purchased from Aldrich Chemical Co.
[15] Dehydrated DMF was purchased from Wako Pure Chemical Industries Ltd., and stored with 4-Å molecular sieves.

Highly 1,2-*trans* Stereoselective Allylations of 1,2-*O*-Isopropylidene-Protected Glycofuranosides**

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

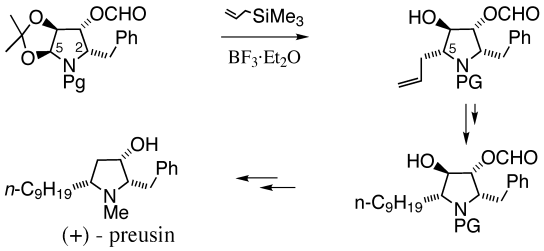
Dedicated to Professor Antonio González on the occasion of his 83rd birthday

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 proceeds via a cyclic oxocarbenium ion, which undergoes nucleophilic attack in a stereoelectronically controlled manner to provide the product with high stereoselectivity.[3–5] Conformational effects have been invoked to explain the stereoselective reactions of substituted five-membered-ring oxocarbenium ions (Scheme 1 a).[4]



Scheme 1. a) The postulated stereoelectronic model for reactions of substituted five-membered-ring oxocarbenium ions. 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 form. b) Schematic representation of the *exo* facial template effect exercised by the 1,2-*O*-isopropylidene protecting group. The nucleophilic attack is directed by the acetal onto the *exo* face of the molecule to give the 1,2-*trans* product.

Because of the biological and chemical importance of C-glycofuranosides,[2, 6] we undertook a 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 C5 nonyl chain with the required *R* configuration (Scheme 2).[8] We hypothesized that the high



Scheme 2. The formal stereoselective synthesis of (+)-preusin. The alkyl chain at C5 is introduced with the required *R* configuration by diastereoselective allylation of the bicyclic 1,2-*O*-isopropylidene-protected dihydroxypyrrolidine intermediate. PG = protecting group.

diastereoselectivity obtained in this experiment was due to the bicyclic nature of these acetals, which confers an intrinsic and general *exo*-facial bias to the incoming nucleophile, regardless of the other substituents on the heterocyclic ring (Scheme 1 b). If this were the case, then this template effect of the bicyclic acetal should be general for any 1,2-*O*-isopropylidene-protected glycofuranoside, and thus provide invariable 1,2-*trans* stereoselectivity for nucleophilic substitution at the anomeric center. Here 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 protecting group.

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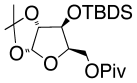
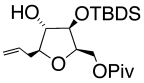
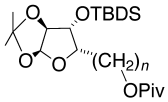
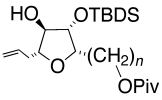
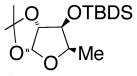
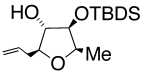
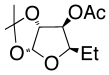
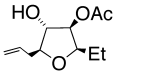
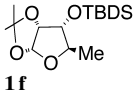
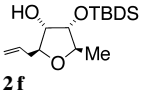
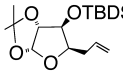
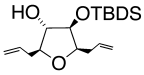
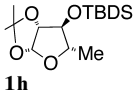
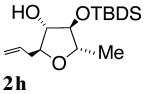
We prepared the structurally related 1,2-*O*-isoprolylidene-protected furanosides **1a**–**h**[9] and carried out a systematic study of their allylation reactions (Table 1). Remarkably, 1,2-*trans* selectivity was achieved in all of the experiments carried out with $BF_3 \cdot Et_2O$ or $TiCl_4$ as the Lewis acid and allyltrimethylsilane as the nucleophile (Scheme 3; Table 2).[10] In general, the yields ranged from modest to good and the reaction conditions were sufficently mild to be supported by other acid-sensitive groups present in the molecule. The reduced reactivity of these acetals with regard to other anomeric activating groups[2c, 6a] meant that the reaction had to be conducted at room temperature in the case of $BF_3 \cdot Et_2O$ and at 0 °C for $TiCl_4$.

Examination of the results depicted in Table 1 reveals the following features: 1) the nucleophile always adds to the *exo* face of the bicyclic acetal; 2) the stereochemical outcome of the reaction depends on neither the size nor the configuration of the substituents on the ring; 3) the yield of the reaction decreases with the bulkiness of the C4 alkyl group (compare **1a** and **1e** with **1d**) and increases with the length of the alkyl chain (compare **1a**, **1b**, and **1c**); and 4) the C3 alkoxy group behaves as a mere spectator, in sharp contrast with the well-established influence of this group for the 1,3-*syn* stereoselectivity found in the C-glycosidation of ribose derivatives.[4]

