Synthesis of Valiolamine and Some Precursors for Bioactive Carbaglycosylamines from (−)-*vibo*-Quercitol Produced by Biogenesis of *myo*-Inositol[⊥]

Seiichiro Ogawa* and Miki Kanto

Department of Biosciences and Informatics, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama, 223-8522 Japan

A convenient and practical synthesis of valiolamine (**4**) and its related carbaglycosylamine glycosidase inhibitors from (−)-*vibo*-quercitol (**13**), a compound readily produced by biogenesis of *myo*-inositol (**9**), is described.

Carbaglycosylamines (aminocyclitols),[1] such as validamine (**2**), valienamine (**3**), valiolamine (**4**), and their analogues, were first isolated as the components of the antibiotic validamycin A (**1**) and its homologues[2] and fully characterized to possess more or less enzyme inhibitory activity toward certain glycosidases. Therefore, they have been important lead compounds for the development of potent and specific inhibitors of glycosidases involved in the intestinal metabolism of sugars. Since among them valiolamine (**4**) possesses very potent activity against maltase and sucrase, extensive chemical modification was carried out, leading to the discovery of voglibose[3] (**5**), a clinically useful remedy to control diabetes (Figure 1).

We became interested in the structural features of validamine (**2**) and valienamine (**3**), which would match structurally the respective ground-state and transition-state mimics of the glucopyranosyl cation postulated to be involved in the hydrolysis of glucosides.[4] Among several analogues of validamine (**2**) synthesized, 5a-carba-α-L-fucopyranosylamine[5] (**6**) was demonstrated to be a very strong α-fucosidase inhibitor. Interestingly, the corresponding D-enantiomer was shown to exhibit potent inhibitory activities against two enzymes, β-galactosidase and β-glucosidase. The design and synthesis of the N-linked carbaglucosyl- and galactosylceramides introduced a new type of inhibitor, which possesses potent and specific activity toward the respective glycocerebrosidases. Further attempts[7] to replace the ceramide moieties with simpler N-alkyl and phenylalkyl chains resulted in the elaboration of N-octyl-β-valienamine (**7**, NOV) and β-epivalienamine (**8**, NOEV), which have improved potency in addition to ready accessibility. They have now become good candidates for a new molecular therapeutic approach (chemical chaperone therapy),[8] particularly to G_{M1}-gangliosidosis caused by β-galactosidase deficiency.

Therefore, the present situation would be greatly benefited by provision of a large quantity of such biologically active aminocyclitols for detailed biochemical and biological assay of the compounds. For this purpose, it may be very attractive to develop a facile preparative route, starting from readily available optically active cyclitol derivatives.

myo-Inositol (**9**) is the most abundant cyclitol occurring in Nature. Among nine stereoisomers, seven are meso compounds. Synthetic studies on inositol derivatives have often been accompanied with some difficulty to obtain the optically active compounds desired. When *myo*-inositol is chosen as a starting material, chemical synthesis regarding modification and/or substitution of one of the
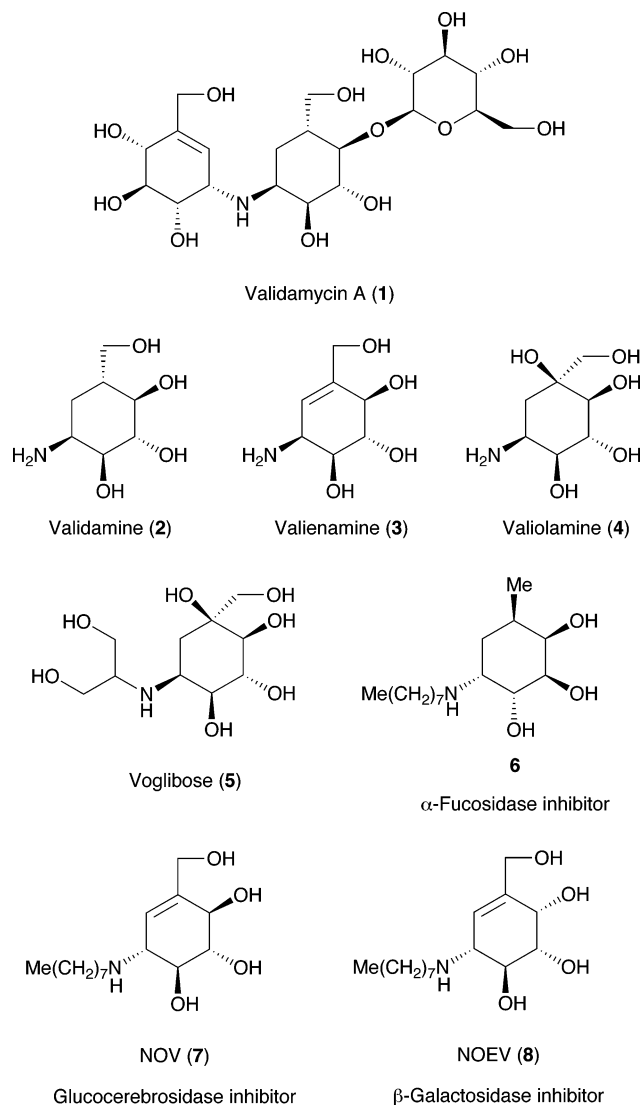
Figure 1. Validamycin A and essential degradation products of validamycins, and some synthetic biologically active 5a-carbaglycosylamine derivatives.

