Pergamon

Tetrahedron Letters, Vol. 37, No. 33, pp. 5921-5924, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01277-4

Two Efficient Routes for Construction of Amidine-Linked Pseudo-disaccharide

Katsuhiko Suzuki, Takashi Fujii,[#] Ken-ichi Sato,[#] and Hironobu Hashimoto*

Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama, 226 Japan

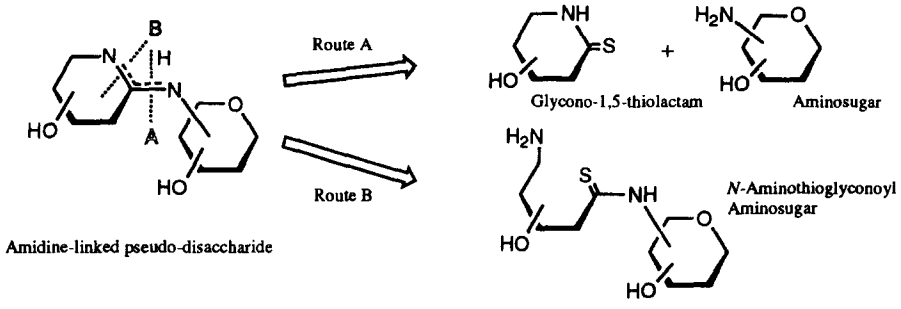
[#] Laboratory of Organic Chemistry, Faculty of Engineering, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama, 221 Japan

Abstract: Two routes for the synthesis of the amidine-linked pseudo-disaccharide were developed. The amidine linkage was constructed by the intermolecular or intramolecular coupling between thioamide and amine in the presence of mercury (II) chloride. The former construction from D-arabinono-1,5-thiolactam and 6-amino-6-deoxy-D-glucoside gave the corresponding pseudo-disaccharide. The latter construction of the amidine linkage was demonstrated in the case of 4-(5-amino-5-deoxy-D-thioarabinononyl)amino-4-deoxy-D-glucoside.

Amidine pseudo-saccharide,[1] whose acetal moiety is substituted with an amidine structure, has been proved to be a powerful inhibitor against *exo*-glycosidases. The inhibitory activity is ascribed to the positive charge as well as the half-chair conformation which mimics the oxocarbenium ion in the transition state. Pseudo-oligosaccharides having an interglycosidic amidine linkage are a potential candidate as a specific inhibitor against glycosidases which recognize both the glycosidic linkage and aglycon moiety. Recently, 1,6-amidine-linked pseudo-mannobioside[2] which has a different selectivity from monosaccharidic mannoamidines has been shown to be a good competitive inhibitor of α-mannosidase. Although this pseudo-disaccharide could be obtained at an elevated temperature by a similar method to that used for the preparation of monosaccharidic amidines[3], construction of the amidine linkage between two sugar moieties remained unexplored. Very recently, synthesis of glycoamidines using a mercury-promoted reaction of the corresponding thioamides with amines was reported.[4] It has been known that some reactions of organosulfur compounds can be activated by soft metal ions.[5] This fact prompted us to apply the method to the construction of the amidine-linkage. In this paper, an efficient methods for the construction of the amidine-linkage was described.

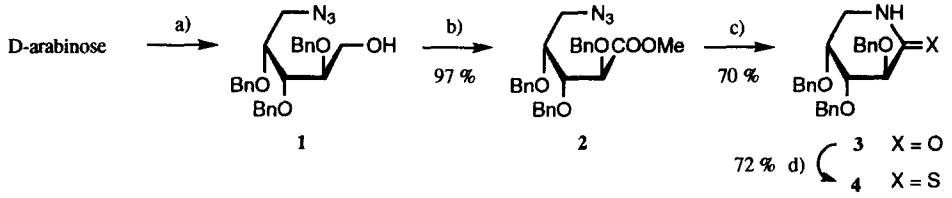
N,N'-Di-substituted amidines are most conveniently prepared from amide derivatives.[6] Two types of thioamides, glycono-1,5-thiolactam and *N*-aminothioglyconoyl aminosugar, were selected as precursors of the amidine-linked pseudo-disaccharide according to our retrosynthetic strategy as shown in Scheme 1.

The construction of the amidine-linkage was demonstrated by intermolecular coupling (route A) and intramolecular cyclization (route B).



