Properties and Production of Valienamine and Its Related Analogues

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I. Introduction

Valienamine, [(1*S*,2*S*,3*S*,4*R*)-1-amino-5-(hydroxymethyl)cyclohex-5-ene-2,3,4-triol], was first isolated from the microbial degradation of validoxylamine A with *Pseudomonas denitrificans*.[1,2] Later, it was produced from the degradation of validoxylamine A with *Flavobacterium saccharophilum*[3−5] or from the *N*-bromosuccinimide (NBS) cleavage of validoxylamine A or its derivatives.[6,7] Its related pseudo-aminosugars include valiolamine [(1*S*)-(1(OH),2,4,5/1,3)-5-amino-1-hydroxymethyl-1,2,3,4-cyclohexanetetrol],[8−12] validamine [(1*S*)-(1,2,4/3,5)-1-amino-5-hydroxymethyl-2,3,4-cyclohexanetriol],[13,14] hydroxyvalidamine [1-amino-5-hydroxymethyl-2,3,4,6-cyclohexanetetrol],[14] and epi-valiolamine [5-amino-1-hydroxymethyl-1,2,3,4-cyclohexanetetrol].[9,10]

The absolute configurations of valienamine and its related pseudo-sugars are similar to that of α-D-glucose. Thus, they demonstrate strong glucosidase inhibitory activity.[8,15−17] There has been increasing interest in the chemistry and biochemistry of glycosidase inhibitors because of their potential use as chemotherapeutic agents. Glycosidases are enzymes for the cleavage of glycosidic bonds and are responsible for glycoprotein processing on the surface of the cell wall and for carbohydrate digestion in animals. Inhibition of these enzymes has significant implications for both antiviral and antidiabetic chemotherapy.[18] Plasma levels of D-glucose and insulin are usually high in diabetics, especially after food ingestion. Limiting intestinal digestion of dietary carbohydrates by inhibition of intestinal α-glucosidases has been suggested as a possible means of controlling diabetes mellitus and obesity. Thus, α-D-glucosidase inhibitors are thought to be valuable aids in the treatment of diabetes. They act by delaying the absorption of carbohydrates, thereby inhibiting postprandial hyperglycemia and hyperinsulinemia. Furthermore, several studies have confirmed the value of the inhibitors of the processing enzyme glucosidase I in the treatment of cancer[19,20] and in inhibiting the human immunodeficiency virus (HIV) replication-etiologic agent for acquired immune deficiency syndrome (AIDS) and AIDS-related complex.[21] It has also been demonstrated that inhibition of the glycoprotein-processing enzyme mannosidase I may provide leads for the treatment of AIDS.[22] In the pseudo-aminosugars, valienamine also showed antibiotic activity against *Bacillus* species.[15]

The methods for the production of valienamine and its related pseudo-sugars can be divided mainly into four kinds. First, valienamine and validamine were produced from the degradation of validoxylamine A or validamycin A with microbes, such as *P. denitri-*

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ficans,[1,2] *F. saccharophilum*,[3−5] or from the NBS cleavage of validoxylamine A or its derivatives.[6,7] Second, valienamine, valiolamine, validamine, and hydroxyvalidamine were isolated from the fermentation broth of *Streptomyces hygroscopicus* ssp. *limoneus*.[8] Third, validamine and hydroxyvalidamine were prepared by hydrogenolysis of validamycin A and validamycin B, respectively. Finally, valienamine and its related pseudo-sugars could be chemically synthesized from L-quebrachitol, (−)-quinic acid, D-glucose derivatives, and other substrates.[23−70]

Valienamine has been found to be a key component for biological activities in pseudo-aminosugars and pseudo-oligosaccharides such as validamycins,[1,2,8,14,71−80] acarbose,[81] amylostatins,[82] adiposins,[83] acarviosin,[84] and trestatins.[85] These pseudo-oligosaccharides exhibit stronger enzyme inhibitory activities than valienamine itself. Valienamine and its related pseudo-sugars could also synthesize their *N*-substituted branch-chain derivatives,[9,80,88−91] such as acarbose, acarviosin, voglibose {1,*N*-[2-hydroxy-1-(hydroxymethyl)ethyl]valiolamine, AO128, Basen}, and so on, some of which have very strong enzyme inhibitory activity for different glucoside hydrolases.

Therefore, valienamine and its related pseudo-aminosugars suppress blood-sugar elevation and are useful in treating symptoms of hyperglycemia and various disorders caused by hyperglycemia, such as obesity, adiposity, hyperlipemia (arteriosclerosis), diabetes, and prediabetes, as well as diseases attributable to sugar metabolism by microorganisms in the oral cavity, such as prophylaxis of dental caries. They also have value as inhibitors of the processing enzyme glucosidase I in the treatment of cancer and as inhibitors of the HIV replication-etiologic agent for AIDS and AIDS-related complex. They are also very important chemical intermediates in the synthesis of other strong α-glucosidase inhibitors, such as acarbose, adiposins, acarviosin, trestatins, voglibose, and so on.

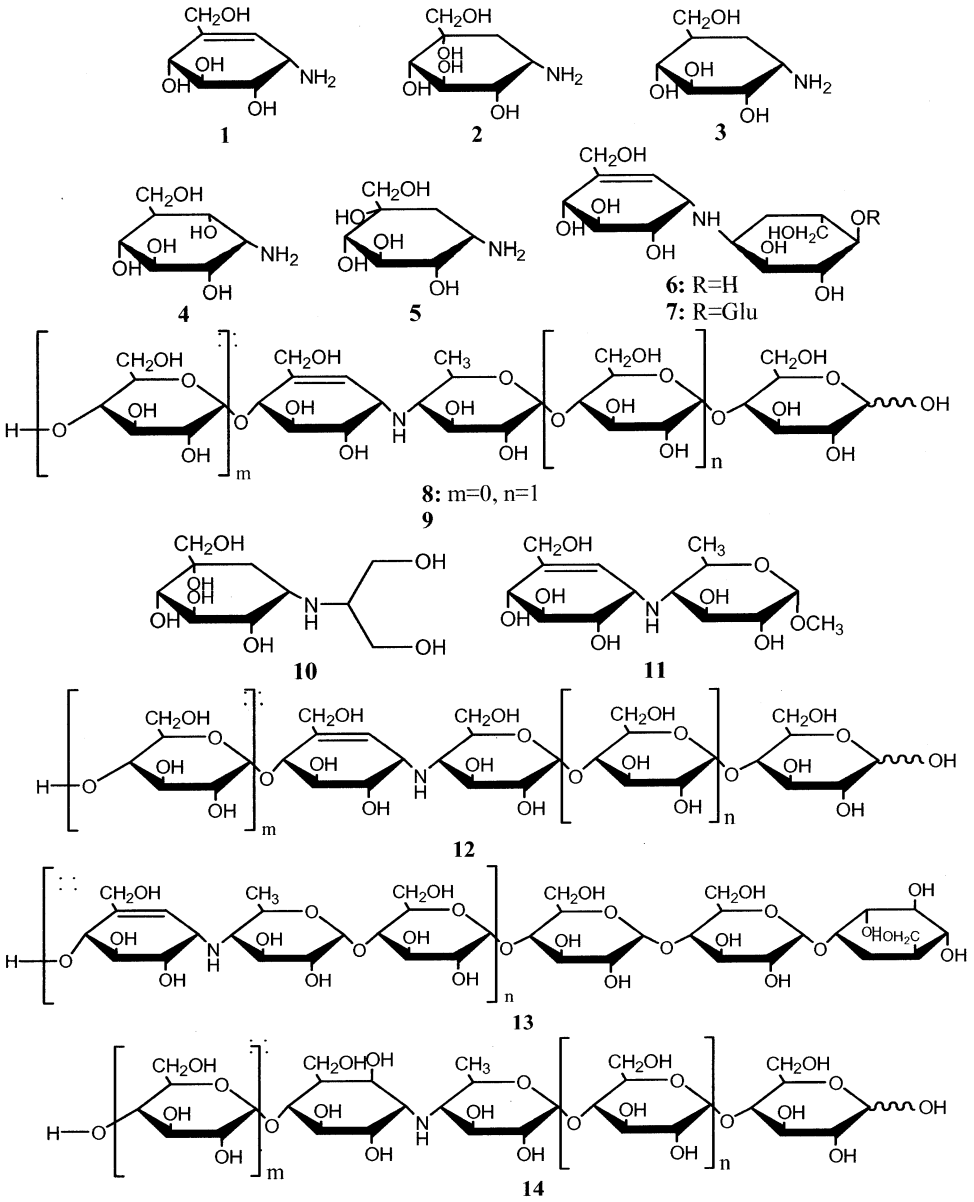


Figure 1. Chemical structures of various glucosidase inhibitors.

II. Chemical Structures of Various Pseudo-aminosugar Glucosidase Inhibitors

The structures of valienamine (**1**), valiolamine (**2**), validamine (**3**), hydroxyvalidamine (**4**), epi-valiolamine (**5**), validoxylamine A (**6**), validamycin A (**7**), acarbose (**8**), amylostatins (**9**), voglibose (AO128, **10**), acarviosin (**11**), adiposins (**12**), trestatins (**13**), and oligostatins (**14**) are shown in Figure 1.

III. Properties of Valienamine and Its Related Pseudo-aminosugars

A. Physicochemical Properties[1,9,10,14]

Valienamine has the molecular formula $C_7H_{15}NO_4$ and contains one primary $-NH_2$ (Van Slyke), one C=C, one $-CH_2OH$, and three secondary $-OH$ groups: monohydrochloride ($C_7H_{13}NO_4 \cdot HCl$), $[\alpha]^{23}_D$ +68.6° (1N-HCl); pentaacetate, mp 95 °C, $C_{17}H_{23}NO_9$, $[\alpha]^{23}_D$ +30.2° ($CHCl_3$), pK_a' 8.4; positive to ninhydrin and Lemieux tests, negative to anthrone and Fehling tests.

Validamine has the molecular formula $C_7H_{15}NO_4$ and contains one primary $-NH_2$ (Van Slyke), one $-CH_2OH$, and three secondary $-OH$ groups: monohydrochloride ($C_7H_{15}NO_4 \cdot HCl$), mp 229−232 °C dec, $[\alpha]^{23}_D$ +57.4° (1N-HCl), $[\alpha]^{21}_D$ +60.6° (H_2O), pK_a' 8.2; positive to ninhydrin and Lemieux tests, negative to anthrone and Fehling tests.

Hydroxyvalidamine has the molecular formula $C_7H_{15}NO_5$ and contains one primary $-NH_2$ (Van Slyke), one $-CH_2OH$, and four secondary $-OH$ groups: crystal, mp 164−165 °C, $[\alpha]_D$ +80.7° (H_2O), pK_a' 7.0; positive to ninhydrin and Lemieux tests, negative to anthrone and Fehling tests.

The physicochemical properties of valiolamine and epi-valiolamine are described in Table 1.

B. Enzyme Inhibitory Activities[8,15−17]

The inhibitory activities (IC_{50}, the molar concentration required to give 50% inhibition) against D-glucose hydrolases of valienamine were examined, and the results appear in Table 2.

Table 1. Physicochemical Properties of Valiolamine and Epi-valiolamine

	valiolamine	epi-valiolamine
appearance	both hygroscopic, white powder	
element analysis	Calcd for $C_7H_{15}NO_5 \cdot H_2O$: C, 39.80; H, 8.11; N, 6.63. Found: C, 39.35; H, 7.82; N, 6.59.	Calcd for $C_7H_{15}NO_5 \cdot H_2O$: C, 39.80; H, 8.11; N, 6.63. Found: C, 39.55; H, 8.32; N, 6.50.
specific rotation	$[\alpha]^{20}_D$ +18.8° (*c* 1, H_2O)	$[\alpha]^{20}_D$ +18.2° (*c* 1, H_2O)
UV absorption spectrum	no absorption maximum[a]	
IR absorption spectrum[b]	3340, 2920, 1575, 1500−1300, 1090, 1045, 910, and 815 cm^{-1}	3340, 2920, 1570, 1500−1300, and 1045 cm^{-1}
^1H NMR[c]	δ 1.65 (1H, dd, J = 3.8, 15.2), 1.90 (1H, dd, J = 2.9, 15.2), 3.33 (1H, m), 3.40 (1H, d, J = 9.5), 3.48 (2H), 3.56 (1H, dd, J = 3.9, 9.5), 3.83 (1H, t, J = 9.5)	δ 1.72 (1H, dd, J = 4.6, 14.3), 1.96 (1H, dd, J = 6.6, 14.3), 3.42 (1H, m), 3.58 (1H, d, J = 6.6), 3.60 (2H, d, J = 3.1), 3.76 (1H, dd, J = 4.0, 6.6), 4.00 (1H, t, J = 6.6)
^{13}C NMR[d]	δ 35.06 (t), 52.94 (d), 68.24 (t), 73.88 (d), 76.30 (d), 76.47 (d), 78.71 (s)	δ 37.16 (t), 48.79 (d), 67.93 (t), 74.27 (d), 75.44 (d), 77.03 (d), 77.85 (s)
solubility	both are soluble in water, dimethyl sulfoxide, and methanol both are sparingly soluble or insoluble in ethanol, ethyl acetate, chloroform, and acetone	
color reactions	both are positive to ninhydrin reaction and Greig−Leaback reagent and negative to Naphthoresorcinol−sulfuric acid	

[a] For both aminosugars, the aqueous solution does not exhibit any characteristic absorption maximum in the region 200−360 nm except end absorption. [b] The IR absorption spectrum was measured by the KBr method. The wavenumbers of the main absorption peaks are given. [c] The ^1H NMR spectrum was measured in D_2O at 100 MHz. The chemical shift δ values and coupling constants J (hertz) are given. [d] The ^{13}C NMR spectrum was measured in D_2O at 100 MHz under decoupling conditions. The chemical shift δ values, as well as the splitting patterns as measured under the off-resonance conditions, are given.

Table 2. Inhibition Effects of Valienamine on Various Glucoside Hydrolases

enzyme (origin)	substrate	IC_{50} (M)
α-glucosidase (yeast)	*p*-nitrophenyl-α-D-glucoside	1.7×10^{-4}
α- glucosidase (yeast)	maltose	1.8×10^{-5}
β- glucosidase (almond)	*p*-nitrophenyl-α-D-glucoside	2.2×10^{-3}
β- glucosidase (almond)	cellobiose	8.8×10^{-3}
sucrase (yeast)	sucrose	1.8×10^{-3}
sucrase (porcine)	sucrose	5.3×10^{-5}
α-glucoamylase (*Rhizopus* sp.)	*p*-nitrophenyl-α-D-glucoside	3.5×10^{-4}
α-glucoamylase (*Rhizopus* sp.)	starch	6.8×10^{-3}
α-amylase (porcine)	starch	none[a]
β-amylase (sweet potato)	starch	1.8×10^{-2}
β-amylase (barley)	starch	1.7×10^{-2}
maltase (porcine)	maltose	3.4×10^{-4}
isomaltase (porcine)	isomaltose	1.0×10^{-3}

[a] No inhibition was observed at a concentration of 2×10^{-2} M.

Table 3. Inhibitory Effects of Valienamine and Its Related Aminocyclitols against Various Glucose Hydrolases

		IC_{50} (M)[a]			
enzyme (origin)	substrate	valienamine	valiolamine	validamine	hydroxyvalidamine
α-glucosidase (yeast)	maltose	1.8×10^{-5}	1.9×10^{-4}	5.8×10^{-4}	3.6×10^{-4}
β-glucosidase (almond)	cellobiose	8.8×10^{-3}	8.1×10^{-3}	1.5×10^{-3}	7.4×10^{-3}
sucrase (yeast)	sucrose	1.8×10^{-3}	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$
sucrase (porcine)	sucrose	5.3×10^{-5}	4.9×10^{-8}	7.5×10^{-6}	4.2×10^{-4}
glucoamylase (*Rhizopus* sp.)	starch	6.8×10^{-3}	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$
α-amylase (porcine)	starch	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$
β-amylase (sweet potato)	starch	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$	$>1.0 \times 10^{-2}$
maltase (porcine)	maltose	3.4×10^{-4}	2.2×10^{-6}	1.1×10^{-4}	8.3×10^{-3}
isomaltase (porcine)	isomaltose	1.0×10^{-3}	2.7×10^{-6}	1.3×10^{-4}	$>1.0 \times 10^{-2}$

[a] Molar concentration required to give 50% inhibition.

