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Asymmetric synthesis of the L-*fuco*-nojirimycin, a nanomolar α-L-fucosidase inhibitor

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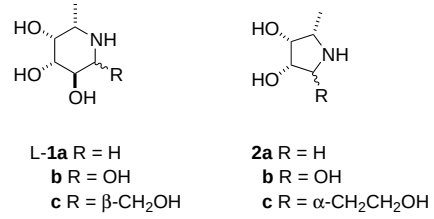
Abstract—We describe the asymmetric synthesis of the 5-amino-5-deoxy-L-fucose (L-*fuco*-nojirimycin) which appears as a very potent fucosidase inhibitor with a K_i value of 1 nM.

The L-fucose is a more lipophilic sugar and has unusual properties. It is implicated in polysaccharide motives, as Sialyl Lewis X, which are important for inflammation processes and tumour migration.[1–3] The design of fucose mimics or the synthesis of nonhydrolysable analogues may be of biological importance.

Potent fucosidase inhibitors have already been described in L-fucose and L-lyxose series (Scheme 1). 1-Deoxy- or homo-L-*fuco*-nojirimycin derivatives L-**1a**, L-**1c** are nanomolar inhibitors of α-L-fucosidase from various sources.[4–8] Amino-L-lyxose sugar **2b**[9,10] and its 1-deoxy-derivative **2a**[9–11] are likewise potent inhibitors of the α-L-fucosidase of bovine kidney; the α-homo derivative **2c** has also a K_i value in the nanomolar range.[12]

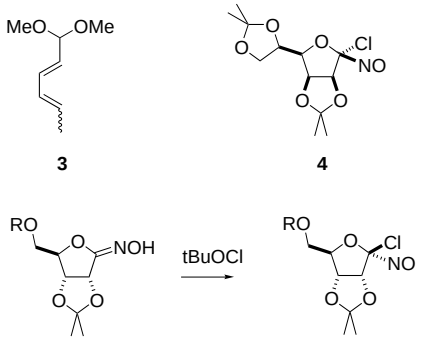


L-**1a** R = H
b R = OH
c R = β-CH_2OH

2a R = H
b R = OH
c R = α-CH_2CH_2OH

Scheme 1.

We describe the asymmetric synthesis and the enzymatic evaluation of the L-*fuco*-nojirimycin L-**1b**, which is a new analogue of nojirimycin and which looks like a promising fucosidase inhibitor. We had already described the synthesis of its D-enantiomer D-**1b** via an asymmetric hetero-Diels–Alder reaction between sorbaldehyde dimethylacetal (**3**) and the chloro-nitroso dienophile **4** in the D-mannose series[13,14] (Scheme 2). This chiral dienophile had been developed by Kresze and Vasella.[15] Using the same methodology and the previously reported concurrent chloro-nitroso dienophiles **6a**,**b** in the 5-*O*-trityl-[16] and the 5-*O*-acetyl-D-ribose[17] series, respectively, the enantiomeric adduct has been prepared. An interesting comparison of these parent dienophiles is now possible.



3 **4**

5a R = CPh_3
b R = Ac

6a R = CPh_3
b R = Ac

Scheme 2.

Diels–Alder reaction of hexadienal dimethylacetal (**3**)[18] with chloro-nitroso dienophiles **6a**,**b** was carried out as

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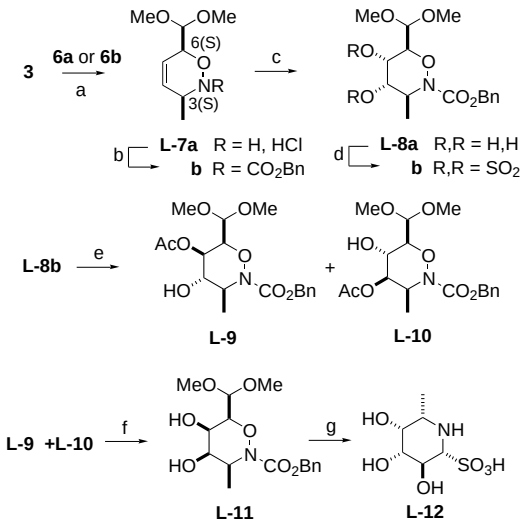


