Carbohydrates as Chiral Templates: Stereoselective Synthesis of (*R*)-Homoallyl Amines Using L-Fucose as the Auxiliary Formally Enantiomeric to D-Galactose

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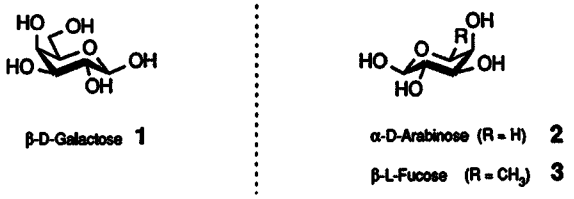
Abstract: (*R*)-Homoallyl amines are synthesized with high asymmetric induction using the diastereoselective Lewis acid induced addition of allylsilanes and allylstannanes to Schiff bases of *O*-acyl protected fucopyranosylamine.

Chiral homoallyl amines are interesting functionalized synthons. They can be transformed, for instance, to non-proteinogenic β-amino acids which are precursors for the synthesis of β-lactams.[1] According to our concept of using carbohydrates as chiral auxiliaries we recently found a diastereoselective synthesis of (S)-homoallyl amines consisting in the Lewis acid-induced addition of allylsilanes and -stannanes to Schiff bases of O-pivaloylated galactosylamines.[2] The absolute configuration of the preferably formed N-galactosyl-homoallyl amines was assigned by the conversion of the 1-phenyl-homoallyl amine into the known β-amino acid (S)-β-phenyl-β-alanine.

We here report on the stereoselective synthesis of homoallyl amines with opposite enantiomeric configuration. In general, the reversal of the stereochemical course of a reaction can be achieved by two different methods. The first one consists in the appropriate modification of the catalyst/solvent systems. In contrast to results obtained in Strecker-syntheses on carbohydrate templates[3], the selectivity of the Lewis acid-induced addition of allylsilanes to N-glycosyl imines cannot be influenced by changing the solvent. The second method to reverse the stereochemical pathway includes the use of the enantiomeric auxiliary. Of course, the L-galactose derivative cannot be considered as a practical enantiomeric template of the O-pivaloylated D-galactose **1**. However, nature presents two other carbohydrate derivatives which can be considered as formal enantiomers of β-D-galactose **1**, i.e. α-D-arabinose **2** and β-L-fucose **3** (Scheme 1).



Scheme 1

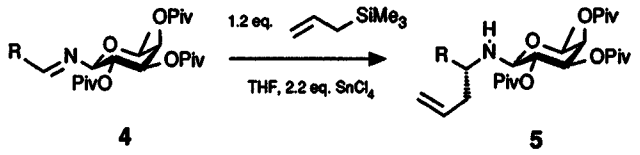
Astonishingly, the imines derived from the O-pivaloylated α-D-arabinosylamine do not react either with allyltrimethylsilane or allyltributylstannane in THF in the presence of $SnCl_4$. Beside the starting materials, only products of anomerization and decomposition of the Schiff bases can be detected. This result stands in remarkable contrast to the experiences collected in Ugi-syntheses of α-amino acid amides[4] in which the arabinosylamine revealed to be a very useful mirror image of D-galactosylamine in order to achieve the reversed stereochemical induction.