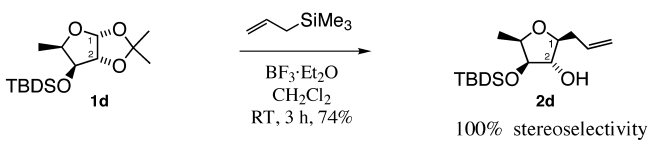
The effect of the C4 alkyl substituents on the yield of the reaction can be interpreted in terms of the destabilizing 1,3-diaxial interaction beteween the nucleophile and the alkyl group. From the model illustrated in Scheme 1b, it is clear that an increase in the size of the alkyl group at C4 produces greater steric congestion on the *exo* face of the bicyclic molecule. Lengthening of the alkyl chain places the bulky pivaloyloxy group further away from the anomeric position, reducing the steric congestion at this center.

The combined use of trimethylsilyl triflate and $BF_3 \cdot Et_2O$ as the Lewis acid (applied for the substrate **1a**, see Table 1) deserves comment. The strong Lewis acid character of this mixture is benficial for the reaction (the yield increases to about 20%), but disadvantageous for the diastereoselctivity (25%). If the starting bicyclic acetal is cleavaged before nucleophilic attack can take place, no template effect can be exercised and the stereochemical outcome of the reaction would be directed by the conforma-

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]
	$BF_3 \cdot Et_2O$	A	40[d]	
1a	$BF_3 \cdot Et_2O$/TMSOTf (8/2)	A	59 (α/β = 1/3)	**2a**
	$BF_3 \cdot Et_2O$	A	42[d]	
1b (n = 2)	$BF_3 \cdot Et_2O$	B	62	**2b** (n = 2)
1c (n = 3)	$BF_3 \cdot Et_2O$	A	89	**2c** (n = 3)
	$BF_3 \cdot Et_2O$	A	74	
1d	$TiCl_4$	C	83	**2d**
	$BF_3 \cdot Et_2O$	A	39[e]	
1e	$BF_3 \cdot Et_2O$	D	39[f]	**2e**
	$BF_3 \cdot Et_2O$	A	47	
1f				**2f**
	$BF_3 \cdot Et_2O$	A	55	
1g				**2g**
	$BF_3 \cdot Et_2O$	A	68	
1h				**2h**

[a] See the Experimental Section. [b] Yields of isolated compounds. [c] All the new compounds gave physical and spectroscopic data in accordance with the proposed structures. [d] Starting material was recovered (38%). [e] Starting material was recovered (25%). [f] Starting material was recovered (56%). TBDS = *tert*-butyldimethylsilyl, Piv = trimethylacetyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate.



Scheme 3. 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. See Table 2 for physical data of the product **2d**.

Table 2. Selected physical data for **2d** (diacetate).

$[\alpha]_D^{20} = -27.8$ (c = 0.56 in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 3H; MeSi), 0.10 (s, 3H; MeSi), 0.90 (s, 9H; tBuSi), 1.21 (d, J = 6.2 Hz, 3H; Me), 2.04 (s, 3H; AcO), 2.44 (m, 2H; CH_2–CH=CH_2), 3.80 (td, J = 6.9, 2.2 Hz, 1H; H-1), 3.88 (dd, J = 3.2, 0.9 Hz, 1H; H-3), 4.00 (qd, J = 6.2, 3.2 Hz, 1H; H-4), 4.77 (dd, J = 2.2, 0.9 Hz, 1H; H-2), 5.07 (m, 2H; CH_2=CH–), 5.81 (m, 1H; –CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −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): $\tilde{\nu}$ = 3080, 1735, 1643 cm^{-1}; MS (870 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 $C_{16}H_{30}O_4Si$: C 61.11, H 9.61; found: C 61.40, H 9.78. The configuration assigned at C1 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

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tion of the 2-trimethylsilyoxy-substituted five-membered-ring oxocarbenium ion. We believe that this is the case as the low stereoselectivity is in good accordance with those reported for some C2-substituted furanosides[11] and γ-lactols.[4b]

To the best of our knowledge, this is the first case in which a 1,2-*O*-isoprolylidene group is used to activate the carbohydrate anomeric position and to direct the stereochemical outcome of the reaction on this center.[13] 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 the moderate reactivity of the bicyclic acetals, we believe that they are reactive enough 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) was dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0 °C, and allyltrimethylsilane (0.4 mmol) was added. The homogeneous solution was stirred for 10 min, and $BF_3 \cdot Et_2O$ (0.2 mmol) was added. 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 (0.1 mL) the reaction mixture was poured into more aqueous saturated sodium bicarbonate and extracted with CH_2Cl_2. 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 purified by flash chromatography.

