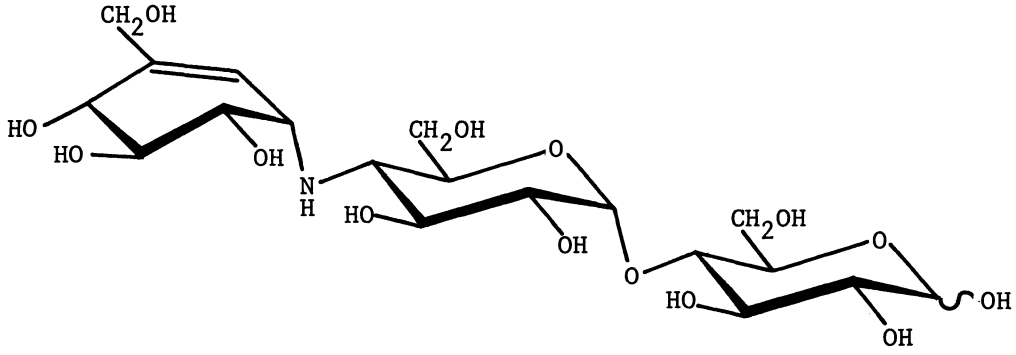
CHEMISTRY LETTERS, pp. 337-340, 1983.

SYNTHESIS OF ADIPOSIN-1, α-GLUCOSIDE HYDROLASE INHIBITOR

Seiichiro OGAWA, Yoshikazu IWASAWA, Tatsushi TOYOKUNI,
and Tetsuo SUAMI*
Department of Applied Chemistry, Faculty of Science and
Technology, Keio University, Hiyoshi, Yokohama 223

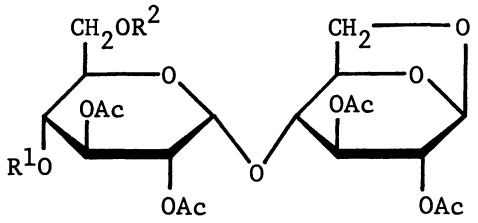
Adiposin-1, the common constituent of pseudo-oligosaccharidic α-glucoside hydrolase inhibitor, adiposin, has been synthesized by coupling of the disaccharide epoxide and the protected DL-valienamine, followed by deblocking.

Recently, several pseudo-oligosaccharidic α-glucosidase inhibitors have been discovered and much interest has been arisen in the biological study[1] and chemical synthesis.[2] In connection with the preceding paper,[3] this communication describes the first synthesis of such an α-glucoside hydrolase inhibitor, adiposin-1 (1), which is isolated from an inhibitor complex, adiposin, produced by *Streptomyces calvus* TM-521.[4] The synthesis involved a coupling of the disaccharide epoxide 4 with the protected DL-valienamine 6.[5] Four products (7a,b and 8a,b) could successfully be separated as a penta-O-acetyl derivative by chromatography on silica gel. Removal of the protecting groups, followed by the conventional acetylation, afforded the peracetyl derivatives of pseudo-trisaccharide, one of which was converted into a free pseudo-trisaccharide, identical with an authentic sample of 1.



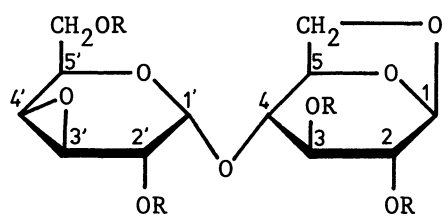
Adiposin-1 (1)

2,2',3,3'-Tetra-O-acetyl-1,6-anhydro-β-maltose (2)[6] was treated with benzoyl chloride (1.1 molar equiv.) in pyridine at room temperature for 4 d. Without separation, a monobenzoate thus formed was successively treated with excess p-toluenesulfonyl chloride (room temperature, 5 d) to produce, after purification by a silica gel chromatography, 2,2',3,3'-tetra-O-acetyl-1,6-anhydro-6'-O-benzoyl-



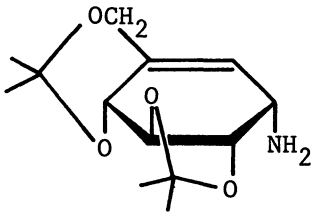
2 $R^1 = R^2 = H$

3 R^1 = Ts, R^2 = Bz

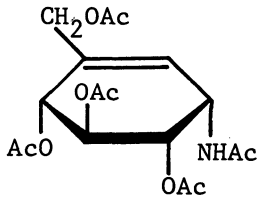


4 R = H

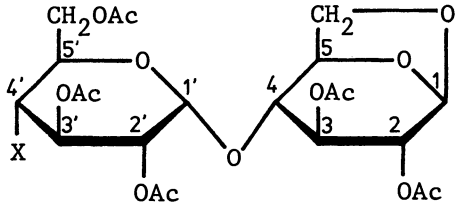
5 R = Ac



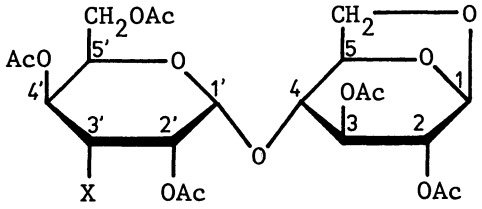
6 (racemate)