hydroxyl groups at C-1, 3, 4, and 6 leads to compounds of racemic modification. In order to obtain the desired compounds, their optical resolution would be needed at an early stage of the preparative processing, followed by determination of absolute structures. The bioconversion of inositols has offered therefore a very advantageous route to provide several optically pure raw materials for cyclitol synthesis, although some difficulty would be encountered in the

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* Author to whom correspondence should be addresssed. Tel: +81 (45)-566-1788. Fax: +81 (45)-566-1789. E-mail: ogawa@bio.keio.ac.jp; sogawa379@ybb.ne.jp

isolation and purification of these compounds when a complex mixture of products is formed in fermentation broths.

We have been engaged in developing effective routes to connect the readily available *myo*-inositol to optically active carbasugars.[1,8] In practical terms, a number of carbaglycosylamines can be furnished[9] through chemical modification of the products obtained by degradation and/or biogenesis of antibiotic validamycins. In recent years, optically active carbasugars have been synthesized starting from common hexopyranose derivatives,[10] (−)-shikimic acid, (−)-quinic acid,[11] and other substances. However, no process has been successfully employed for the production of large quantities of the desired carbasugars.

We review here the synthesis of (−)-β-valiol (**19**) and (−)-valiolamine (**4**) accomplished[12] by the chemical transformation of (−)-*vibo*-quercitol (**13**), obtained by biogenesis of *myo*-inositol. The present route establishes a link between naturally abundant meso cyclitol and chiral carbasugars, being generally applicable for the provision of large quantities of desired aminocyclitols and carbasugars of biological interest.

