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TOTAL SYNTHESIS OF (±)-2-*EPI*-VALIDAMINE

Hiroaki Okamura,* Hiroshi Nagaike, Nsiama Tienabe Kipassa, Tetsuo Iwagawa, and Munehiro Nakatani

Department of Chemistry and Bioscience, Faculty of Science, Kagoshima University, Korimoto 1-21-35, Kaghoshima 890-0065, Japan. e-mail address: okam@sci.kagoshima-u.ac.jp

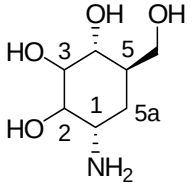
Abstract – (±)-Validamine and its epimers, (±)-2-*epi*-validamine ($_{DL}$-5a-carba-α-mannopyranosylamine) and (±)-2-*epi*-3-*epi*-validamine ($_{DL}$-5a-carba-α-altropyranosylamine) were synthesized from a poly-functionalized bicyclolactam that obtained by a base-catalyzed Diels-Alder reaction of *N*-tosyl-3-hydroxy-2-pyridone and methyl acrylate. All isomers were prepared via a common key intermediate in six or seven steps.

INTRODUCTION

Pseudo-sugars (carbasugars) and *pseudo*-aminosugars (carba-aminosugars), which have a methylene group instead of the oxygen in a furanose or pyranose ring, are important sugar mimics showing various biological activities including strong inhibition against glycosidases and related enzymes, and some of them have been used as drugs or their components.[1]

Validamine (**1**)[2,3] is one of the well known biologically active *pseudo*-aminosugars, isolated as a degradation product of a strong antibiotic, validamycin A in 1971.[2] Later in 1984, it was found in broth of *Streptomyces hygroscopicus* along with the structurally related compounds, valiolamine, valienamine, and hydroxyvalidamine.[3] All of these compounds showed strong α-glucosidase inhibitory activity.

Because of their interesting biological activities and molecular structures which have five or six stereogenic centers in a six membered ring, much interest has been attracted for the synthesis of this class of compounds. Since the first synthesis of **1** was reported in 1977,[4] active synthetic studies have been continued by several groups.[5] In addition, synthesis of stereoisomers of **1**, including

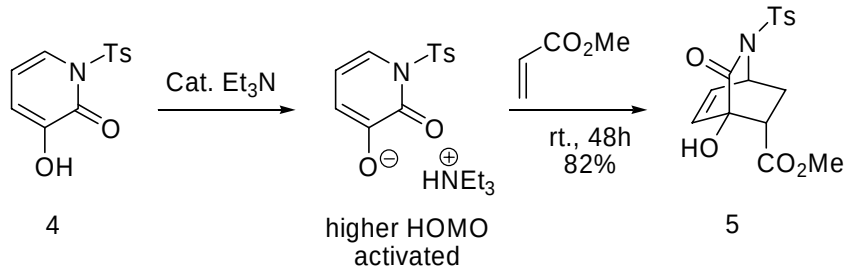


1: 2α–, 3β-, validamine
2: 2β-, 3β-, 2-*epi*-validamine
3: 2β-, 3α-, 2-*epi*-3-*epi*-validamine

