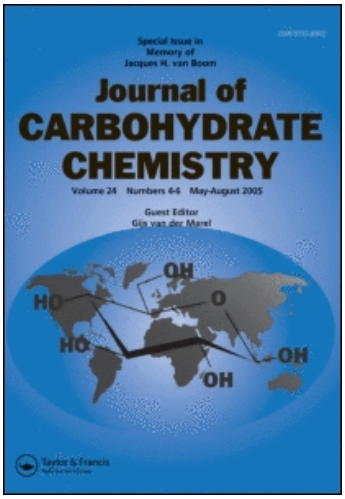

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Preparation of Versatile Synthetic Precursors of Optically Active 5a-Carba-sugars from (-)-*vibo*-Quercitol

Seiichiro Ogawa[a]; Miwako Asada[a]; Yoriko Ooki[b]; Midori Mori[b]; Masayoshi Itoh[b]; Takashi Korenaga[b]
[a] Department of Biosciences and Informatics, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama, Japan [b] Department of Chemistry, Tokyo Metropolitan University, Minami-Ohsawa, Hachioji, Tokyo, Japan

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Seiichiro Ogawa and Miwako Asada

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

Yoriko Ooki, Midori Mori, Masayoshi Itoh, and Takashi Korenaga

Department of Chemistry, Tokyo Metropolitan University, Minami-Ohsawa, Hachioji, Tokyo, Japan

The spiro-epoxide derived from (−)-2-deoxy-*scyllo*-inosose was converted into the iodide **2**, which was directly subjected to elimination conditions, affording the key methylene compound **4**. Successive cyclohexylidenation of the tetrol obtained from **4**, selective benzoylation, and conventional tosylation gave the homoallyl tosylate **11**, which would be a versatile intermediate for preparation of biologically active 5a-carbahexopyranosylamines and their unsaturated congeners.

Keywords Cyclitols, Inositols, Bioconversion, Carbohydrate mimics, Carba-sugars, Carba-glycosylamines

INTRODUCTION

We have been engaged in developing effective routes to connect readily available *myo*-inositol to optically active carba-sugars[1] of biologic interest. Practically, a number of carba-glycosylamines can be furnished[2] by chemical

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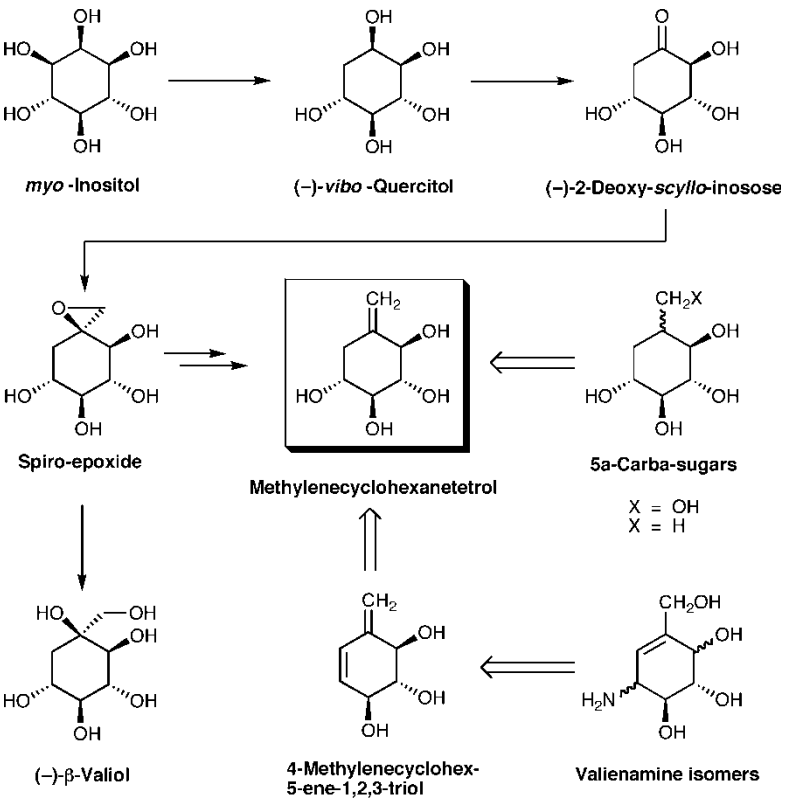
Address correspondence to Seiichiro Ogawa, Department of Biosciences and Informatics, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan. E-mail: ogawa@bio.keio.ac.jp

degradation and/or biogenesis of antibiotic validamycins. In recent years optically active carba-sugars have been totally synthesized[3] starting from common hexopyranose derivatives, (−)-shikimic acid, and so on. However, no process has been successfully employed for the production of large quantities of desired carba-sugars.