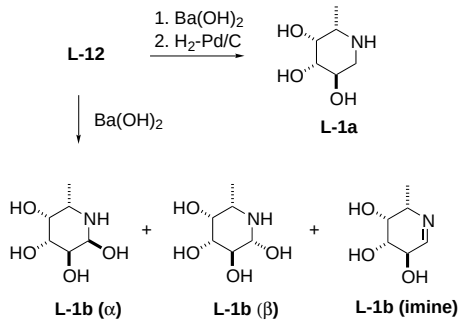
Scheme 3. Reagents and conditions: (a) $HC(OMe)_3$, MeOH, −10 °C, 16–24 h; (b) aq Na_2CO_3, $ClCO_2Bn$, 0 °C, 16 h; (c) cat. OsO_4, *N*-methyl-morpholine *N*-oxide, acetone/H_2O, 40 °C, 16 h, yield 10% or 17% from **3**; (d) 1—$SOCl_2$, CH_2Cl_2, NEt_3, 2—$RuCl_3$, $NaIO_4$, yield 90%; (e) 1—$AcONH_4$, DMF, 70 °C; 2—cat. H_2SO_4, dioxane; (f) 1—Tf_2O, CH_2Cl_2, pyridine; 2—$NaNO_2$, DMF, 30 °C; 3—Na_2CO_3, MeOH, yield 65% from L-**8b**; (g) 1—H_2-Pd/C, EtOH, 50 °C; 2—SO_2, H_2O, 6 days, 40 °C, yield 60%.

Table 1. Comparison of data ($[\alpha]_D$, overall yield, enantiomeric excess (ee) value) for the obtained chiral diol L-**8a** with those of the known enantiomer D-**8a**[13] depending on the used dienophiles **4, 6a**,**b**

Starting nitroso derivative	**4**[13]	**6a**	**6b**
Obtained chiral diol	D-**8a**	L-**8a**	L-**8a**
$[\alpha]_D^{25}$ value (*c* 1, $CHCl_3$)	−33	+28	+30
Yield of diol **8a** from **3**	35%	10%	17%
ee % value	>99	96	95

previously described with the mannose-derived dienophile **4**[13] (Schemes 2 and 3): diene **3** (1–1.5 equiv) was reacted with dienophiles **6a**,**b** (1 equiv) in a mixture of MeOH/methyl orthoformate at − 10 °C for 24 h. Compounds **6a**,**b** were prepared just before use by oxidation of the corresponding oximes **5a**,**b** with *t*-butyl hypochlorite. The adduct was recovered as hydrochloride L-**7a** in the aqueous phase after dilution with ether and extraction with an aqueous NaCl solution. Addition of excess Na_2CO_3 to this aqueous solution of L-**7a** and acylation with benzyl chloroformate (1 equiv) under good stirring for 5 h furnished, after extraction with CH_2Cl_2, the crude N-protected adduct L-**7b** (crude yield ca. 50%). Subsequent bis hydroxylation as previously reported in D-series[13] gave the stable diol L-**8a** after chromatographic purification (AcOEt/cyclohexane, 1/1) in 10% or 17% yield according to the used nitroso dienophile (Table 1).

Table 1 compiles some data for the diol L-**8a** in comparison with those obtained for its enantiomer D-**8a** already prepared from the nitroso-D-mannose-derivative **4**.[13] Lower overall yield was observed when the trityl derivative **6a** was used as a dienophile. This is probably due to the difficulty in purifying the amorphous initial oxime **5a**, compared to the nicely crystallised acetylated



Scheme 4.

one **5b**.[17] Determined enantiomeric excess (ee)[19] of L-**8a** was good (ca. 95%) and independent of the 5-substitution of the dienophile. This ee was similar to the one observed when hexadienoic acid was reacted with the dienophile **6b**.[17] Regarding the overall yields and the ee values which are given in Table 1, the mannose derivative **4** gave the best results among these dienophiles.