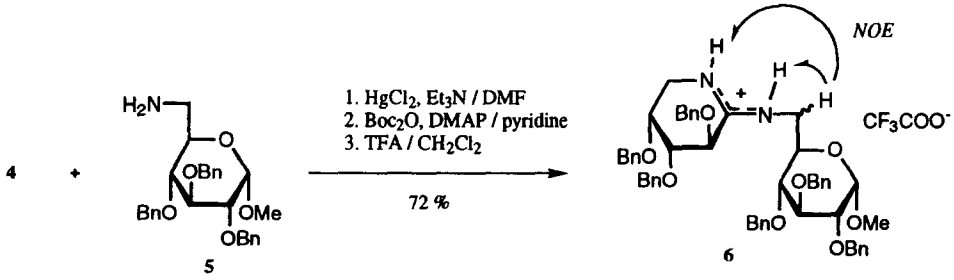
Scheme 1

The route A was accomplished using D-arabinono-1,5-thiolactam **4**, which was synthesized from D-arabinose as shown in Scheme 2. Coupling of **4** with 6-amino-6-deoxy-D-glucoside[3a] **5** with the assistance of mercury (II) chloride gave the corresponding amidine-linked pseudo-disaccharide[8] **6** in 72% yield (Scheme 3).[9] The ^{1}H-NMR spectrum of **6** in 2 : 1 DMSO-d_6-C_6D_6 indicates a single isomer and two kinds of characteristic NH protons, suggesting the protonated amidine structure. The counter anion, trifluoroacetate, was confirmed by the ^{19}F-NMR spectrum. The structure of **6** was further supported by NOE observed between H-6 and protonated two NH signals (Scheme 3) and HRMS (FAB).



a) Ref. 7 ; b) 1. $(COCl)_2$, DMSO, Et_3N / CH_2Cl_2 -78°C, 2. Br_2, $NaHCO_3$ / MeOH-H_2O ;
c) PPh_3, H_2O / benzene ; d) Lawesson's reagent / toluene.

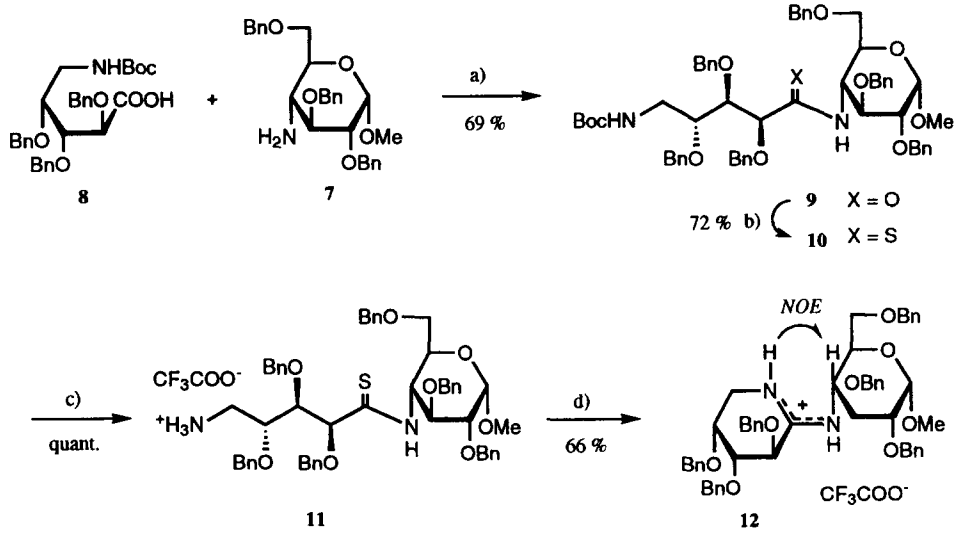
Scheme 2



Scheme 3

Coupling of **4** with 4-amino-4-deoxy-D-glucoside[3a] **7** under the same conditions, however, did not proceed at all. On the other hand, the intramolecular construction of the amidine linkage (route B) was

successful and proved to be widely applicable (Scheme 4). 5-*N*-Boc-D-arabinono-1,5-lactam prepared by treatment of **3** with Boc_2O in the presence of DMAP was converted to 5-*N*-Boc-glyconic acid **8** in good yield by hydrolysis in 1M aq. NaOH. Condensation of **8** with **7** using *N*-ethyl-*N*'-3-dimethylamino-propylcarbodiimide (EDC) hydrochloride and 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOOBt)[10] gave the corresponding *N*-(5-amino-5-deoxy-D-arabinonoyl) derivative **9**. Thionation of an amide **9** using Lawesson's reagent[11] gave a thioamide **10** in 72% yield. The *N*-Boc group of **10** was cleaved smoothly with TFA to give **11** quantitatively. Intramolecular construction of the amidine linkage was achieved using the same conditions as used for the route A. The structure of **12** was supported by characteristic NH signals observed at 10.37 and 9.91 ppm and also by NOE observed between H-4 and *endo* NH signal.[8] The interglycosidic amidine linkage of this pseudo-disaccharide was proved to be stable enough for *O*-debenzylation by catalytic hydrogenolysis.[3a]



a) EDC hydrochloride, HOOBt / CH_2Cl_2 ; b) Lawesson's reagent / toluene ; c) TFA / CH_2Cl_2 ; d) 1. $HgCl_2$, Et_3N / DMF, 2. Boc_2O, DMAP / pyridine, 3. TFA / CH_2Cl_2 .

Scheme 4

Thus, an efficient synthesis of the amidine-linked pseudo-disaccharide was achieved and this strategy may be applicable to synthesis of the amidine-linked pseudo-disaccharide having a wide variety of amino sugars at the reducing end. Inhibitory activities of the pseudo-disaccharides are currently being evaluated.

