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Total Synthesis of Trehalase Inhibitor Salbostatin

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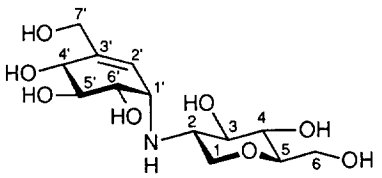
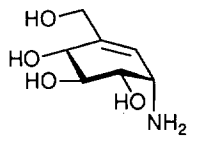
Abstract: Trehalase inhibitor salbostatin has been completely synthesized by coupling of 1,5:2,3-dianhydro-D-mannitol and di-*O*-isopropylidene-α-valienamine followed by deprotection.

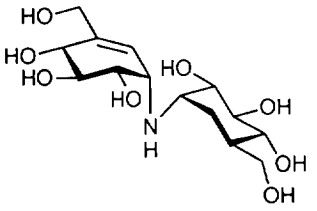
Very recently, new trehalase inhibitor salbostatin (**1**) was discovered[1] as a novel metabolite of *Streptomyces albus*, ATCC 21838, and the structure has been established[2] mainly on the basis of ^{1}H NMR spectroscopic data. Salbostatin inhibits trehalase from porcine kidneys with an inhibition constant $Ki = 1.8 \times 10^{-7}$ M, and possesses a very unique pseudo-disaccharide structure composed of 2-amino-1,5-anhydro-2-deoxy-D-glucitol to which an unsaturated 5a-carba-sugar, α-valienamine (**2**) residue, is attached by way of an imino bridge. Similar pseudo-disaccharidic glycosidase inhibitors containing **2**, validoxylamine A[3] (**3**) and methyl α-acarviosin[4] (**4**), a core component of acarbose, have been known so far. The former is a potent trehalase inhibitor and its dihydro derivative[3] more likely mimicking substrate α,α'-trehalose-structure exhibits also high inhibitory activity.