The inversion of the two hydroxyl groups in positions 4 and 5 of diol L-**8a** was carried out as for the D-enantiomer[14] (Scheme 3). The cyclic sulphate L-**8b** was obtained in 90% yield by reaction with $SOCl_2$ and oxidation of the resulting cyclic sulfite isomers with perruthenate ion. Opening of the sulphate L-**8b** with acetate anion following by acidolysis furnished two isomeric acetate alcohols L-**9** and L-**10** which were not separated. Their hydroxyl group was inverted by action of nitrite anion on the triflate and a subsequent methanolysis of the acetate group afforded the inverted diol L-**11** in 65% yield from sulphate L-**8b** (60% from diol L-**8a**).

Hydrogenolysis over Pd/C of the *N*-CO_2Bn group and of the N–O bond of the diol L-**11** followed by hydrolysis of the acetal group with SO_2 in water at 40 °C gave the crystalline L-*fuco*-nojirimycin sulfite adduct L-**12**, which was isolated after dilution with EtOH in 60% yield from diol L-**11**.

Hydrolysis of this sulfite adduct L-**12** with baryte gave the L-*fuco*-nojirimycin L-**1b** in aqueous solution as a mixture of the imine form and of both the α- and β-anomers in 11%, 46% and 43% proportion, respectively, at 295 K as in D-series[14] (Scheme 4). Hydrogenolysis over Pd/C of this mixture led to the known deoxy-derivative L-**1a**.[4–7,20–22]

Analytical data[23] of compounds L-**1b**, L-**8a**, L-**8b**, L-**11** and L-**12** were in agreement with those of the corresponding D-enantiomers[13,14] as well as data of the L-**1a** with those of the literature.[4,20–22]

Table 2. Inhibition of α-L-fucosidase from bovine kidney (K_i in μM)[24] with compounds L-**1a**, L-**1b** and L-**12** as well as with their D-enantiomers[14] D-**1a**, D-**1b** and D-**12**

Compound	**1a**	**1b**	**12**
L-Series	0.003[a]	0.001	0.001
D-Series	660	3	13

[a] IC_{50} = 5 nM.

Inhibition properties of the L-*fuco*-nojirimycin L-**1b**, its deoxy-derivative L-**1a** and its sulfite adduct L-**12** were determined against α-L-fucosidase activity[24] as well as those of their corresponding D-enantiomers[14] (Table 2).

All these compounds proved to be competitive inhibitors. L-*fuco*-Nojirimycin L-**1b** and its sulfite adduct L-**12** appear to be very potent α-L-fucosidase inhibitors with a K_i value of 1 nM. The deoxy-derivative L-**1a** is a less potent inhibitor and its potency is in agreement with the literature data against α-L-fucosidase of bovine epididymis.[4–7] Their D-enantiomers are comparatively poor inhibitors, particularly the 1-deoxy-derivative D-**1a**.

We have described the asymmetric synthesis of the most potent nanomolar α-L-fucosidase inhibitor, the L-*fuco*-nojirimycin (L-**1b**, L-fucose analogue of nojirimycin), in a 7% overall yield from hexadienal acetal (**3**) or in a 36% yield from the chiral diol L-**8a**. The increase of the inhibition potency for the amino-sugars L-**1b**, D-**1b** compared to their deoxy-derivatives L-**1a**, D-**1a** points out the importance of the anomeric hydroxyl group in the enzyme recognition as reported for other amino-sugars.[25]