Kameda et al. studied the different inhibitory activities against D-glucose hydrolases of valienamine, valiolamine, validamine, and hydroxyvalidamine. The results are shown in Table 3. Valienamine, with IC_{50} values in the range of 10^{-3}−10^{-5} mol/L against porcine intestinal maltase, sucrase, and isomaltase, was more active than hydroxyvalidamine, less active than valiolamine, and similar to validamine.

Table 4 shows the kinetic constants (apparent K_m and V_{max} values) for activities of carbohydrases in rat small intestine brush border membrane.

To characterize the mechanism of inhibition by valienamine, validamine, and valiolamine, Takeuchi et al. studied their inhibition kinetics. Obtained from the calculation of the Lineweaver−Burk plots, the K_i values of valienamine for inhibition of the activities of sucrase, maltase, glucoamylase, isomaltase, and trehalase are shown in Table 5. The apparent K_i

Table 4. Kinetic Constants[a] of Carbohydrase Activities in Rat Intestinal Brush Border Membranes

enzyme	substrate	K_m (M)	V_{max}[b]
sucrase	sucrose	3.4×10^{-2}	85.6
maltase	maltose	2.2×10^{-3}	237
glucoamylase	soluble starch	7.7×10^{-3} [c]	119[d]
isomaltase	isomaltose	5.7×10^{-3}	15.8
trehalase	trehalose	1.1×10^{-2}	10.3
lactase	lactose	2.4×10^{-2}	13.7

[a] The apparent K_m and V_{max} values are the averages of five determinations with different preparations of brush border membranes. [a] Micromoles of hydrolyzed substrate per milligram of protein per hour. [b] Milligrams per milliliter. [c] Micromoles of released glucose per milligram of protein per hour.

Table 5. Inhibitory Constants (K_i)[a] of Valienamine and Its Related Pseudo-aminosugars on Activities of Carbohydrases in Rat Intestinal Brush Border Membranes

		K_i		
enzyme	substrate	valienamine	validamine	valiolamine
sucrase	sucrose	3.0×10^{-4}	3.2×10^{-5}	3.2×10^{-7}
maltase	maltose	9.6×10^{-4}	1.8×10^{-4}	2.9×10^{-6}
glucoamylase	soluble starch	8.9×10^{-4}	1.6×10^{-4}	1.2×10^{-6}
isomaltase	palatinose	7.6×10^{-4}	8.8×10^{-5}	9.1×10^{-7}
trehalase	trehalose	8.8×10^{-4}	2.7×10^{-4}	4.9×10^{-5}
lactase	lactose	none[b]	none[b]	none[b]

[a] The apparent K_i value was calculated from the Lineweaver−Burk plots. The value given is the average of two determinations with different concentrations of inhibitors. [b] No inhibition was detected with 2×10^{-3} M pseudo-aminosugars.

Table 6. Antibiotic Activity of Valienamine against *Bacillus subtilis* by the Cylinder-Agar Plate Method

concentration of valienamine (mg/mL)	diameter of inhibition zone (mm)
16	20
8	16
4	12

Table 7. Reversal of Valienamine Inhibition by Various Sugars

sugar (1 mg/mL)	diameter of inhibition zone (mm)[a]
none	19
D-glucose	0
D-fructose	0
D-galactose	19
maltose	(13)[b]
cellobiose	14
lactose	20
sucrose	{12}[b]
D-mannitol	0
D-sorbitol	(16)[b]

[a] Valienamine, 10 mg/mL. [b] Inhibited incompletely.

values of valienamine and its related pseudo-aminosugars for sucrase, isomaltase, glucoamylase, maltase, and trehalase activities are $10^{-7}-10^{-1}$ times smaller than the apparent K_m values.

C. Antibiotic Activity of Valienamine against *Bacillus* Species[15]

Valienamine showed antibiotic activity against *Bacillus* species such as *B. subtilis* and *B. cereus* on bouillon medium by the cylinder-agar plate method. The results are shown in Table 6. However, the activity was not observed with D-glucose, D-fructose, D-mannitol, and D-glucosamine. The addition of D-galactose and lactose had no effect on the activity, and that of maltose, sucrose, cellobiose and D-sorbitol had some effects, as shown in Table 7. This phenomenon may be due to the antagonism of inhibition on the sugar metabolism.

IV. Production of Valienamine and Its Related Pseudo-aminosugars

A. Microbial Degradation of Validamycin A To Produce Valienamine and Validamine

1. Degradation of Validamycin A by Pseudomonas denitrificans[1,2]

The microbial hydrolysis by *P. denitrificans* is nonspecific for α- and β-glucosidic linkages, and validamycin A is hydrolyzed to D-glucose and validoxylamine A in the first step. The further decomposition of validoxylamine A proceeds via valienamine and validamine, which can be isolated as the intermediate products.

The degradation procedure was carried out with resting cells. The resting cells were obtained as follows. A cell suspension of *P. denitrificans* from the agar slant was inoculated in 20 mL of a medium which contained glucose 2%, yeast extract 0.1%, peptone 1%, K_2HPO_4 0.5%, KH_2PO_4 0.1%, NaCl 0.2%, $MgSO_4 \cdot 7H_2O$ 0.02%, pH 7.2, in a 100-mL Erlenmeyer flask and cultured on a rotary shaker at 28 °C for 24 h. The broth was transferred to a 1-L Erlenmeyer flask containing 300 mL of the medium and incubated on a rotary shaker at 28 °C for 72 h. The cells were harvested by centrifugation and washed several times with water.

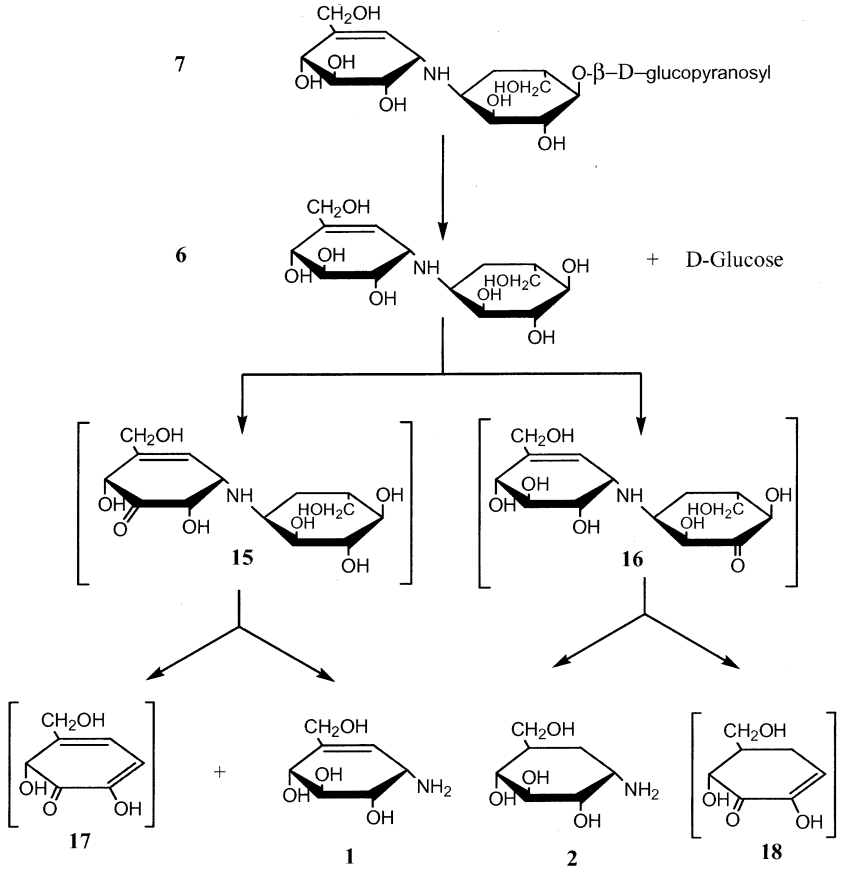
Validamycin A (2.03 g) was then dissolved in water (2 L), and the resting cells harvested from the culture solution (4 L) of *P. denitrificans* were suspended in the reaction solution (pH 7.1). The incubation was carried out at 28 °C for 8 h under shaking conditions, and then the mixture was centrifuged. The cells were discarded, and the supernatant solution was passed through a column of Amberlite IRC-50 (H^+ form, 300 mL) to adsorb the basic degradation products. The column was eluted with 0.5 N ammonia water, and the eluate was concentrated to dryness. The residue was separated by Dowex 1 × 2 (OH^- form) ion-exchange resin chromatography, using water as the developing solvent, into three components: valienamine, validamine, and validoxylamine A.

2. Degradation of Validamycin A by Flavobacterium saccharophilum[3−5]

F. saccharophilum, which was isolated from the rice fields of Kanazawa City, Japan, was found to decompose validamycin A efficiently. For the preparation of valienamine and validamine, *F. saccharophilum* was cultured at 27 °C for 4 days on a shaker in a medium consisting of validamycin A 1%, $(NH_4)_2SO_4$ 1%, K_2HPO_4 0.7%, KH_2PO_4 0.3% and $MgSO_4 \cdot 7H_2O$ 0.01%, pH 7.1. Two liters of the broth was passed through a column of Amberlite IRC-50 (NH_4^+ form, 500 mL), which was eluted with 0.5 N aqueous ammonia. The concentrate of the eluate was chromatographed on a column of Dowex 1 × 2 (OH^- form, 500 mL) column and developed with water to give valienamine and validamine.

The resting cells of *F. saccharophilum* could also be used to degrade validamycin A. At first, *F.*

Scheme 1. Proposed Degradation Pathway of Validamycin A by *Flavobacterium saccharophilum*



saccharophilum was cultured in nutrient broth with shaking at 27 °C for 24 h. The cells were harvested by centrifugation at 20000*g*. The washed cells (50 g, wet weight) were suspended in 1000 mL of 0.05 M phosphate buffer, pH 7.0, containing 10 g of validamycin A, and the suspension was incubated at 27 °C for 48 h under shaking conditions. The isolation method was as described above.

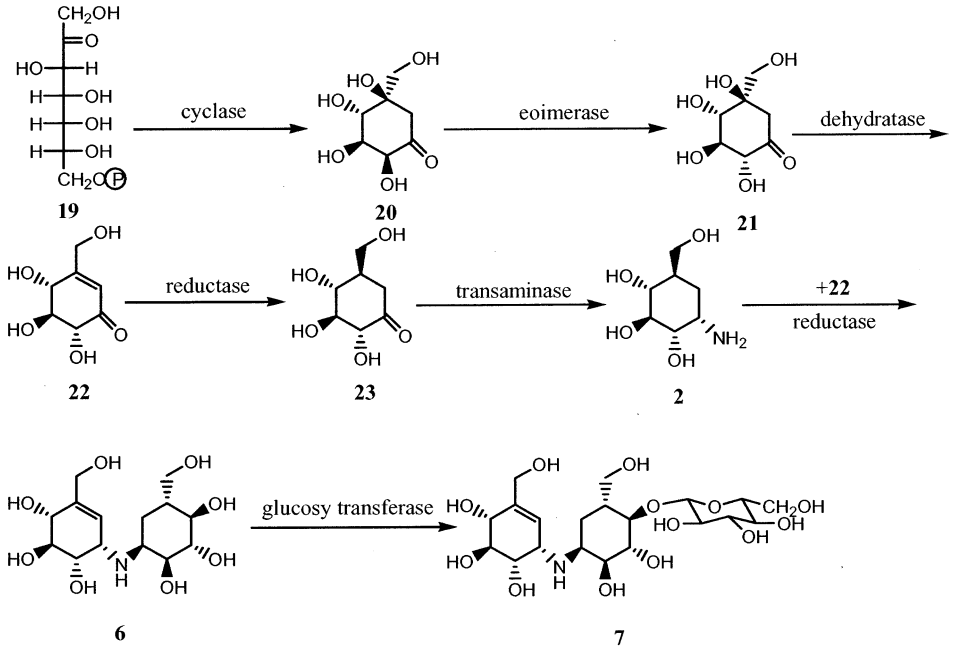
Asano et al.[5] studied the proposed degradation pathway of validamycin A by *F. saccharophilum* (Scheme 1). Validamycin A is first hydrolyzed to D-glucose and validoxylamine A. Validoxylamine A undergoes oxidation at the C-3 position of the validamine or valienamine moiety by 3-dehydrogenase to form two keto−enol compounds, in addition to validamine and valienamine. Validamine and valienamine are also deaminated to form the keto−enol compounds. The resulting keto−enol compounds could be degradated by the some hydrolase into open-chain compounds and further into low-molecular-weight compounds.

B. Isolation from the Fermentation Broth of *Streptomyces hygroscopicus* Subspecies *limoneus*[8−10]

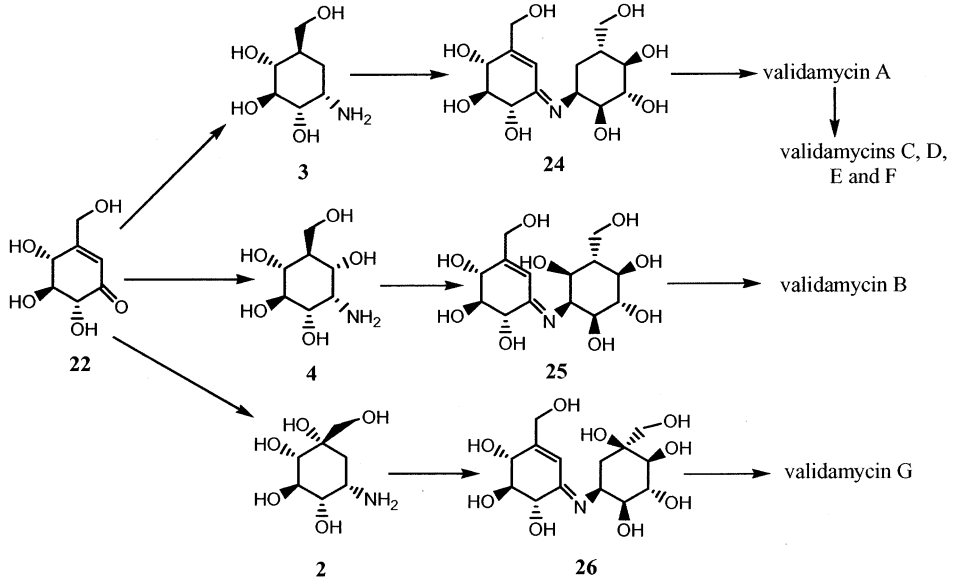
In recent studies,[75,76] the proposed biosynthetic pathway of validamycin A was investigated with a number of potential precursors of the antibiotic synthesized in ^{2}H-, ^{3}H-, or ^{13}C-labeled form. The precursors were fed to the cultures of *S. hygroscopicus* var. *limoneus*. At the end of the fermentation, the resulting validamycin A from each of these feeding experiments was isolated, purified, and analyzed by liquid scintillation counting, ^{2}H or ^{13}C NMR, or selective ion monitoring mass spectrometry (SIM-MS) techniques. The results show that 2-epi-5-epivalionone is specifically incorporated into **7** and labels both cyclitol moieties. A more proximate precursor of **7** is valienone **22**. The proposed pathways for the biosynthesis of validamycin A and other validamycins are shown in Schemes 2 and 3. So, valienamine (**1**), valiolamine (**2**), validamine (**3**), and hydroxyvalidamine (**4**) are all present in the fermentation broth of *S. hygroscopicus* var. *limoneus*.

