Synthetic Studies on the Validamycins. 10. Total Synthesis of DL-Validoxylamines A and B[1,2]

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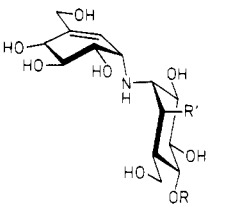
The first synthesis of racemic validoxylamine A (3) and B (4), constituents of antibiotic validamycins, is described. For construction of these types of pseudodisaccharides containing an imino linkage, a coupling reaction of the protected anhydro derivative of DL-pentahydroxy(hydroxymethyl)cyclohexane (5) with the DL-trihydroxy(hydroxymethyl)cyclohexylamine or -cyclohexenylamine (6 or 7) was undertaken. All possible diastereoisomers (four pairs of enantiomers) formed by the reaction of 5 with 6, employed for synthesis of 4, could be separated by chromatography on silica gel, and the relative configurations in two of the enantiomeric pairs, deduced on the basis of ^{1}H NMR spectroscopy, were confirmed by identification of one pair with an authentic chiral sample 4. On the other hand, the intermediate enantiomeric pair **13a** obtained by a coupling of the appropriate epoxide 5 and amine 7 underwent mainly dehydration with sulfuryl chloride in pyridine to give the pair of enantiomers **19a**, one of which was the protected derivative of 3. In contrast, the diastereoisomeric pair of enantiomers **13b** yielded selectively the chloride **18b**, which was then transformed into the enantiomeric pair **21b** by dehydrochlorination followed by deprotection.

Validamycins A (1), B (2), C, D, E, and F and validoxylamines A (3) and B (4) (Chart I), isolated from the culture of *Streptomyces hygroscopicus* var. *limoneus*,[3,4] have been found to be effective in control of sheath blight of rice plants. All validamycins except 2 are D-glycopyranosides possessing 3 as an aglycon and differ in activities depending on the site and/or type of glycosidic bond to 3. Although validamycins C and D as well as 3 and 4 show very low activity (less than $^1/_{1000}$ of that of 1) by the "dendroid test method", they show considerable activity by the green house test.[4]

In a continuation of the previous paper of this series,[1c] we describe the details of the first total synthesis of racemic 3 and 4. The present synthesis involved coupling reactions of the protected anhydro derivative of DL-pentahydroxy(hydroxymethyl)cyclohexane (5) with the protected DL-trihydroxy(hydroxymethyl)cyclohexylamine (7) or -cyclohexenylamine (6) to construct the pseudodisaccharide structures containing an imino linkage. [Since each of the two initial reactants is a racemic modification, each set of subsequent products or intermediates, depicted by **8a,b**–**21a,b**, consists of four compounds, **a** and **b**, each being a two-component racemic modification, and each enantiomeric component in **a** being a diastereoisomer of the two enantiomers in **b** (and vice versa). However, for each formula number, only one structural formula, rather than four, is shown.]

Synthesis of DL-Validoxylamine B. Validoxylamine B (4) was first obtained, along with D-glucose, from the acid hydrolysate of 2,[5] and later isolated as well as 3 from the fermentation broth of validamycin producing microorganism.[4] Hydrogenolysis of 4 gave (1*S*)-(1,2,4/3,5,6)-2,3,4,6-tetrahydroxy-5-(hydroxymethyl)cyclohexylamine [(+)-hydroxyvalidamine], (1*S*)-(1,3,4/2)-4-(hydroxymethyl)-1,2,3-cyclohexanetriol [(+)-validatol], and (+)-deoxyvalidatol.[5,6] The structure of 2 was assigned as the β-D-glucopyranoside of 4, that is, the 6-hydroxy analogue of 1.

Chart I



	R	R'
1	β-D-Glucopyranosyl	H
2	β-D-Glucopyranosyl	OH
3	H	H
4	H	OH

We attempted a coupling reaction of DL-3,4-di-*O*-acetyl-1,2-anhydro-5,7-*O*-benzylidene-(1,2,4,6/3,5)-1,2,3,4,5-pentahydroxy-6-(hydroxymethyl)cyclohexane (5)[7] with DL-4,7:5,6-di-*O*-isopropylidene-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenylamine (6)[8] for direct construction of the pseudodisaccharide structure identical with 4 (Chart II).

When molar equivalents of 5 and 6 were heated in a small amount of 2-propanol in a sealed tube at 120 °C, after 7 days, the formation of two major components along with several minor components was shown by TLC. The product mixture was chromatographed on silica gel to give the protected pseudodisaccharides **8a**, **8b**, **9a**, and **9b** as crystals in 9%, 2%, 11%, and 18% yields, respectively, along with a 23% yield of recovered 5. Alternatively, the mixture after treatment with 70% aqueous acetic acid to remove the benzylidene and isopropylidene groups was

(1) For a preliminary communication, see: (a) Ogawa, S.; Toyokuni, T.; Iwasawa, Y.; Abe, Y.; Suami, T. *Chem. Lett.* **1982**, *279*. (b) Ogawa, S.; Ogawa, T.; Chida, N.; Toyokuni, T.; Suami, T. *Ibid.* **1982**, 749. The previous paper in this series: (c) Toyokuni, T.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2999.

(2) The nomenclature and numbering of cyclitols used in this paper follow IUPAC and IUB tentative rules for cyclitol nomenclature (*J. Biol. Chem.* **1968**, *243*, 5809). All compounds described in this paper are racemic, and the formulas depict only one of the respective enantiomers.

(3) (a) Iwasa, T.; Higashide, E.; Sibata, M. *J. Antibiot.* **1971**, *24*, 114. (b) Iwasa, T.; Kameda, Y.; Asai, M.; Horii, S.; Mizuno, K. *Ibid.* **1971**, *24*, 119.

(4) Horii, S.; Kameda, Y.; Kawahara, K. *J. Antibiot.* **1972**, *25*, 48.

(5) Horii, S.; Iwasa, T.; Kameda, Y. *J. Antibiot.* **1971**, *24*, 57.

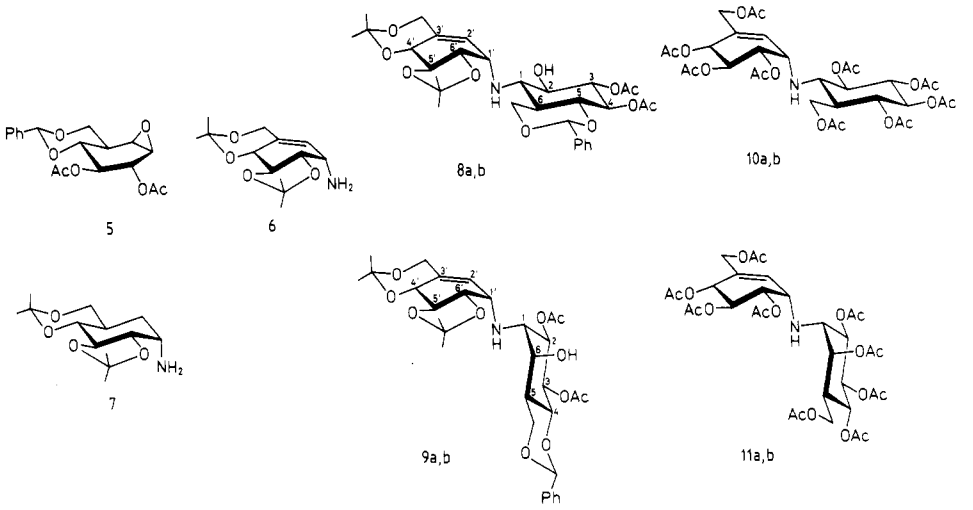
(6) Horii, S.; Iwasa, T.; Mizuta, E.; Kameda, Y. *J. Antibiot.* **1971**, *24*, 59.

