Asymmetric Synthesis of D-Fucosamine and *N*-Methyl-D-Fucosamine

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Abstract: (+)-D-fucosamine and (+)-*N*-methyl-D-fucosamine (the amino sugar moiety of neocarzinostatin) have been synthesized from known building blocks derived from natural amino acids. Direct and diastereoselective construction of the key intermediate **4** was accomplished by a *syn*-aldol type reaction between Schöllkopf's bislactim ether **2** and the 1,3-dioxolane-4-carboxaldehyde **3**. Reduction and monomethylation of a O'Donnell's Schiff base derived from the common amino ester **7** allows an optional access to the *N*-methyl derivative.

Amino sugars are known as an important class of carbohydrates. Aminoglycosides are found in glycoproteins and glycolipids [1] and as structural components of antibiotics produced from various microorganisms. [2] D-fucosamine (2-amino-2,6-dideoxy-galactose) is a common component of bacterial polysaccharides [3] and its 3-*O*-methyl and *N*-methyl derivatives are also present in elsamicin A [4] and neocarzinostatin [5] antibiotics, respectively. At present, there has been a renewed interest in neocarzinostatin because of its structural, biological and mechanistic similarities with the newly discovered enediyne class of antitumour antibiotics.[6] Neocarzinostatin is a 1:1 noncovalently associated mixture of a carrier protein and a chromophoric molecule (Figure 1). It has been demonstrated that its aminoglycoside moiety (*N*-methyl-D-fucosamine) plays an important role in the binding and activation of the neocarzinostatin chromophore.[7,8]

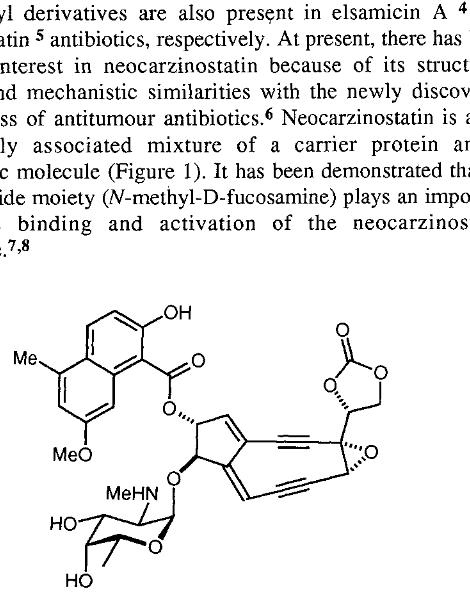
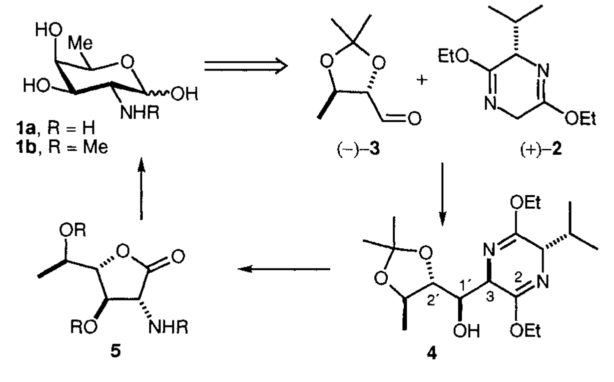


