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Synthesis of Pseudo-Disaccharide Derivative Having D-Manno Configuration, an Acarviosin Analogue

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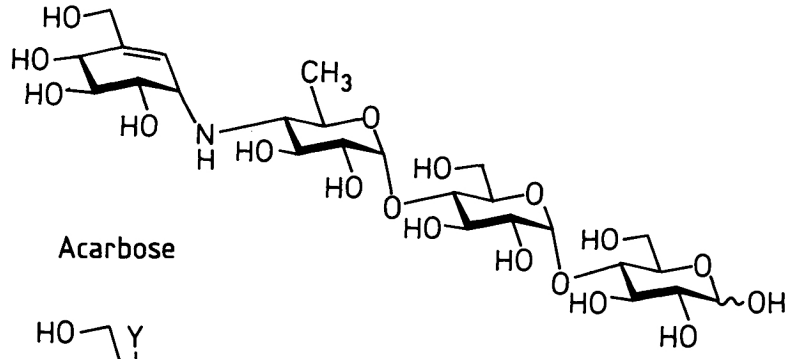
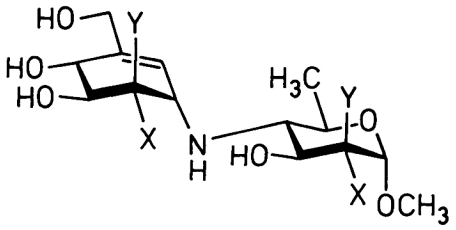
Acarviosin analogue, 4-deoxy-4-{[(1S)-(1,4/5,6)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexen-1-yl]amino}-D-mannopyranose, has been synthesized as the octaacetyl derivative by coupling of 1,6:3,4-dianhydro-2-O-tosyl-β-D-galactopyranose and the cyclohexenylamine derivative, followed by further transformation.

In recent years, much interest has been directed toward elucidation of enzyme-inhibitory mechanism of pseudo-oligosaccharidic α-glucosidase inhibitors.[1] Especially, acarbose,[2] a pseudo-tetrasaccharide α-glucosidase inhibitor, has extensively been studied in pharmacological and clinical aspects. Methanolysis of acarbose produced acarviosin[3] (1), a maltose-type pseudo-disaccharide, which was shown to be five times more potent as the inhibitor than acarbose and has been considered as the essential core structure concerning the inhibitory activity of acarbose and its homologues. Therefore, by analogy with the hypothesis of the inhibitory mechanism, a structurally related pseudo-disaccharide (2), the arrangement of substituents of which resembles that of O-α-D-mannopyranosyl-(1→4)-D-mannopyranose, would be expected to show an inhibitory activity against, for instance, α-mannosidase.

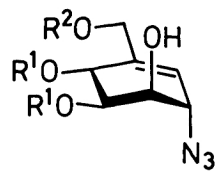
In continuation with the preceding paper,[4] we describe a convenient route to the octaacetyl derivative (13a) of a pseudo-disaccharide with an α-D-mannose type stereochemistry by coupling of a readily available tosylate[5] (8) of 1,6:3,4-dianhydro-β-D-galactopyranose and the protected, racemic trihydroxy(hydroxymethyl)-cyclohexenylamine (6a,b), followed by further transformation.



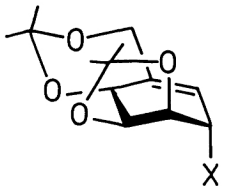
Acarbose



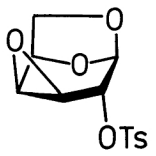
		X	Y
Acarviosin:	1	OH	H
	2	H	OH



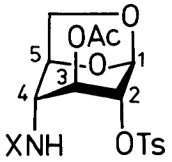
	R^1	R^2
3a,b	Ac	Bz
4a,b	H	H



5a,b X = N_3
6a,b X = NH_2
7a,b X = NHAc

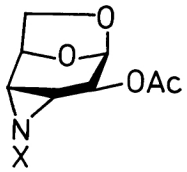


8

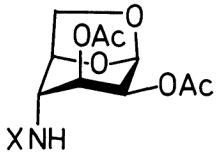


9a,b

10a

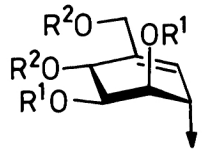


11a

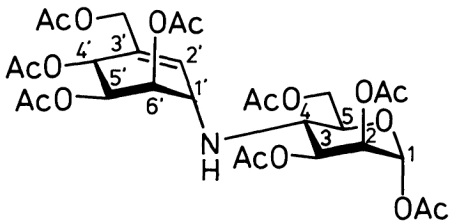


12a

X =



9–11 $R^1, R^1 : R^2, R^2$ = Ip
12 $R^1 = R^2$ = Ac



13a

For convenience, the formulas depict only one structure corresponding to the a series.