Figure 1. validamine and its epimers

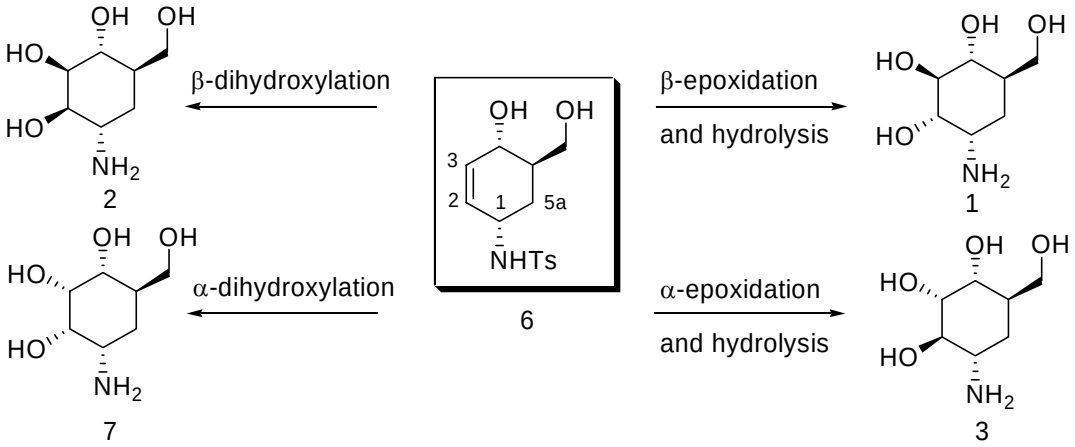
2-*epi*-validamine (5a-carba-α-mannopyranosylamine) (**2**),[6] has also been reported[7] because of their promising potential as therapeutic drugs and/or chemical probes for physiological studies.

Our research group have been developed a base-catalyzed Diels-Alder (DA) reaction of 3-hydroxy-2-pyridone derivative (**4**) and electron deficient dienophiles.[8] Usually, catalytic DA reactions proceed by a combination of a diene and a dienophile that is activated by a Lewis acid catalyst to lower the LUMO level. Interestingly, however, the base-catalyzed DA reaction goes with an opposite combination, a catalytically activated diene having higher HOMO level and a dienophile.[9] In addition to the mechanistic interests, the resulting product of this reaction is a highly functionalized bicyclic lactam (**5**), and thus it can be considered as a useful building block to synthesize *pseudo*-aminosugars. In this paper, we describe an efficient synthesis of (±)-**1** and its epimers, (±)-**2** and (±)-2-*epi*-3-*epi*-validamine (5a-carba-α-altropyranosylamine) (**3**) from **5**.



