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Synthesis of *N*-acetylxylosamidoxime, a potential transition state analog inhibitor of glycosyltransferases

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Abstract

The synthesis of a polyfunctionalized amidoxime is described involving condensation of hydroxylamine on a thioamide deriving from Boc-L-serine. This structure could be an efficient transition state like inhibitor of *N*-acetylglucosaminyltransferases, such as chitin synthase. © 2000 Published by Elsevier Science Ltd. All rights reserved.

Various amidoxime, amidrazone and amidine derivatives of monosaccharide aldonolactams have already been described.[1] These molecules constitute powerful inhibitors of metabolically important glycosyl hydrolases. Their inhibitory activity has been discussed in relation to the proposed oxocarbonium-like transition state along the enzymatic hydrolysis pathway.[2,3] The described derivatives exhibit roughly similar affinities but differ greatly in stability, the amidoxime being the most stable one. This latter functionality has been studied in the *gluco*, *manno* and *galacto* series. We turned our attention on molecules possessing an acetamido function at position 2, to test whether the amidoxime functionality could confer interesting properties towards *N*-acetylglucosamine-specific biosynthesis-glycosyltransferases.

Herein, we describe the synthesis of the *N*-acetylxylosamidoxime **12** in eleven steps starting from the Garner's synthon[4] **1** (Scheme 1).

After homologation of **1** into ester **2** by a Wittig reaction[5] (87%) leading exclusively to the *E* stereomer, chemoselective reduction by DIBAL-H at 0°C gave the allylic alcohol **3** (72%). Mesylation of the alcohol followed by treatment with sodium azide gave allylic azide **4** in moderate yield (67%).

Since asymmetric dihydroxylation according to Sharpless was unsuccessful,[6] the reaction was performed in non-asymmetric conditions and the resulting diastereomers **5a** and **5b**, obtained in a 55:45 ratio (66%), were separated by crystallization.

After benzylation of the diol **5a** in the presence of benzyl bromide (92%) and cleavage of the oxazolidine using Dowex 50 W resin (72%), the alcohol **7** was cleanly oxidized with TEMPO[7] and the resulting acid esterified with diazomethane (51% overall yield).[8]

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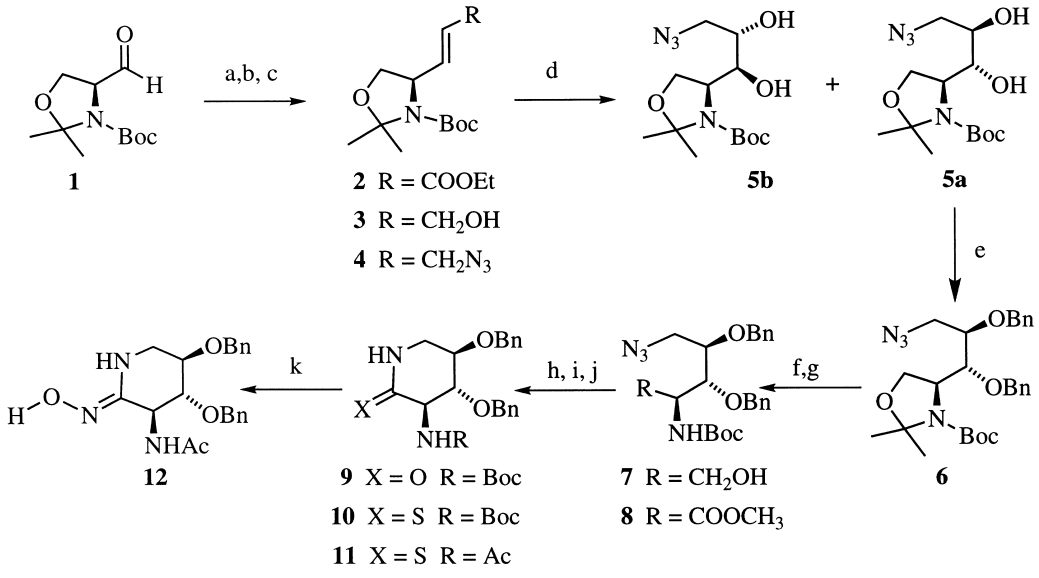

Scheme 1. (a) $\emptyset_3$P=CHCOOEt, THF reflux, 2 h; (b) DIBAL-H 20% wt in toluene, THF, 0°C, 1 h; (c) MsCl, Et_3N, CH_2Cl_2, 0°C, 15 min then NaN_3, DMF, rt, 12 h; (d) OsO_4, MNO, H_2O, *t*BuOH, THF, rt, 12 h; (e) BnBr, DMF then NaH, rt, 2 h; (f) DOWEX 50W (H^+), MeOH, rt, 12 h; (g) $NaHCO_3$ 5% aq., KBr, TEMPO, NaOCl, acetone, 0°C, 1 h then CH_2N_2, MeOH; (h) Pd/$CaCO_3$, H_2, MeOH, rt, 3 h; (i) Lawesson's reagent, pyridine, toluene, reflux, 2 h; (j) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, rt, 30 min then MeOH, Ac_2O, Bu_4NF, rt, 12 h; (k) $NH_2OH.HCl$, $NaHCO_3$, MeOH reflux, 2 h

Reduction of azide **8** by Lindlar catalyst yielded the lactam **9** (86%), which was transformed into thionolactam **10** by Lawesson's reagent[9] (75%). Use of classical Boc deprotection/reacetylation conditions[10] led to degradation products. We thus established a modified version of Ohfune's procedure,[11] based on trapping the amine formed in a protic solvent by acetic anhydride, and obtained the *N*-acetylated thionolactam **11** (46% overall yield).

The amidoxime **12** was finally obtained by condensation of hydroxylamine (2 equivalents) on **11** (55%). This compound is derivatized in a specific manner such that further condensation on the amidoxime hydroxyl function is possible. Such *N*-acetylglucosamidoxime analogs represent potential transition state analog inhibitors of glycosyltransferases specific of *N*-acetylglucosamine derivatives, among which chitin synthase.

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