Also described herein is the ready access to a key intermediate, 1L-(1,3/2,4)-1,2,3,4-tetra-*O*-acetyl-5-methylene-1,2,3,4-cyclohexanetetrol (2,3,4-tri-*O*-acetyl-5a-carba-β-D-*xylo*-5-enopyranose acetate)[13] (**23**), to provide 5a-carbahexopyranoses as well as valienamine-type unsaturated 5a-carbahexopyranosylamines. In this review we have referred to recent results on the bioconversion of *myo*-inositol to the optically pure intermediates utilized for the practical synthesis of biological importance.
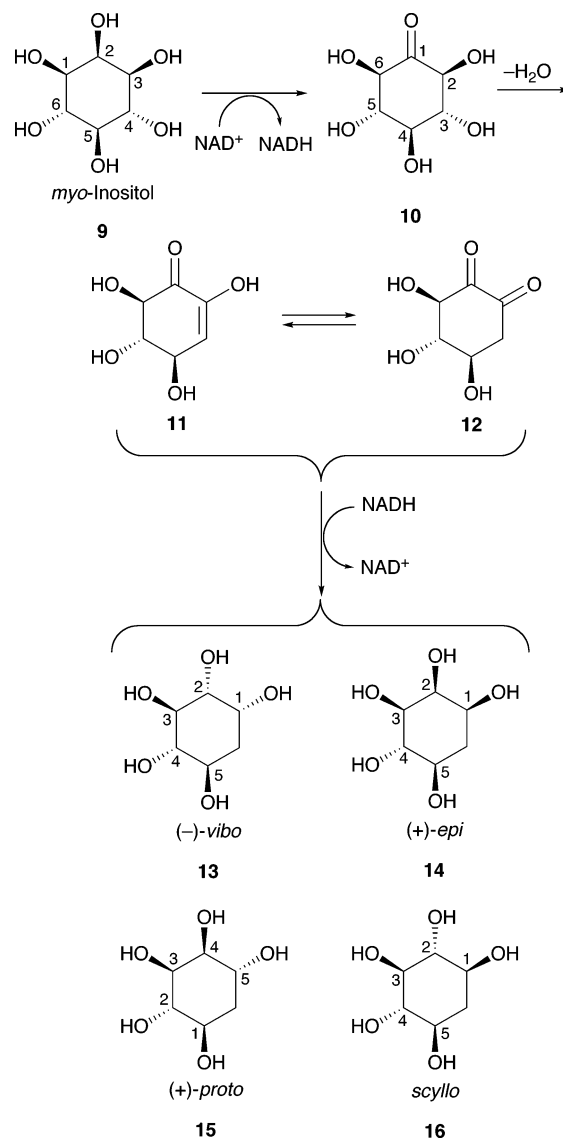
Bioconversion of *myo*-Inositol by *Salmonella typhimurium* Leading to the Production of Three Quercitols (Deoxyinositols)

Angyal et al.[14] studied the chemical behavior of *epi*- and *scyllo*-inososes (**10**) in neutral and aqueous sodium carbonate solution, involving their conversion into unsaturated ketones via dehydration to form an equilibrium mixture of some enol-ketones (**11**) and diketones (**12**) (Figure 2). They confirmed their postulated transformation of *scyllo*-inosose by determining the components through hydrogenation to chemically stable deoxyinositols. Hydrogenation of the reaction mixture was carried out in the presence of platinum catalyst, and the theoretically possible four deoxyinositols (quercitols) were isolated and characterized by chromatography. DL-*epi*-Quercitol (**14**) was shown to be a major product (28%), along with DL-*vibo*- (**13**, 14%), DL-*proto*- (**15**, 3%), and *scyllo*-quercitols (**16**, 3%). These results verified the postulated mechanism of chemical conversion of inososes in aqueous alkaline solution. From the use of Raney nickel catalyst, *epi*-quercitol was obtained mainly in ca. 40% yield.

Recently, Takahashi et al.[15] succeeded in the production of some optically active quercitols by biotransfomation of *myo*-inositol using several strains of *Salmonella typhimurium*. Three quercitols were isolated from fermentation broth, and each was purified by a combination of ion-exchange chromatography and subsequent recrystallization. The major product, (−)-*vibo*-quercitol (**13**), was obtained in 35% yield, together with (+)-*epi*- (**14**, 11%) and (−)-*proto*-quercitol (**15**, 5%). We have become interested in the application of these optically pure cyclitols as potential sources for the development of biologically active compounds. The mechanism of their biotransformation may be proposed as the initial biooxidation of *myo*-inositol (**9**) to *scyllo*-inosose (**10**), followed by dehydration and reduction (Figure 2), as was observed by Angyal et al.[14] concerning *scyllo*-inososes in neutral and alkaline solution.

Synthesis of β-Valiol and Valiolamine

(−)-Valiolamine (**4**) was first isolated from the fermentation broth of antibiotic validamycins and later found[16] to be one of the components of validamycin G. Since **4** was found to possess a potent inhibitory activity against maltase and sucrase, its chemical

Figure 2. Bioconversion of *myo*-inositol. Production of quercitols (deoxyinositols).

modification was carried out extensively, leading to voglibose (**5**), the *N*-(1,3-dihydroxyprop-2-yl) derivative,[4] a clinically very useful drug for the control of diabetes. Several syntheses of **4** have already been accomplished, starting from D-glucose,[17] the Diels−Alder *endo*-adduct[18] of furan and acrylic acid, and L-quinic acid,[11] and by other methods. Valienamine (**3**), derived from the microbiological degradation of the validamycins, has been transformed into **4** through a four-step synthetic reaction, leading to the production of voglibose (**5**).