Scheme 1

RESULTS AND DISCUSSION

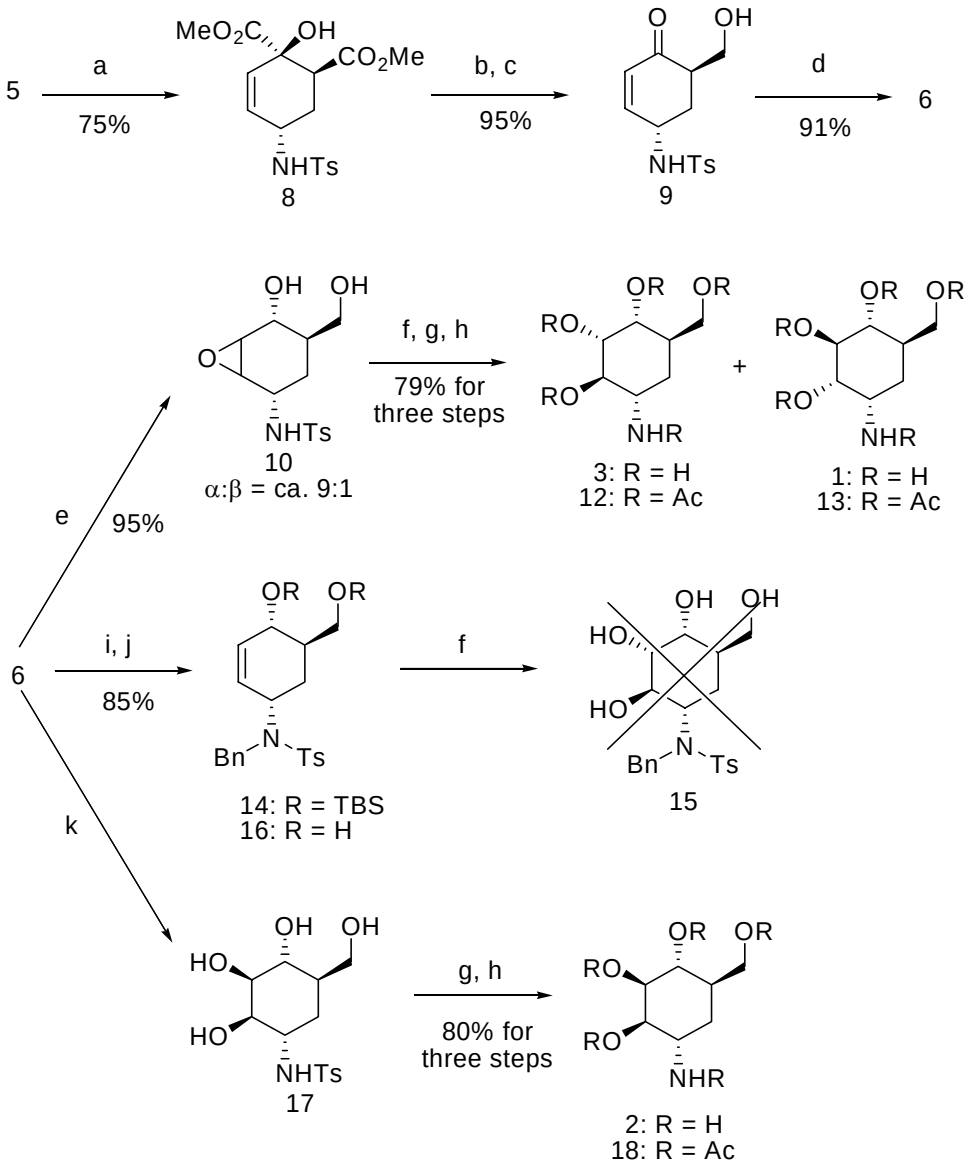


Scheme 2

Our synthetic plan is illustrated in Scheme 2. The common key compound (**6**) seemed to be easily derived from the DA adduct (**5**) by conventional methods, and introduction of the two hydroxyl groups at C-2 and 3 positions (all the carbon numbers referred in this paper are based on *pseudo*-sugar numbering) could be realized by osmium dihydroxylation or epoxidation followed by acid hydrolysis. Since stereo controlled epoxidation and dihydroxylation of cyclic allyl alcohol have already been realized by using hydrogen

bonding or steric hinderance,[10] four stereoisomers (**1**, **2**, **3** and **7**) could be prepared from the same intermediate (**6**).

The synthesis was started from a hydrolysis to open the lactam ring of **5**. To avoid epimerization of carbomethoxy group at C-5, the reaction was carried out at 0 ˚C and stopped within 1 h, even small amount of **5** was still remained. Reduction of **8** followed by oxidative cleavage gave unsaturated ketone (**9**) in excellent yield. Stereoselective reduction of the ketone was achieved by $NaBH(OAc)_3$ reduction[11] under the influence of stereochemistry of neighboring hydroxymethyl group, and the common key intermediate (**6**) was obtained as an exclusive product in good yield.

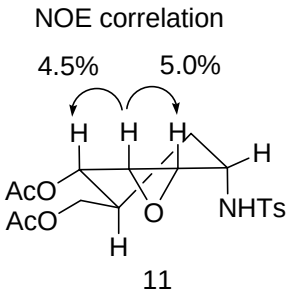


a) MeOH, NaOMe b) $LiBH_4$ c) $NaIO_4$ d) $NaB(OAc)_3H$ e) *m*-CPBA f) aq. H_2SO_4 g) Na, liq. NH_3
h) Ac_2O, pyridine i) TBSCl, imidazole j) BnBr, NaH k) OsO_4, aq. NMO