Acknowledgement

The authors thank Kazuo Tanaka, JEOL Ltd., for recording the MS spectra. This work was supported in part by a Grant-in-Aid (No. 06453212) for Scientific Research on Priority Area from the Japanese Ministry of Education, Science, Sports and Culture.

REFERENCES AND NOTES

1. a) Papandreou G.; Tong M. K.; Ganem B. *J. Am. Chem. Soc.*, **1993**, *115*, 11682-11690. b) Tong M. K.; Papandreou G.; Ganem B. *J. Am. Chem. Soc.*, **1990**, *112*, 6137-6139. c) Tong M. K.; Papandreou G.; Ganem B. *J. Am. Chem. Soc.*, **1991**, *113*, 8984-8985.
2. Bleriot Y.; Dintinger T.; Guillo N.; Tellier C. *Tetrahedron Lett.*, **1995**, *36*, 5175-5178.
3. a) Knapp S.; Choe Yun H.; Reilly E. *Tetrahedron Lett.*, **1993**, *34*, 4443-4446. b) Bleriot Y.; Genre-Grandpierre A.; Tellier C. *Tetrahedron Lett.*, **1994**, *35*, 1867-1870.
4. Avalos M.; Babiano R.; Cintas P.; Durán C. J.; Jiménez J. L.; Palacios J. C. *Tetrahedron*, **1995**, *51*, 8043-8056.
5. a) Satchell D. P. N. *Chem. Soc. Rev.*, **1977**, *3*, 345-371. b) Gautier J.-A.; Miocque M.; Farnoux C. C. Preparation and Synthetic Uses of Amidines In *The Chemistry of Amidines and Imidates*; Patai S. Ed.; John Wiley & Sons, Inc.: New York, 1975; pp. 283-348.
6. a) Weinturb L.; Oles S. R.; Kalish N. *J. Org. Chem.*, **1968**, *33*, 1679-1681. b) Bredereck H.; Gompper R.; Klemm K.; Rempfer H. *Chem. Ber.*, **1959**, *92*, 837-849. c) Besan J.; Kulcsar L.; Kovacs M. *Synthesis*, **1980**, 883-884.
7. Suzuki K.; Hashimoto H. *Tetrahedron Lett.*, **1994**, *35*, 4119-4122.
8. Selected spectral data for **6** : ^{1}H-NMR (DMSO-d_6 : C_6D_6 = 2 : 1) δ 9.76 (br s, 1H, *endo* NH), 9.62 (br dd, 1H, $J_{6a,NH} = J_{6b,NH}$ = 5.49 Hz, *exo* NH), 4.81-4.77 (m, 4H, benzyl, H-1,2'), 4.29 (br d, 2H, J = 5.80 Hz, H-3',4'), 3.94 (dd, 1H, $J_{2,3}$ = 9.46 Hz, $J_{3,4}$ = 9.00 Hz, H-3), 3.84 (ddd, 1-H, $J_{4,5}$ = 9.77 Hz, $J_{5,6a}$ = 4.58 Hz, $J_{5,6b}$ = 4.73 Hz, H-5), 3.70 (br dd, 2H, H-6a,6b), 3.65-3.60 (m, 2H, H-5'a,5'b), 3.59 (dd, 1H, $J_{1,2}$ = 3.36 Hz, H-2), 3.50 (dd, 1H, H-4), 3.22 (s, 3H, OMe). ^{13}C-NMR (DMSO-d_6 : C_6D_6 = 2 : 1) δ 161.31; ^{19}F-NMR ($CDCl_3$) δ -76.86. HRMS (FAB) Calc. for $C_{54}H_{59}O_8N_2$ $(M+H)^+$: 863.4274; Found: 863.4283. **11** : ^{1}H-NMR (DMSO-d_6 : C_6D_6 = 2 : 1) δ 10.37 (br d, 1H, J = 9.00 Hz, *exo* NH), 9.91 (br s, 1H, *endo* NH), 5.04 (d, 1H, J = 3.36 Hz, H-1), 4.82 (d, 1H, $J_{2',3'}$ = 5.34 Hz, H-2'), 4.24-4.12 (m, 4H, H-4,5,3',4'), 4.09 (dd, 1H, $J_{2,3} = J_{3,4}$ = 9.31 Hz, H-3), 3.67 (dd, 1H, H-2), 3.61 (d, 2H, J = 2.44 Hz, H-6a,6b), 3.34-3.43 (m, 2H, H-5'a,5'b), 3.41 (s, 3H, OMe). ^{13}C-NMR (DMSO-d_6 : C_6D_6 = 2 : 1) δ 160.75; ^{19}F-NMR ($CDCl_3$) δ -76.84.
9. This reaction did not proceed in the absence of mercury (II) chloride, which was a sole mercury salt examined. The product was *N-tert*-butoxycarbonylated to facilitate its purification.
10. König W.; Geiger R. *Chem. Ber.*, **1970**, *103*, 2034-2040.
11. Scheibye S.; Pederson B. S.; Lawesson S.-O. *Bull. Soc. Chim. Belg.*, **1978**, *87*, 229-238.

(*Received in Japan* 17 *May* 1996; *revised* 24 *June* 1996; *accepted* 26 *June* 1996)