The isolation and purification of **1**−**4** were carried out as follows. *S. hygroscopicus* var. *limoneus* IFO 12703 was inoculated on a glucose asparagine agar slant for 7 days at 27 °C and then held at 10 °C until used. A loopful of the stock culture was added to 20 mL of the liquid medium in a 100-mL Erlenmeyer flask. This was incubated for 48 h at 27 °C on a rotary shaker (2.0 cm radius) at 220 rpm. The medium for the seed culture consisted of 3.0% glucose, 2.2% soybean flour, 0.3% peptone, and 0.4% calcium carbonate, added after adjustment to pH 7.0. The seed culture was transferred to the 100-mL Erlenmeyer flask containing 20 mL of medium and incubated at 27 °C for 5−7 days on the rotary shaker. The culture filtrate (70 L, pH 6.0) was passed though a column of Amberlite IRC-50 (NH_4^+, 6 L), and the column was eluted with 0.5 N ammonium hydroxide. The eluate was concentrated and rechromatographed on a column of Amberlite CG-50 (NH_4^+, 1 L) with 0.1 N ammonium hydroxide. The eluate was fractionated

Scheme 2. Proposed Biosynthetic Pathway to Validamycin A



Scheme 3. Proposed Mode of Formation of Minor Components, Validamycin B through G



into three fractions in order of elution: fraction I contained **4**, fraction II contained **1** and **3**, and fraction III contained **2**. Fraction II was chromatographed on Dowex 1 × 2 (OH^-, 450 mL) with water to separate **1** (the later fraction) and **3** (the first fraction). Each fraction was rechromatographed on Dowex 1 × 2, and finally **4** (25 mg), **1** (45 mg), **2** (0.25 g), and **3** (1.1 g) were isolated.

C. Hydrogenolysis of Validamycin A and Validamycin B To Give Validamine and Hydroxyvalidamine[13]

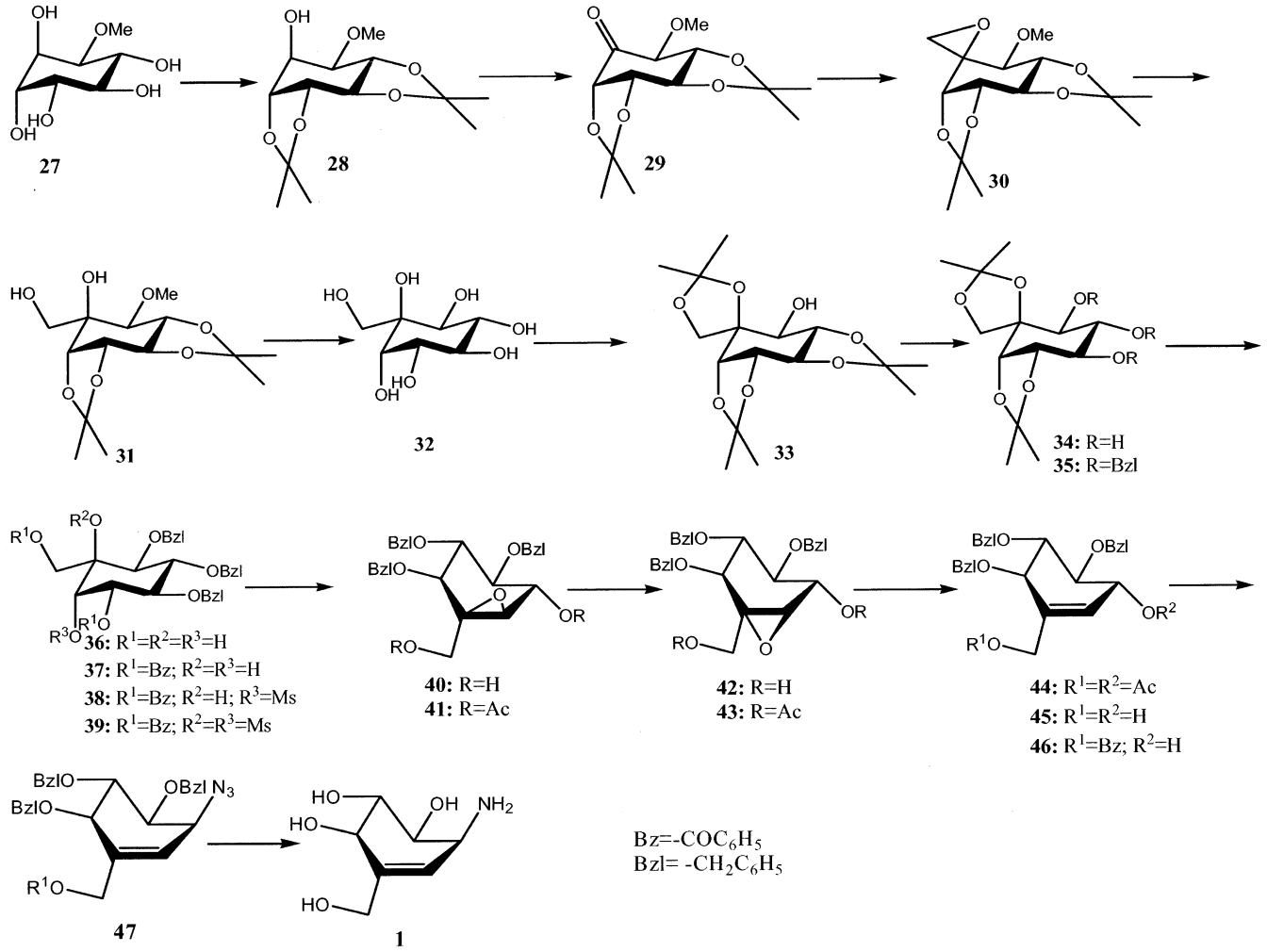
Hydrogenolysis of validamycin A, a main component of the validamycin complex, over platinum oxide results in absorption of approximately 2.3 mol of hydrogen to yield a mixture of several degradation products, including validamine **3** (~55% yield), validatol (~40% yield), and deoxyvalidatol (~15% yield).

Hydrogenolysis of validamycin B, the biologically least active component, by the same procedure as employed with validamycin A, afforded several degradation products, including hydroxyvalidamine **4**, validatol, and deoxyvalidatol.

D. NBS Cleavage of Validoxylamine A or Its Derivatives To Prepare Valienamine and Validamine[6,7]

Cleavage of the C−N bond of validoxylamine A (**6**) with *N*-bromosuccinimide (NBS) in aqueous *N*,*N*-dimethylformamide (DMF), conceivably via *N*-bromination, giving rise to valienamine (**1**), validamine (**3**), and hydroxy (or hydroxymethyl)cyclohexanone and/or -cyclohexenone was investigated. The amines were characterized by converting them into the *N*-acetyl derivatives, which were separable by chromatography on silica gel. This procedure has also

Scheme 4



been applied for chemical degradation of several protected derivatives of **6**, providing the appropriately protected synthons directly. Treatment the octa-acetate of **6** with 3 molar equiv of NBS in aqueous 80% DMF at ambient temperature for 2 d afforded, after chromatography on silica gel, a 45% yield of (4*R*,5*R*)-2,4-diacetoxy-5-acetoxymethylcyclohex-2-en-1-one {$[\alpha]^{23}_D$ +96° (*c* 1.3, chloroform); ^{1}H NMR ($CDCl_3$) δ = 6.47 (1H, d, J = 2.9 Hz, H-3); IR ($CHCl_3$) 1700 cm^{-1} (C═O)}, which was probably obtained by β-elimination of the initially formed tetraacetate in situ or during separation on silica gel. The slower-moving components were acetylated with acetic anhydride in pyridine at ambient temperature to give **54** (14%). On the other hand, **6** readily reacted with 1.5 molar equiv of NBS in water (or aqueous DMF) for 4 h. The reaction mixture was passed through a column of Amberlite CG-50 (NH_4^+) resin, and the effluent was concentrated. The basic compounds were then recovered by elution of the column with aqueous ammonia and were acetylated to afford **54** (9.2%) and **187** (17%).

To prepare the protected derivatives of **1**, **3**, and trihydroxy(hydroxymethyl)cyclohexanone, the per-*O*-benzyl ether {$[\alpha]^{22}_D$ +63° (*c* 1.0, chloroform)} and the hexa-*O*-benzyl-4,7-*O*-benzylidene derivative were subjected to the similar conditions. On treatment with 3 molar equiv of NBS in aqueous 80% DMF at ambient temperature for 3 d, the per-*O*-benzyl ether afforded the cyclohexenone (11%) {$[\alpha]^{22}_D$ −12° (*c* 0.36, chloroform); ^{1}H NMR ($CDCl_3$) δ = 4.07 (^{1}H, d, J = 9.8 Hz, H-6), 6.21 (^{1}H, s, H-2); IR ($CHCl_3$) 1680 cm^{-1} (C═O)} and the cyclohexanone (47%) {$[\alpha]^{23}_D$ +50° (*c* 0.57, chloroform); ^{1}H NMR ($CDCl_3$) δ = 4.13 (^{1}H, d, J = 9.5 Hz, H-2); IR ($CHCl_3$) 1730 cm^{-1} (C═O)}.

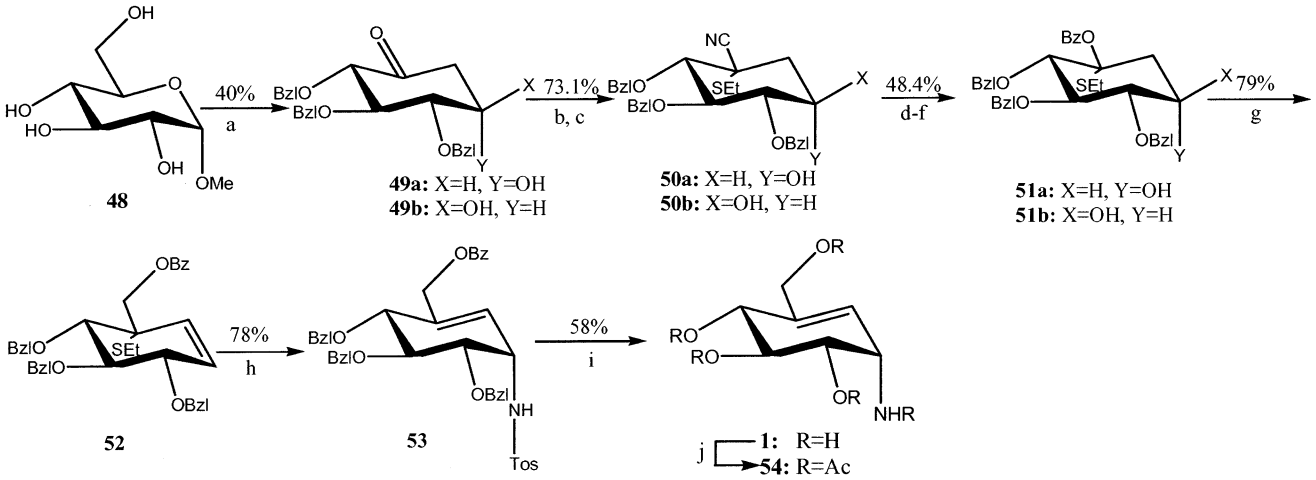
E. Chemical Synthesis of Valienamine and Its Related Pseudo-aminosugars

1. Chemical Synthesis of Valienamine

Since the isolation of valienamine **1** in 1972,[1] many synthetic efforts directed toward **1** have been made. Some afforded the racemate[23−27] or the diastereoisomeric mixture,[28] while others afforded the optically active compound. In this paper, we describe only the optically active **1**, (+)-**1**. On the basis of the different starting materials, the syntheses of **1** are divided into five methods.

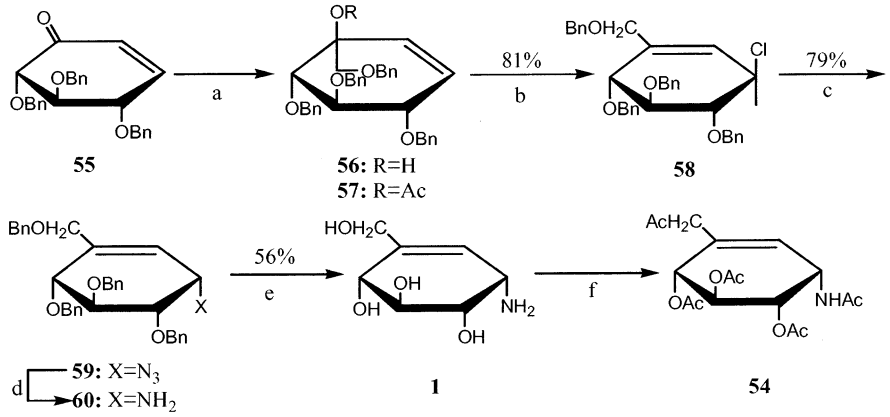
a. Synthesis from L-Quebrachitol.[29,30] L-Quebrachitol (**27**, 2-*O*-methyl-L-chiroinositol) is a byproduct in the production of natural rubber. To incorporate the side chain, **27** was converted with dimethoxypropane into the diisopropylidene compound **28**, which can be catalytically oxidized with ruthenium tetroxide/sodium periodate to the ketone **29** (63%) (Scheme 4). On reaction with dimethyloxosulfonium

Scheme 5[a]



[a] Reagents and conditions: (a) six steps;[38,39] (b) EtSH/MeCH, HCl; Ac_2O, pyridine; (c) Me_3Si-CN, $SnCl_4$, CH_2Cl_2, 0 °C; (d) DIBAH, CH_2Cl_2/petroleum ether, −70 °C to room temperature; (e) $LiAlH_4$, THF, 0 °C to room temperature; (f) BzCN, CH_3CN/NEt_3, −15 °C; (g) PPh_3, DEAD, toluene, room temperature; (h) chloramine T, BTAC, CH_2Cl_2, room temperature; (i) liquid ammonia, Na, −70 °C; (j) Ac_2O, pyridine (quantitative).

Scheme 6[a]



[a] Reagents and conditions: (a) benzyloxymethylmagnesium chloride; (b) thionyl chloride, reflux; (c) sodium azide; (d) hydrogen sulfide in pyridine−water; (e) sodium in liquid ammonia; (f) Ac_2O, pyridine.