O-Deacetylation of DL-2,3-di-O-acetyl-(1,2/3,6)-6-azido-4-benzoyloxymethyl-4-cyclohexene-1,2,3-triol[6] (3a,b) with methanolic sodium methoxide gave the hydroxy compound (4a,b, ca. 100%). This compound was treated with an excess of 2,2-dimethoxypropane in N,N-dimethylformamide (DMF) in the presence of p-toluenesulfonic acid to give the di-O-isopropylidene derivative (5a,b), which was without purification reduced with hydrogen sulfide in aq pyridine to give the protected free base (6a,b, 66% over-all yield) characterized as the N,O-acetate (7a,b).

Coupling of a slight excess of 6a,b and 8 in a 1:1 mixture of 2-propanol and DMF (70 °C, 7 d) proceeded regioselectively to give, after acetylation, a diastereoisomeric mixture of the condensates, which was separated by chromatography on silica gel to afford 9a (20%), $[\alpha]_D^{25}$ -38° ($CHCl_3$), and 9b (19%), $[\alpha]_D^{25}$ -13° ($CHCl_3$). The ^{1}H-NMR spectra of 9a and 9b showed two singlets due to H-2 ($\delta \approx 4.2$) and H-3 ($\delta \approx 4.8$), indicating the presence of the 1,6-anhydroglucopyranose residue. Since it was difficult to discriminate the stereochemistry of 9a and 9b on the basis of optical rotations, they were finally assigned by the preparation of 9a, $[\alpha]_D^{20}$ -35° ($CHCl_3$), by condensing 8 and optically active 6a derived from 3a.[7]

A solution of 9a in methanol was stirred in the presence of Amberlite IRA-400 (OH^-) at room temperature to give a single product, the ^{1}H-NMR spectrum of which showed two epoxide protons as a triplet (δ 3.39, J = 3 Hz) and a doublet (δ 3.11, J = 3 Hz), ascribable to H-2 and H-3, respectively. Without purification, the epoxide 10a was treated with ethanolic potassium hydroxide[8] (70 °C, 20 h) and the product was acetylated to give the aziridine (11a, 83%), $[\alpha]_D^{18}$ -53° ($CHCl_3$). The structure was tentatively assigned by comparison of the ^{1}H-NMR spectrum with those of the related compounds.[9] Compound 11a was then treated with sodium acetate in acetic acid (90 °C, 15 h), and after treatment with aq acetic acid, the product was acetylated to give the hexaacetate (12a, 87%), $[\alpha]_D^{23}$ -56° ($CHCl_3$). Acetolysis of 12a with acetic acid-acetic anhydride-conc sulfuric acid (40:40:1) at room temperature afforded 85% yield of the pseudo-disaccharide octaacetate 13a $[\alpha]_D^{23}$ +25° ($CHCl_3$). The ^{1}H-NMR spectrum[10] (200 MHz) of 13a could be interpreted by first-order assignment, supporting the structure depicted.

References

1) E. Truscheit, W. Frommer, B. Junge, L. Müller, D. D. Schmidt, and W. Wingender, Angew. Chem., Int. Ed. Engl., 20, 744 (1981) and references cited therein.

2) D. D. Schmidt, W. Frommer, B. Junge, L. Müller, W. Wingender, E. Truscheit, and D. Schafer, Naturwissenschaften, 64, 535 (1977) and references cited therein.

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4) S. Ogawa and H. Sugizaki, Carbohydr. Res., in press.

5) L. L. Carlson, J. Org. Chem., 30, 3953 (1965).

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7) Compound 3a, $[\alpha]_D^{20}$ +46° ($CHCl_3$), was prepared from (1R)-3,4-di-O-acetyl-1,2-anhydro-(1,2,3/4)-5-benzoyloxymethyl-5-cyclohexene-1,2,3,4-tetrol: S. Ogawa and T. Takagaki, J. Org. Chem., 50, 2356 (1985).

8) M. Černý, I. Černý, and J. Pacák, Collect. Czech. Chem. Commun., 41, 2942 (1976).

9) S. Ogawa, K. Yasuda, and H. Sugizaki, unpublished results.

10) Partial ^{1}H-NMR data ($CDCl_3$, 200 MHz): δ 6.05 (1H, d, J = 1.6 Hz, H-1), 5.83 (1H, d, J = 2.7 Hz, H-2'), 5.52 (1H, d, J = 5.7 Hz, H-4'), 5.32 (1H, dd, J = 2.5 and 5.9 Hz, H-5'), 5.19 (1H, br dd, J = 1.6 and 3.2 Hz, H-2), 5.17 (1H, br dd, J = 3.2 and 10.3 Hz, H-3), 4.96 (1H, dd, J = 2.5 and 5.9 Hz, H-6'), 3.82 (1H, dq, J = 2, 4.8, and 10.3 Hz, H-5), 3.51 (1H, br t, J = 2.7 Hz, H-2'), 3.31 (1H, t, J = 10.3 Hz, H-4). The assignment of two coupled, broad signals due to H-2 and H-3 has further been confirmed by comparison with the data of the other diastereoisomer 13b: δ 5.18 (1H, dd, J = 2 and 3.2 Hz, H-2), 5.13 (1H, dd, J = 3.2 and 10.4 Hz, H-3).

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