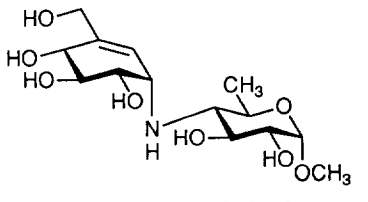
Salbostatin: **1**



α-Valienamine: **2**



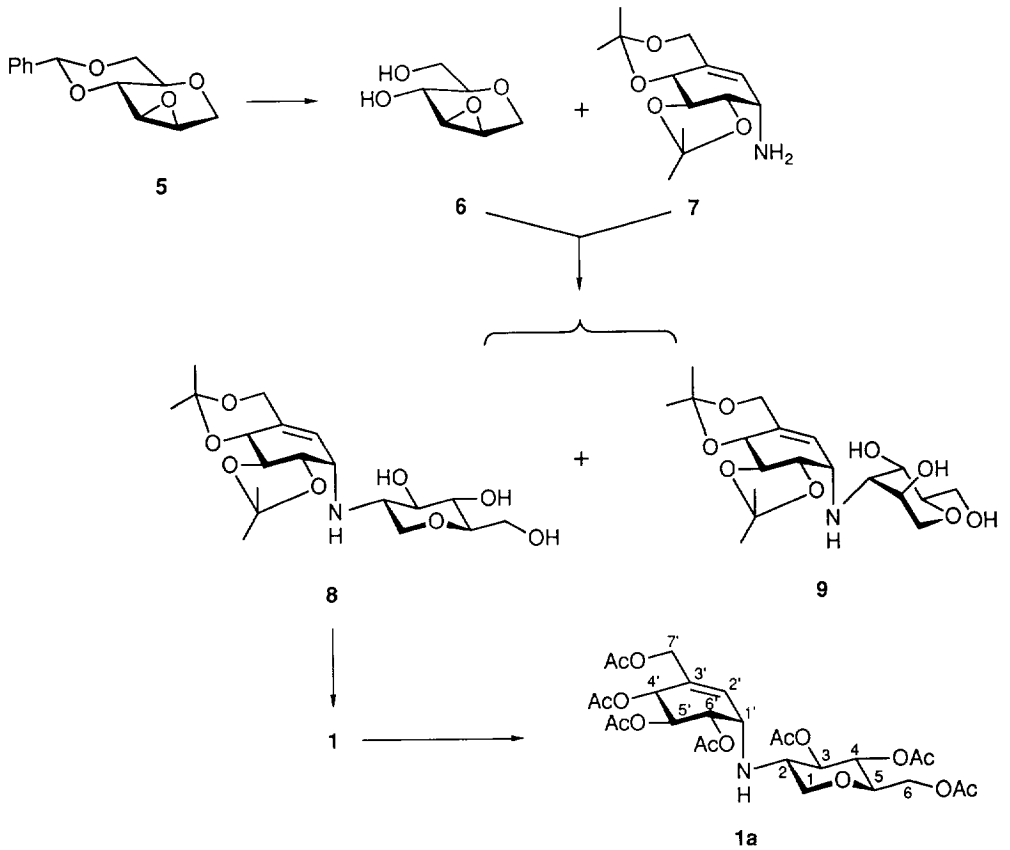
Validoxylamine A: **3**



Methyl α-acarviosin: **4**

We have been studying a structure-inhibitory activity relationship of this type of inhibitors[5] and, especially, our interests now have been focused on trehalase inhibitors such as **3** and trehazolin[3,6]. In this paper, convenient total synthesis of salbostatin has been attempted in order both to confirm the structure proposed and to elaborate a general method for the preparation of salbostatin analogues. The method involves coupling of an anhydro sugar between versatile carba-sugar donor 2,3:4,6-di-*O*-isopropylidene-α-valienamine[7] (**7**).

As anhydro sugar acceptor, we chose the unprotected 1,5:2,3-dianhydro-D-mannitol (**6**), which was readily derived (95%) by hydrogenolysis (10% Pd/C) of the known corresponding 4,6-*O*-benzylidene derivative[8] (**5**). Removal of the benzylidene group of **5** seemed to enhance reactivity of the 2,3-epoxide and, hopefully, to improve desired regioselectivity of its cleavage by the bulky amine, owing to relief from the structural rigidity. Coupling of a slight excess of **6** (1.3 molar equivalent) and **7** was thus carried out conventionally[9] in 2-propanol in a sealed tube for 4 days at 120°C. TLC showed as had been expected a formation of two coupling products. Chromatography of the mixture on a silica gel column with butanone–toluene (3:1, v/v) as an eluent afforded the diequatorial-opening product **8** (58%) and the diaxial-opening product **9**



(25%), the structures of which were tentatively assigned as depicted in Scheme on the basis of the ^{1}H NMR spectra. The spectrum (270 MHz, $CDCl_3$) of **8** was well resolved, being amenable to a first-order analysis. Thus, the coupled signals due to 1,1-H and 2-H appeared as a doublet of doublets (δ 4.08, J = 4.8 and 11.0 Hz), a triplet (δ 3.19, J = 11.0 and 11.0 Hz), and a doublet of doublets of doublets (δ 2.80, J = 4.8, 9.2, and 11.0 Hz), respectively, supporting an 1,5-anhydro-glucitol structure of the sugar moiety. Preferential attack of the amine at C-2 may be due to the C-1 position being unsubstituted, and might be further rationalized by assuming that 6-hydroxyl group of **6** involves in stabilizing the favorable transition state that leads to diequatorial product.[7,10] *O*-Deisopropylidenation of **8** was effected in aqueous 70% acetic acid for 1 h at 60°C to give, after purification by a column of Dowex 50W-X2 (H^+) resin with *N* aqueous ammonia, salbostatin **1** in 97% yield. The ^{13}C and ^{1}H NMR spectra[11] were in good accordance with those of an authentic sample.[2] The synthetic **1** was further characterized as the hepta-*O*-acetyl derivative **1a**, the ^{1}H NMR spectrum[12] of which was shown to be superimposable on that reported.[2,13]

The present synthesis constitutes the first total synthesis of the inhibitor salbostatin **1**, thereby confirming the structure proposed, and also provides one of the convenient methods for preparation of its analogues useful for elucidation of the structure-activity relationship.