1L-(1,2,4/3,5)-1,2,3,4,5-Cyclohexanepentol[13] (**13**), (−)-*vibo*-quercitol, which is easily obtained by the stereospecific microbial dehydration of *myo*-inositol, is biochemically oxidized under the influence of a slant culture of *Gluconobacter* sp. AB10277 to produce crude (−)-2-deoxy-*scyllo*-inosose[19] (**17**), 2L-(2,4/3,5)-2,3,4,5-tetrahydroxycyclohexan-1-one, in ca. 80% yield (Figure 3). On the scrutiny of its ^{1}H NMR spectroscopic data, this compound was shown to be a mixture of the keto and hydrate forms in water, but the former seemed to be the major component when dissolved in DMSO. Although several possible synthetic procedures have been considered for a C−C bond formation at the keto function of cyclitol derivatives, very few are likely to be applicable without protection of the hydroxyl groups. In fact, direct protection such as conventional acylation or etherification of inososes often results in serious structural changes via epimerization and/or elimination. Therefore,
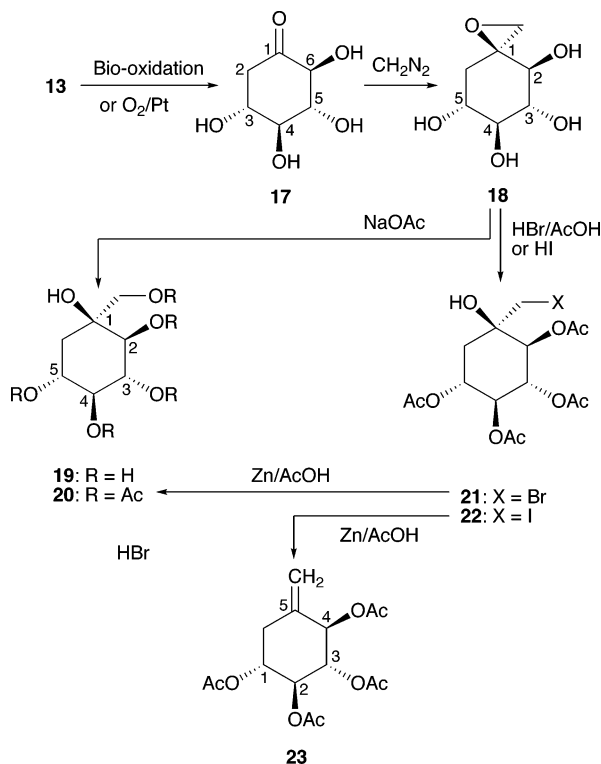
Figure 3. Preparation of (1,3/2,4)-1,2,3,4-tetra-*O*-acetyl-5-methylene-1,2,3,4-cyclohexanetetrol from (−)-*vibo*-quercitol.

we attempted to subject the crude ketone directly to a simple C−C bond formation, among the conditions of which a reaction with diazomethane would be considered to work in polar and protic solvents. Treatment of **17** with 2 molar equiv of diazomethane−diethyl ether was carried out in methanol at room temperature. On addition of excess diethyl ether, a sole spiro epoxide, **18**, crystallized out in pure form from the reaction mixture in 44% yield. The isolated yields of crystalline **18** are rather variable, partly depending on the purity of crude inosose **17** as well as the ratio of the keto and hydrate forms of **17** in the reaction medium. Diazomethane is likely to attack the carbonyl group on a rear side of the adjacent 2-hydroxyl group in an equatorial orientation. Hydrolysis of **18** with 3 M aqueous potassium hydroxide at 100 °C gave, after chromatography, the crystalline (−)-β-valiol[20] (**19**) in 32% yield. On the other hand, nucleophilic substitution of **18** with an excess of sodium acetate in 80% aqueous DMF at 120 °C gave, after acetylation with acetic anhydride in pyridine, the penta-*O*-acetyl derivative of **19** (**20**) quantitatively. Thus, optically active β-valiol (**19**) is readily available from *myo*-inositol (**9**) via a four-step reaction.