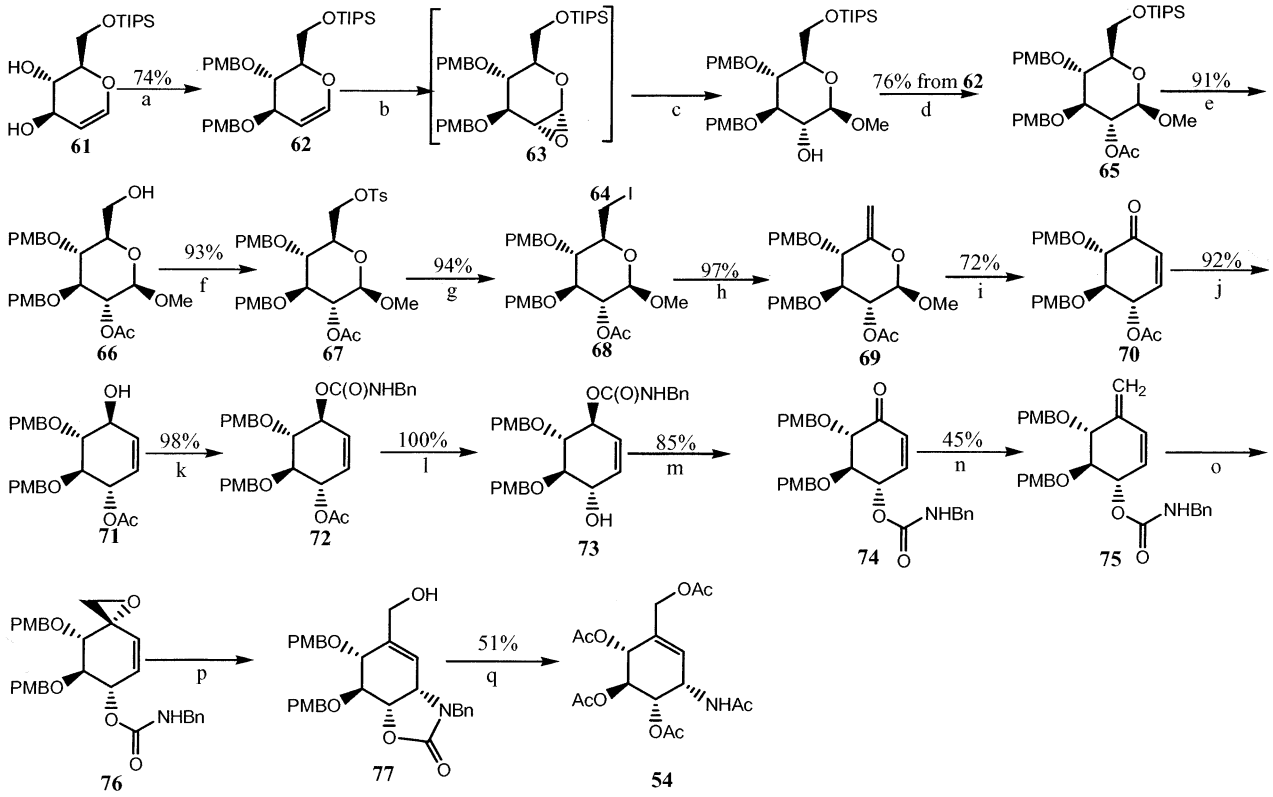
methylide, **29** stereoselectively formed the epoxide **30** (57%). Reaction of **31** with the anion of the dithiane analogue *N*-methylthioformaldine (5-methylperhydro-1,3,5-dithiazine) then afforded the product with the other (undesired) stereochemistry at the branching site. The ring-opening product **31** (89%) could be obtained by hydrolysis of **30** with aqueous alkali. Since the stereochemistry of the side chain in **31** was fixed, the methyl ether could now be cleaved; on reaction with boron tribromide, the completely deblocked product **32** was formed. Reaction of **32** with dimethoxypropane yielded the triisopropylidene compound **33**. Selective hydrolysis of the *trans*-isopropylidene group led to formation of **34**, from which the tribenzyl ether **35** (75%) could be obtained. The benzoylation of the tetrol **36**, obtainable from **35** by acid hydrolysis, could be steered so that it selectively furnished the dibenzoate **37** (82%). The OH group at the branching site and the 6-OH group were considerably less reactive. On mesylation of **37**, an inseparable mixture of monomesylate **38** and dimesylate **39** (Ms = CH_3SO_3) was obtained. Treatment of this mixture with sodium ethoxide afforded a mixture of the epoxides **40** and **42**, which are isolated as the acetates **41** and **43**. The double bond was incorporated by reaction of **41** and **43** with sodium iodide, followed by elimination with phosphorus oxide trichloride; this led uniformly to the olefin **44** (69%).

For the introduction of the amino group, the side chain, after hydrolysis of **44** to **45**, was protected by selective benzoylation to **46**. It was possible to convert the free hydroxy group at the allyl position into an azido group with hydrazoic acid/triphenylphosphane/azodicarboxylate to give **47** (72%), which had the stereochemistry of valienamine. The azido group in **47** was converted with triphenylphosphane into the phosphinimide, which could be hydrolyzed to the amino group. Cleavage of the benzyl ether protecting groups was achieved with sodium in liquid ammonia: valienamine **1** was isolated as the hydrochloride.

b. Synthesis from D-Glucose. This method involves different key steps, including a Ferrier rearrangement,[31−33] an aldol-type cyclization of a nitrofuranose,[34] an intramolecular Horner−Emmons reaction,[35] a ring-closing alkene metathesis,[36] and an aldol condensation of a sulfone.[37]

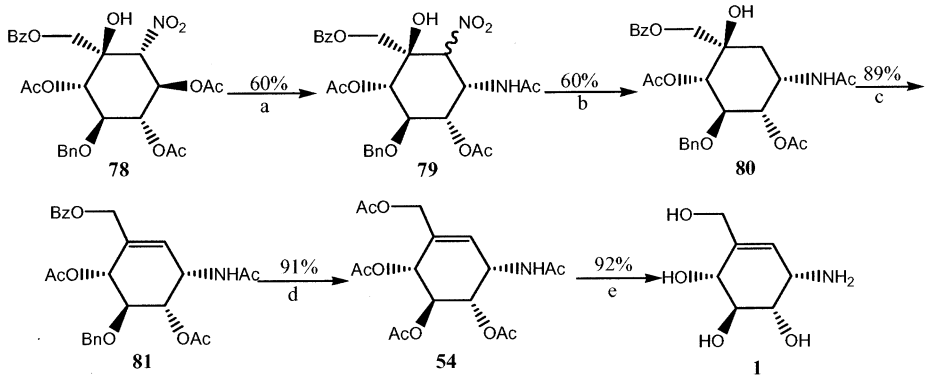
With the Ferrier rearrangement as the key step, Schmidt and Kohn[31] reported a 15-step method (Scheme 5) with an overall yield of 5.06%. Synthesis

Scheme 7[a]



[a] Reagents and conditions: (a) NaH, PMBCl; (b) dimethyldioxirane, acetone−CH_2Cl_2; (c) MeOH, room temperature; (d) Ac_2O, DMAP; (e) TBAF, THF−EtOAc; (f) TsCl, pyridine, DMAP; (g) KI, DMF, 100 °C, 2 h; (h) AgF, pyridine, room temperature, 1 day; (i) $HgCl_2$, acetone−water, reflux, 4 h and MaCl, DMAP, pyridine, room temperature, 5 h; (j) $NaBH_4$−$CeCl_3$, EtOH, −78 °C, 10 min; (k) benzyl isocyanate, benzene, reflux, overnight; (l) K_2CO_3, MeOH (quantitative); (m) PDC, AcOH, EtOAc, room temperature, overnight; (n) CH_2I_2, Zn, $TiCl_4$, THF, 15 min; (o) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (p) KHMDS, 18-crown-6, THF, −78 °C to room temperature, 2.5 h; (q) (1) Na, NH_3−THF, −78 °C; (2) LiOH, 30% H_2O−EtOH, reflux; (3) Ac_2O, pyridine, overnight.

Scheme 8[a]



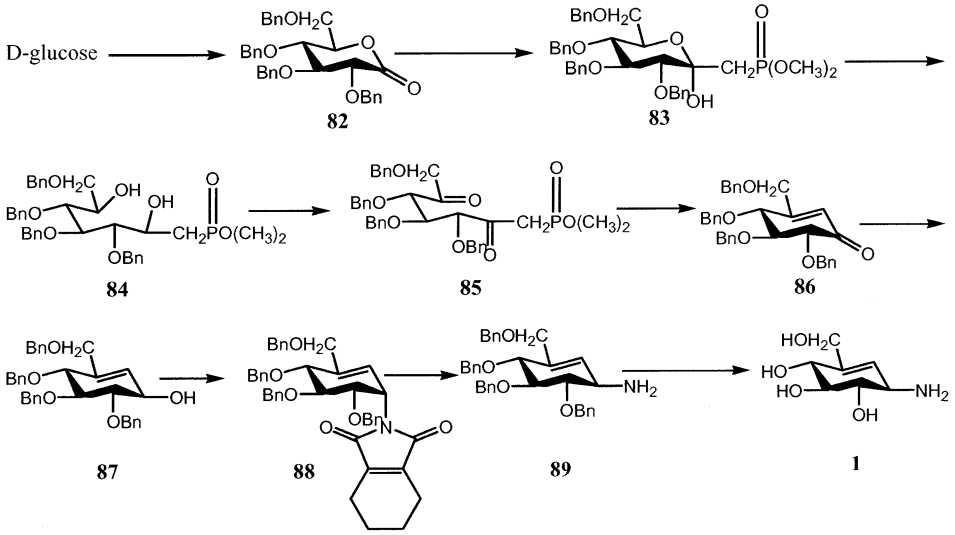
[a] Reagents and conditions: (a) liquid NH_3/THF (−78 °C); Ac_2O/*p*-TaOH·H_2O; (b) *n*-Bu_3SnH/AIBN/benzene; (c) $SOCl_2$/pyridine; (d) 1% NaOH−MeOH; Na/liquid NH_3; Ac_2O/pyridine; (e) 10% NaOMe−MeOH; 80% aqueous NH_2NH_2.

of valienamine with a total yield of 22% was achieved by Nicotra et al.,[32] using enone **56** as the starting material (Scheme 6). Pak and Danishefsky[33] investigated the synthesis by an S_N2 reaction (Scheme 7), obtaining an overall yield of <5.50%.

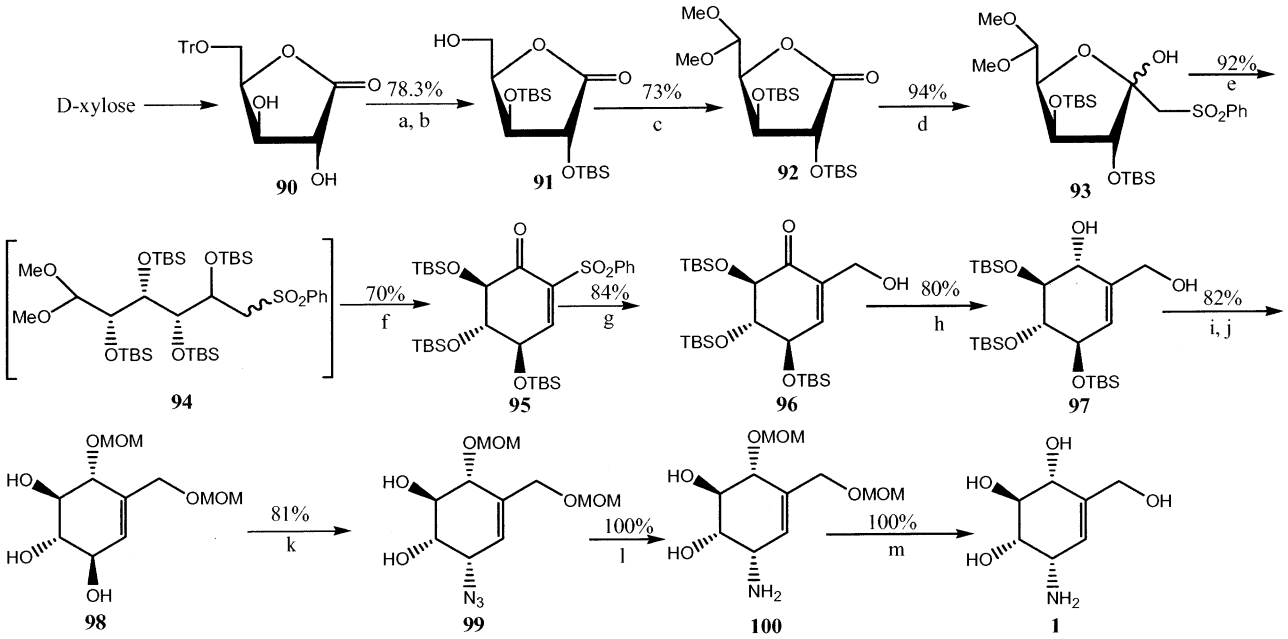
The aldol-type cyclization of a nitrofuranose was the key step in the synthesis of valienamine reported by Yoshikawa et al.[34] In the synthesis, optically active valienamine was obtained via a Michael-type addition to nitroolefins or via substitution for an acetoxyl residue at the β-position of the nitro group in the pseudo-nitrosugar (Scheme 8), with an overall yield of 26.82% from **78**.

The intramolecular Horner−Emmons reaction, starting from tetra-*O*-benzyl-D-glucono-1,5-lactone, which is readily available from D-glucose, was carried out by Fukase and Horii[35] (Scheme 9). In the first step, **82** was treated with 2 equiv of lithium dimethyl methylphosphonate to yield the (dimethoxyphosphoryl)heptulopyranose derivative **83**. Before, oxidation, the pyranose ring of the heptulose derivative **83** was reductively opened with sodium borohydride ($NaBH_4$), to give the heptitol derivative **84**. The newly formed C-2 and the released C-6 hydroxyl groups of **84** were oxidized with a reagent combination of DMSO, trifluoroacetic anhydride (TFAA), and Et_3N. The in-

Scheme 9



Scheme 10[a]

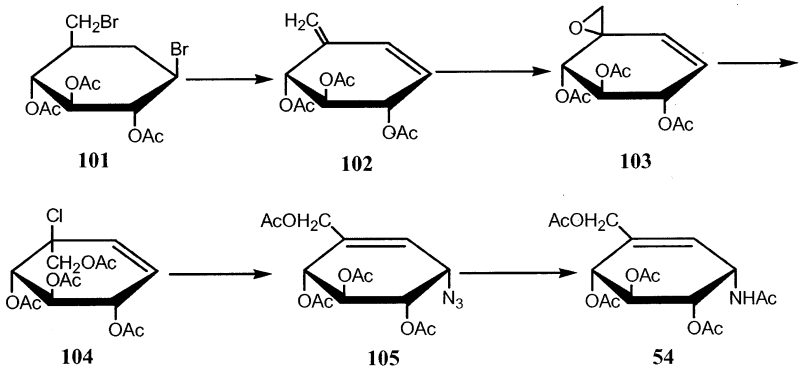


[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine/CH_2Cl_2, room temperature, 4 h; (b) H_2, Pd−C/$CHCl_3$, room temperature, 12 h; (c) (1) DCC, Py·TFA, DMSO/Et_2O, room temperature, 30 min; (2) CSA, $HC(OMe)_3$/MeOH, 50 °C, 15 h; (d) $MeSO_2Ph$, *n*-BuLi/THF, −78 °C, 30 min; (e) TBSOTf, 2,6-lutidine/CH_2Cl_2, 40 °C, 2 days; (f) $SnCl_4/CH_2Cl_2$, −78 °C, 3 h; (g) *n*-Bu_3SnLi, HCHO/THF, −78 °C to 40 °C, 3 days; (h) $Zn(BH_4)_2$/ether, 0 °C, 1 h; (i) MOMCl, *n*-Bu_4NI, DIPEA, CH_2ClCH_2Cl, 50 °C, 24 h; (j) TBAF/THF, room temperature, 3 h; (k) NH_3, Ph_3P, DEAD/THF, room temperature, 1 h; (l) H_2, Raney Ni/H_2O/1,4-dioxane, room temperature, 3 h; (m) 3% HCl−MeOH, 50 °C, 3 h.

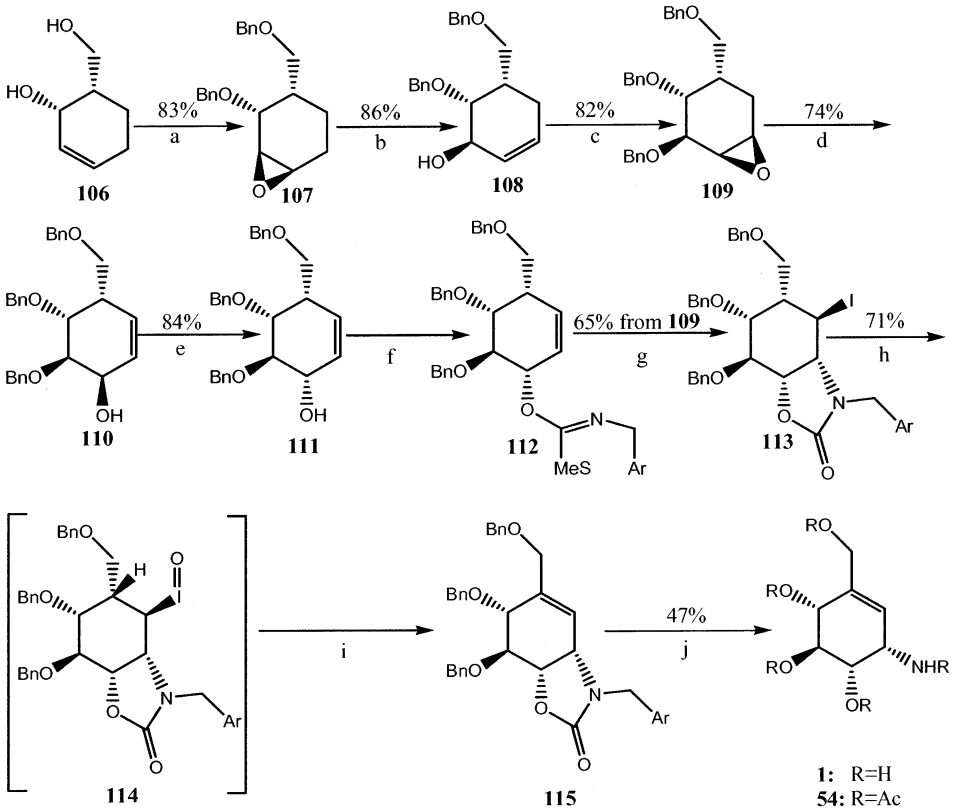
tramolecular cyclization of the resulting 2,6-heptodiulose derivative **85** was accomplished with potassium carbonate in the presence of 18-crown-6, to give the branched unsaturated inosose derivative **86**. Next, the oxo group of **86** was converted to the axial amino group, to give **1** in the following manner. The α,β-unsaturated keto group of **86** was reduced stereoselectively to an allylic equatorial secondary hydroxyl group with $NaBH_4$/cerous chloride in ethanol, followed by cooling in a dry ice−acetone bath. The resulting branched unsaturated inositol derivative **87** was converted to the phthalimido derivative **88** by employing a Mitsunobu reaction that proceeded with complete inversion of the configuration; namely, the free hydroxyl group at the allylic position was replaced with a phthalimido group using the diethylazodicarboxylate (DEAD)/triphenylphosphane (Ph_3P) system. Removal of the phthaloyl group of the phthalimido derivative **88** with hydrazine, and subsequent removal of the *O*-benzyl protecting groups with sodium in liquid ammonia, gave an unsaturated pseudo-aminosugar that was identical to naturally occurring **1**. However, no further information about the yields was provided.