Table I. Synthesis of N-fucosyl-homoallyl amines **5**

amine	R	temp. [°C]	time	yield [%]	$[\alpha]_D^{22}$ 3)	(R) : (S)
5a	C_6H_5	1) 0, 2) rt	1) 2 h, 2) 4 d	44 1)	- 17.4°	23 : 1
5b	4-Cl-C_6H_4	1) 0, 2) rt	1) 2 h, 2) 3 d	86 1)	- 8.3°	8 : 1
5c	2-Cl-C_6H_4	1) 0, 2) rt	1) 2 h, 2) 3 d	69	- 23.0°	3.3 : 1
5c	2-Cl-C_6H_4	1) -10, 2) rt	1) 6.5 h, 2) 2.5 d	59	- 7.7°	> 100 : 1
5d	4-NO_2-C_6H_4	1) 0, 2) rt	1) 1 h, 2) 2 d	68 1)	- 10.8°	20 : 1
5e	4-MeO_2C-C_6H_4	1) -10, 2) rt	1) 26 h, 2) 3.5 d	53 1)	- 15.4°	17 : 1
5f	4-NC-C_6H_4	1) 0, 2) rt	1) 1 h, 2) 2d	56 1)	- 8.5°	13 : 1
5f	4-NC-C_6H_4	1) -10, 2) rt	1) 26 h, 2) 15 h	42 1)	- 8.1°	28 : 1
5g	4-Me-C_6H_4	1) 0, 2) rt	1) 1 h, 2) 60 h	43 1)	- 3.7°	49 : 1
5h	2-naphthyl	1) 0, 2) rt	1) 3 h, 2) 3 d	40	- 25.1°	12 : 1
5i	n-Pr 2)	1) -78, 2) -30	1) 11 h, 2) 36 h	26	- 91.3°	4.5 : 1 4)

1) Crystalline product.
2) Allyltributylstannane is used instead of allyltrimethylsilane.
3) (c = 1.00; $CHCl_3$).
4) The product contains 29 % of the corresponding α-anomer which displays the identical (R/S)-diastereomeric ratios.

However, using the corresponding β-L-fucosyl imines[5] **4** instead of the α-D-arabinosyl imines in the allylic addition the (R)-configurated homoallyl amines **5** can be isolated in high diastereoselectivities.[6] The obtained results are summarized in Scheme 2 and Table I.



Scheme 2

Performing the reaction at lower temperature results in increased diastereoselectivities (e.g. **5c** and **5f**). The decreased yields of homoallyl amines **5** at lower temperatures are caused by partial anomerization of the Schiff bases which becomes a reaction competing to the allylic addition[2]. It should also be noted that the fucosylamine as a chiral auxiliary in the allylic addition has an important advantage in comparison to the corresponding galactosylamine: In most cases the N-fucosyl-homoallyl amines **5** are crystalline products. This allows the purification and the enrichment of the diastereomers by a single recrystallization.

In conclusion, chiral homoallyl amines can be prepared stereoselectively and alternatively in both enantiomeric configurations by the appropriate choice of the chiral auxiliary. Whereas the Lewis acid-induced addition of allylsilanes to O-pivaloylated N-galactosylimines preferably gives the (S)-N-glycosyl-homoallyl amines, the use of the O-pivaloylated N-fucosylimines allows the synthesis of (R)-N-glycosyl-homoallyl amines with high stereoselectivity. N-Fucosylimines derived from aliphatic aldehydes only react with allyltributylstannane to furnish the corresponding homoallyl amines with lower stereoselectivity.

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(6) *General Procedure:* To a solution of 0.5 mmol of the N-fucosylimine **4** in 5 ml dry tetrahydrofuran allyltrimethylsilane (0.6 mmol) and $SnCl_4$ (1.1 mmol) are added at low temperature [Table I, temperature 1)] and the mixture is stirred [time 1)]. Then the reaction is completed at room temperature [time 2)]. After hydrolysis by addition of 2 N NaOH (50 ml) the tetrahydrofuran is evaporated in vacuo and the aqueous solution is extracted three times with chloroform. Usual work-up of the chloroform solution and flash-chromatography of the crude product delivers the analytically pure N-fucosyl-homoallyl amines **5**. The ratio of diastereomers is obtained from the crude product by HPLC on reversed phase columns using acetonitrile/water (30-40 %) as the eluent.
The major diastereomers of **5** give typical NMR-signals: 400 MHz-^{1}H-NMR ($CDCl_3$): δ = 3.65 - 3.70 (d, $J_{1,2}$ = 8.5 - 9.0 Hz, 1 H, 1-H); 100.6 MHz-^{13}C-NMR ($CDCl_3$): δ = 85 - 86 (C-1) ppm. The corresponding signals of the educts **4** show typical downfield shift: 400 MHz-^{1}H-NMR: δ = 4.65 - 4.90 (d, $J_{1,2}$ = 8.5 - 9.0 Hz, 1 H, 1-H); 100.6 MHz-^{13}C-NMR: δ = 92.5 - 95 (C-1) ppm.