Scheme 3

Next, stereoselective introduction of diol at C-2 and 3 positions was examined. Epoxidation using *m*-CPBA gave epoxide (**10**) as an inseparable diastereomer mixture. Although the isomer ratio was not

clear at this stage, it could be estimated as 9:1 in according to the ratio of the final products (*vide infra*). The conformation and orientation of the major isomer was suggested by NOE correlation of corresponding diacetate (**11**) as shown in Figure 2. After acid hydrolysis and subsequent de-tosylation by Na-liq. NH_3 reduction[12] of **10**, the corresponding mixture of *pseudo*-aminosugars (**1** and **3**) were obtained. Since the products were very polar and difficult to purify, they were further converted to their pentaacetates (**12** and **13**), which were separated by silica gel column chromatography to give pure products in 9:1 ratio. The ^{1}H-NMR spectrum of the minor product (**13**) was completely identical to that of validamine pentaacetate.[2] The stereochemistry of the major isomer (**12**) was also established from detailed ^{1}H-NMR analysis as 2-*epi*-3-*epi*-validamine pentaacetate. The formation of these products was well explained by trans-diaxial opening of epoxide ring in major isomer (**10**α) and minor isomer (**10**β).



11

Figure 2. Stereochemistry of **11**

The stereoselectivity in the epoxidation of **6** can be rationalized from a hydrogen bonding of *m*-CPBA and the amide proton and hydroxyl proton in **6**. And thus, we next tried the epoxidation of fully protected compound (**14**) to prepare β-epoxide that was expected to give **1** as the major isomer. However, the epoxidation was very slow and the subsequent acid hydrolysis only afforded small amounts of complex mixtures and recovered diol (**16**). This is probably due to a serious steric hindrance around C-2, 3 double bond, which interfered an approach of mCPBA and acid hydrolysis of the resulting epoxides.

The other stereoisomer (**2**) was successfully synthesized from the common intermediate (**6**). By OsO_4 oxidation, *cis*-diol (**17**) was obtained as a single isomer in good yield. The resulting stereochemistry could be explained by stereoselective approach of the oxidant from β-face to avoid steric influence of both α-oriented hydroxyl and amide groups The resulting product was converted into **2** and its pentaacetate (**18**) as described above. Since the ^{1}H NMR of **18** was identical to that of 2-*epi*-validamine pentaacetate, [6] we have established the stereoselective synthesis of 2-*epi*-validamine.

In conclusion, three validamine type compounds (**1**, **2** and **3**) were synthesized *via* a common intermediate (**6**) that is easily converted from the bicyclic lactam (**5**) obtained by a base-catalyzed DA reaction of *N*-tosyl-3-hydroxy-2-pyridone with methyl acrylate. This synthesis is a short and efficient process to give *pseudo*-aminosugars. Further synthesis of the related compounds including optically active products from an asymmetric DA reaction is now currently investigated.

EXPERIMENTAL

Melting points were measured by Yanagimoto micro melting point apparatus and was uncorrected. IR spectra were determined with JASCO FT/IR 5300 spectrometer. The ^{1}H NMR spectra were recorded by

JEOL GSX400 spectrometer at 400 MHz. FAB mass spectra were obtained from JEOL JMX-SX/SX 102A spectrometer. All reagents were commercially available and used without further purification.

(1*S,2*S**,5*S**)-Dimethyl 2-hydroxy-5-(tosylamino)cyclohex-3-ene-1,2-dicarboxylate (8)**

To a solution of DA adduct **5** (1.00 g, 2.85 mmol) in MeOH (28.5 mL), NaOMe (4.9 M in MeOH, 1.74 mL, 8.55 mmol) was added at 0 °C, and the mixture was stirred for 1 h at the temperature. The reaction mixture was quenched with aqueous H_3PO_4 (5.0%, 10 mL) and water (10 mL), and evaporated to remove MeOH. The resulting mixture was extracted with ethyl acetate (20 mL, three times), washed with brine, and dried over $MgSO_4$. After filtration and evaporation, the resulting syrup was purified by silica gel column chromatography (hexane/AcOEt 1:1 to 3:7, gradient) to give **8** (816 mg, 75%) as a colorless oil. Rf: 0.47 (hexane/AcOEt 3:7); IR (film): 3449, 2361, 2334, 1736, 1640, 1439, 1159 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.70 (dd, *J* = 10.4, 5.1 Hz, 1H), 5.63 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 7.7 Hz, 1H), 3.92 (m, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.30 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.44 (s, 3H), 2.19 (br d, *J* = 13.0 Hz, 1H), 2.11 (ddd, *J* = 13.2, 13.0, 4.4 Hz, 1H); *Anal* Calcd for $C_{17}H_{21}NO_7S$: C, 53.25; H, 5.52; N, 3.65; S, 8.36. Found: C, 52.91; H, 5.40; N, 3.46, S, 8.45.

