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INTRAMOLECULAR AMINO DELIVERY REACTIONS FOR THE SYNTHESIS OF VALIENAMINE AND ANALOGUES

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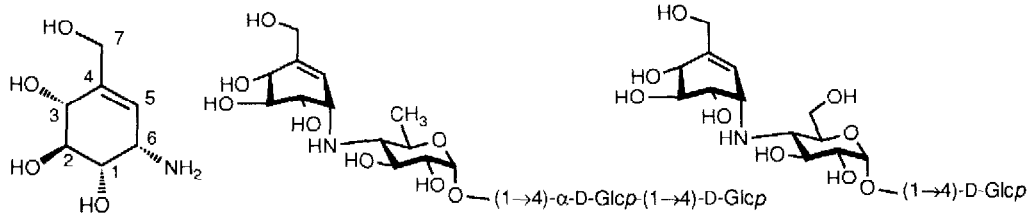
Abstract: *Iodocyclization and [3,3] sigmatropic rearrangement reactions of* N*-substituted carbonimidothioates are used to prepare valienamine (1), 7-*nor*-valienamine (8), and the valienamine-based pseudo-disaccharide 12.*

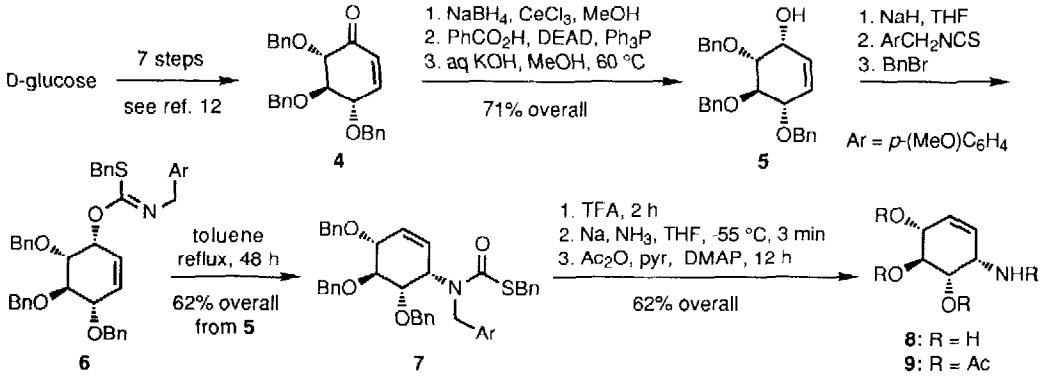
The fermentation-derived aminocyclitol valienamine (**1**)[1] and several close analogues[2] exhibit α-glucosidase inhibitory activity by virtue of a protonated amino group aptly positioned where a protonated interpyranosidic oxygen might bind in the enzyme active site.[3] Valienamine-based *pseudo*-oligosaccharides such as acarbose (**2**),[4] adiposin-1 (**3**),[5] and trestatin A[6] show enhanced α-glycosidase inhibition, presumably because two or more *pseudo*-sugar units bind more strongly than one.[4] Even simple alkyl substitution (e. g. 2-phenethyl or β-hydroxyphenethyl) on the nitrogen of **1** enhances inhibition of porcine maltase and sucrase.[7] Despite extensive investigations into the synthesis of *N*-substituted derivatives of **1**, there is no generally efficient coupling method for forming either C-N bond. Halide displacements[8] and reductive aminations[9] give poor yields, and epoxide aminolysis methods[10] suffer from regioselectivity problems. Our earlier work with *O*-allyl-carbonimidothioate rearrangements and iodocyclizations[11] in simple models suggested that *intramolecular* formation of the cyclitol carbon-nitrogen bond might be possible, even with bulky and/or functionalized *N*-substituents. We undertook the synthesis of **1** and some analogues to test this notion.



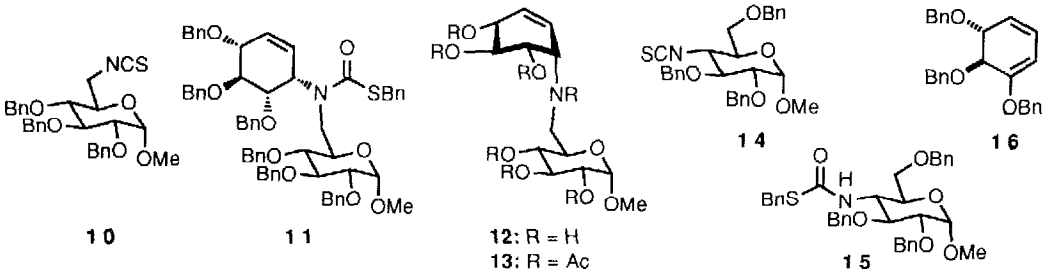
1: valienamine **2**: acarbose **3**: adiposin-1