Vasella et al.[36] reported that **1** was prepared in seven steps and in an overall yield of 17% from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose. Stereoselective addition of vinylmagnesium bromide to the 1,3,4,5-tetra-*O*-benzyl-6,7-dideoxy-L-*xylo*-hept-6-en-2-ulose gave the diene (86%). Ring-closing alkene metathesis of the diene in the presence of 0.15 equiv of Grubb's catalyst gave the cyclohexene

Scheme 11



Scheme 12[a]



[a] Reagents and conditions: (a) BnBr, NaH, THF, HMPA; *m*-CPBA, CH_2Cl_2, −10 °C; (b) PhSeNa, EtOH, THF; *m*-CPBA, CH_2Cl_2, −40 °C; 45 °C, toluene, I−Pr_2EtN; (c) *m*-CPBA, CH_2Cl_2, 0 °C; NaH, BnBr, THF, HMPA; (d) PhSeNa, EtOH, THF; *m*-CPBA, CH_2Cl_2, −40 °C; 70 °C, toluene, *i*-Pr_2EtN; (e) $PhCO_2H$, DEAD, PPh_3; KOH, THF, aqueous EtOH; (f) KH, THF; $ArCH_2NCS$; MeI; (g) I_2, THF, sieves; aqueous Na_2SO_3; (h) *m*-CPBA, CH_2Cl_2, −10 °C, 2.5 days; (i) −HOI; (j) CAN, SiO_2, aqueous CH_3CN; KOH, aqueous MeOH, reflux; Na, NH_3, THF, −60 °C; Ac_2O, pyr, DMAP.

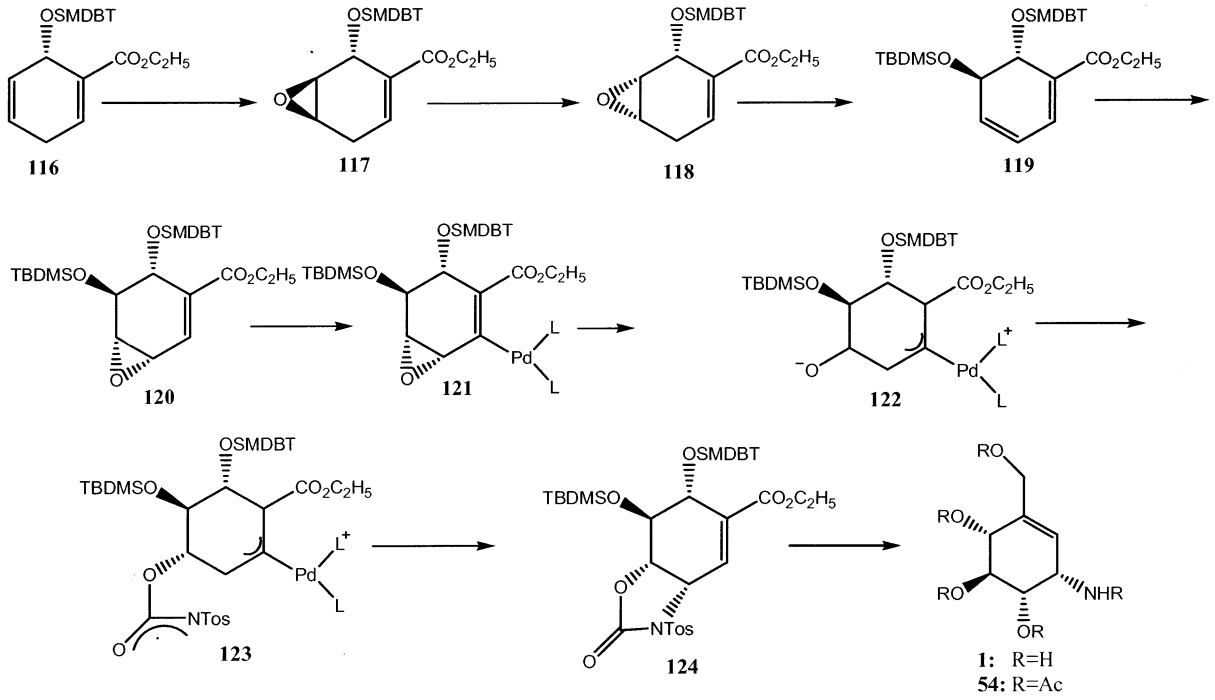
(58%), which was converted into **1** in three steps and in 47% yield. Similarly, ring-closing alkene metathesis of the D-mannose-derived diene gave the cyclohexene (89%).

c. Synthesis from D-Xylose. Tatsuta et al.[37] synthesized valienamine by using D-xylose as the starting material, with an aldol condensation of a sulfone as the key step (Scheme 10). The overall yield in the synthesis from **90** to **1** was 15.44%.

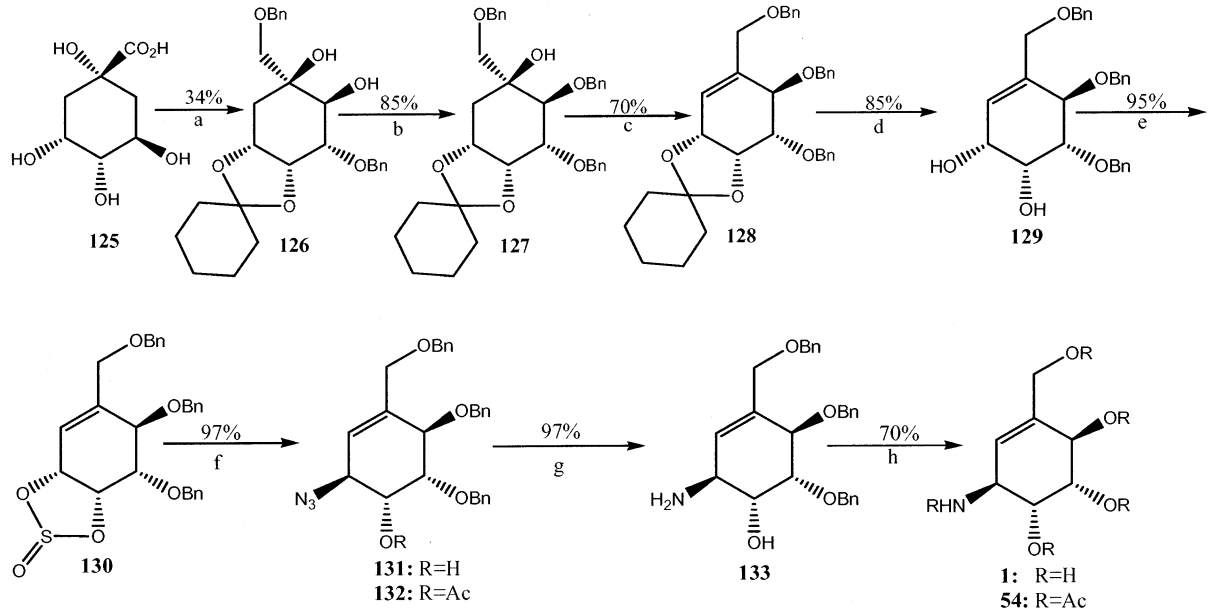
d. Synthesis from Cyclohexane Skeleton. (1*R*)-(−)-1,2,3-Tri-*O*-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**101**) was used by Ogawa et al.[40] as the starting material to synthesize valienamine (Scheme 11). Dehydrobromination of **101** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene afforded exclusively the diene **102**, which was, without purification, treated with an equimolar amount of *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane to oxidize the *exo*-methylene group. A mixture of the products was fractionated on a silica gel column to give the spiro oxiranes **103** (27%). Chlorination of **103** with concentrated hydrochloric acid in tetrahydrofuran (THF), followed by acetylation, gave the chloride **104** in 92% yield. Treatment of **104** with sodium azide in DMF at 60 °C gave selectively the azide **105** in quantitative yield. Reduction of **105** with hydrogen sulfide, followed by the conventional acetylation, gave **54** in 94% yield. From **101**, **54** was prepared in five steps, with a total yield of 24.11%.

Knap et al.[41] utilized the diol **106** as the starting material to give the compound valienamine (Scheme

Scheme 13



Scheme 14[a]

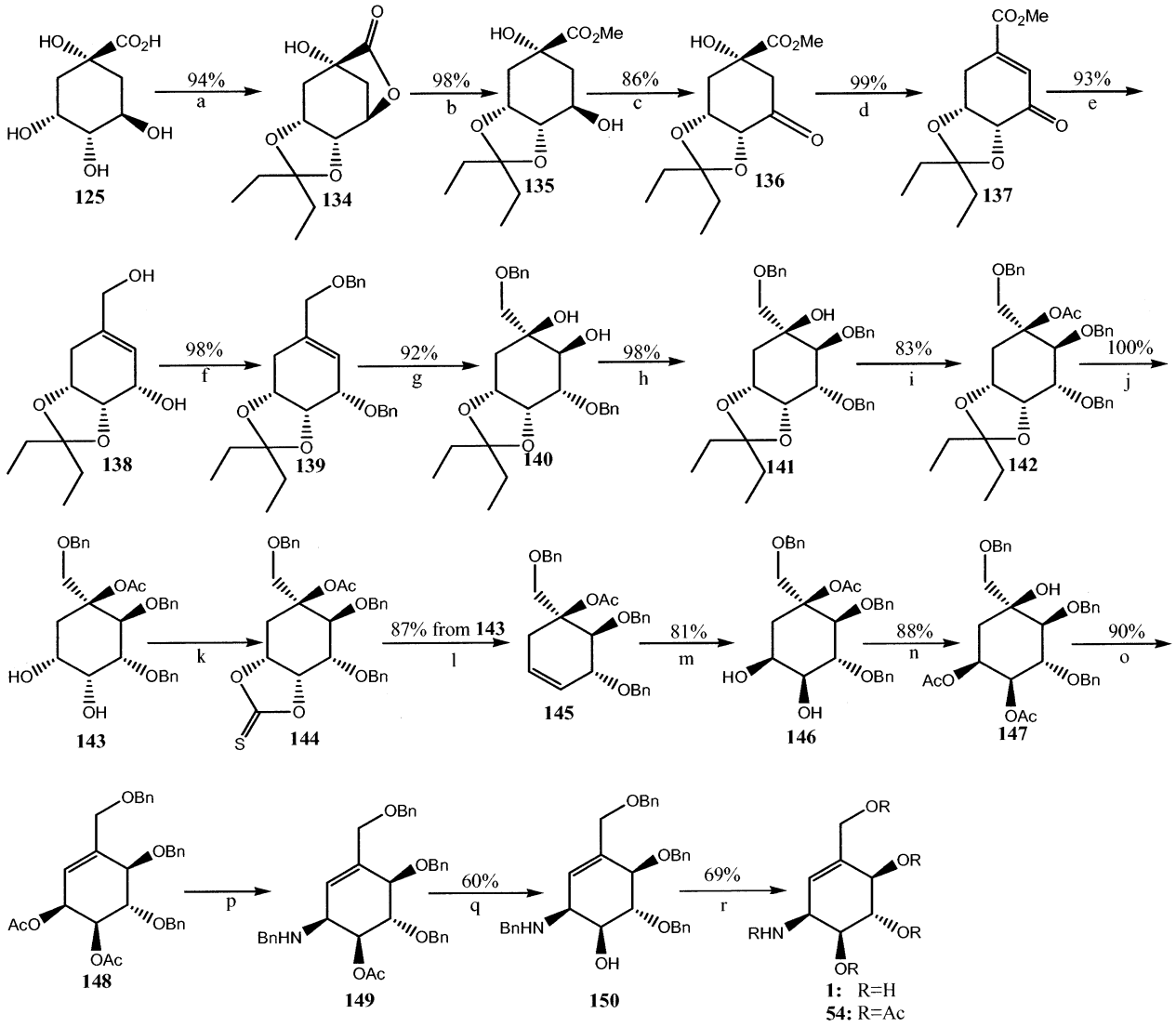


[a] Reagents and conditions: (a) six steps;[43] (b) NaH, THF, 0 °C; BnBr, *n*-Bu_4NI; (c) pyridine, CH_2Cl_2, $SOCl_2$, 0 °C; (d) TFA, H_2O, CH_2Cl_2; (e) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; (f) LiN_3, DMF, 80 °C; (g) PPh_3, pyridine; (h) Na, NH_3, −78 °C; Ac_2O, pyridine.

12). The hydroxyls of **106** were *O*-benzylated, and the double bond was epoxidized with 3.5:1 selectivity. The major epoxide **107** was isomerized to allylic alcohol **108** by the Sharpless−Reich protocol, with 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 **109**, which was rearranged to the allylic alcohol **110** by another application of the Sharpless−Reich procedure. Inversion of the allylic hydroxyl was accomplished by a Mitsunobu sequence, giving the desired allylic alcohol substrate **111** in about 23% overall from **106**. Condensation of the potassium salt of **111** with *p*-methoxybenzyl isothiocyanate, followed by iodomethane quench, led to the carbonimidothioate **112**, iodocyclization of which gave, after aqueous sodium sulfite quench, the iodo oxazolidinone **113**. Oxidation of **113** to the corresponding iodoso compound **114** resulted in spontaneous syn elimination of HOI, with formation of the unsaturated oxazolidinone **115**. Finally, oxidative removal of the *N*-*p*-methoxybenzyl group, basic hydrolysis of the oxazolidinone, and debenzylation gave **1**, which was isolated and characterized as its known peracetate **54**. Therefore, **54** was synthesized in 10 steps with an overall yield of 7.89%.