Figure 1

Carbohydrate based syntheses of biological significant fucosamines have been reported in the literature,[9] but to the best of our knowledge, only an asymmetric synthesis of *N*-methyl fucosamine has been described.[10] In this communication we present a new diastereoselective synthesis of D-fucosamine (**1a**, see scheme 1) and its *N*-methyl derivative **1b**, by extending the applicability of our amino acid based convergent approach to 2-amino-2,6-dideoxy-hexoses.[11] Our strategy is based on a direct and highly stereoselective construction of the 2-amino-2,6-dideoxy-galactose backbone, by using a *syn*-aldol type reaction between Schöllkopf's bislactim ether **2** and a 1,3-dioxolane-4-carboxaldehyde **3**, both derived from natural amino acids (glycine, valine and threonine). As enolate and aldehyde form a matched-pair, a double asymmetric induction of the 3,1'-*syn*-1',2'-*anti* configuration allows the stereoselective formation of the adduct **4**. The conversion of this key intermediate to both fucosamines requires the removal of the chiral auxiliary group, a partial reduction at C-2 and an optional and selective monomethylation of the amino group. Thus, after the protection of the hydroxyl group at position 1', the selective hydrolysis of the pyrazino moiety should enable the methylation of the amino group. In addition, the reduction of a lactone intermediate like **5** would avoid the manipulation of compounds with 2-aminoaldehyde functions, of known instability [12].



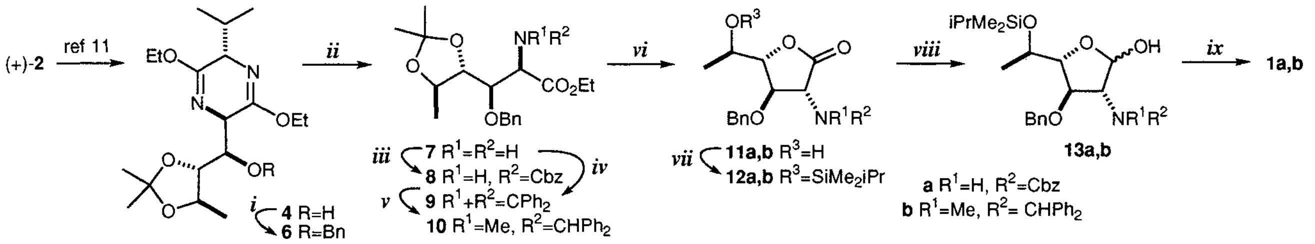
Scheme 1

According to the literature, L-threonine was converted into the (4*S*)-*trans*-2,2,5-trimethyl-1,3-dioxolane-4-carboxaldehyde (**3**),[13] and (3*S*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine (**2**) was prepared from glycine and L-valine.[14] Following our recently reported procedure, [11] the addition of freshly distilled **3** to the lithium salt of bislactim ether **2** (THF, -78°C) led, after chromatography, to the isolation of adduct **4** in good yield. Protection of the hydroxyl group at position 1' was accomplished by treatment of **4** with sodium hydride and benzyl bromide (THF, 0°C to RT, 85%).[15] Selective hydrolysis of the pyrazino moiety of **6** in the presence of the isopropylidene ketal (0.25 N HCl, EtOH, RT, 14 h)[16] yielded, after removal of the auxiliary valine ester by simple chromatography, the amino ester **7** in high yield. Protection of the amino group of **7** as benzyloxycarbonyl was accomplished in an almost quantitative yield under standard conditions.

For the synthesis of the *N*-methyl derivative the attempts to methylate the benzylcarbamate **8** under various conditions were unsuccessful[17] However, protection and monomethylation was finally accomplished in a one pot procedure by the reduction of a O'Donnell's Schiff base followed by reductive methylation of the corresponding secondary amine.[10,18] Thus, the imino ester **9** was obtained in good yield by treatment of amino ester **7** with diphenylketimine and anhydrous *p*-toluensulfonic acid as catalyst. [19] Reduction of the Schiff base under anhydrous acidic conditions to generate benzhydryl secondary amine and subsequent reductive methylation enable the isolation of the monomethylamine **10**. [20]