Conversion of the spiro-epoxide **18** into the *exo*-methylene compound **23** was attempted through an elimination reaction of the halides obtained (Figure 3). Thus, treatment of the epoxide **18** with 20% HBr−AcOH at 50 °C gave the 7-bromide **21** selectively in 80% yield, which was then subjected to conventional elimination conditions with zinc powder in refluxing acetic acid. However, a main product was shown to be penta-*O*-acetyl-(−)-β-valiol (**20**, 58%), resulting from substitution at C-7 with an acetate ion. Alternatively, the epoxide **18** was treated with concentrated hydroiodic acid in acetic acid at room temperature to give the iodide **22** (∼100%). Interestingly, under similar elimination conditions to those above, compound **22** was converted preferentially into the desired *exo*-methylene compound **23** in 85% yield.

We therefore intended to establish a facile synthesis of the biologically valuable valiolamine (**4**) from **19** (Figure 4). An important key step was considered to be the incorporation of an amino function at C-5 by replacement of the 5-hydroxyl group via Walden inversion. In the initial attempts, the primary 7-hydroxyl group was first protected with a triphenylmethyl group, and the
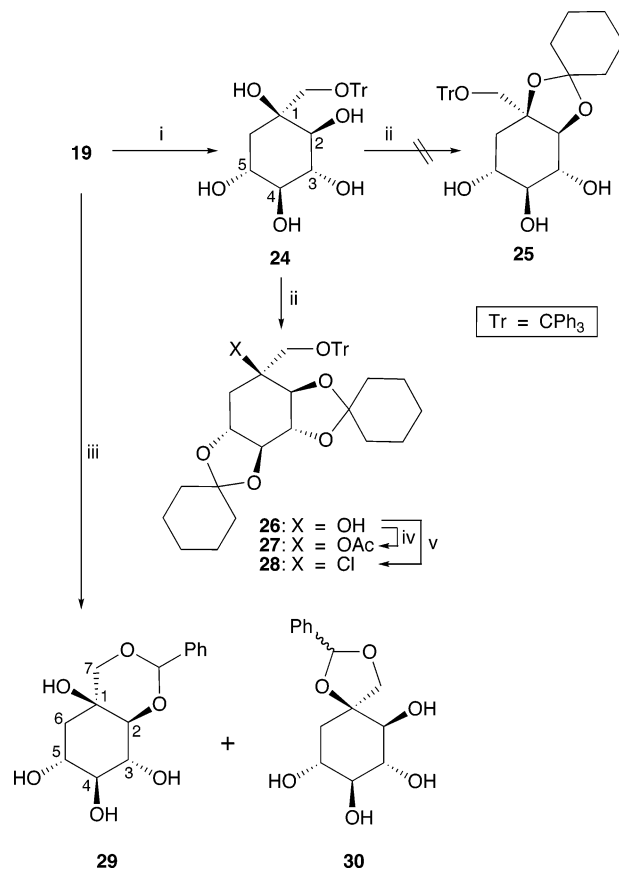

Figure 4. Preparation of protected derivatives of (−)-β-valiol. Reagents and conditions: (i) TrCl, pyridine; (ii) α,α-(MeO)₂C₆H₁₀, TsOH·H₂O, DMF, rt; (iii) PhCH(OMe)₂, TsOH·H₂O, DMF, 50 °C; (iv) Ac₂O, pyridine; (v) SO₂Cl₂, pyridine.

trityl ether obtained was subjected to conventional cyclohexylidenation conditions, expecting preferential formation of the cis-ketal function. However, unexpectedly, a major product was found to be the 2,3:4,5-di-*O*-cyclohexylidene derivative, **26**, the structure of which was confirmed by converting it into the acetyl derivative, **27**. Interestingly, conventional chlorination of **26** with SO₂Cl₂ in pyridine gave the chloride **28**. Neither the desired 1,2:3,4- nor the 1,2:4,5-di-*O*-cyclohexylidene derivative was produced through an initial formation of the 1,2-*O*-cyclohexylidene derivative **25**. Then, selective benzylidenation of **19** was carried out by treatment with α,α-dimethoxytoluene and TsOH·H₂O in dry DMF for 4 h at room temperature, giving the desired 2,7-*O*- (**29**) (59%) and a spiro-type 1,7-*O*-benzylidene derivative, **30** (26%). Compounds **29** and **30** were converted into the tri- and tetra-*O*-acetyl derivatives, respectively, and their structures established. Compound **30** was convertible to **29** by regeneration of **19**, followed by benzylidenation.