Method B: Under a nitrogen atmosphere, the 1,2-*O*-isopropylidene glycofuranoside (0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0 °C, and allyltrimethylsilane (0.1 mmol) was added. The homogeneous solution was stirred for 10 min, and $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 (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. Three more portions of allyltrimethylsilane (0.1 mmol) and $BF_3 \cdot Et_2O$ in CH_2Cl_2 (0.1 mL) were added at intervals of 0.5 h, and the solution was stirred at room temperature for a further 2 h. More allyltrimethylsilane (4×0.1 mmol) and $BF_3 \cdot Et_2O$ in CH_2Cl_2 (4×0.1 mL) were 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) was dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0 °C, and allyltrimethylsilane (0.4 mmol) was added. The homogeneous solution was stirred for 10 min and $TiCl_4$ (0.2 mmol) in CH_2Cl_2 (1 mL) was added through a cannula. The reaction mixture was stirred for 10 min at this temperature and then quenched and worked up as in method A.

Method D: Under a nitrogen atmosphere, the 1,2-*O*-isopropylidene glycofuranoside (0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL) and cooled to 0 °C, and allyltrimethylsilane (0.4 mmol) was added. The homogeneous solution was stirred for 10 min, and $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 (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. Three more portions of $BF_3 \cdot Et_2O$ in CH_2Cl_2 (0.1 mL) were added at intervals of 0.5 h, and the solution was stirred at room temperature for a further 1 h. The reaction mixture was quenched and worked up as in method A.

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[1] I. Fleming, *Comprehensive Organic Synthesis, Vol. 2* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, pp. 576 – 594; b) P. Mangeney, *Tetrahedron: Asymmetry* **1990**, *8*, 477.

[2] M. H. D. Postema, *C-glycoside synthesis*, CRC, Boca Raton, FL, **1995**; b) E. D. Levy, C. Tang, *The chemistry of C-glycosides*, Pergamon, Oxford, **1995**; c) For the synthesis of 2,5-disubstituted tetrahydrofurans, see J. C. Harmange, B. Figadere, *Tetrahedron: Asymmetry* **1993**, *4*, 1711 – 1754.

[3] For six-membered-ring oxocarbenium ions, see T. Harada, T. Nakamura, M. Kinugasa, A. Oku, *J. Org. Chem*. **1999**, *64*, 7594 – 7600, and references therein; T. Sammakia, R. S. Smith, *J. Am. Chem. Soc*. **1992**, *114*, 10998 – 10999; S. E. Denmark, N. G. Almstead, *J. Am. Chem. Soc.* **1991**, *113*, 8089 – 8110.

[4] For five-membered-ring oxocarbenium ions, see a) C. H. Larsen, B. H. Ridway, J. T. Shaw, K. A. Woerpel, *J. Am. Chem. Soc.* **1999**, *121*, 12208 – 12209; J. T. Shaw, K. A. Woerpel, *Tetrahedron* **1999**, *55*, 8747 – 8756; b) A. Schmitt, H.-U. Reissig, *Synlett* **1990**, 40 – 42.

[5] For acyclic acetals, see K. Manju, S. Trehan, *Chem. Commun.* **1999**, 1929 – 1930.

[6] P. Collins, R. Ferrier, *Monosacharides: Their chemistry and their roles in Natural Products*, Wiley, New York, **1995**; b) A. Cavé, D. Cortés, B. Frigadere, R. Hocquemiller, O. Laprévot, A. Laurens, M. Leboeuf, *Phytochemical Potential of Tropical Plants*; *Recent Advances in Phytochemistry*, *Vol. 27* (Eds.: K. R. Bownum, J. Romeo, H. H. A. Stafford), Plenum, New York, **1993**.

[7] Many stereocontrolled approaches to these structures have been reported. Among them, nucleophilic substitution at the anomeric center of a furanoid glycal or a furanosyl halide appears to be a general strategy for preparing the corresponding 2-substituted tetrahydrofuran (see ref. [2]).

[8] P. Armas, F. García-Tellado, J. J. Marrero-Tellado, J. Robles, *Tetrahedron Lett.* **1998**, *39*, 131 – 134.

[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 protocal of Suárez et al., 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 configuration assigned to each newly created stereogenic center was confirmed by nOe spectroscopic analysis.

[11] P. Kozikowski, K. L. Sorgi, *Tetrahedron Lett.* **1983**, *24*, 1563 – 1566.

[12] P. Armas, C. G. Francisco, E. Suárez, *J. Am. Chem. Soc*. **1993**, *115*, 8865 – 8866.

[13] A series of 3-alkoxymethyl-5-alkoxy-2,7-dioxabicycle[2.2.1]heptane acetals derived from 6-O-protected D-galactal have been used as electrophilic substrates for C-glycosidation.[14] The bicycle does not seem to play a 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]

[14] V. Jaouen, A. Jégou, L. Lemée, A. Veyrières, *Tetrahedron* **1999**, *55*, 9245 – 9260.

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