(7) Ogawa, S.; Chida, N.; Suami, T. *Chem. Lett.* **1980**, 1559; *J. Org. Chem.* **1983**, *48*, 1203.

(8) Toyokuni, T.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1161.

0022-3263/84/1949-2594$01.50/0

Chart II[a]



[a] For convenience, only one diastereoisomer (**8a**-**11a**) is shown.

acetylated to give the peracetates of pseudodisaccharide. Successive column chromatography on silica gel afforded crystalline **10a**, **10b**, **11a**, and **11b** in 8%, 6%, 12%, and 12% yields, respectively. Compounds **8a** and **9a** were convertible into **10a** and **11a**, respectively, by treatment with aqueous acetic acid followed by acetylation.

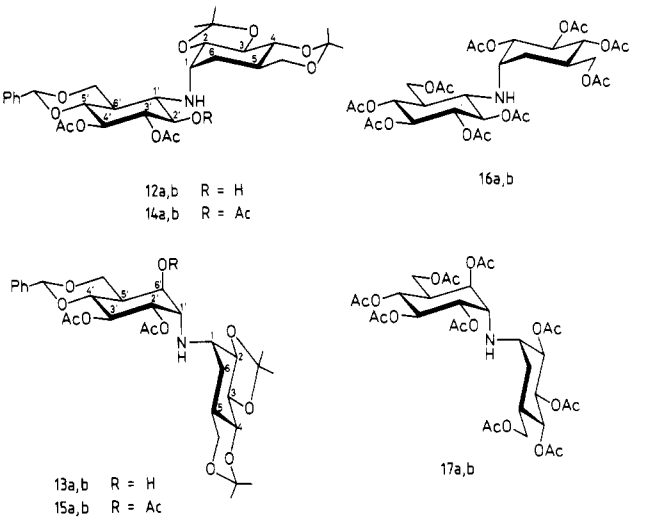
The structures of the condensation products were supported by their elemental analyses and ^{1}H NMR spectra. In particular, the ^{1}H NMR spectrum of **10a** revealed upon deuteration a triplet (δ 2.83, J = 9.8 Hz) which was attributed to the C-1 axial proton attaching to the carbon atom bonding to the imino group, indicative of the axial–axial–axial conformation for H-6, H-1, and H-2. In contrast, in the spectrum of **11a**, the corresponding signal appeared as a triplet (δ 3.29, J = 3.6 Hz), suggesting that the C-1 proton was in the equatorial position. The spectra of **10b** and **11b** were quite similar to those of **10a** and **11a**, respectively. Therefore, **8a** and **8b** have been formed by diequatorial cleavage of the epoxide ring of **5**, while **9a** and **9b** have been derived by the diaxial opening.

Hydrolysis of **11a** with 4 M hydrochloric acid at reflux for 50 min followed by treatment with Amberlite IRA 400 (OH^-) resin gave free pseudodisaccharide racemic modification **4a**, whose ^{1}H NMR spectrum was shown to be superimposable on that of an authentic chiral sample of **4**.[9] Similarly, the racemic modification **4b** was obtained from **11b**. Accordingly, the structures of **9a** and **9b** were fully confirmed. On the other hand, ^{1}H NMR data did not allow definitive assignment of structural formula **8** to the racemic modification **8a** rather than to **8b**, a reverse assignment being possible.

Synthesis of DL-Validoxylamine A. Acid hydrolysis of **1** produced validoxylamine A (**3**) which, on hydrogenolysis, gave (1*S*)-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexylamine [(+)-validamine] and (+)-validatol.[4,5] On the other hand, microbial degradation of **1** or **3** gives (1*S*)-(1,2,4/3)-2,3,4-trihydroxy-5-(hydroxymethyl)-5-cyclohexenylamine [(+)-valienamine].[10] The structure of **3** was elucidated as that shown in Chart I.[11]

Our synthesis of **3** consisted of the initial construction of a saturated pseudodisaccharide structure having the proper stereochemistry, followed by dehydration of the α,β-positions of the imino group. Thus, condensation of the racemic modification **5** with DL-2,3:4,7-di-*O*-isopropylidene-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)validamine] (**7**)[1c] was carried out in 2-propanol in a sealed tube at 120 °C. After 9 days, TLC indicated disappearance of **5** and **7** and formation of two major components. Column chromatography of the condensates on silica gel afforded two four-component, diastereomeric mixtures, one consisting of the enantiomeric pairs **12a** and **12b**, the other, **13a** and **13b**, as crystals in 16% and 44% yields, respectively (Chart III). The mixture of **12a** and **12b** was treated with acetic anhydride in pyridine at ambient temperature to give the corresponding triacetates, which were separated by chromatography to give **14a** (25%) as crystals and **15b** (26%) as an oil. Alternatively, the mixture of **12a** and **12b** was treated with 80% aqueous acetic acid followed by acetylation to give **16a** (43%) and **16b** (36%) as crystals after chromatography. Compound **14a** could be converted to **16b**. On the other hand, the mixture of **13a** and **13b** was acetylated to give, after chromatography, the corresponding triacetate **15a** (39%) and **15b** (26%), each as a glassy product. Compounds **15a** and **15b** were similarly transformed into the nonaacetate

Chart III[a]



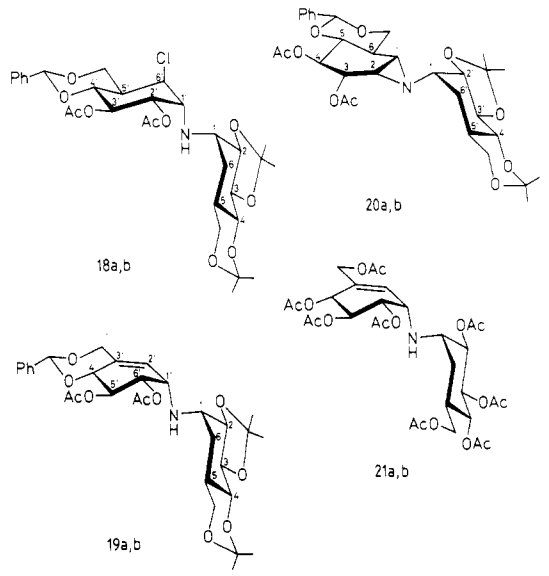
[a] For convenience, only one diastereoisomer (**12a**-**17a**) is shown.