(4*S,6*R**)-6-(Hydroxymethyl)-4-(tosylamino)cyclohex-2-enone (9)**

To a solution of **8** (1.45 g, 3.8 mmol) in THF (38 mL) was added $LiBH_4$ (413 mg, 19 mmol) at 0 °C, and the mixture was stirred for 1.5 h at the temperature. The mixture was quenched with aqueous H_3PO_4 (5.0%, 10 mL) and water (40 mL). To the resulting suspension, $NaIO_4$ (814 mg, 3.8 mmol) was added and stirred for additional 12 h at 0 °C. The mixture was extracted with AcOEt (60 mL, three times), washed with brine, and dried over $MgSO_4$. After conventional work-up and purification as described above, compound **9** was obtained as colorless oil (953 mg, 95% from **8**). Rf: 0.42 (hexane/AcOEt 3:7); IR (film): 3508, 3264, 2928, 1674, 1601, 1329, 1157 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.61 (dd, *J* = 9.9, 4.8 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 5.01 (d, *J* = 8.1 Hz, 1H), 4.20 (m, 1H), 3.77-3.65 (m, 2H), 2.68 (m, 1H) 2.45 (s, 3H), 2.10-1.98 (m, 2H); HRFABMS $(M+H)^+$ calcd for $C_{14}H_{18}NO_4S$ 296.0957, found 296.0956.

(1*S,4*S**,6*R**)-6-(Hydroxymethyl)-4-(tosylamino)cyclohex-2-enol (6)**

To a solution of **9** (83 mg, 0.28 mmol) in AcOH (4.0 mL), $NaBH(OAc)_3$ (108 mg, 0.42 mmol) was added at rt, and stirred for 2 days. The mixture was poured into saturated $NaHCO_3$ (10 ml) and the whole mixture was extracted with AcOEt (10 mL, three times). After conventional work-up and purification as described above, key intermediate (**6**) was obtained as white solid (79 mg, 91%). mp 165-167 °C; Rf: 0.36 (AcOEt/acetone 3:1); IR (KBr): 3420, 2924, 1647, 1447, 1321, 1155 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.71 (d, *J* = 9.9 Hz, 1H), 5.38 (d, *J* = 9.9 Hz, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 3.75 (br s, 1H), 3.62 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.55 (dd, *J* = 10.6, 7.3 Hz, 1H), 2.44

(s, 3H), 1.75 (m, 1H), 1.66 (br d, *J* = 13.9 Hz, 1H), 1.40 (ddd, *J* = 13.6, 13.2, 4.8 Hz, 1H); HRFABMS $(M+H)^+$ calcd for $C_{14}H_{20}NO_4S$ 298.1113, found 298.1115.

(1*R,4*S**,6*R**)-2,3-Epoxy-6-(hydroxymethyl)-4-(tosylamino)cyclohexane-1-ol (10)**

To a solution of **6** (50 mg, 0.17 mmol) in MeOH (0.3 mL) and CH_2Cl_2 (1.7 mL), *m*-CPBA (58 mg, 0.34 mmol) was added ar rt and stirred for 12 h. The excess mCPBA was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and the mixture was extracted with AcOEt (5 mL, three times). After conventional work-up and purification as described above, epoxide (**10**) and its diastereomer were obtained as an inseparable mixture (50 mg, 95%). Rf: 0.52 (CH_2Cl_2/MeOH 10:1); IR (KBr): 3376, 2948, 1599, 1497, 1424, 1159 cm^{-1}; ^1H NMR for major isomer ($CDCl_3$): δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 3.85-3.75 (m, 2H), 3.70-3.50 (m, 2H), 3.34 (m, 1H), 3.12 (m, 1H), 2.43 (s, 3H), 2.40 - 2.20 (br s, 2H), 1.75 (m, 1H), 1.48 (d, *J* = 13.0 Hz, 1H), 1.25 (m, 1H).