Treatment of **29** with 2.5 molar equiv of 2-methoxypropene in the presence of TsOH·H₂O in DMF for 4 h at room temperature gave a mixture of products (Figure 5), which was easily fractionated using a silica gel column to give the 3,4- (**31**) and 4,5-*O*-isopropylidene (**35**) derivatives in 41% and 36% yield, respectively. The structures of these compounds were established by converting them into the acetyl derivatives **32** and **36**, respectively.

Treatment of **31** with an excess of *p*-toluenesulfonyl chloride in pyridine gave the tosylate **33** (∼100%). Direct nucleophilic substitution of **33** with an azide anion in the presence of 15-crown-5 ether in DMF proceeded smoothly at 120 °C to afford a single azide, **37** (88%). Formation of any elimination products was not observed in these conditions. Hydrogenation of **37** with Raney nickel catalyst in ethanol in the presence of excess acetic anhydride gave the amide **38** (76%). This compound was deacylated with 2 M hydrochloric acid at 80 °C to give, after purification over a
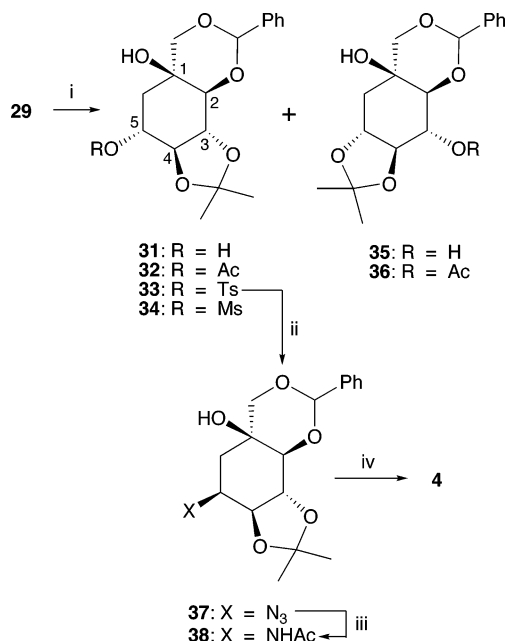
Figure 5. Synthesis of (−)-valiolamine. Reagents and conditions: (i) 2-methoxypropene (2.5 molar equiv), TsOH·H₂O, DMF, rt; (ii) NaN₃ (4 molar equiv), DMF, 120 °C; (iii) H₂, Raney nickel, EtOH, Ac₂O; (iv) 2 M HCl, 80 °C; Dowex 50 W × 2 (H⁺) resin, aqueous 1% NH₃.
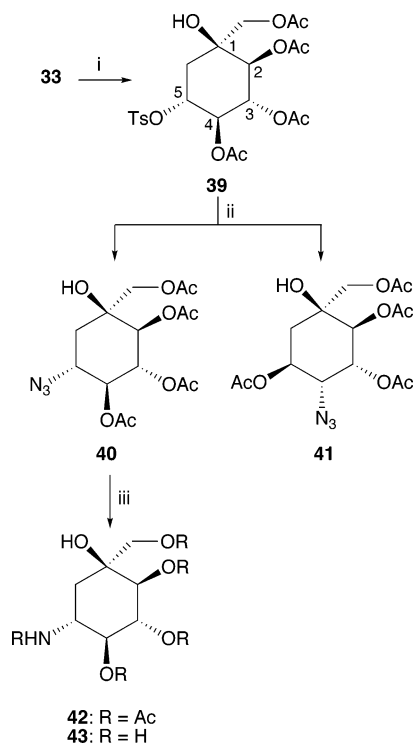
Figure 6. Synthesis of (−)-epivaliolamine (**43**). Reagents and conditions: (i) 2 M HCl, 60 °C; Ac₂O, pyridine; (ii) NaN₃ (4 molar equiv), aqueous 90% 2-methoxyethanol, 120 °C; (iii) H₂, Raney Ni, EtOH, Ac₂O.

column of Dowex 50 W × 2 (H⁺) resin with 5% aqueous ammonia, (−)-valiolamine (**4**, 90%) as a syrup. Synthetic (−)-valiolamine was further characterized as the penta-*N,O*-acetyl derivative.[21] Thus, valiolamine (**4**) was successfully synthesized from the crude deoxyinosose **13** through eight steps in more than 10% total yield.