References and Notes

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11. Data for salbostatin (**1**): $[\alpha]_D^{25}$ +130° (c = 1.2, H_2O) [ref.[2] $[\alpha]_D^{20}$ +115° (c = 1, H_2O)], ^{1}H NMR (270 MHz, [D_6]DMSO–D_2O, 4:1, v/v) δ 5.81 (d, $J_{1',2'}$ = 3.3 Hz, 1 H, 2'-H), 4.05 and 3.99 (2 d, $J_{7'gem}$ = 14.4 Hz, each 1 H, 7',7'-H), 3.91 (dd, $J_{1eq,2}$ = 4.6, J_{1gem} = 11.2 Hz, 1 H, 1eq-H), 3.79 (d, $J_{4',5'}$ = 5.5 Hz, 1 H, 4'-H), 3.69 (d, $J_{5,6a}$ = ~0, J_{6gem} = 12.1 Hz, 1 H, 6a-H), 3.48 (dd,

$J_{4',5'}$ = 5.5, $J_{5',6'}$ = 8.8 Hz, 1 H, 5'-H), 3.45 (dd, $J_{5,6b}$ = 5.9, J_{6gem} = 12.1 Hz, 1 H, 6b-H), 3.41 (dd, $J_{1',6'}$ = 4.8, $J_{5',6'}$ = 8.8 Hz, 1 H, 6'-H), 3.23 (br dd, $J_{1',2'}$ = 3.3, $J_{1',6'}$ = 4.8 Hz, 1 H, 1'-H), 3.16–3.11 (m, 3 H, 3,4,5-H), 3.02 (dd, $J_{1ax,2}$ = 10.8, J_{1gem} 11.2 Hz, 1 H, 1ax-H), 2.66 (ddd, $J_{1ax,2}$ = 10.8, $J_{1eq,2}$ = 4.6, $J_{2,3}$ = 10.3 Hz, 1 H, 2-H). ^{13}C-NMR (67.5 MHz, [D$_6$]DMSO) δ 140.38, 120.17, 81.67, 76.60, 72.90, 70.90, 70.47, 70.15, 68.97, 61.37, 61.25, 57.54, 52.76

12. Data for the hepta-*O*-acetyl derivative **1a**: $[\alpha]_D^{24}$ +66.6° (*c* = 0.75, $CHCl_3$), ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.86 (br d, $J_{1',2'}$ = 4.8 Hz, 1 H, 2'-H), 5.53 (d, $J_{4',5'}$ = 6.6 Hz, 1 H, 4'-H), 5.48 (dd, $J_{4',5'}$ = 6.6, $J_{5',6'}$ = 9.7 Hz, 1 H, 5'-H), 4.97 (dd, $J_{1',6'}$ =4.0, $J_{5',6'}$ = 9.7 Hz, 1 H, 6'-H), 4.95 (dd, $J_{3,4}$ = 9.3, $J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 4.87 (dd, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, 1 H, 3-H), 4.64 and 4.36 (2 d, $J_{7'gem}$ = 13.2 Hz, each 1 H, 7',7'-H), 4.21 (dd, $J_{5,6a}$ = 4.8, J_{6gem} = 12.5 Hz, 1 H, 6a-H), 4.09 (dd, $J_{5,6b}$ = 2.2, J_{6gem} = 12.5 Hz, 1 H, 6b-H), 4.08 (dd, $J_{1eq,2}$ = 4.8, J_{1gem} = 11.7 Hz, 1 H, 1eq-H), 3.65 (br dd, $J_{1',2'}$ = 4.8, $J_{1',6'}$ = 4.0 Hz, 1 H, 1'-H), 3.54 (ddd, $J_{4,5}$ = 9.3, $J_{5,6a}$ = 4.8, $J_{5,6b}$ = 2.2 Hz, 5-H), 3.14 (dd, $J_{1ax,2}$ = 11.0, J_{1gem} = 11.7 Hz, 1 H, 1ax-H), 2.88 (ddd, $J_{1ax,2}$ = 11.0, $J_{1eq,2}$ = 4.8, $J_{2,3}$ = 9.3 Hz, 1 H, 2-H), 2.10, 2.09, 2.06, 2.04, 2.03, and 2.02 (6 s, 3, 6, 3, 3, 3, and 3 H, 7 Ac).

13. We express our sincere thanks to Dr. L. Vértesy (Hoechst AG, Frankfurt am Main, FRG) for identification of the synthetic **1** and **1a** with a natural compound and its derivative by comparison of their ^{1}NMR spectra.

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