Penta-N,O-acetylvalienamine

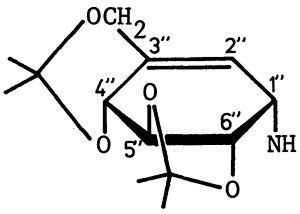


7a,b

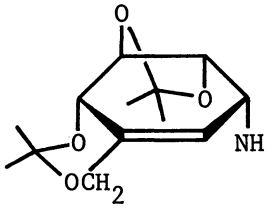


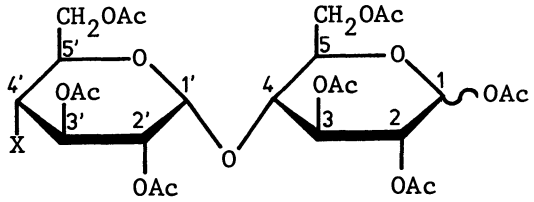
8a,b

a: X =



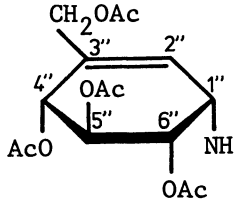
b: X =



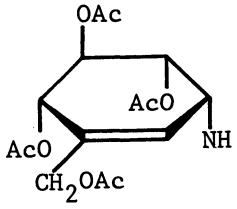


9a,b

a: X =



b: X =



4'-O-p-tolylsulfonyl-β-maltose (3, oil, $[\alpha]_D^{19}$ +46.6 °, 85%).[7] Treatment of 3 with an excess amount of methanolic sodium methoxide in methanol (0 °C, 2 h) gave, after chromatography on silica gel, a single crystalline epoxide [4, mp 155–157 °C, $[\alpha]_D^{20}$ +18 ° (MeOH), 71%].[8] Compound 4 was further characterized as the tetra-O-acetyl derivative (5, oil, $[\alpha]_D^{20}$ +26 °): ^{1}H NMR ($CDCl_3$, 90 MHz) δ = 3.26 (2H, s, H-3' and H-4').

A coupling reaction of 4 with DL-2,3:4,7-di-O-isopropylidene-(1,2,4/3)-4-hydroxymethyl-4-cyclohexenylamine (6)[5] was carried out in 2-propanol in a sealed tube at 120 °C for 50 h and then the products were treated with acetic anhydride in pyridine. After having been roughly separated by chromatography, the products were treated with 70% aqueous acetic acid (50 °C, 1.5 h) and then acetylated. As expected, formation of four components was observed by TLC [silica gel, 2-butanone–toluene (1:2)]. Fractionation of the mixture by use of a silica gel column with a mixture of 2-butanone and toluene as an eluent afforded the protected pseudo-trisaccharides 7a ($[\alpha]_D^{22}$ +61 °, 13%), 7b ($[\alpha]_D^{22}$ +8 °, 14%), 8a ($[\alpha]_D^{22}$ +28 °, 21%), and 8b ($[\alpha]_D^{22}$ -6 °, 16%). The structures of 7a,b and 8a,b were tentatively assigned on the basis of ^{1}H NMR spectroscopy and optical rotation. Thus, the ^{1}H NMR spectra ($CDCl_3$, 90 MHz) of 7a and 7b revealed the signals for H-4' as triplets (J = 9.8 Hz) at δ 2.76 and 2.72, and those for H-2" as doublets (J = 5.1–5.3 Hz) at δ 5.94 and 5.80, respectively.[9] Whereas, the spectra of 8a and 8b indicated the signals for H-3' as triplets (J = 4.2 Hz) at δ 3.15 and 3.07, and those for H-2" as doublets (J = 4.7–5.0 Hz) at δ 5.97 and 6.12, respectively. Since penta-N,O-acetylvalienamine[10] possesses $[\alpha]_D$ +30.2 °, the diastereomer with higher positive rotation was considered to contain the unsaturated cyclitol portion whose absolute configuration was related to that of the natural compound.

The 7a and 7b were subjected to acetolysis [concd. sulfuric acid–acetic acid–acetic anhydride (1:70:30), room temperature, 2 h] to give 9a, $[\alpha]_D^{17}$ +93 °, and 9b, $[\alpha]_D^{17}$ +47 °, in quantitative yields, which showed one major (α-anomer) and one minor (β-anomer) spots at Rf 0.43 and 0.46, and Rf 0.39 and 0.42, respectively, on TLC [silica gel, EtOH–toluene (1:7)]. The ^{1}H NMR spectra ($CDCl_3$, 200 MHz) of 9a and 9b could be fully interpreted by a first-order method, being consistent with the assigned structures.[11] O-Deacetylation of 9a with methanolic sodium methoxide (room temperature, 2 h) gave a free pseudo-trisaccharide, $[\alpha]_D^{21}$ +127 ° (H_2O) [TLC (silica gel), Rf 0.45 in n-BuOH–pyridine–H_2O (12:8:5) and Rf 0.35 in n-BuOH–EtOH–H_2O (3:2:2)], which was identified with an authentic sample by comparison of the ^{1}H NMR spectra (D_2O, 400 MHz).[12]