A route to *N*-substituted-7-*nor*-valienamine analogues (valienamine numbering used throughout) was developed based on [3,3]-sigmatropic rearrangements of *N*-substituted carbonimidothioates derived from the allylic alcohol **5** (mp 50-51 °C), which was prepared from D-glucose[12] as shown below. Condensation of the sodium salt of **5** with *p*-methoxybenzylisothiocyanate, followed by quenching with benzyl bromide, led to the carbonimidothioate **6**, which underwent rearrangement in refluxing toluene to give the thiocarbamate **7**. The analogous *N*-benzyl- and *N*-(3,4-dimethoxybenzyl)-carbonimidothioates also rearranged smoothly, hence

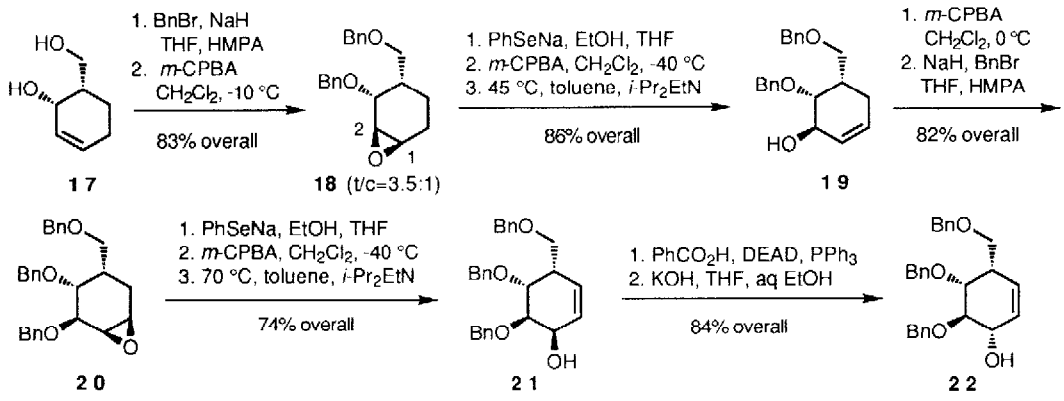
other simple *N*-alkyl substituents should probably also survive the rearrangement. Removal of the *N*-(*p*-methoxybenzyl) group, followed by exhaustive debenzylation, provided 7-*nor*-valienamine **8**, isolated as its peracetate **9**.[13] To our knowledge this represents the first synthesis of this potentially useful aminocyclitol.



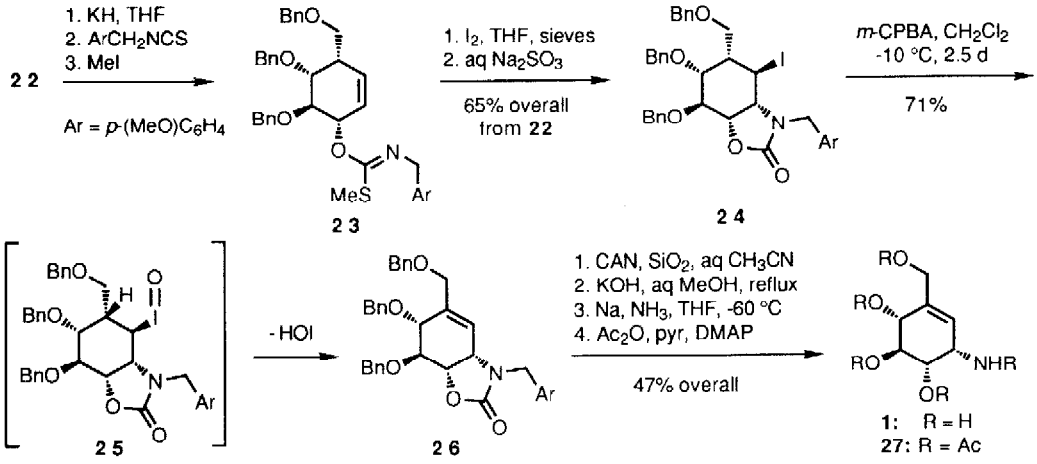
An analogous sequence using the glucose-derived isothiocyanate **10**[14] led to a carbonimidothioate that rearranged to **11** (52% overall). Exhaustive debenzylation gave the *pseudo*-α-D-Glc*p*(1→6)-D-Glc*p* disaccharide **12**, isolated and characterized as its peracetate **13** (80% overall, two amide rotamers, 5:1).[13] The *pseudo*-disaccharide **12** structurally resembles the linkage cleaved by a glycogen (1→6)-debranching enzyme.[15] A rearrangement was attempted with the carbonimidothioate derived from the 4-isothiocyanatoglucopyranoside **14**,[14] but only fragmentation leading to **15** and **16** was observed. No improvement was realized under conditions of mercury or palladium[16] promotion, or 13 Kbar pressure, signifying that **14** may represent the steric limit for *N*-substituents in this rearrangement.