The 1-epimer **43** of **4**, (−)-β-valiolamine, was also synthesized from the tosylate **39** (Figure 6). Hydrolysis of **33** followed by conventional acetylation gave the tetra-acetyl tosylate, **39**. Treatment
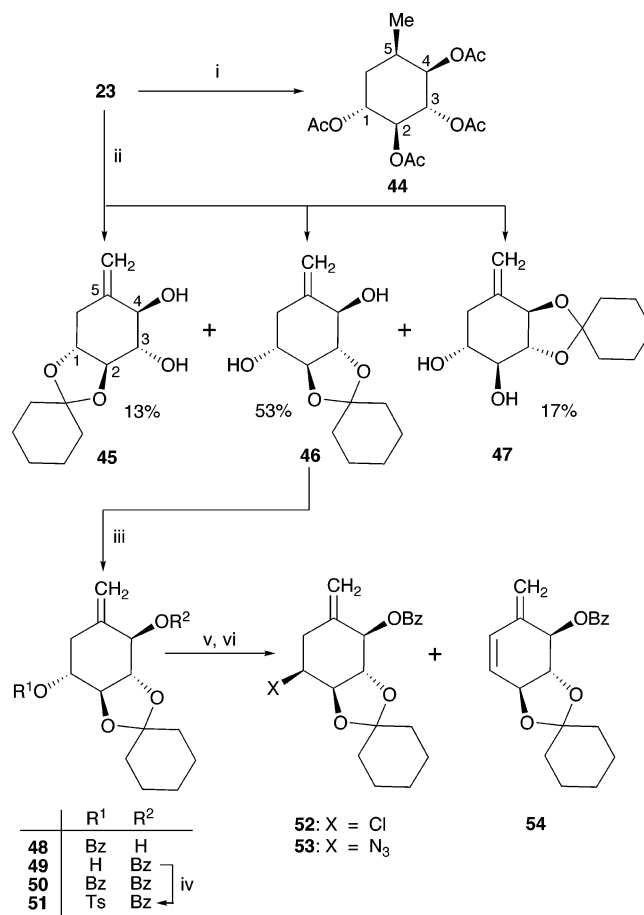
Figure 7. Preparation of versatile precursors for carbaglycosyl-amines of biological interest. Reagents and conditions: (i) H₂, Pd/C, EtOH; (ii) α,α-(MeO)₂C₆H₁₀ (ca. 10 molar equiv), TsOH·H₂O, DMF, rt; (iii) benzoic acid (1.2 molar equiv), Et₃N, EDC·HCl (1.2 molar equiv), DMAP, CH₂Cl₂, 2 days, rt; (iv) TsCl, DMAP, pyridine; (v) LiCl (30 molar equiv), Et₃N, DMF, 85 °C; (vi) NaN₃ (10 molar equiv), DMF, 85 °C.

of **39** with sodium azide in aqueous 90% 2-methoxyethanol proceeded via formation of intermediate acetoxonium ion by neighboring participation of 4-acetoxyl at C-5 to give rise to two products, the 5-azide, **40** (65%), and the 4-azide, **41** (28%). Compound **40** was similarly hydrogenolyzed and the penta-*N,O*-acetyl derivative **42** (68%) isolated and converted into the free (−)-epivaliolamine (**43**), which showed a moderate inhibitory activity toward α-glucosidase (IC₅₀ 36 μM, Baker's yeast).

Synthesis of Versatile Precursors for Carbaglycosylamines of Biological Interest

The spiro-epoxide derived from (−)-2-deoxy-*scyllo*-inosose (**17**) was converted into the iodide **22**, which was directly subjected to elimination conditions, affording the key methylene compound **23**. Hydrogenation of **23** gave a single 6-deoxycarbahexose derivative **44**. Successive cyclohexylidenation of the tetrol obtained from **23**, selective benzoylation, and conventional tosylation gave the ho-moallyl tosylate **51**, which would be a versatile intermediate for preparation of biologically active 5a-carbahexopyranosylamines and its unsaturated congeners.