In a preceding paper,[4] we documented transformation of (−)-2-deoxy-*scyllo*-inosose derived by bio-oxidation of (−)-*vibo*-quercitol[5] into a single crystalline spiroepoxide, from which (−)-β-valiol[6] and clinically important (−)-valiolamine[7] were prepared, thus establishing a link between cyclitols and chiral carba-sugars. This process might also be applicable for provision of branched-chain cyclitol derivatives and carba-sugars.

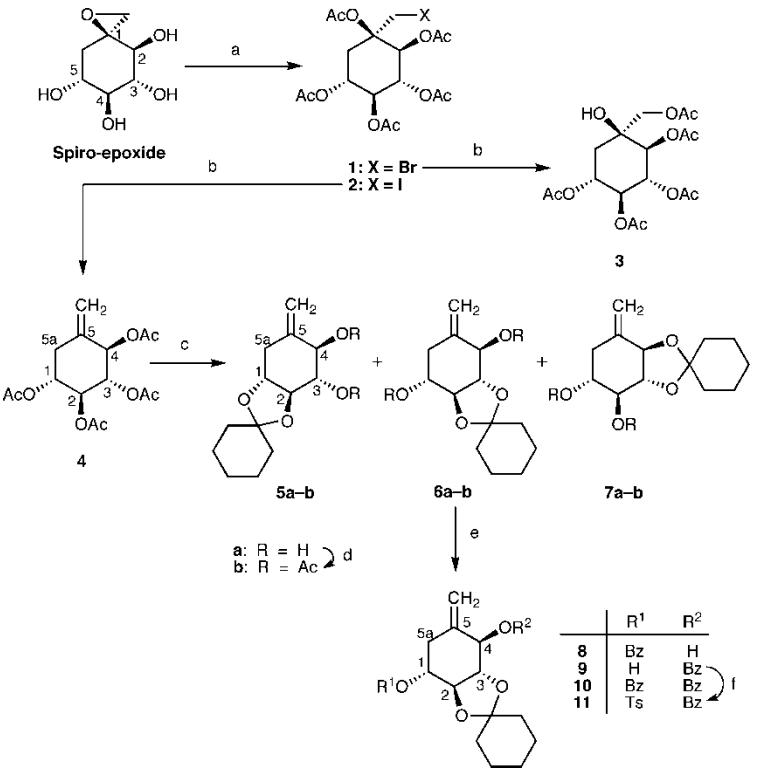
We report here ready synthesis of a key intermediate, 1L-(1,3/2,4)-5-methylene-1,2,3,4-cyclohexanetetrol (2,3,4-tri-*O*-acetyl-5-deoxy-5a-carba-β-D-*xylo*-5-enopyranose acetate)[8] (**4**), to provide 5a-carba-hexopyranoses as well as valienamine type unsaturated 5a-carba-hexopyranosylamines[9,10] of biological importance (Sch. 1).



Scheme 1: Synthetic routes to biologically interesting 5a-carba-sugar derivatives from *myo*-inositol.

RESULTS AND DISCUSSION

Conversion of the spiro-epoxide[4] into the *exo*-methylene compound **4** was attempted through an elimination reaction of the halides obtained from it (Sch. 2). Thus, treatment of the epoxide with 20% HBr-AcOH at 50°C gave the 7-bromide **1** selectively in 80% yield, which was then subjected to conventional elimination conditions[11] with zinc powder in refluxing acetic acid. However, a major product was shown to be penta-*O*-acetyl-(−)-β-valiol **3** (58%), resulting from substitution at C-7 with an acetate ion. Alternatively, the epoxide was treated with concd. hydroiodic acid in acetic acid at rt to give the iodide **2** (∼100%). Interestingly, under similar elimination conditions as above, compound **2** was converted into the desired *exo*-methylene compound **4** preferentially in 85% yield. The structure of **4** was confirmed by its ^{1}H NMR spectrum, with signals due to H-4 and H-5a protons as a doublet ($J = 9.8$ Hz)



Scheme 2: Synthesis of the key intermediates **4** and **11** from the spiro-epoxide. Conditions and reagents: (a) 20% HBr-AcOH, 50°C (→**1**); HI (2 molar equiv.), AcOH, r.t. (→**2**); (b) Zn powder, AcOH, 2 hr, reflux temp; (c) NaOMe, MeOH; α,α-dimethoxycyclohexane (∼10 molar equiv.), TsOH · H_2O (0.2 molar equiv.), DMF, 8 hr, rt; (d) Ac_2O, pyridine, rt; (e) benzoic acid (1.2 molar equiv.), Et_3N (1.2 molar equiv.), EDC · HCl (1.2 molar equiv.), DMAP (0.2 molar equiv.), CH_2Cl_2, 2 days, rt; (f) TsCl, DMAP, pyridine.