(9) The ^{1}H NMR spectrum of an authentic sample (chiral) was kindly provided by Dr. Satoshi Horii (Takeda Chemical Ind. Inc., Osaka, Japan).

(10) Kameda, Y.; Horii, S. *J. Chem. Soc., Chem. Commun.* **1972**, 746. Kameda, Y.; Asano, N.; Teranishi, M.; Matsui, K. *J. Antibiot.* **1980**, *33*, 1573.

(11) Horii, S.; Kameda, Y. *J. Chem. Soc., Chem. Commun.* **1972**, 747.

Chart IV[a]



[a] For convenience, only one diastereoisomer (18a–21a) is shown.

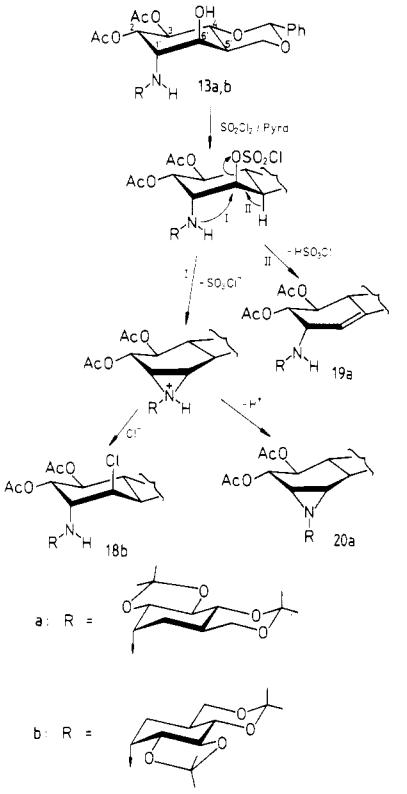
17a and 17b in good yields, respectively.

The ^{1}H NMR spectra of **15a** and **15b** revealed two signals due to the protons on the carbon atoms (C-2′ and C-6′) bearing the acetoxyl groups as doublets and doublets (J = 4.5 and 10.5 Hz) and triplets (J = 3 Hz) at δ 5.09–5.10 and 4.79–5.02, respectively. On the other hand, in the spectra of **16a** and **16b**, the broad quartet (J = ca. 10 Hz) at δ 2.83–2.88 can be ascribed to the axial protons on the carbon atoms (C-1′) attached to the imino group. Accordingly, **12a** and **12b** were formed by diequatorial opening of the epoxide ring of **5**, and **13a** and **13b** by diaxial opening.[12]

Attempts to introduce a double bond between C-5′ and C-6′ through an elimination reaction of the C-6′ chlorosulfate ester of **13a** and **13b** were then conducted. Although a nucleophilic attack at C-6′ by the nitrogen at C-1′ was expected as a competing side reaction, attempted deactivation of the imino group was unsuccessful. The mixture **13a** and **13b** was therefore directly treated with an excess of sulfuryl chloride in pyridine at −15 °C for 2 h, followed by at 3 °C overnight (Chart IV). At that time, TLC showed the two major components and two minor components. Chromatography of a mixture of products on silica gel afforded crystalline chloride **18b** and aziridine **20a** in 42% and 4% yields, respectively, along with oily **19a** contaminated with trace of unidentified compounds. When the mixture of **13a** and **13b** was treated with methanesulfonyl chloride in pyridine, only **18b** and **20a** were obtained in rather low yields.

The structure of **18b** was confirmed by the ^{1}H NMR spectrum, which showed a narrow triplet (δ 4.00, J = 3 Hz), attributable to the equatorial proton on the carbon atom carrying the chlorine atom. This was also verified by the following reaction. Dehydrochlorination of **18b** was effected by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene for 3 h to give crystalline

Scheme I. Postulated Mechanism of Reaction of 13a,b with Sulfuryl Chloride in Pyridine[a]



[a] For convenience, only one diastereoisomer is shown.

olefin **19b** and aziridine **20b** in 56% and 31% yields, respectively.

The ^{1}H NMR spectrum of **20b** showed the signals due to the aziridine protons (H-1 and H-2) as a doublet (δ 1.23, $J_{1,2}$ = 6 Hz) and a doublet (δ 2.42, $J_{1,2}$ = 6 Hz, $J_{2,3}$ = 4 Hz), respectively. These data correspond to the dihedral angle $\Phi_{1,6}$ (90°) ($J_{1,6}$ = ca. 0 Hz) deduced from a molecular model. The ^{1}H NMR spectrum of **20a** was similar to that of **20b** except for a small difference in the chemical shifts of the signals due to the aziridine protons.

The crude **19a** was hydrolyzed with 1 M hydrochloric acid at 90 °C followed by acetylation to give **21a** as an oil in 9% yield based on **5** used. The ^{1}H NMR spectrum of **21a** was superimposable on that of an authentic chiral sample derived from **3**.[13] Compound **19b** was also converted into **21b** in 78% yield. Due to the close similarity of the ^{1}H NMR spectra, **21a** and **21b** were diastereoisomers.

The above results suggest that the reactions of the intermediate chlorosulfate esters of **13a** and **13b** proceed in diastereoselective fashion (Scheme I). In the case of **13b**, the chlorosulfate ester is converted selectively into the intermediate aziridinium ion through nucleophilic attack by the imino group. The intermediate is then diaxially cleaved by a chloride ion generated in situ to give **18b**. This assumption is supported by the retention of the configuration at C-6′.[14] The chlorosulfate ester of **13a** undergoes preferential elimination of chlorosulfonic acid to give **19a**, along with **20a** which is formed through

(12) The structures of **14a** and **14b** could not be distinguished on the basis of almost identical ^{1}H NMR spectra. Therefore, the structures exhibited in Chart III may be reversed. Compounds **15a** and **15b** have been correlated to neither **21a** nor **21b** yet. However, the ^{1}H NMR spectra of **15a** and **15b** revealed the signals due to the C-6′ equatorial protons as doublets of doublets at δ 5.02 and 4.79, respectively. The deshielding effect observed for **15a** might be attributable to the close proximity of the oxygen atom of the dioxolane ring to H-6′.

(13) An authentic sample of **3** was provided by Dr. Satoshi Horii, to whom our thanks are due.

(14) Chlorination of an secondary alcohol with sulfuryl chloride in pyridine proceeds through an S_N2 reaction, in which an intermediate chlorosulfate ester is attacked by a chloride ion, resulting in the inversion of the configuration: Jennings, H. J.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 2372 and references are cited therein.

neighboring group participation. Attack of a chloride ion at the aziridinium ion seems to be hampered by steric hindrance in this case. In view of the stringent conditions required for the dehydrochlorination of **18b** by DBU, formation of **19a** via an intermediate **18a** is unlikely under these reaction conditions.

In order to accomplish the total synthesis of chiral **3** and **4** as well as to offer further evidence for the postulated reaction mechanism, utilization of chiral **6** and **7** in the coupling reactions is being carried out.