Finally, Trost et al.[42] synthesized valienamine with **116** as the starting material (Scheme 13). In the

Scheme 15[a]



[a] Reagents and conditions: (a) 3-pentanone, H_3PO_4, Dean−Stark; (b) NaOMe, MeOH; (c) PDC, CH_2Cl_2, CH_3CO_2H, room temperature; (d) $POCl_3$, pyridine, 0 °C; (e) DIBALH, toluene, −40 °C to 0 °C; (f) NaH, THF, 0 °C; BnBr, Bu_4NI OsO_4, NMO, acetone−H_2O (4:1); (g) NaH, BnBr, THF, Bu_4NI, 0 °C to room temperature, 2.5 h; (h) Ac_2O, pyridine, reflux; (i) TFA, H_2O, CH_2Cl_2; (j) 1,1′-thiocarbonyldiimidazole, PhMe, reflux; (k) $P(OM_3)_3$, reflux; (l) catalytic, $RuCl_3 \cdot 3H_2O$, EtOAc−CH_3CN−H_2O, $NaIO_4$, 0 °C; (m) catalytic K_2CO_3, MeOH; Ac_2O, pyridine, catalytic DMAP, CH_2Cl_2; (n) Martin sulfurane, dehydrating agent; (o) Martin sulfurane, dehydrating agent; (p) catalytic $(Ph_3P)_4Pd$, Ph_3P, $BnNH_2$, CH_3CN, reflux; (q) NaOMe, MeOH; (r) NH_3, THF, Na; pyridine, Ac_2O.

procedure, a new protocol invoking the importance of cocatalysis for the palladium-based *cis*-hydroxyamination sequence and a new application of the asymmetric palladium-catalyzed hydroxycarboxylation sequence evolved.

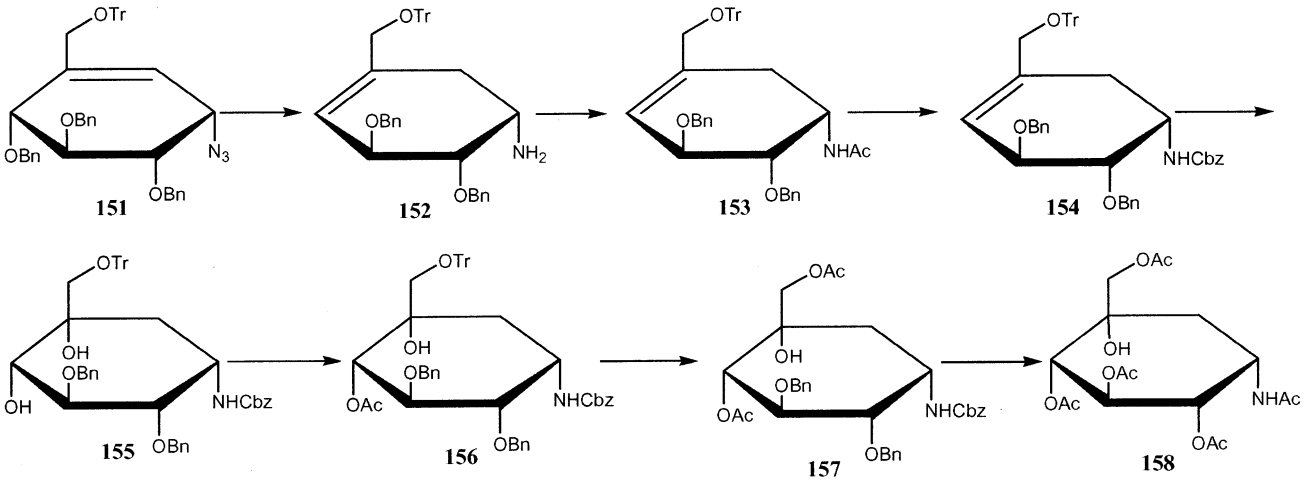
e. Synthesis from (−)-Quinic Acid. The research group of Professor Shing reported the synthesis of valienamine with (−)-quinic acid (**125**) as the starting material.[39,43−53] First, they described the versatility of this approach for the facile and enantiospecific synthesis of valienamine, involving a regioselective cyclic sulfite opening as the key step (Scheme 14). The synthesis of **54** was carried out in 16 steps with a total yield of 6.25%. Later, valienamine was produced directly from a cyclohexane precursor bearing an allylic acetate moiety. A regio- and stereospecific palladium-catalyzed reaction was proven to effectively install the amino function (Scheme 15). At last, **54** was synthesized from (−)-quinic acid in 20 steps with an overall yield of 11%.

2. Chemical Synthesis of Valiolamine

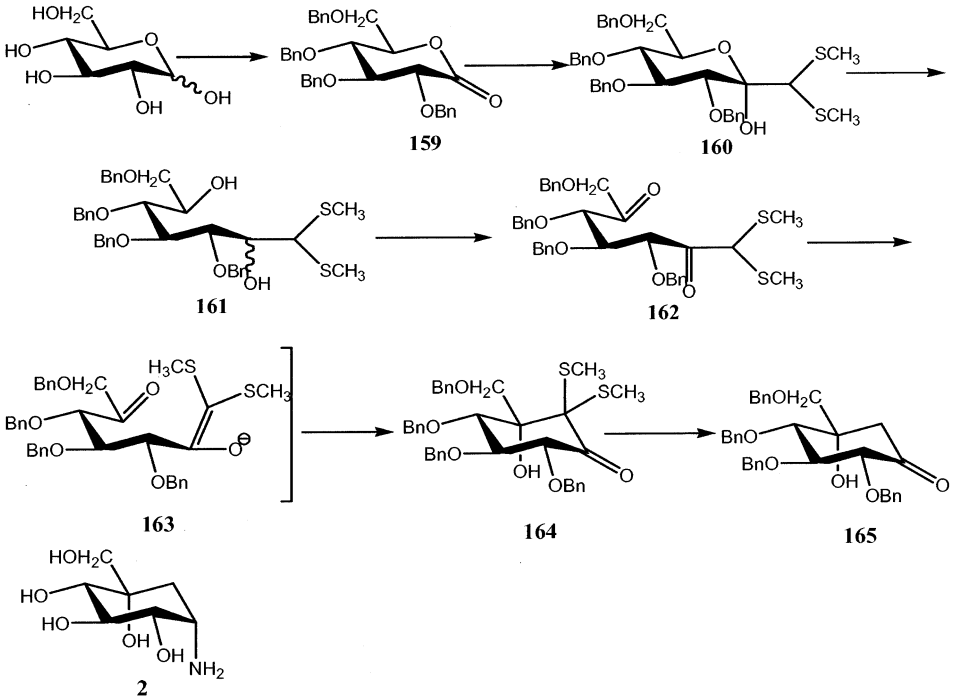
Since the discovery of valiolamine, five total syntheses of valiolamine **2** have been reported: (i) starting from a Diels−Alder (furanacrylic acid) cycloadduct;[54] (ii) from D-glucose via a Ferrier rearrangement;[55] (iii) from 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone,[12] employing an aldol reaction as the key step; (iv) from (−)-quinic acid (**125**) via the approach in the facile synthesis, a novel acetyl migration, and internal displacement reactions involving neighboring group participation; and (v) from validamine and valienamine via the stereoselective conversion.

a. Synthesis from D-Glucose. (1*L*)-(1,3,4/2)-4-Azido-1,2,3-tri-*O*-benzyl-6-(trityloxymethyl)-5-cyclo-

Scheme 16



Scheme 17



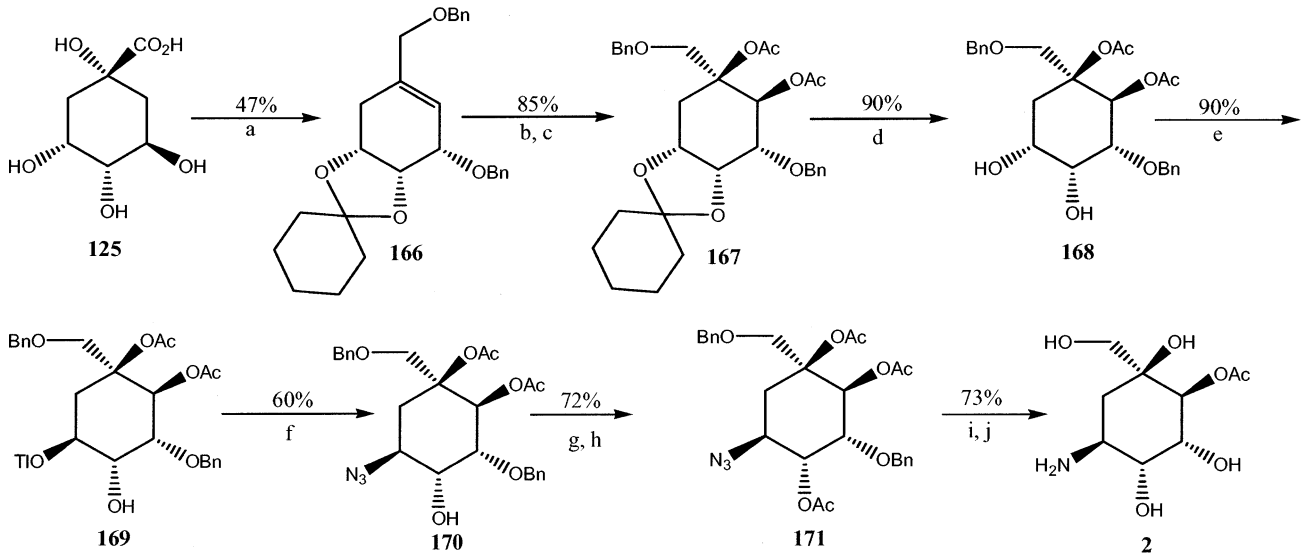
hexene-1,2,3-triol (**151**), which was derived from D-glucose, was utilized as the synthetic precursor to synthesize chiral **2** (Scheme 16).[62] **151** was reduced with lithium aluminum hydride in boiling diethyl ether, unexpectedly, to give (1*D*)-(1/2,3)-3-amino-1,2-di-*O*-benzyl-5-(trityloxymethyl)-6-cyclohexene-1,2-diol (**152**) as the major product. Its *N*-acetyl and *N*-benzyloxycarbonyl derivatives, **153** and **154**, were obtained. Compound **154** was oxidized at 60−70 °C with a catalytic amount of osmium tetroxide in the presence of trimethylamine *N*-oxide, giving a valiolamine derivative **155** in 58% yield. Compound **155** underwent acetylation of only the secondary hydroxyl group at C-2 by treatment with acetic anhydride and base, giving **156**. The trityl group of **156** was removed with acetic acid, and the resulting primary hydroxyl group was acetylated to give the diacetate **157**. **157** was catalytically hydrogenated with palladium-on-carbon for simultaneous removal of the benzyl and the benzyloxycarbonyl groups, and the product was then acetylated in the usual way, giving **158**.

2,3,4,6-Tetrabenzyl-D-glucono-1,5-lactone was another intermediate which is derived from D-glucose and readily available.[12] With it as the starting material, valiolamine could be synthesized (Scheme 17).

b. Synthesis from (−)-Quinic Acid.[44,48] (−)-Quinic acid was utilized as the starting material to synthesize valiolamine, as reported by Shing et al. (Scheme 18), in which the total yield was 8.1% after 14 steps.

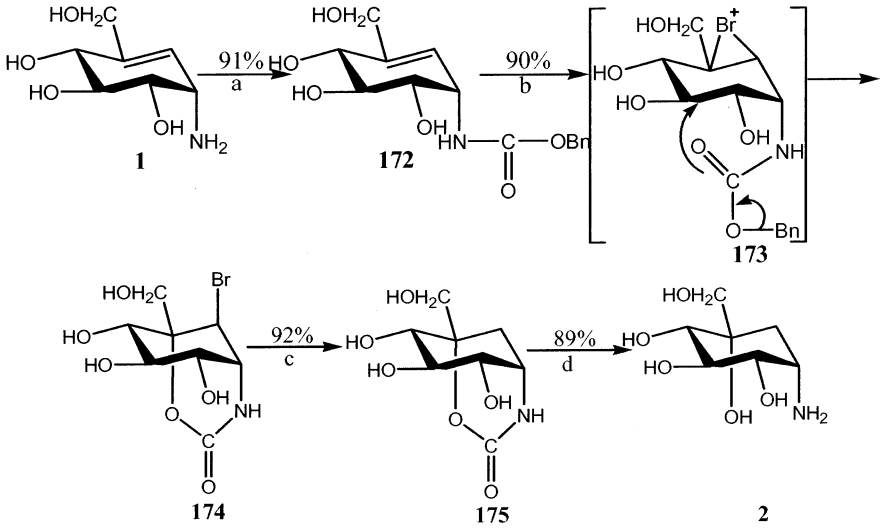
c. Synthesis from Valienamine and Validamine.[12,56] Valiolamine (**2**) was stereoselectively synthesized from valienamine (**1**) in a good yield of 67.06%, as shown in Scheme 19. *N*-(Benzyloxycarbonyl)valienamine (**172**), an acyclic carbamate derivative of valienamine, was treated with bromine to afford the bromocyclitol cyclic carbamate **174**. This cyclization reaction is thought to proceed by a mechanism similar to halolactonization, as illustrated in

Scheme 18[a]



[a] Reagents and conditions: (a) five steps;[52,53] (b) OsO_4, H_2O, Me_3NO, pyridine, *n*-BuOH, reflux; (c) Ac_2O, DMAP, Et_3N, reflux; (d) TFA, H_2O, CH_2Cl_2; (e) Tf_2O (1 equiv), pyridine, CH_2Cl_2, 0 °C; (f) NaN_3, benzo[15]crown-5, DMF; (g) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (h) *n*-Bu_4NOAc, THF; (i) K_2CO_3, MeOH; (j) H_2, $Pd(OH)_2$, EtOH.

Scheme 19[a]



[a] Reagents: (a) CabzCl, $NaHCO_3$; (b) Br_2; (c) $NaBH_4$; (d) $Ba(OH)_2$.

Scheme 19. This regioselective intramolecular cyclization reaction is explained by Markovnikov's rule. The bromocyclitol cyclic carbamate **174** was dehalogenated reductively with sodium borohydride, and the resulting dehalogenated cyclic carbamate **175** was hydrolyzed with barium hydroxide to give **2**.

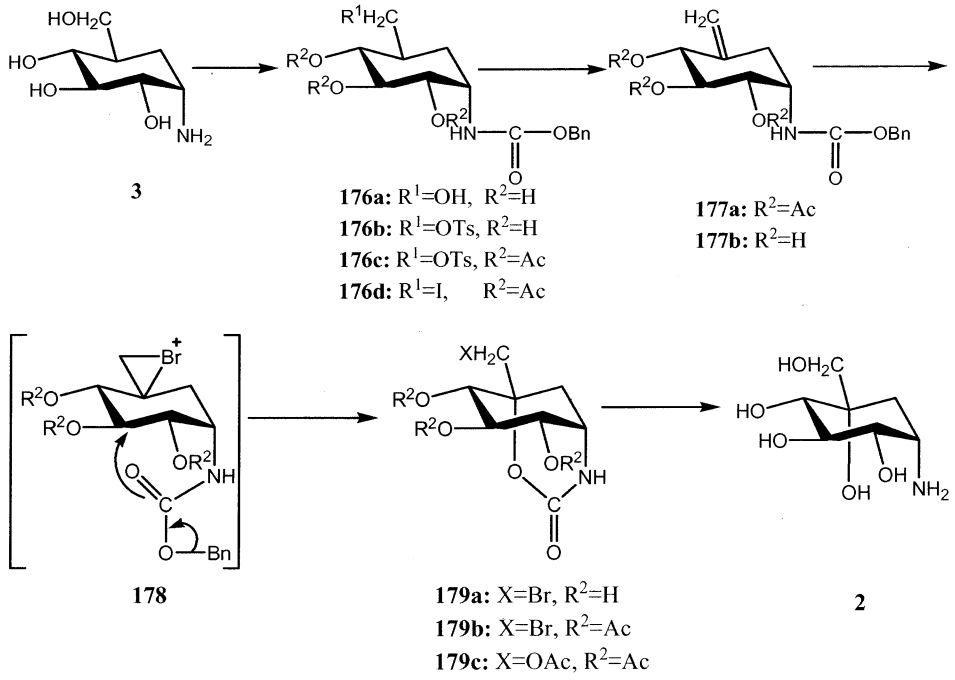
Validamine (**3**) could also be converted into **2**, as shown in Scheme 20. The 7-deoxy-7-iodo derivative **176d** of tri-*O*-acetyl-*N*-(benzyloxycarbonyl)validamine, prepared from **3** by a four-step sequence via **176a**−**176c**, was treated with silver fluoride in pyridine to give the *exo*-methylene derivative **177a**. Hydrolysis of **177a** with ammonium hydroxide gave the de-*O*-acetate **177b**. The *exo*-methylene derivatives **177a** and **177b** were treated with bromine to give the (bromomethyl)cyclitol cyclic carbamates **179b** and **179a**, respectively, presumably via the transient intermediate **178**. The (bromomethyl)cyclitol cyclic carbamate **179b** was treated with silver acetate to give the acetoxymethyl derivative **179c,** which was identical to the tetra-*O*-acetate of **175**, derived from **1**. Hydrolysis of **179a** and **179c** with barium hydroxide gave **2**.