Compound **23** was O-deacetylated with methanolic sodium methoxide, and the resultant tetrol was allowed to react with 1,1-dimethoxycyclohexane (23 molar equiv) in DMF in the presence of TsOH·H₂O (0.2 molar equiv) at room temperature, to give, after fractionation over a column of silica gel, the 1,2-, 2,3-, and 3,4-*O*-cyclohexylidene derivatives **45**, **46**, and **47** in 13, 53, and 17% yield, respectively (Figure 7). Their structures were clearly estab-

lished on the basis of ^{1}H NMR spectroscopic data of their respective di-*O*-acetyl derivatives. In practice, the tetrol generated by hydrolysis of compounds **45** and **47** was again subjected to cyclohexylidenation conditions to improve the yield of **46**.

Next, selective benzoylation of **46** was attempted by treatment with benzoic acid (1.2 molar equiv) in the presence of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 1.2 molar equiv), Et$_3$N (1.2 molar equiv), and DMAP (0.2 molar equiv) in CH$_2$Cl$_2$ for 2 days at −30 °C to room temperature, to afford, after fractionation over a silica gel column, the 1-*O*, 4-*O*-, and 1,4-di-*O*-benzoyl derivatives **48**, **49**, and **50** in 13, 35, and 27% yield, respectively. On conventional tosylation, the major benzoate **49** was converted into the reactive intermediate tosylate **51** (∼100%), the structure of which was established by its ^{1}H NMR spectrum, exhibiting a signal due to H-4 as a doublet ($J = 10.6$ Hz) at δ 5.62. This compound is equivalent to the corresponding 1-bromide that was effectively utilized as the intermediate for preparation of β-valienamine and its 4-epimer. In order to improve the practical yield of **49**, compounds **48** and **50** were found to be readily convertible into **46** by O-debenzoylation with MeONa in MeOH.

Reactivity of the homoallyl tosylate **51** toward common nucleophiles was first studied in order to assess reaction conditions to facilitate elimination and/or substitution reactions as selectively as possible (Figure 7). Treatment of **51** with a large excess of lithium chloride (30 molar equiv) in DMF in the presence of triethylamine was carried out at 85 °C to afford the chloride **52** (62%) and the elimination product **54** (15%). Conventional azidolysis of **51** gave the azide **53** (77%). These results indicated **51** to be a good candidate for direct nucleophilic substitution at C-1, while **52** is considered to be equivalent to the 1-epimer of **51**, which would produce likewise the epimeric azide. These azides would provide the versatile intermediates for some validamine and valiolamine isomers. The alkadiene **54**, obtainable mainly by treatment of **51** with DBU in toluene, would offer key intermediates[21] for preparation of α- and β-valienamine derivatives.

Summary and Conclusions

The present synthetic methodology has demonstrated that optically active cyclitol derivatives generated by biotransformation of *myo*-inositol would be promising key intermediates for the preparation of biologically interesting carba-amino sugar derivatives. Two racemic 5a-carbahexopyranoses (pseudosugars) were first synthesized from *myo*-inositol by Suami and one of us 30 years ago.[22] Although the present synthetic work was based substantially on precedent methods, it has been demonstrated that the availability of the crystalline unprotected spiro-epoxide **18**, newly derived from *myo*-inositol, would improve the previous route and would be more generally applicable for the provision of optically pure 5a-carbasugars and derivatives. Alternatively, compound **18** has been shown to be readily convertible to the 5-methylene compound **23**, which would be useful for synthesis of optically pure 5a-carbasugars and derivatives thereof.

Recently, the 1L-(1,2/3,4)-isomer of 5-methylene-1,2,3,4-cyclohexanetetrol was prepared[23] from a D-mannitol derivative through a multistep sequence and demonstrated to be utilized as a versatile intermediate for preparation of 5a-carbafucopyranose. In conclusion, the optically active 1L-(1,3/2,4)-isomer, **23**, obtained directly from *myo*-inositol, through a bioconversion combined with conventional synthetic procedures, promises to be a key compound convertible to quantities of optically pure carbasugars, allowing the ready design and synthesis of biologically active carbasugar derivatives.

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