Experimental Section

Melting points were determined on a Büchi 510 capillary melting point apparatus or a Mitamura Riken micro hot stage and are uncorrected. ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) or JEOL FX-200 (200 MHz) spectrometer in chloroform-*d* with tetramethylsilane as an internal standard. The peak positions are given in terms of δ values, and values given for coupling constants are of first order. TLC was performed on precoated silica gel 60 F-254 plates (Merck, Darmstadt, 0.25-mm thickness). The silica gel used for column chromatography was Wakogel C-300 (Wako Pure Chemical Industries, Ltd., Osaka). Organic solutions were dried over anhydrous sodium sulfate. Solutions were concentrated below 50 °C under reduced pressure.

Condensation of DL-3,4-Di-*O*-acetyl-1,2-anhydro-5,7-*O*-benzylidene-(1,2,4,6/3,5)-1,2,3,4,5-pentahydroxy-6-(hydroxymethyl)cyclohexane (5) with DL-4,7:5,6-Di-*O*-isopropylidene-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenylamine [DL-Di-*O*-isopropylidenevalienamine] (6). (a) A mixture of **5** (327 mg, 0.94 mmol) and **6** (240 mg, 0.94 mmol) in 2-propanol (3 mL) was heated in a sealed tube at 120 °C for 7 days. TLC indicated the formation of two major products (R_f 0.33 and 0.30) and two minor products (R_f 0.35 and 0.39), along with **5** (R_f 0.54), in 1:10 ethanol–toluene. The reaction mixture was concentrated to give a brown residue (567 mg), which was transferred on a silica gel column (25 g) and eluted with 2:11 acetone–toluene. The first fraction (R_f 0.54) gave 74 mg (23% recovered yield) of **5**. The second fraction (R_f 0.39) gave 40 mg (9%) of ***N*-[(1*SR*)-4,7:5,6-di-*O*-isopropylidene-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*SR*)-3,4-di-*O*-acetyl-5,7-*O*-benzylidene-(1,2,4/3,5,6)-2,3,4,5-tetrahydroxy-6-(hydroxymethyl)cyclohexylamine (8a)** as prisms: mp 272 °C dec; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.65–7.25 (m, 5, phenyl), 5.49–5.40 (m, 1, $C_{2'}$ H), 5.45 (s, 1, benzylic), 5.14 (dd, 1, J = 9.3 and 9.8 Hz) and 5.02 (t, 1, J = 9.3 Hz) (C_3 H, C_4 H), 2.11 (s, 3) and 2.06 (s, 3) (OAc), 1.59 (s, 3), 1.53 (s, 3), 1.50 (s, 3), and 1.47 (s, 3) (isopropylidene).

The third fraction containing three components (R_f 0.35, 0.33, and 0.30) was concentrated to give a pale yellow oil (420 mg), which was crystallized from ethanol to give 130 mg of crystalline mixture. Fractional crystallization from ethyl acetate gave 79 mg (18%) of **DL-*N*-[(1*SR*)-4,7:5,6-di-*O*-isopropylidene-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*RS*)-2,3-di-*O*-acetyl-4,7-*O*-benzylidene-(1,2,4/3,5,6)-2,3,4,6-tetrahydroxy-5-(hydroxymethyl)cyclohexylamine (9b)** as prisms: mp 257–257.5 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.30–7.26 (m, 5, phenyl), 5.76–5.29 (m, 4, C_2 H, C_3 H, $C_{2'}$ H, benzylic), 2.74–2.32 (m, 1, C_2 H), 2.06 (s, 3) and 2.03 (s, 3) (OAc), 1.53 (s, 3) and 1.44 (s, 9) (isopropylidene).

The mother liquor from **9b** was concentrated and the residue was crystallized from ethanol (3 mL) to give 10 mg (2%) of the diastereoisomer **8b** of **8a** as needles: mp 255–265 °C dec; R_f 0.35 in 1:10 ethanol-toluene; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.53–7.20 (m, 5, phenyl), 5.61–5.41 (m, 1, $C_{2'}$ H), 5.43 (s, 1, benzylic), 5.23 (dd, 1, J = 8.3 and 9.3 Hz) and 5.05 (t, 1, J = 9.3 Hz) (C_3 H, C_4 H), 2.51 (dd, 1, J = 9.6 and 11.3 Hz, C_6 H), 2.08 (s, 3) and 2.02 (s, 3) (OAc), 1.54 (s, 3), 1.49 (s, 6), and 1.40 (s, 3) (isopropylidene).

The mother liquor of 130 mg of crystals was concentrated and the residue was crystallized from methanol to give 72 mg of crude crystals of the diastereoisomer **9a** of **9b**. It was purified by a silica gel column (3 g) with 2:9 2-butanone–toluene as an eluant and then recrystallized from ethanol to give 48 mg (11%) of **9a** as prisms: mp 232–233 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.65–5.27 (m, 4, C_2 H, C_3 H, $C_{2'}$ H, benzylic), 3.58–3.17 (m, 2, C_1 H, $C_{1'}$ H), 2.90–2.44 (m, 1, C_5 H), 2.10 (s, 3) and 2.03 (s, 3) (OAc), 1.55 (s, 3), 1.53 (s, 3), and 1.44 (s, 6) (isopropylidene).

Anal. Calcd for $C_{31}H_{41}NO_{11}$: C, 61.68; H, 6.85; N, 2.32. Found for **8a**: C, 61.42; H, 6.83; N, 2.33. Found for **8b**: C, 61.79; H, 6.70; N, 2.35. Found for **9a**: C, 61.40; H, 6.77; N, 2.41. Found for **9b**: C, 61.44; H, 6.92; N, 2.25.

(b) A mixture of **5** (684 mg) and **6** (500 mg, molar equiv) was treated as described above to give, after chromatographic purification, 547 mg of condensates. It was heated with 80% aqueous acetic acid (40 mL) at 60 °C for 13 h. The reaction mixture was concentrated and the residue was treated with acetic anhydride (8 mL) and pyridine (8 mL) at ambient temperature for 2 days. TLC showed the presence of one major (R_f 0.35) and three minor components (R_f 0.50, 0.44, and 0.36) in 1:3 2-butanone–toluene. The oily mixture (647 mg) obtained was fractionated by a silica gel column (32 g) with 1:8 2-butanone-toluene as an eluant. The first fraction gave 86 mg of an oily product, whose ^{1}H NMR spectrum showed the presence of a benzylidene group (δ 5.60, s, 1, benzylic). Therefore, the oil was treated with 1 M hydrochloric acid (3 mL) at reflux for 1 h, then treated with Amberlite IRA 400 (OH^-) resin, and acetylated in the usual way. The product was purified by a short column of alumina with chloroform and crystallized from ethanol to give 77 mg (7.8%) of ***N*-[(1*SR*)-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*SR*)-(1,3,5/2,4,6)-2,3,4,5-tetrahydroxy-6-(hydroxymethyl)cyclohexylamine nonaacetate (10a)** as prisms: mp 150–151 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.99 (d, 1, J = 6 Hz, $C_{2'}$ H), 5.79–5.54 (m, 2, $C_{4'}$ H, $C_{5'}$ H), 5.28–4.82 (m, 5, C_2 H, C_3 H, C_4 H, C_5 H, $C_{6'}$ H), 4.63 (d, 1) and 4.30 (d, 1) (J = 13.4 Hz, C=CCH_2OAc), 4.26 (br s, 2, CHCH_2OAc), 3.77 (t, 1, J = 6 Hz, $C_{1'}$ H appears upon deuteration), 2.83 (t, 1, J = 9.8 Hz, C_1 H appears upon deuteration), 2.81–1.86 (m, total 27, OAc).