3. Chemical Synthesis of Validamine

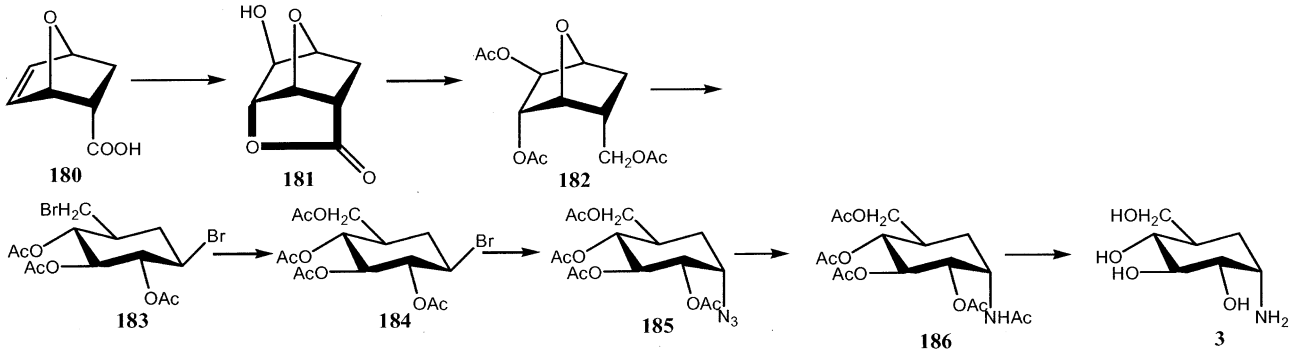
Since the discovery of validamine, there several methods for validamine syntheses have been reported, including racemic[57−61] and optically active validamine.[34,62−64] But in this review, only the optically active validamine, (+)-validamine, is discussed.

a. Synthesis from (−)-7-*endo*-Oxabicyclo[2.2.1]-hept-5-ene-2-carboxylic Acid.[64] With (−)-7-*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**180**) as the starting material, the optically active validamine was formed (Scheme 21) in seven steps with a total yield of <17.49%. The synthesis was carried out in

Scheme 20



Scheme 21

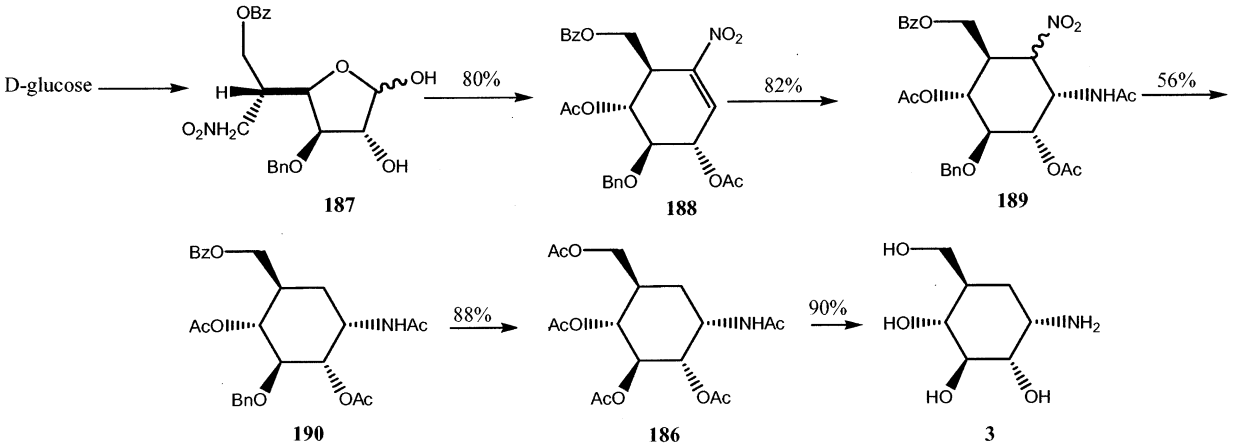


the following sequence. Treatment of **180** with 90% formic acid and 35% hydrogen peroxide gave the hydroxy lactone **181** in 66% yield. Compound **181** was reduced with lithium aluminum hydride in THF and then acetylated to give the triacetate **182** which, without purification, was directly subjected to acetolysis to give a mixture of fully acetylated derivatives of pseudo-sugars. Next, treatment of the triacetate **182** with 20% hydrogen bromide at 85 °C for 20 h gave the crystalline dibromide **183** in 53% yield. Compound **183** was selectively converted into the bromide **184** by treatment with sodium acetate in 90% aqueous 2-methoxyethanol at 85 °C, followed by acetylation. The secondary bromo group was then displaced with an azide ion via an S_N2 reaction to give the azide **185**, which was hydrogenated in the presence of Raney nickel and acetylated to give the penta-*N*,*O*-acetate **186** in 50% yield. Finally, de-*O*-acetylation of **186** with 10% NaOMe-MeOH (25 °C, 3 h), followed by de-*N*-acetylation with 80% aqueous NH_2NH_2 in a sealed tube (100 °C, 72 h), furnished **3**.

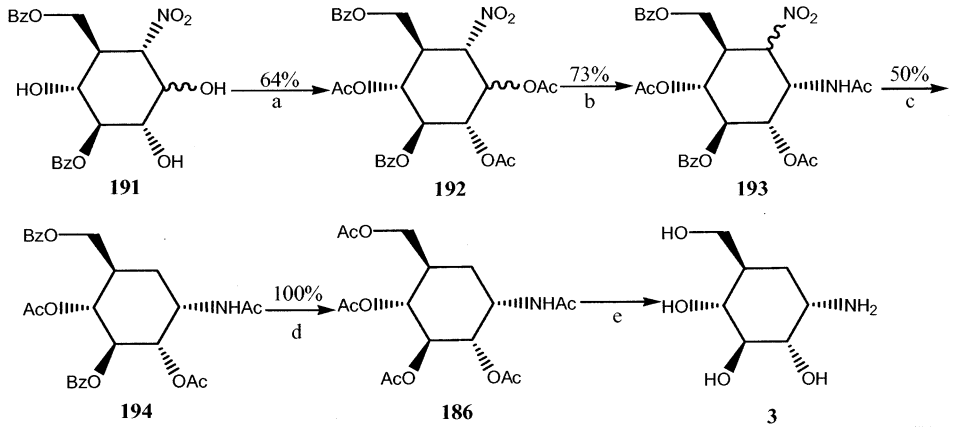
b. Synthesis from D-Glucose.[63] With D-glucose as the starting material, validamine was synthesized by Yoshikawa et al. (Scheme 22). Treatment of a nitrofuranose derivative, **187**, with KF in DMF in the presence of 18-crown-6 (23 °C, 3 h) yielded a nitroolefin, **188**. When **188** was treated with 28% liquid NH_3 in THF at −78 °C for 2 h and the product was acetylated with Ac_2O and *p*-TsOH·H_2O, 1α-acetamide **189** was obtained. Elimination of the nitro group in **189** with *n*-Bu_3SnH in benzene in the presence of azobisisobutyronitrile (AIBN) (80 °C, 3 h) formed **190**. After removal of the acetyl groups and the benzoyl group in **190** with 1% NaOH−MeOH, the product was subjected to debenzylation (Na, liquid NH_3, −78 °C, 30 min) and subsequent acetylation with Ac_2O in pyridine, to provide pentaacetylvalidamine (**186**). Finally, de-*O*-acetylation of **174** with 10% NaOMe−MeOH (25 °C, 3 h), followed by de-*N*-acetylation with 80% aqueous NH_2NH_2 in a sealed tube (100 °C, 72 h), furnished **3**. So, the synthesis of validamine from **187** was achieved with an overall yield of 29.09%.

c. Synthesis from Nitrofuranose. Yoshikawa et al. reported the synthesis of validamine from the nitrocyclitol, which is an intermediate in the synthesis of pseudo-D-glucopyranose (Scheme 23).[34] The synthesis was accomplished in five steps from **191** to **186** with an overall yield of 23.36%.

Scheme 22

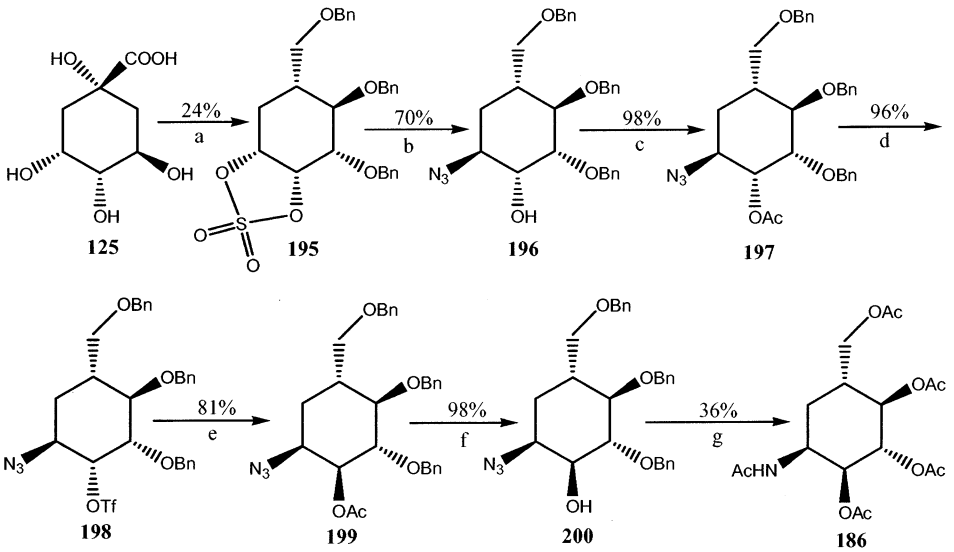


Scheme 23[a]



[a] Reagents and conditions: (a) *p*-TsOH, Ac_2O; (b) liquid NH_3, THF, −78 °C; *p*-TsOH, Ac_2O; (c) *n*-Bu_3SnH, AlBN; toluene, heat; (d) 1% NaOMe−MeOH; Ac_2O, pyridine; (e) 1% NaOMe−MeOH; 80% aqueous NH_2NH_2, 100 °C.

Scheme 24[a]

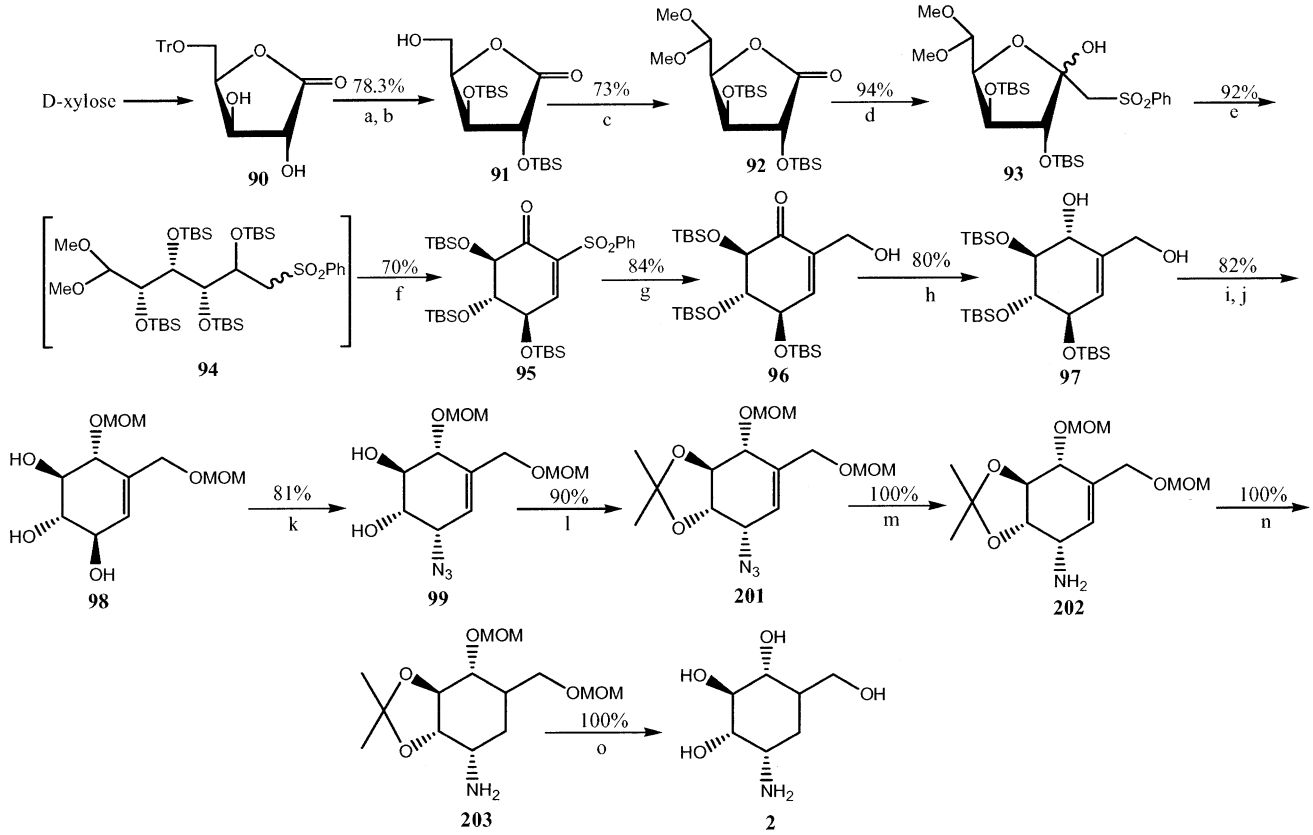


[a] Reagents and conditions: (a) nine steps;[66,67] (b) LiN_3, DMF, 105 °C; H_2SO_4, H_2O, THF; (c) Ac_2O, pyridine, CH_2Cl_2; (d) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (e) *n*-Bu_4NOAc, THF, 80 °C; (f) NaOMe, MeOH, room temperature; (g) H_2, Raney Ni, EtOAc, room temperature; Na/NH_3, THF, −78 °C; Ac_2O, pyridine, DMAP.

d. Synthesis from (−)-Quinic Acid.[65] In this synthesis, a regioselective cyclic sulfate opening was the key step (Scheme 24), and the penta-*N*,*O*,*O*,*O*,*O*-acetate **186** was the product. The preparation of **186** was carried out in 15 steps with a total yield of 1.06%. The product, **186**, could be deacetylated smoothly to give the free target molecule **3** in quantitative yield.

e. Synthesis from D-Xylose. Compound **90**, which was derived from D-xylose, was utilized for the synthesis of validamine by Tatsuta et al. (Scheme

Scheme 25[a]



[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine/CH_2Cl_2, room temperature, 4 h; (b) H_2, Pd−C/$CHCl_3$, room temperature, 12 h; (c) (1) DCC, Py·TFA, DMSO/Et_2O, room temperature, 30 min; (2) CSA, $HC(OMe)_3$/MeOH, 50 °C, 15 h; (d) $MeSO_2Ph$, *n*-BuLi/THF, −78 °C, 30 min; (e) TBSOTf, 2,6-lutidine/CH_2Cl_2, 40 °C, 2 days; (f) $SnCl_4/CH_2Cl_2$, −78 °C, 3 h; (g) *n*-Bu_3SnLi, HCHO/THF, −78 °C to 40 °C, 3 days; (h) $Zn(BH_4)_2$/ether, 0 °C, 1 h; (i) MOMCl, *n*-Bu_4NI, DIPEA, CH_2ClCC, H_2Cl, 50 °C, 24 h; (j) TBAF/THF, room temperature, 3 h; (k) HN_3, Ph_3P, DEAD/THF, room temperature, 1 h; (l) $Me_2C(OMe)_2$, CSA/DMF, 90 °C, 3 h; (m) H_2, Raney Ni/H_2O/1,4-dioxane, room temperature, 2 h; (n) 3 atm H_2, Raney Ni/H_2O/1,4-dioxane, room temperature, 10 h; (o) 3% HCl−MeOH, 50 °C, 3 h.