References

1) E. Truscheint, W. Frommer, B. Junge, L. Müller, D. D. Schmidt, and W. Wingender, Angew. Chem. Int. Ed. Engl., 20, 744 (1981).
2) Very recently, amylostatin (XG) has been synthesized by Sakairi and Kuzuhara: Tetrahedron Lett., in press. The authors wish to thank Dr. Hiroyoshi Kuzuhara for sending reprint of his work prior to publication.
3) S. Ogawa, Y. Iwasawa, T. Toyokuni, and T. Suami, Chem. Lett., 1982, 1729.
4) H. Seto, N. Furihata, T. Otake, S. Namiki, K. Kangouri, H. Hara, K. Mizogami,

and S. Omura, presented at the 223rd Sci. Meet. Japan Antibiot. Res. Assoc., Tokyo, March 27, 1981; S. Namiki, K. Kangouri, T. Nakate, H. Hara, K. Sugita, and S. Omura, J. Antibiot., 35, 1234 (1982). Adiposin-1 and 2 were found to be identical with two of the amylase inhibitor, described by Otani et al.: M. Otani, T. Saito, S. Saito, J. Mizoguchi, and N. Muto, Japan Kokai 54-92,909, 1979.

5) S. Ogawa, T. Toyokuni, Y. Iwasawa, Y. Abe, and T. Suami, Chem. Lett., 1982, 279.

6) M. Mori, M. Haga, and S. Tejima, Pharm. Bull. Chem., 23, 1480 (1975).

7) Optical rotations were determined on a Jasco DIP-4 polarimeter, unless otherwise noted, in chloroform. ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) or a JEOL FX-200 (200 MHz) spectrometer in chloroform-d with reference to tetramethylsilane as an internal standard. TLC was performed on precoated silica gel 60 F-254 plates (Merck, Darmstadt; 0.25 mm thickness). The silica gel used for a column chromatography was Wakogel C-300 (Wako Pure Chemical Ind. Ltd.).

8) Under these reaction conditions, the epoxidation seems to proceed smoothly to give a sole product. A trace of a stereoisomer of the epoxide, formed by an epoxide group migration, was detected by TLC.

9) Observed signals due to H-4' of 7a and 7b were shown to be in accord with the corresponding signal of C-4 proton of methyl oligobiosaminide (δ 2.34, t, J = 10 Hz): S. Omoto, K. Iwamatsu, N. Nishizawa, and S. Inouye, J. Antibiot., 34, 1429 (1981).

10) Y. Kameda and S. Horii, J. Chem. Soc., Chem. Commun., 1972, 746.

11) ^{1}H NMR ($CDCl_3$, 200 MHz) for 9a: δ= 1.94–2.13 (27H, m), 2.15 (3H, s), and 2.21 (3H, s) (OAc), 2.81 (1H, t, J = 10 Hz, H-4'), 3.64 (1H, br d, J = 10 Hz, H-5'), 3.69 (1H, t, J = 5.6 Hz, H-1''), 3.97 (1H, dd, J = 10 and 8.8 Hz, H-4), 4.07 (1H, br d, J = 10 Hz, H-5), 4.16 (1H, dd, J = 12.4 and 4 Hz), 4.22 (1H, dd, J = 13.2 and 4 Hz), 4.33 (2H, d, J = 13.2 Hz), 4.46 (1H, dd, J = 12.4 and 2 Hz), and 4.61 (1H, d, J = 13.2 Hz) (CH_2OAc), 4.81 (1H, dd, J = 10.4 and 2 Hz, H-2'), 4.89 (1H, dd, J = 10 and 4 Hz, H-6''), 4.94 (1H, dd, J = 10 and 4 Hz, H-2), 5.18 (1H, t, J = 10 Hz, H-3'), 5.30 (1H, d, J = 4 Hz, H-1'), 5.47 (1H, dd, J = 10 and 8.8 Hz, H-3), 5.5–5.6 (2H, m, H-4'' and H-5''), 5.71 (a trace, d, J = 8.4 Hz, H-1,β), 5.94 (1H, d, J = 5.6 Hz, H-2''), and 6.21 (1H, d, J = 4 Hz, H-1,α). Although the spectrum of 9b is substantially very similar to that of 9a, there are some differences in chemical shifts and coupling constants of the following signals: δ = 2.76 (1H, t, J = 10.4 Hz, H-4''), 3.59 (1H, t, J = 4.8 Hz, H-1''), and 5.83 (1H, d, J = 4.8 Hz, H-2''). All signals were assigned on the basis of decoupling experiments as well as the spectral data of methyl oligobiosaminide.[9]

12) The authors express their sincere thanks to Dr. Sadafumi Omura (Taisho Pharmaceutical Co. Ltd., Ohmiya, Saitama) for providing the ^{1}H NMR spectrum of an authentic sample of adiposin-1.

(Received December 28, 1982)