Compound **10a** was identical with the nonaacetate derived from **8a** by similar treatment with 1 M hydrochloric acid followed by acetylation.

The second fraction gave 59 mg of an oily product, whose ^{1}H NMR spectrum also showed the presence of the benzylidene group. O-Debenzylidenation followed by acetylation as described above gave 59 mg (6%) of the diastereoisomer **10b** of **10a** as prisms: mp 175–176 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.90 (d, 1, J = 4.2 Hz, $C_{2'}$ H), 5.51–4.86 (m, 5, C_2 H, C_3 H, C_4 H, C_5 H, $C_{6'}$ H), 4.65 (d, 1) and 4.34 (d, 1) (J = 12 Hz, C=CCH_2OAc), 4.48 (dd, 1, J = 4 and 12 Hz) and 4.22 (dd, 1, J = 2.7 and 12 Hz) (CHCH_2OAc), 3.81 (t, 1, J = 4.2 Hz, $C_{1'}$ H), 2.92 (t, 1, J = 10.5 Hz, C_1 H), 2.23–1.96 (m, total 27, OAc).

The third fraction gave 314 mg of an oily product, whose ^{1}H NMR spectrum showed the two doublets (J = ca. 5 Hz) at δ 6.00, indicative of being a mixture of **11a** and **11b**. Fractional crystallization from ethanol and then from methanol gave 120 mg (12%) of ***N*-[(1*SR*)-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*SR*)-(1,2,4/3,5,6)-2,3,4,6-tetrahydroxy-5-(hydroxymethyl)cyclohexylamine nonaacetate (11a)** as thin needles, mp 172.5–173.5 °C, and 120 mg (12%) of the diastereoisomer **11b** of **11a** as needles, mp 146.5–147 °C. **11a**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.98 (d, 1, J = 5.5 Hz, $C_{2'}$ H), 5.49–4.88 (m, 7, C_2 H, C_3 H, C_4 H, C_6 H, $C_{4'}$ H, $C_{5'}$ H, $C_{6'}$H), 4.68 (d, 1) and 4.36 (d, 1) (J = 13.5 Hz, C=CCH_2OAc), 4.19 (dd, 1, J = 9.2 and 11.3 Hz) and 3.97 (dd, 1, J = 4.5 and 11.3 Hz) (CHCH_2OAc), 3.56 (t, 1 J = 4.8 Hz, $C_{1'}$ H appears upon deuteration), 3.29 (t, 1, J = 3.6 Hz, C_1 H appears upon deuteration), 2.89–2.54 (m, 1, C_5 H), 2.16–1.95 (m, total 27, OAc). **11b**: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.93 (d, 1, J = 4.9 Hz, $C_{2'}$ H), 5.56–5.04 (m, 7, C_3 H, C_4 H, C_6 H, $C_{4'}$ H, $C_{5'}$ H, $C_{6'}$ H), 4.68 (d, 1) and 4.39 (d, 1) (J = 13 Hz, C=CCH_2OAc), 4.14 (dd, 1, J = 8.4 and 11.7 Hz) and 3.93 (dd, 1, J = 4.6 and 11.7 Hz) (CHCH_2OAc), 3.62 (t, 1, J = 4.5 Hz, $C_{1'}$ H appears upon deuteration), 3.36 (t, 1, J = 3.8 Hz, C_1 H appears upon deuteration), 2.96–2.58 (m, 1, C_5 H), 2.24–1.95 (m, total 27, OAc).

Compound **11a** was identical with the nonaacetate derived from **9a**.

Anal. Calcd for $C_{32}H_{43}NO_{18}$: C, 52.67; H, 5.94; N, 1.92. Found for **10a**: C, 52.34; H, 5.91; N, 1.80. Found for **10b**: C, 52.42; H, 5.84; N, 1.99. Found for **11a**: C, 52.65; H, 5.86; N, 1.89. Found for **11b**: C, 52.74; H, 5.98; N, 1.95.

A mixture of **11a** (31 mg) and 4 M hydrochloric acid (2 mL) was refluxed for 50 min, and then diluted with methanol and the solution was passed through a coulmn of Amberlite IRA 400 (OH^-)

resin (15 mL). The filtrate was concentrated to give 14 mg (100%) of the free base: R_f 0.34 in 4:1:1 1-propanol–water–acetic acid; ^{1}H NMR (D_2O, 90 MHz) δ 6.18 (d, 1, J = 5 Hz, $C_{2'}$ H), 2.28–1.91 (m, 1, C_5 H). The ^{1}H NMR spectrum was identical with that of an authentic sample of **4**.

A mixture of **11b** (20 mg) and 4 M hydrochloric acid (2 mL) was refluxed for 50 min. The reaction mixture was processed as described above to give an oil (9 mg, 100%) of a racemic diastereoisomer of **4**: R_f 0.27 in 4:1:1 1-propanol–water–acetic acid; ^{1}H NMR (D_2O, 90 MHz) δ 5.88 (d, 1, J = 4 Hz, $C_{2'}$ H), 2.08–1.64 (m, 1, C_5 H).

Condensation of 5 with DL-2,3:4,7-Di-*O*-isopropylidene-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexylamine [DL-Di-*O*-isopropylidenevalidamine] (7). A mixture of **5** (0.27 g, 0.78 mmol) and **7** (0.20 g, 0.78 mmol) in 2-propanol (1.5 mL) was heated in a sealed tube at 120 °C for 9 days. TLC showed the formation of two major components (R_f 0.40 and 0.32 in 1:10 ethanol–toluene). The reaction mixture was concentrated and the residue (0.47 g) was chromatographed on a silica gel column (23 g) with 2:9 2-butanone–toluene as an eluant. The first fraction gave 75 mg (16%) of a mixture of ***N*-[(1*SR*)-3,4-di-*O*-acetyl-5,7-*O*-benzylidene-(1,3,5/2,4,6)-2,3,4,5-tetrahydroxy-6-(hydroxymethyl)cyclohexyl]-(1*SR*)-2,3:4,7-di-*O*-isopropylidenevalidamine (12a)** and the diastereoisomer (**12b**) as colorless prisms. Recrystallization from ethanol gave an analytical sample (64 mg): mp 234–237 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.68–7.05 (m, 5, phenyl), 5.43 (s, 1, benzylic), 4.53 (dd, 1, J = 5 and 11 Hz, $C_{7'}$ H_{eq}), 2.05 (s, 3) and 2.01 (s, 3) (OAc), 1.47 (s, 3) and 1.40 (s, 9) (isopropylidene).