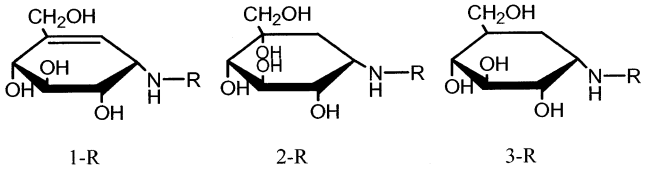


Figure 2.

25).[37] The synthesis of validamine was achieved in 15 steps with an overall yield of 13.90%.

V. Derivatives of Valienamine and Its Related Pseudo-aminosugars

Valienamine and its related pseudo-aminosugars could be reacted with alkyl halides and epoxides, condensed with aldehydes (or ketones), and reduced to give *N*-alkyl- and *N*-aralkylvalienamines and other related pseudo-aminosugars, some of which are strong glucosidase inhibitors.

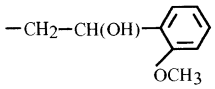
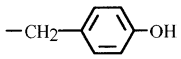
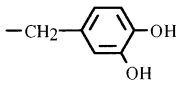
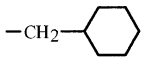
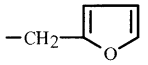
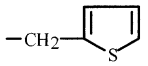
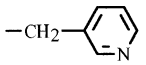
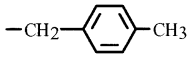
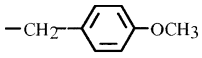
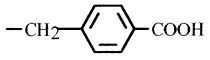
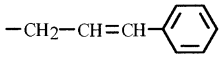
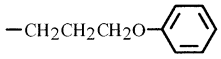
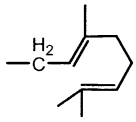
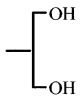
A. Derivatives of Valienamine[79,80]

N-Alkyl- and *N*-aralkylvalienamine (Figure 2) were synthesized by (a) the reaction of valienamine with an alkyl halide, (b) condensation of valienamine with an aldehyde (or a ketone) and reduction of the resulting Schiff base, or (c) reaction of valienamine with an epoxide. The inhibitory activity of the derivatives against glucosidase from yeast was measured at pH 6.8 in 0.02 M phosphate buffer, with 0.05 M maltose as the substrate. The inhibitory activity of the derivatives against sucrase and maltase, prepared from porcine intestinal mucosa, was measured at pH 6.0 in 0.02 M phosphate buffer, with 0.05 M sucrose or maltose as the substrate, respectively. The liberated D-glucose was determined by the D-glucose oxidase method to calculate the 50% inhibition concentration (IC_{50}). Table 8 shows IC_{50} values of *N*-alkyl- and *N*-aralkylvalienamines for the glucosidase from yeast, maltase, and sucrase from the porcine intestinal mucosa. Their $[\alpha]^{25}_D$ values are also shown in Table 8.

From Table 1, we can see that some *N*-alkyl- and *N*-aralkylvalienamines have stronger inhibitory activity against glucosidase (yeast), sucrase (porcine), and maltase (porcine) than the parent valienamine. The highest inhibitory activity was observed in the Ph-$(CH_2)_n$ substituent series. Furthermore, the inhibitory activity tends to increase with introduction of hydroxyl groups into the alkyl or phenyl moiety. But the conversion of the phenyl group in the aralkyl substituent moiety to a heterocyclic group, such as a furyl, thienyl, or pyridyl group, did not improve the inhibitory activity. On the other hand, *N*-acylvalienamines, unlike *N*-alkyl- and *N*-aralkylvalienamines, are lacking or very low in inhibitory activity.

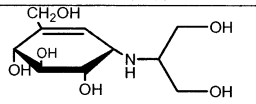
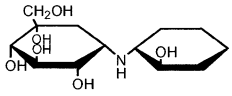
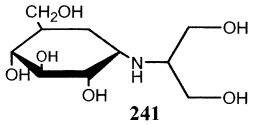
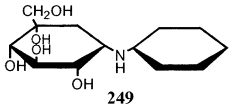
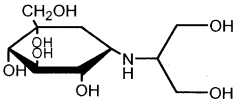
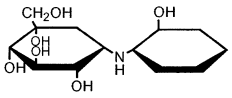
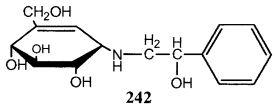
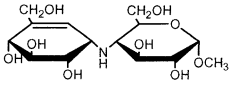
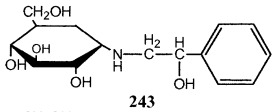
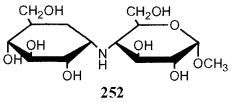
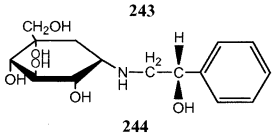
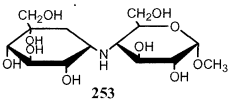
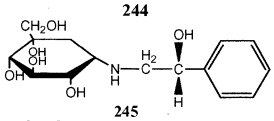
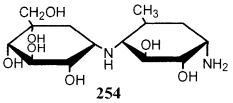
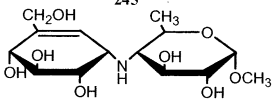
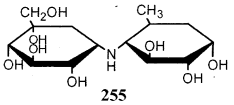
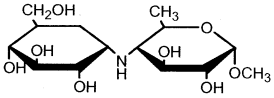
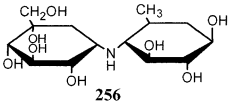
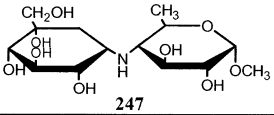
Except for the *N*-substituted derivatives, valienamine was converted into glucoside derivatives with

Table 8. $[\alpha]^{25}_D$ and IC_{50} Values of *N*-Alkyl- and *N*-Aralkylvalienamines

compound			IC_{50}		
R	no.	$[\alpha]^{25}_D$	glucosidase	maltase	sucrase
−H	**1**	+80.5° (H_2O)		3.4×10^{-4}	5.3×10^{-5}
-$OCCH_3$	**204**	+141.4° (H_2O)		$>1.0 \times 10^{-3}$	4.5×10^{-4}
-$OCCH_2CH_3$	**205**	+145.5° (H_2O)		$>1.0 \times 10^{-3}$	$>1.0 \times 10^{-3}$
-$OCCH_2CH_2CH_3$	**206**	+158.1° (H_2O)		$>1.0 \times 10^{-3}$	$>1.0 \times 10^{-3}$
−CH_2CH_3	**207**	+122.7° (H_2O)		3.4×10^{-4}	3.4×10^{-5}
−$CH_2CH_2CH_3$	**208**	+119.3° (H_2O)		3.4×10^{-4}	5.5×10^{-5}
−$CH_2CH_2CH_2CH_3$	**209**	+115.4° (H_2O)	2.1×10^{-5}	4.9×10^{-5}	5.6×10^{-6}
−CH_2-Ph	**210**	+80.5° (H_2O)	9.2×10^{-6}	6.4×10^{-5}	2.4×10^{-6}
−CH_2CH_2-Ph	**211**	+127.5° (H_2O)	1.8×10^{-6}	4.6×10^{-6}	1.8×10^{-6}
−$CH_2CH_2CH_2$-Ph	**212**	+103.0° (H_2O)	2.2×10^{-6}	8.5×10^{-6}	2.4×10^{-6}
−$CH_2CH_2CH_2CH_2$-Ph	**213**	+95.2° (H_2O)	9.8×10^{-7}	3.4×10^{-5}	8.1×10^{-6}
−$(CH_2)_5$-Ph	**214**	+36.7° (CH_3OH)	7.5×10^{-7}	5.9×10^{-5}	6.0×10^{-6}
−$(CH_2)_6$-Ph	**215**	+65.0° (CH_3OH)		1.7×10^{-5}	4.2×10^{-6}
−$CH(CH_3)$-Ph	**216**	+91.9° (H_2O)	1.3×10^{-5}	1.5×10^{-4}	1.7×10^{-5}
−CH_2−$CH(Ph)_2$	**217**	+78.1° (CH_3OH)	3.8×10^{-8}	1.9×10^{-4}	3.5×10^{-5}
−CH_2−$CH(CH_3)$-Ph	**218**	+79.2° (CH_3OH)	1.3×10^{-5}	1.7×10^{-4}	3.2×10^{-6}
−$CH(CH_3)$−CH_2-Ph	**219**	+94.7° (CH_3OH)		1.0×10^{-5}	1.3×10^{-6}
−CH_2−CH(OH)-Ph	**220**	+101.4° (H_2O)	1.1×10^{-6}	1.4×10^{-6}	1.9×10^{-7}
	**221**	+119.8° (H_2O)	3.8×10^{-7}	1.3×10^{-5}	6.3×10^{-6}
−CH(CH_2OH)-Ph	**222**	+120.6° (H_2O)		1.4×10^{-5}	1.8×10^{-6}
−CH(CH_2OH)−CH(OH)-Ph	**223**	+34.4° (H_2O)		9.6×10^{-6}	5.8×10^{-6}
	**224**	+149.8° (H_2O)	5.0×10^{-6}	1.9×10^{-5}	1.4×10^{-6}
	**225**	+76.7° (H_2O)		8.1×10^{-6}	6.2×10^{-7}
	**226**	+110.8° (H_2O)		5.5×10^{-4}	4.1×10^{-6}
	**228**	+112.2° (H_2O)		3.1×10^{-4}	3.8×10^{-6}
	**229**	+94.0° (H_2O)	3.8×10^{-7}	1.5×10^{-4}	1.5×10^{-5}
	**230**	+129.8° (H_2O)	1.5×10^{-4}	3.0×10^{-4}	1.6×10^{-5}
	**231**	+126.8° (H_2O)	3.8×10^{-5}	1.5×10^{-4}	6.0×10^{-6}
	**232**	+123.6° (H_2O)	5.6×10^{-5}	5.1×10^{-4}	1.2×10^{-5}
	**233**	+123.6° (CH_3OH)	2.0×10^{-5}		
	**234**	+108.8° (CH_3OH)	1.8×10^{-5}		
	**235**	+84.0° (H_2O)	1.5×10^{-4}		
	**236**	+112.2° (CH_3OH)	2.0×10^{-5}		
	**237**	+83.1° (CH_3OH)	1.1×10^{-6}		
	**238**	+90.3° (CH_3OH)	1.7×10^{-6}	5.2×10^{-6}	
	**239**	+111.0° (CH_3OH)	6.6×10^{-5}	1.4×10^{-5}	

enzyme synthesis by Furumoto et al.[12,84,88] The inhibitory activity of these compounds against maltase and sucrase was not high; some of them were weaker than valienamine.

Table 9. Inhibitory Effects (IC_{50}, M) of *N*-Substituted Valienamine, Validamine, and Valiolamine Derivatives on Porcine Maltase and Sucrase

Derivatives	Maltase	Sucrase	Derivatives	Maltase	Sucrase
 **240**	5.9×10^{-6}	1.8×10^{-7}	 **248**	6.1×10^{-9}	5.2×10^{-9}
 **241**	5.5×10^{-7}	1.3×10^{-8}	 **249**	4.1×10^{-7}	1.5×10^{-8}
 **10**	1.5×10^{-8}	4.6×10^{-9}	 **250**	1.6×10^{-6}	1.6×10^{-7}
 **242**	1.4×10^{-6}	1.9×10^{-7}	 **251**	7.2×10^{-6}	3.2×10^{-7}
 **243**	1.7×10^{-6}	2.2×10^{-8}	 **252**	4.4×10^{-6}	5.8×10^{-7}
 **244**	5.8×10^{-9}	2.9×10^{-9}	 **253**	7.2×10^{-8}	8.0×10^{-8}
 **245**	5.0×10^{-8}	1.9×10^{-8}	 **254**	2.8×10^{-8}	7.5×10^{-9}
 **11**	3.2×10^{-6}	7.0×10^{-7}	 **255**	6.8×10^{-8}	3.6×10^{-8}
 **246**	1.8×10^{-6}	7.4×10^{-7}	 **256**	7.0×10^{-8}	3.5×10^{-8}
 **247**	4.9×10^{-9}	1.0×10^{-8}			

B. Inhibitory Effects of *N*-Substituted Valienamine, Validamine, and Valiolamine Derivatives[12,74]

The porcine maltase and sucrase inhibitory effects of *N*-substituted valienamine, validamine, and valiolamine derivatives were compared. As shown in Table 9, the valiolamine derivatives are more potent than the corresponding valienamine and validamine derivatives as well as the parent valiolamine, valienamine, and validamine.

The stereochemistry of the hydroxyl group on the cyclohexyl unit of *N*-(hydroxycyclohexyl)valiolamines also influences the activity. The hydroxy group of the *N*-[(1*R*,2*R*)-2hydroxycyclohexyl] isomer **248** exerts a positive effect on the activity, while the hydroxyl group of the *N*-[(1*S*,2*S*)-2-hydroxycyclohexyl] isomer **250** exerts a negative effect on the activity, in comparison with the nonsubstituted cyclohexyl derivative **249**. The inhibitory activity tends to increase, especially against porcine maltase, with the introduction of a hydroxyl group into the proper position on the alkyl, cyclohexyl, or aralkyl moiety of the *N*-substituted group, which is supposed to interact with the aglycon binding subsite of the enzyme.

Replacement of the valienamine unit of acarviosin (**11**) and its 6′-hydroxy derivative **246**, the key pseudo-disaccharides of naturally occurring oligosaccharide α-D-glucosidase inhibitors, with a valiolamine unit leads to a remarkable increase in porcine maltase and sucrase inhibitory activity, especially the maltase inhibitory activity (compounds **247** and **253**). The pseudo-disaccharides **255** and **256**, which were formed by coupling two pseudo-sugar units, valiolamine and 7-deoxy-pseudo-D-glucopyranose, by an −NH− bond, showed undiminished potency as compared to the valiolamine analogue of **11**, **247**. The enzyme inhibitory activity was not greatly affected by the functional group (hydroxyl or amino group) or the stereochemistry(α or β) of the C-1′ carbon,

which corresponds to the anomeric carbon atom of the reducing end-group of **11**.

Synthetically, especially for large-scale preparation, the *N*-[2-hydroxy-1-(hydroxymethyl)ethyl] derivative is more attractive than the derivatives that have an asymmetric carbon in their *N*-substituted moieties and require stereoresolution. After taking into consideration the ease of preparation and the safety of the possible metabolites of the *N*-substituted moiety in the living body, voglibose (**10**), the *N*-substituted moiety of which is derived from glycerol, was selected for further biological evaluation over the other *N*-substituted valiolamine derivatives which showed high α-D-glucosidase inhibitory activity.[50]

VI. Prospects for Valienamine and Its Related Pseudo-aminosugars

In recent years, valienamine and its related pseudo-aminosugars have aroused great interest in researchers and scholars all over the world. These compounds are very important, not only because they suppress blood-sugar elevation and are useful in treating symptoms of hyperglycemia and various disorders caused by hyperglycemia, such as obesity, adiposity, hyperlipemia (arteriosclerosis), diabetes, and prediabetes, as well as diseases attributable to sugar metabolism by microorganisms in the oral cavity, such as prophylaxis of dental caries, but they also have value as inhibitors of the processing enzyme glucosidase I in inhibiting the human immunodeficiency virus (HIV) replication-etiologic agent for acquired immune deficiency syndrome (AIDS) and AIDS-related complex. Furthermore, several studies have confirmed the value of the inhibitors of the processing enzyme glucosidase I in the treatment of cancer. Most importantly, they are very important chemical intermediates in the syntheses of their *N*-substituted derivatives with even stronger α-glucosidase inhibition, such as acarbose, adiposins, acarviosin, trestatins, voglibose, and so on.

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