A complementary route based on the carbonimidothioate iodocyclization reaction was developed for the synthesis of valienamine (**1**) and *N*-substituted analogues. The requisite allylic alcohol **22** was prepared from resolved diol **17**[17] by the efficient sequence shown below. The hydroxyls of **17** were *O*-benzylated, and the double bond epoxidized with 3.5 : 1 selectivity.[18] The major epoxide **18** was isomerized to allylic alcohol **19** by the Sharpless-Reich protocol,[19] attack by PhSeNa occurring virtually exclusively at C-1 because of steric hindrance to attack at C-2. Hydroxyl-directed epoxidation followed by *O*-benzylation gave the epoxide **20**, which was rearranged to the allylic alcohol **21** by another application of the Sharpless-Reich[19] procedure. Here the observed 5 : 1 selectivity may be attributed to a more favorable trans-diaxial cyclohexane epoxide-opening conformation for attack at C-6. Inversion of the allylic hydroxyl was accomplished by a Mitsunobu sequence, giving the desired allylic alcohol substrate **22** in about 23% overall yield from **17**.



Condensation of the potassium salt of **22** with *p*-methoxybenzylisothiocyanate, followed by iodomethane quench, led to the carbonimidothioate **23**, iodocyclization of which gave after aqueous sodium sulfite quench the iodo oxazolidinone **24**. Although not yet investigated, other simple alkyl *N*-substituents should tolerate the iodocyclization as well. Oxidation of **24** to the corresponding iodoso compound **25** resulted in spontaneous *syn* elimination[20] of HOI, with formation of the unsaturated oxazolidinone **26**. Finally, oxidative removal of the *N*-*p*-methoxybenzyl group, basic hydrolysis of the oxazolidinone, and debenzylation gave valienamine (**1**), isolated and characterized as its known peracetate (+)-**27**.[21]



In summary, intramolecular formation of the C(6)-N bond of valienamine and 7-*nor*-valienamine by an iodocyclization and [3,3]-sigmatropic rearrangement sequence, respectively, has been demonstrated. In the rearrangement, a primary but not secondary carbohydrate *N*-substituent is tolerated. Further extension of the iodocyclization sequence to complex *N*-substituents such as those represented by the isothiocyanates **10** and **14** is under investigation.

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13. Compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (ddd, *J* = 10.0, 4.9, 1.7, H-5), 5.72 (ddd, *J* = 10.0, 2.6, 0.7, H-4), 5.62 (br d, *J* = 9.0, N-H), 5.37 (dd, *J* = 10.2, 5.9, H-2), 5.29 (dddd, *J* = 5.9, 2.6, 1.7, 0.7, H-3), 5.06 (dd, *J* = 10.2, 4.8, H-1), 4.99 (ddt, *J* = 9.2, 4.7, 0.7, H-6), 2.01, 2.02, 2.06, 2.07 (s, 4 $COCH_3$'s); IR (thin film) 3390, 3300, 3060, 1760, 1679, 1666, 1540 cm^{-1}; $[\alpha]_D$ -7.1° (25 °C, c=0.15, $CHCl_3$). Compound **13**: ^{1}H NMR (major rotamer, $CDCl_3$, 400 MHz) δ 5.89 (d, 1 H, *J* = 9.5), 5.77 (d, 1 H, *J* = 9.7), 5.67 (br s, 1 H), 5.37 - 5.50 (m, 3 H), 5.22 - 5.28 (m, 1 H), 4.95 (br s, 1 H), 4.80 - 4.88 (m, 2 H), 3.93 (t, 1 H, *J* = 9.1), 3.62 (dd, 1 H, *J* = 9, 14), 3.38 - 3.45 (m, 1 H), 3.37 (s, 3 H), 2.22, 2.09, 2.08, 2.05, 2.03, 2.02, 1.98 (s, 7 X 3 H); IR (thin film) 1751, 1655 cm^{-1}; $[\alpha]_D$ +108.1° (25 °C, c=0.16, $CHCl_3$); EI-MS *m/z* 615 (M+), 556 [(M - OAc)+]. Exact mass calcd for [(M - OAc)+], $C_{25}H_{34}NO_{13}$: 556.2030. Found: 556.2034.
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18. The minor epoxide was independently converted to **19** (58% overall): (1) *t*-$BuMe_2Si$-OTf, 2,6-lutidine, -30 °C (attack by TfO^- at C-1); (2) DBU, toluene, 45 °C; (3) *n*-Bu_4NF, THF; (4) $PhCO_2H$, DEAD, PPh_3; (5) KOH, aq EtOH, THF.
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