After acetylation by Ac_2O and pyridine and further purification, major isomer (**11α**) that satisfied its elemental analysis was obtained. ^1H NMR ($CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 5.18 (d, *J* = 9.2 Hz, 1H), 4.96 (dd, *J* = 9.9, 1.8 Hz, 1H), 4.00 (dd, *J* = 11.4, 5.1 Hz, 1H), 3.89-3.83 (m, 2H), 3.42 (dd, *J* = 4.1, 1.8 Hz, 1H), 3.09 (dd, *J* = 4.1, 3.7 Hz, 1H), 2.43 (s, 3H), 2.11 (s, 3H), 2.11-2.02 (m, 1H), 2.02 (s, 3H), 1.74-1.65 (m, 1H), 1.50 (dt, *J* = 1.8, 5.9 Hz, 1H); *Anal* Calcd for $C_{18}H_{23}NO_7S$: C, 54.40; H, 5.83; N, 3.52; S, 8.07. Found: C, 54.18; H, 5.65; N, 3.42; S, 8.25

(±)-Validamine pentaacetate (13) and (±)-2-*epi*-3-*epi*-validamine pentaacetate (12)

Aqueous H_2SO_4 (10%, 5 mL) and MeOH (5 mL) was added to the mixture of the epoxides (**10**) (91 mg, 0.29 mmol), and stirred for 12 h at rt. The reaction mixture was poured into aqueous KOH (10%, 5 mL) and whole mixture was extracted with *t*-BuOH (20 mL, five times). The combined organic layer was concentrated to give a crude mixture of tetraol.

To the mixture of the crude tetraol and liquid NH_3 (*ca.* 10 mL), small pieces of sodium metal were added at -78 °C until blue color persisted. After stirring for 20 min powdered NH_4Cl was added until the blue color disappeared. Evapolation of liquid NH_3 gave crude mixture of **1** and **3**. To establish their structures, the crude product was directly acetylated by Ac_2O (1.0 ml) and pyridine (1.0 ml) to give the corresponding pentaacetates. After conventional work up and silica gel column chromatography, **12** (80 mg, 71%) and **13** (9.0 mg, 7.9%) were obtained separately. **12**: IR (film): 3376, 1746, 1663, 1589, 1368, 1231 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.85 (br d, *J* = 8.4 Hz, 1H), 5.31 (dd, *J* = 5.1, 3.3 Hz, 1H), 5.08 (dd, *J* = 8.4, 8.0 Hz, 1H), 4.25 (ddd, *J* = 8.4, 8.0, 4.4 Hz, 1H), 4.17 (m, 2H), 2.29 (m, 1H), 2.11, 2.08, 2.08, 2.05, 1.95 (s, 3H for each signals), 1.83 (m, 1H). HRFABMS $(M+H)^+$ calcd for $C_{17}H_{26}NO_9$ 388.1608, found 388.1610. **13**: mp: 195-197 °C (lit.,[5] 197-198 °C); ^1H NMR was identical to the previous data.[2]

(±)-2-*Epi*-validamine pentaacetate (18)

To a solution of **6** (95 mg, 0.32 mmol) and *N*-methylmorpholine-*N*-oxide (82 μL, 50 % in H_2O) in THF (3.0 mL), OsO_4 (0.02 M in *t*-BuOH, 318 μL) was added at rt, and stirred for 1 day. After adding 2-methyl-2-butene (1 mL) to quench the excess oxidant, the whole mixture was evapolated. The resulting crude tetraol (**17**) was de-tosylated in according to the same procedure described above to give **2**. To established the structure, the product was acetylated and purified with the same procedure described above to give **18** (99 mg, 80%) as an colorless oil. ^{1}H NMR was identical to the previous data.[6]

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