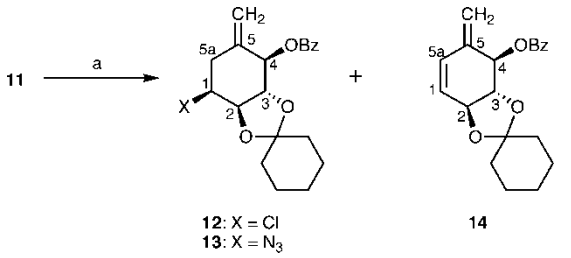
and two resonated doublets of doublets ($J = 5.4$, 13.2 Hz and $J = 11.7$, 13.2 Hz) at δ 5.39, 2.82, and 2.25, respectively.

Compound **4** 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 $TsOH \cdot H_2O$ (0.2 molar equiv.) at rt to give, after fractionation over a column of silica gel, the 1,2-, 2,3-, and 3,4-*O*-cyclohexylidene derivatives[a] **5a**, **6a**, and **7a** in 13%, 53%, and 17% yields, respectively. Their structures were clearly established on the basis of ^{1}H NMR spectral data of their respective di-*O*-acetyl derivatives **5b**, **6b**, and **7b**. For example, the structure of **6b** was assigned on the basis of its spectrum, which indicated signals due to H-1 and H-4 as a doublet of doublets of doublets ($J = 5.4$, 9.9, 10.0 Hz) and a doublet ($J = 10.5$ Hz) at δ 4.86 and 5.41, respectively. Practically, the tetrol obtained by hydrolysis of compounds **5a** and **7a** was again subjected to cyclohexylidenation conditions to improve the yield of **6a**.

Next, selective benzoylation of **6a** was attempted by treatment with benzoic acid (1.2 molar equiv.) in the presence of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride ($EDC \cdot HCl$, 1.2 molar equiv.), Et_3N (1.2 molar equiv.), and DMAP (0.2 molar equiv) in CH_2Cl_2 for two 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 **8**, **9**, and **10** in 13%, 35%, and 27% yields, respectively. On conventional tosylation, the major benzoate **9** was converted into reactive intermediate tosylate **11** ($\sim$100%), the structure of which was established by its ^{1}H NMR spectrum, exhibiting a signal due to H-4 as a doublet ($J = 10.6$ Hz) at δ 5.62. This compound is equivalent to the corresponding 1-bromide that was effectively utilized[12] as the intermediate for preparation of β-valienamine and its 4-epimer. To improve the practical yield of **9**, compounds **8** and **10** were readily convertible into **6a** by *O*-debenzoylation with MeONa in MeOH.

Reactivity of the homoallyl tosylate **11** toward common nucleophiles was first studied to assess reaction conditions to facilitate elimination and/or substitution reactions as selectively as possible (Sch. 3). Treatment of **11** 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 **12** (62%) and the elimination product **14** (15%). The structure of the chloride **12** was assigned by the ^{1}H NMR signals for H-2 and H-3 at δ 3.58 and 4.25 as doublets of doublets ($J = 3$, 9.5 Hz) and ($J = 9.5$, 10.3 Hz), respectively. The structure of the alkadiene **14** was also assigned by the ^{1}H NMR spectrum, which contained a doublet ($J = 8.4$ Hz) and a doublet of doublets ($J = 8.4$, 11.2 Hz) at δ 4.43 and 3.93 due to H-2 and H-3 signals, respectively. Alternatively, azidolysis of **11** with 10 molar equiv. of sodium azide in DMF at 85°C produced the α-azide **13** (77%)

[a]All compounds **4**–**14** are designated the derivatives of 5a-carba-hexopyranose.



Scheme 3: Reactions of the tosylate **11**. Conditions and reagents: (a) LiCl (30 molar equiv.), Et_3N, DMF, 85°C (**11** → **12**); NaN_3 (10 molar equiv.), DMF, 85°C (**11** → **13**).

along with **14** (12%). The ^{1}H NMR spectrum of **13** contained two resonated doublets of doublets at δ 3.86 ($J = 2.7$, 9.3 Hz) and 4.14 ($J = 9.3$, 10.4 Hz), attributable to H-2 and H-3, confirming the assigned structure. These results indicated **11** as a nice candidate for direct nucleophilic substitution at C-1. Compound **12** is considered to be equivalent to the α-anomer of **11**, which would produce the β-azide by azidolysis. All reaction conditions have not been optimized yet. The alkadiene **14**, obtainable mainly by treatment of **11** with DBU in toluene, offered a key intermediate[13] for preparation of β-valienamine derivatives. Selected ^{1}H NMR data for key compounds are presented below.[b]