The second fraction gave 0.21 g (44%) of a mixture of ***N*-[(1*SR*)-2,3-di-*O*-acetyl-4,7-*O*-benzylidene-(1,2,4/3,5,6)-2,3,4,6-tetrahydroxy-5-(hydroxymethyl)cyclohexyl]-(1*SR*)-2,3:4,7-di-*O*-isopropylidenevalidamine (13a)** and the diastereoisomer (**13b**) as colorless needles. Recrystallization from ethanol gave an analytical sample (0.18 g): mp 255–257 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.57–7.20 (m, 5, phenyl), 5.49 (s, 1, benzylic), 2.08 (s, 3) and 2.03 (s, 3) (OAc), 1.48 (s, 6) and 1.43 (s, 6) (isopropylidene).

Anal. Calcd for $C_{31}H_{43}NO_{11}$: C, 61.47; H, 7.16; N, 2.31. Found for **12a,b**: C, 61.60; H, 7.18; N, 2.18. Found for **13a,b**: C, 61.57; H, 7.16; N, 2.43.

A mixture of **12a,b** (0.12 g) was treated with acetic anhydride (5 mL) and pyridine (5 mL) at ambient temperature overnight. TLC indicated the formation of two components (R_f 0.37 and 0.33 in 1:3 2-butanone–toluene. The reaction mixture was concentrated to give a solid residue which was dissolved in chloroform and passed through a short column of alumina. The filtrate was concentrated and the residue was chromatographed on a silica gel column (6 g) with 2:9 2-butanone–toluene as an eluent. The first fraction gave crystals (34 mg) which were recrystallized from ethanol to give 32 mg (25%) of ***N*-[(1*SR*)-2,3,4-tri-*O*-acetyl-5,7-*O*-benzylidene-(1,3,5/2,4,6)-2,3,4,5-tetrahydroxy-6-(hydroxymethyl)cyclohexyl]-(1*SR*)-2,3:4,7-di-*O*-isopropylidenevalidamine (14a)** as needles: mp 280–282 °C dec; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.51–7.17 (m, 5, phenyl), 5.44 (s, 1, benzylic), 4.62 (dd, 1, J = 5 and 11 Hz, $C_{7'}$ H_{eq}), 2.05 (s, 3), 2.01 (s, 3), and 1.99 (s, 3) (OAc), 1.43 (s, 3) and 1.39 (s, 9) (isopropylidene).

The second fraction gave 33 mg (26%) of the diastereoisomer (**14b**) as a colorless glass: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.62–7.18 (m, 5, phenyl), 5.45 (s, 1, benzylic), 4.62 (dd, 1, J = 5 and 11 Hz, $C_{7'}$ H_{eq}), 2.06 (s, 3), 2.02 (s, 3), and 1.99 (s, 3) (OAc), 1.47 (s, 3) and 1.40 (s, 9) (isopropylidene).

Anal. Calcd for $C_{33}H_{45}NO_{12}$: C, 61.19; H, 7.00; N, 2.16. Found for **14a**: C, 60.94; H, 6.86; N, 2.26. Found for **14b**: C, 60.88; H, 6.90; N, 2.01.

A mixture of **13a,b** (68 mg) was acetylated in the usual way described in the preparation of **14a** and **14b**. The product was shown to contain two components by TLC (R_f 0.49 and 0.46 in 1:10 ethanol–toluene). Chromatography on silica gel (4 g) with 1:10 2-butanone–toluene as an eluant gave, as the first fraction, 28 mg (39%) of ***N*-[(1*SR*)-2,3,6-tri-*O*-acetyl-4,7-*O*-benzylidene-(1,2,4/3,5,6)-2,3,4,6-tetrahydroxy-5-(hydroxymethyl)cyclohexyl]-(1*SR*)-2,3:4,7-di-*O*-isopropylidenevalidamine (15a)** as a glass: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.47–7.17 (m, 5, phenyl), 5.34 (dd, 1, J = 8.3 and 10.5 Hz, $C_{3'}$ H), 5.34 (s, 1, benzylic), 5.09 (dd, 1, J = 4.5 and 10.5 Hz, $C_{2'}$ H), 5.02 (t, 1, J = 3 Hz, $C_{6'}$ H), 2.08 (s, 3), 2.02 (s, 3), and 2.00 (s, 3) (OAc), 1.47 (s, 6), 1.43 (s, 3), and 1.40 (s, 3) (isopropylidene).

The second fraction gave 19 mg (26%) of the diastereoisomer (**15b**) as a glass: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.50–7.23 (m, 5, phenyl), 5.38 (dd, 1, J = 9 and 10.5 Hz, $C_{3'}$ H), 5.38 (s, 1, benzylic), 5.10 (dd, 1, J = 4.5 and 10.5 Hz, $C_{2'}$ H), 4.79 (t, 1, J = 3 Hz, $C_{6'}$ H), 3.38 (dd, 1, J = 4 and 9 Hz, C_2 H), 2.09 (s, 3), 2.02 (s, 3), and 2.00 (s, 3) (OAc), 1.47 (s, 3) and 1.43 (s, 9) (isopropylidene).

Anal. Calcd for $C_{33}H_{45}NO_{12}$: C, 61.19; H, 7.00; N, 2.16. Found for **15a**: C, 61.14, H, 6.99; N, 2.06. Found for **15b**: C, 61.41; H, 6.93; N, 2.12.

***N*-[(1*SR*)-(1,3,5/2,4,6)-2,3,4,5-Tetrahydroxy-6-(hydroxymethyl)cyclohexyl]-(1*SR*)-validamine Nonaacetate (16a) and the Diastereoisomer (16b).** A mixture of **12a,b** (182 mg) was treated with 80% aqueous acetic acid (10 mL) at 90 °C overnight. The reaction mixture was concentrated and the residue was acetylated in the usual way. TLC showed the formation of two components (R_f 0.16 and 0.13 in 1:3 2-butanone-toluene). The product (207 mg) was chromatographed on silica gel (10 g) with 1:3 2-butanone–toluene as an eluant. The first fraction gave 95 mg (43%) of crystals, which were recrystallized from ethanol to give 81 mg of a pure sample of **16a** as prisms: mp 213–214 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.33 (t, 1, J = 10 Hz, C_3 H), 4.95 (t, 1, J = 10 Hz, C_4 H), 4.91 (dd, 1, J = 4.5 and 10 Hz, C_2 H), 4.41 (dd, 1) and 4.24 (dd, 1) (J = 3.5 and 12 Hz, CH_2OAc), 4.10 (dd, 1) and 3.77 (dd, 1) (J = 3 and 12 Hz, CH_2OAc), 3.59 (br q, 1, J = 3 Hz, C_1 H), 2.83 (m, 1, $C_{1'}$ H), 2.05, 2.01, 1.99, 1.98, and 1.96 (m, total 27, OAc).

The second fraction gave 79 mg (36%) of crystals which were recrystallized from ethanol to give 65 mg of **16b** as plates: mp 208–208.5 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 5.32 (t, 1, J = 10 Hz, C_3 H), 4.93 (t, 1, J = 10 Hz, C_4 H), 4.91 (dd, 1, J = 3 and 10 Hz, C_2 H), 4.44 (dd, 1) and 4.10 (dd, 1) (J = 3.5 and 12 Hz, CH_2OAc), 4.08 (dd, 1) and 3.87 (dd, 1) (J = 3.5 and 12 Hz, CH_2OAc), 3.35 (br q, 1, J = 3 Hz, C_1 H), 2.88 (br q, 1, J = 10 Hz, $C_{1'}$ H), 2.05, 2.04, 2.03, 1.99, 1.95, and 1.93 (m, total 27, OAc).