Hydrolysis of the isopropylidene ketal of **8** and **10** in acidic media (THF/TFA/H_2O 6:6:1, RT, 3 h.) led to the simultaneous formation of the γ-lactones **11a,b** [21] in good yield. Treatment of lactones **11a,b** with dimethylisopropylsilyl chloride (imidazole, THF, RT) afforded the corresponding silyl ethers **12a,b** in excellent yield.[22] Partial reduction of **12a,b** (DIBALH, THF:toluene 1:2, -78°C) led to the mixtures of furanoses **13a,b** within combined yields higher than 80%. Finally, deprotection of lactols **13a,b** by catalytic hydrogenation in acidic media (MeOH:HCl 0.25N 2:1) allowed, after ion-exchange chromatography (Dowex 50x8-200, H^+), the isolation of the free amino sugars **1a,b**. Treatment of **1a** with HCl and purification by reverse phase flash chromatography (H_2O, RP-18 230-400 mesh) afforded fucosamine as its hydrochloride salt in an almost quantitative yield.[23]

The present asymmetric synthesis of D-fucosamine (**1a**) and *N*-methyl-D-fucosamine (**1b**) from natural amino acids requires rather



i NaH, BnBr, NBu_4I, THF, RT, 12h, 85%. *ii* HCl 0.25 N, EtOH, RT, 12h, 88%. *iii* Na_2CO_3, $NaHCO_3$, BnOCOCl, dioxane:H_2O 1:1, RT, 2h, 94%. *iv* Ph_2CNH, TsOH, CH_2Cl_2, RT, 14h, 81%. *v* $NaBH_3CN$, H_2CO, pH~7, CH_3CN, 15h, 82%. *vi.* TFA:THF:H_2O 6:6:1, RT, 3h, 85% for **8**, 80% for **10**. *vii.* 1.25 *i*-$PrMe_2SiCl$, 2 imidazole, THF, RT, 1h, 95% for **a**, 90% for **b**.*viii* 2.1 DIBALH, -78°C, toluene:THF 2:1, 6h, 80% for **a**, 85% for **b**. *ix* *1* H_2, Pd/C 10%, Patm, MeOH:HCl 0.25N 2:1, RT, 6h. *2* Dowex , 1% aq. NH_3, 87% for **a**, 85% for **b**.

Scheme 2

inexpensive reagents and operatively simple reaction conditions, and proves the versatility of our recently reported approach to the 2-amino-2,6-dideoxy-galactose backbone. Work is now underway to extend this methodology to the synthesis of biologically interesting polyhydroxylated piperidines an pyrrolidines.

Acknowledgements

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(14) *Cyclo*[(2*S*)-val-gly] was obtained as described by Rose *et al.* Treatment of this compound with triethyloxonium tetrafluorborate allowed the preparation of the 2,5-diethoxy pyrazine derivative. See Rose, J.E., Leeson, P.D.; Gani, D. *J. Chem. Soc. Perkin Trans 1* **1995**, 157. Alternatively, both enantiomers of the related 2,5-dimethoxy-3-isopropyl-3,6-dihydropyrazine can be purchased from E. Merck.

(15) All new compounds have been isolated in a pure analytical form after chromatography (on SiO_2 or RP-18), and their spectral data (FABMS, NMR and IR) were consistent with the proposed structure. Selected data for compound **6**: $[\alpha]^{22}_D$ +65.2 (c 1.5, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ : 0.68 (d, 3H, *J* = 6.8 Hz, $(C\underline{H}_3)_2CH$); 1.05 (d, 3H, *J* = 6.8 Hz, $(C\underline{H}_3)_2CH$); 1.22-1.35 (m, 9H, $C\underline{H}_3CH_2O$ and $C\underline{H}_3CH$); 1.40 (s, 3H, $(C\underline{H}_3)_2C$), 1.43 (s, 3H, $(C\underline{H}_3)_2C$); 2.31 (dsp, 1H, *J* = 6.8, 3.6 Hz, $(CH_3)_2C\underline{H}$); 3.91 (t, 1H, *J* = 3.6 Hz, H-6); 3.98-4.30 (m, 8H); 4.43,4.50 (AB system, 2H, *J* = 9.1 Hz, CH_2Ph); 7.18-7.35 (m, 5H, ArH).