Acknowledgments

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19. Determination conditions of the enantiomeric excess: column Chiralpak AD Daicel, eluent: 2-propanol/heptane 20/80, flow rate: 1 ml/min, 25 °C, λ = 260 nm. Analytical parameters: retention time for L(+)-**8a** Rt_1 = 9.4 min, for D(−)-**8a** Rt_2 = 11.2 min; $k'_1 = 2.26$, $k'_2 = 2.81$, $k'_2/k'_1 = 1.24$, Resolution = 1.33.
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23. L-**1a**. Same ^{1}H NMR data as in[20,21] and for D-**1a**[14]; $[\alpha]_D^{20} = -52$ (*c* 1, H_2O) {lit.[4] $[\alpha]_D^{20} = -48.8$ (*c* 0.64, H_2O); lit.[20] $[\alpha]_D^{20} = -48$ (*c* 0.2, H_2O); lit.[21] $[\alpha]_D^{20} = -46.9$ (*c* 0.61, H_2O); lit.[22] $[\alpha]_D = -50$ (*c* 1, D_2O); lit.[14] +49 (*c* 1, H_2O) for D-**1a**}.
L-**1b**. Same ^{1}H NMR data of the imine form, α- and β-anomers as for D-**1a**.[14]
L-**8a**. $[\alpha]_D^{25} = +30$ (*c* 1, $CHCl_3$) {lit.[13] $[\alpha]_D^{20} = -33$ (*c* 1, $CHCl_3$) for the D-enantiomer}. Same IR and ^{1}H NMR data as for D-**8a**;[13] ^{13}C NMR ($CDCl_3$, 100 MHz, 295 K): 156.4 (CO); 136.1 (Car-s); 128.6 (2 Car-m, Car-p); 128.2 (2 Car-o); 104.3 (*CH*(OMe)$_2$); 75.8 (C(6)); 68.8 (C(4)); 67.9 (*CH*$_2$Ph); 64.8 (C(5)); 56.4 (OMe); 55.4 (C(3); 53.3 (OMe); 14.4 (Me-3). HR-MS (Q-Tof), calcd for $C_{16}H_{23}NO_7$: 341.1475; found: 341.1431. Anal. calcd for $C_{16}H_{23}NO_7$ (341.36): C, 56.29; H, 6.79; N, 4.10. Found: C, 56.1; H, 7.1; N, 4.1.
L-**8b**. $[\alpha]_D^{20} = +63$ (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{20} = -68$ (*c* 2, $CHCl_3$) for D-**8b**}. Same IR and ^{1}H NMR data as for D-**8b**;[14] ^{13}C NMR ($CDCl_3$, 100 MHz, 295 K): 154.5 (CO); 135.2 (Car-s); 128.7 (2 Car-m); 128.6 (Car-p); 128.3 (2 Car-o); 101.8 (*CH*(OMe)$_2$); 79.7 (C(4)); 76.9 (C(6)); 74.7 (C(5)); 68.6 (*CH*$_2$Ph); 55.8, 55.3 (OMe, C(3)); 51.1(OMe); 14.2 (Me-3). HR-MS (Q-Tof), calcd for $C_{16}H_{21}NO_9S$: 403.0937; found: 403.0909. Anal. calcd for $C_{16}H_{21}NO_9S$ (403.41): C, 47.64; H, 5.25; N, 3.47. Found: C, 47.6; H, 5.5; N, 3.4.
L-**11**. $[\alpha]_D^{20} = +24$ (*c* 1, $CHCl_3$) {lit.[14] $[\alpha]_D^{20} = -19$ (*c* 1, $CHCl_3$) for D-**11**}. Same IR and ^{1}H NMR data as for D-**11**[14]; ^{13}C NMR ($CDCl_3$, 100 MHz, 295 K): 154.9 (CO); 135.8 (Car-s); 128.5 (2 Car-m); 128.3 (Car-p); 128.1 (2 Car-o); 101.9 (*CH*(OMe)$_2$); 81.3 (C(6)); 67.9, 67.5, 67.3 (*CH*$_2$Ph, C(4), C(5)); 55.8 (OMe); 54.1, 53.3 (C(3), OMe); 12.0 (Me-3). HR-MS (Q-Tof), calcd for $C_{16}H_{23}NO_7$: 341.1475; found: 341.1436.
L-**12**. Mp = 242–250 °C (dec.), (lit.[14] 240–250 °C, dec. for D-**12**). $[\alpha]_D^{20} = -8.2$ (*c* 1, H_2O) {lit.[14] $[\alpha]_D^{20} = +9$ (*c* 1, H_2O) for D-**12**}. Same IR, ^{1}H NMR and ^{13}C NMR data as for D-**12**.[14] Anal. calcd for $C_6H_{13}NO_6S$ (227.23): C, 31.71; H, 5.77; N, 6.16; S, 14.11. Found: C, 31.8; H, 5.8; N, 6.0; S, 14.2.
24. Inhibition determination conditions: acetate buffer, pH 5.5, K_m = 0.15 mM, 30 °C; all measured compounds were stable under these conditions.
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