Anal. Calcd for $C_{32}H_{45}NO_{18}$: C, 52.53; H, 6.20; N, 1.91. Found for **16a**: C, 52.48; H, 6.14; N, 1.83. Found for **16b**: C, 52.52; H, 6.20; N, 1.97.

Compound **14b** could be converted into **16b** by treatment with aqueous acetic acid followed by acetylation in the usual way.

***N*-[(1*SR*)-(1,2,4/3,5,6)-2,3,4,6-Tetrahydroxy-5-(hydroxymethyl)cyclohexyl]-(1*SR*)-validamine Nonaacetate (17a) and the Diastereomer (17b).** A mixture of **15a** (73 mg) and 80% aqueous acetic acid (5 mL) was heated at 70 °C for 3 h and then concentrated. The residue was acetylated in the usual way and the product was purified by a silica gel column (4 g) with 1:3 2-butanone–toluene as an eluant to give 64 mg (78%) of **17a** as a white powder: R_f 0.21 in 1:3 2-butanone–toluene; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.26–3.80 (m, 4, CH_2OAc), 3.21 (m, 2, C_1 H, $C_{1'}$ H), 2.07, 2.05, 2.02, and 2.00 (m, total 27, OAc).

Similarly, **15b** (78 mg) was converted into **17b** (61 mg, 70%) as a white powder: R_f 0.25 in 1:3 2-butanone–toluene; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.20–3.70 (m, 4, CH_2OAc), 3.15 (m, 2, C_1 H, $C_{1'}$ H), 2.06, 2.03, 2.01, 2.00, 1.99, and 1.97 (m, total 27, OAc).

Anal. Calcd for $C_{32}H_{45}NO_{18}$: C, 52.53; H, 6.20; N, 1.91. Found for **17a**: C, 52.34; H, 6.07; N, 1.76. Found for **17b**: C, 52.35; H, 6.12; N, 1.79.

Reaction of 13a,b with Sulfuryl Chloride. To a stirred mixture of **13a,b** (254 mg) in pyridine (10 mL) was added, dropwise over a period of 5 min, sulfuryl chloride (80 μL, molar equiv) at −15 °C, and then the reaction mixture was stirred at the same temperature for 2 h followed by stirring at 3 °C overnight. TLC showed the formation of two major components (R_f 0.45 and 0.40) and two minor components (R_f 0.36 and 0.34) in 1:10 ethanol–toluene. The reaction mixture was filtered to remove an insoluble material and concentrated. The residue was extracted with ethyl acetate (50 mL) and the extracts were washed with saturated sodium hydrogen carbonate and water thoroughly. The organic layer was dried and concentrated to give a pale yellow oil (232 mg), which was chromatographed on a silica gel column (12 g) with 2:9 2-butanone–toluene as an eluant. The first fraction gave 109 mg (42%) of ***N*-[(1*RS*)-2,3-di-*O*-acetyl-4,7-*O*-benzylidene-(1,2,4/3,5,6)-6-chloro-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexyl]-(1*RS*)-2,3:4,7-di-*O*-iso-**

propylidenevalidamine (18b) as an oil, which was crystallized from ethanol to give 93 mg of prisms: mp 185–187 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50–7.38 (m, 2) and 7.38–7.28 (m, 3) (phenyl), 5.52 (s, 1, benzylic), 4.00 (t, 1, J = 3 Hz, $C_{6'}$ H), 3.88 (t, 1, J = 9 Hz, C_3 H), 3.53 (m, 1, $C_{1'}$ H), 3.48 (dd, 1, J = 4 and 9 Hz, C_2 H), 3.26 (br t, 1, C_1 H), 2.82 (ddt, 1, J = 3, 5, and 10 Hz, $C_{5'}$ H), 2.08 (s, 3) and 2.05 (s, 3) (OAc), 1.49 (s, 3), 1.45 (s , 6), and 1.43 (s, 3) (isopropylidene).

Anal. Calcd for $C_{31}H_{42}NClO_{10}$: C, 59.66; H, 6.78; N, 2.24; Cl, 5.68. Found: C, 59.38; H, 6.84; N, 2.47; Cl, 5.40.

The second fraction gave 76 mg of oily ***N*-[(1*SR*)-5,6-di-*O*-acetyl-4,7-*O*-benzylidene-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*SR*)-2,3:4,7-di-*O*-isopropylidenevalidamine (19a)**, which was contaminated with a trace of an unidentified compound: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.55–7.14 (m, 5, phenyl), 5.77 (br d, J = ca. 6 Hz, $C_{2'}$ H), 5.51 (s, 1, benzylic), 4.94 (dd, J = 6 and 10.5 Hz, $C_{6'}$ H), 3.04–2.59 (m, 1, C_5 H), 2.06 (s, 3) and 2.02 (s, 3) (OAc), 1.48 (s, 3), 1.45 (s, 3), and 1.43 (s, 6) (isopropylidene).

The third fraction gave 11 mg (4%) of **(1*SR*)-[*N*-[2,3:4,7-di-*O*-isopropylidene-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexyl]epimino]-(1*SR*)-3,4-di-*O*-acetyl-5,7-*O*-benzylidene-(1,2,3,5/4,6)-3,4,5-trihydroxy-6-(hydroxymethyl)cyclohexane (20a)** as needles. Recrystallization from ethanol gave pure sample: mp 217–221 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44–7.27 (m, 5, phenyl), 5.47 (s, 1, benzylic), 4.41 (dd, 1, J = 5 and 11 Hz, C_7 H), 4.43 (t, 1, J = 9 Hz, $C_{3'}$ H), 3.47 (dd, 1, J = 3 and 9 Hz, $C_{2'}$ H), 3.41 (t, 1, J = 10.5 Hz, C_5 H), 2.29 (td, 1, J = 5, 11, and 11 Hz, C_6 H), 2.12 (s, 3) and 2.05 (s, 3) (OAc), 1.44 (s, 3), 1.52 (s, 3), and 1.50 (s, 6) (isopropylidene), 1.37 (dt, 1, J = 3, 3, and 13.5 Hz, $C_{6'eq}$ H), 1.13 (td, 1, J = 3, 13.5, and 13.5 Hz, $C_{6'ax}$ H).

Anal. Calcd for $C_{31}H_{41}NO_{10}$: C, 63.36; H, 7.03; N, 2.38. Found: C, 63.08; H, 6.98; N, 2.47.