(16) Prolonged reaction times or the use of ethers as the solvent resulted in a complete hydrolysis to the corresponding 2-amino-4,5-dihydroxy acid, isolated in low yields. Lactonization of this compound was not efficiently achieved.

(17) Attempts to achieve the *N*-methylation of the benzylcarbamate **8** under several conditions (sodium hydride or potassium carbonate and methyl iodide) resulted in recovered starting material or decomposition compounds after prolonged reaction times. See also note 21.

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(20) Selected data for compound **10**: $[\alpha]^{24}_D$ +77.1 (c 1.9, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ : 1.21 (d, 3H, *J* = 5.9 Hz, $C\underline{H}_3CH$); 1.31 (t, 3H, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$); 1.36 (s, 3H, $(C\underline{H}_3)_2C$), 1.49 (s, 3H, $(C\underline{H}_3)_2C$); 2.55 (s, 3H, $NC\underline{H}_3$); 3.68 (d, 1H, *J* = 6.1 Hz, H-2); 3.91 (dd, 1H, *J* = 7.9, 6.6 Hz); 4.07-4.34 (m, 4H); 4.69, 4.83 (AB system, 2H, *J* = 11.1 Hz, CH_2Ph); 5.00 (s, 1H, $CHPh_2$); 7.10-7.51 (m, 15H, ArH).

(21) Treatment of compound **11a** with sodium hydride and methyl iodide (THF, -15°C) led to the exclusive formation of a 3-amino-5*H*-furan-2-one derivative (by *syn* elimination of the bencyloxy group at position 4) instead of the desired *N*-methyl derivative.

(22) Selected data for lactones **12**. **12a**: $[\alpha]^{22}_D$ -26.7 (c 1.0, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ : 0.03 (s, 3H, $(C\underline{H}_3)Si$); 0.06 (s, 3H, $(C\underline{H}_3)Si$); 0.70-0.96 (m, 7H, $(CH_3)_2CHSi$); 1.26 (d, 3H, *J* = 6.4 Hz, $C\underline{H}_3CH$); 3.91-4.12 (m, 1H); 4.10 (t, 1H, *J* = 5.4 Hz); 4.21-4.25 (m, 1H); 4.50-4.60 (m, 1H); 4.55, 4.76 (AB system, 2H, *J* = 11.9 Hz, OCH_2Ph); 5.13, 5.21 (AB system, 2H, *J* = 12.2 Hz, CO_2CH_2Ph); 5.21 (d, 1H, NH); 7.31 (s, 5H, ArH); 7.37 (s, 5H, ArH). **12b**: $[\alpha]^{22}_D$ +8.5 (c 2.7, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ : 0.07 (s, 3H, $(C\underline{H}_3)Si$); 0.09 (s, 3H, $(C\underline{H}_3)Si$); 0.70-0.91 (m, 1H, CHSi); 0.91-1.04 (m, 6H, $(C\underline{H}_3)_2CHSi$); 1.26 (d, 3H, *J* = 6.7 Hz, $C\underline{H}_3CH$); 2.40 (s, 3H, NCH_3); 3.90-4.05 (m, 3H); 4.49 (dd, 1H, *J* = 8.0, 6.6 Hz); 4.79, 5.11 (AB system, 2H, *J* = 11.3 Hz, OCH_2Ph); 5.42 (s, 1H, $CHPh_2$); 7.20-7.56 (m, 15H, ArH).

(23) Optical rotation for *N*-methyl-D-fucosamine: $[\alpha]^{23}_D$ +69.0 (final, c 0.1, H_2O) {lit (ref. 5) $[\alpha]^{25}_D$ +73.1 (final, c 0.1, H_2O)}. Optical rotation for D-fucosamine hydrochloride: $[\alpha]^{23}_D$ +76.1 (final, c 0.6, H_2O) {lit (ref. 9a) $[\alpha]_D$ +81.0 (final, c 0.2, H_2O)}.