Recently, the 1L-(1,2/3,4)-isomer of 5-methylene-1,2,3,4-cyclohexanetetrol was prepared[14] 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

[b]Specific rotations and ^{1}H NMR data follow **4**: $[\alpha]_D^{22} = +5.5°$ ($c = 1.8$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.39 (d, 1H, $J_{3,4}$ 9.8 Hz, H-4), 5.28 (dd, 1H, $J_{1,2} = J_{2,3}$ 9.8 Hz, H-2), 5.05 (m, 3H, H-3, 2 × H-6), 4.82 (ddd, 1H, $J_{1,5a(eq)}$ 5.4 Hz, $J_{1,2}$ 9.8 Hz, $J_{1,5a(ax)}$ 11.7 Hz, H-1), 2.82 [dd, 1H, $J_{1,5a(eq)}$ 5.4 Hz, J_{5agem} 13.2 Hz, H-5a(eq)], 2.25 (dd, 1H, $J_{1,5a(ax)}$ 11.7 Hz, J_{5agem} 13.2 Hz, H-5a(ax)], 2.12, 2.03, 2.02, 2.01 (4 s, each 3H, 4 × OAc). **6b**: $[\alpha]_D^{22} = -27°$ ($c = 0.52$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.41 (d, 1H, $J_{3,4}$ 10.5 Hz, H-4), 5.08, 4.95 (2 s, each 1H, 2 × H-6), 4.86 (ddd, 1H, $J_{1,5a(eq)}$ 5.4 Hz, $J_{1,2}$ 9.9 Hz, $J_{1,5a(ax)}$ 10.0 Hz, H-1), 3.76 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{1,2}$ 9.9 Hz, H-2), 3.48 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 10.5 Hz, H-3), 2.92 [dd, 1H, $J_{1,5a(eq)}$ 5.4 Hz, J_{5agem} 13.9 Hz, H-5a(eq)], 2.14 [m, 1H, H-5a(ax)], 2.21, 2.11 (2 s, each 3H, 2 × OAc), 1.67 (m, 10 H, C_6H_{10}). **11** $[\alpha]_D^{20} = -15°$ ($c = 2.8$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12–7.26 (m, 9 H, Ph), 5.62 (d, 1H, $J_{3,4}$ 10.6 Hz, H-4), 5.11, 5.05 (2 s, each 1H, 2 × H-6), 4.57 (ddd, 1H, $J_{1,5a(eq)}$ 5.4 Hz, $J_{1,2}$ 9.8 Hz, $J_{1,5a(ax)}$ 10.3 Hz, H-1), 3.74 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{1,2}$ 9.6 Hz, H-2), 3.51 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 10.6 Hz, H-3), 3.01 [dd, 1H, $J_{1,5a(eq)}$ 5.4 Hz, J_{5agem} 14.4 Hz, H-5a(eq)], 2.51 [dd, 1H, $J_{1,5a(ax)}$ 10.3 Hz, J_{5agem} 14.4 Hz, H-5a(ax)], 2.44 (s, 3H, PhCH_3), 1.32 (m, 10 H, C_6H_{10}). **13**: $[\alpha]_D^{20} = -9.6°$ ($c = 1.1$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (m, 2 H, Ph), 7.54 (m, 3H, Ph), 5.65 (d, 1H, $J_{3,4}$ 10.4 Hz, H-4), 5.09 (br s, 2 H, 2 × H-6), 4.29 (m, 1H, H-1), 4.14 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 10.4 Hz, H-3), 3.86 (dd, 1H, $J_{1,2}$ 2.7 Hz, $J_{2,3}$ 9.3 Hz, H-2), 2.54 [m, 2 H, H-5a(ax), H-5a(eq)], 1.71 (m, 10 H, C_6H_{10}). **14**: $[\alpha]_D^{20} = +47°$ ($c = 0.13$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (m, 2 H, Ph), 7.62–7.45 (m, 3H, Ph), 6.13 (m, 3H, H-1, H-4, H-5a), 5.25, 5.12 (2 s, each 1H, 2 × H-6), 4.43 (d, 1H, $J_{2,3}$ 8.4 Hz, H-2), 3.93 (dd, 1H, $J_{2,3}$ 8.4 Hz, $J_{3,4}$ 11.2 Hz, H-3), 1.64 (m, 10 H, C_6H_{10}).

4, obtained directly from *myo*-inositol through bioconversion combined with conventional synthetic procedures, promises to be a key compound convertible to quantities of optically pure carba-sugars, allowing us readily to design and synthesize biologically active carba-sugar derivatives with ease.

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