Reaction of 13a,b with Methanesulfonyl Chloride. To a stirred solution of **13a,b** (100 mg, 0.17 mmol) in pyridine (5 mL, 0.66 mmol) was added dropwise methanesulfonyl chloride (52 μL, 0.66 mmol) at 0 °C, and then the mixture was stirred at the same temperature for 1 h followed by stirring at 3 °C overnight. TLC showed the presence of two major components (R_f 0.40 and 0.34) in 1:10 ethanol–toluene. The reaction mixture was diluted with ethyl acetate (20 mL) and washed thoroughly with water and dried. The organic layer was concentrated to give a pale yellow oil, which was chromatographed on silica gel (6.5 g) with 2:9 2-butanone-toluene as an eluant. The first fraction gave 14 mg (13%) of crystals, which was identical with **18b** obtained before. The second fraction gave 7 mg of an oil, which was not further characterized because of a minute quantity. The third fraction gave 20 mg (21%) of crystals, which was identical with **20a** obtained before.

Reaction of 18b with DBU. To a solution of **18b** (110 mg, 0.18 mmol) in toluene (5 mL) was added DBU (78 μL, 0.52 mmol) and the mixture was refluxed for 3 h. At that time, TLC showed the formation of two major components (R_f 0.41 and 0.33) in 1:10 ethanol–toluene. The reaction mixture was concentrated and the residue (150 mg) was chromatographed on silica gel (10 g) with 2:9 2-butanone–toluene as an eluant. The first fraction gave 75 mg (56%) of crystals, which were recrystallized from ethanol to give 47 mg of ***N*-[(1*SR*)-5,6-di-*O*-acetyl-4,7-*O*-benzylidene-(1,4,6/5)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*RS*)-2,3:4,7-di-*O*-isopropylidenevalidamine (19b)** as prisms: mp 211–212 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 7.54–7.12 (m, 5, phenyl), 5.69 (d, 1, J = 5 Hz, $C_{2'}$ H), 5.63 (s, 1, benzylic), 5.55 (dd, 1, J = 6.5 and 9 Hz, $C_{5'}$ H), 5.08 (dd, 1, J = 5 and 9 Hz, $C_{6'}$ H), 4.48 (br s, 2, C≡CCH_2O), 4.39 (d, 1, J = 6.5 Hz, $C_{4'}$ H), 4.01 (t, 1, J = 9 Hz, C_3 H), 2.07 (s, 6, OAc), 1.49 (s, 3) and 1.42 (s, 9) (isopropylidene).

Anal. Calcd for $C_{31}H_{41}NO_{10}$: C, 63.36; H, 7.03; N, 2.38. Found: C, 63.06; H, 6.90; N, 2.49.

The second fraction gave 32 mg (31%) of crystals, which were recrystallized from ethanol to give 21 mg of **(1*SR*)-[*N*-[2,3:4,7-di-*O*-isopropylidene-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexyl]epimino]-(1*RS*)-3,4-di-*O*-acetyl-5,7-*O*-benzylidene-(1,2,3,5/4,6)-3,4,5-trihydroxy-6-(hydroxymethyl)cyclohexane (20b)** as needles: mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.47 (s, 1, benzylic), 5.35 (dd, 1, J = 4 and 9.5 Hz, C_3 H), 5.19 (t, 1, J = 9.5 and 10 Hz, C_4 H), 4.32 (t, 1, J = 9 Hz, $C_{3'}$ H), 3.46 (dd, 1, J = 3 and 9 Hz, $C_{2'}$ H), 3.45 (t, 1, J = 10 Hz, C_5 H), 2.42 (dd, 1, J = 4 and 6 Hz, C_2 H), 2.30 (ddd, 1, J = 5, 11, and 11 Hz, C_6 H), 2.21 (q, 1, J = ca. 3 Hz, $C_{1'}$ H), 2.12 (s, 3) and 2.02 (s, 3) (OAc), 1.53 (s, 6), 1.50 (s, 3), and 1.41 (s, 3) (isopropylidene), 1.23 (d, 1, J = 6 Hz, C_1 H), 1.21 (td, 1, J = 3, 14, and 14 Hz, $C_{6'ax}$ H).

Anal. Calcd for $C_{31}H_{41}NO_{10}$: C, 63.36; H, 7.03; N, 2.38. Found: C, 62.54; H, 6.87; N, 2.59.

***N*-[(1*SR*)-(1,4,6/5)-4,5,6-Trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*SR*)-validamine Octaacetate (Validoxylamine A Octaacetate) (21a).** Crude **19a** (76 mg) was treated with 1 M hydrochloric acid (4 mL) at 90 °C for 4 h. After neutralization with Amberlite IRA-400 (OH^-), the solution was concentrated and the residue was acetylated in the usual way. TLC of the product showed the presence of two components (R_f 0.36 and 0.30) in 1:10 ethanol–toluene. Chromatography on silica gel (4 g) with 2:9 2-butanone–toluene as an eluant gave, as the first fraction, 26 mg (9% based on **13a,b** used) of **21a** as an oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.00 (br d, 1, J = 5 Hz, $C_{2'}$ H), 4.66 (d, 1) and 4.39 (d, 1) (J = 13 Hz, C=CCH_2OAc), 4.14 (dd, 1, J = 4 and 11 Hz) and 3.90 (dd, 1, J = 3 and 11 Hz) (CHCH_2OAc), 3.55 (m, 1, $C_{1'}$ H), 3.38 (br m, 1, C_1 H), 2.10, 2.09, 2.08, 2.07, 2.04, and 2.00 (m, total 24, OAc).

Anal. Calcd for $C_{30}H_{41}NO_{16}$: C, 53.65; H, 6.15; N, 2.09. Found: C, 53.38; H, 6.16; N, 2.10.

The ^{1}H NMR spectrum was superimposable on that of an authentic chiral sample of validoxylamine A octaacetate. TLC showed a single spot, R_f 0.36, in 1:10 ethanol–toluene, and R_f 0.39, in 2:3 2-butanone–toluene.

The second fraction gave 49 mg of an unidentified compound.

***N*-[(1*SR*)-(1,4,6/5)-4,5,6-Trihydroxy-3-(hydroxymethyl)-2-cyclohexenyl]-(1*RS*)-validamine Octaacetate (21b).** Compound **19b** (47 mg) was treated with 1 M hydrochloric acid (3 mL) at 90 °C for 4 h, and then the reaction mixture was neutralized with Amberlite IRA-400 (OH^-). The solution was concentrated and the product was acetylated in the usual way. Purification by a short column of alumina with chloroform as an eluant gave 42 mg (78%) of **21b** as an oil: R_f 0.39 in 2:3 2-butanone–toluene; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.88 (br d, 1, J = 4 Hz, $C_{2'}$ H), 4.66 (d, 1) and 4.40 (d, 1) (J = 13 Hz, C=CCH_2OAc), 4.12 (dd, 1, J = 4.5 and 11 Hz) and 3.91 (dd, 1, J = 3 and 11 Hz) (CHCH_2OAc), 3.58 (m, 1, $C_{1'}$ H), 3.46 (m, 1, C_1 H), 2.40 (m, 1, C_5 H), 2.08 2.06, 2.05, 2.03, and 2.00 (m, total 24, OAc).

Anal. Calcd for $C_{30}H_{41}NO_{16}$: C, 53.65; H, 6.15; N, 2.09. Found: C, 53.29; H, 6.09; N, 1.97.

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