Synthesis of Streptolidine from D-Xylose

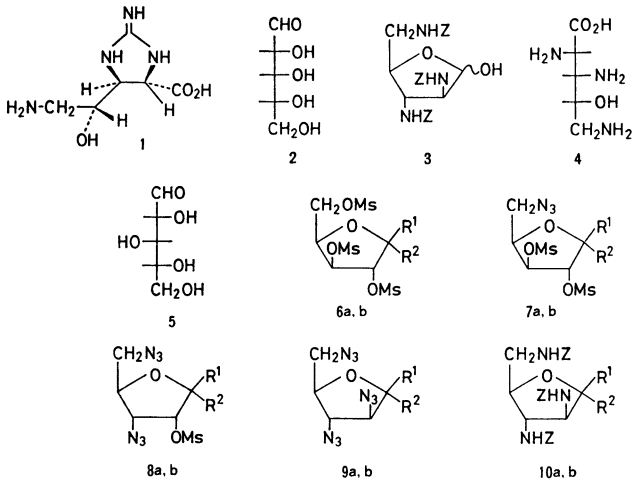
Shoichi KUSUMOTO, Shinichi TSUJI, Keiyuu SHIMA, and Tetsuo SHIBA

Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560

(Received June 21, 1976)

An alternative total synthesis of streptolidine (roseonine, geamine) was achieved starting from D-xylose. Direct azidolysis of methyl 2,3,5-tri-*O*-mesyl-α-D-xylofuranoside (**6a**) afforded methyl 2,3,5-triazido-2,3,5-trideoxy-α-D-arabinofuranoside (**9a**), whereas the β-anomer of **6a** gave only 3,5-diazido-3,5-dideoxy-2-*O*-mesyl-β-D-ribofuranoside (**8b**) indicating that the glycosidic configuration in the furanoside system has a decisive influence on the reactivity of the 2-mesyloxy group. However, the β-anomer of diazide (**8b**) was anomerized to α-anomer which readily undergoes azidolysis to give the triazide (**9a**). The triazide was successively hydrogenated, benzyloxycarbonylated, and then hydrolyzed to give 2,3,5-tris(benzyloxycarbonylamino)-2,3,5-trideoxy-D-arabinofuranose, which was identical with that prepared from D-ribose. Streptolidine could be synthesized from this key intermediate.

In a previous paper,[1] a report was given on the total synthesis of streptolidine (roseonine, geamine)[2] (**1**), a component guanidino amino acid of streptothricin antibiotics, which had been performed starting from D-ribose. Fully controlled substitution of three hydroxyl group in D-ribose (**2**) *via* twelve synthetic steps involving azidolysis of an epimino ring yielded 2,3,5-tris(benzyloxycarbonylamino)-2,3,5-trideoxy-D-arabinofuranose (**3**), which was then oxidized to (2*S*, 3*S*, 4*R*)-2,3,5-triamino-4-hydroxypentanoic acid (**4**) derivative. Guanidination of δ-lactam of **4** with cyanogen bromide afforded streptolidine of the natural configuration. The above complicated synthesis can be improved if simultaneous S_N2 displacement of the three hydroxyl groups on C-2, -3, and -5 of D-xylose (**5**) with nitrogen functions would occur leading to the same key intermediate (**3**). Although a sulfonyloxy group on C-2 of a furanoside or pyranoside resists substitution with azide anion in general, some successful cases of this reaction have recently been reported.[3,4] In the present investigation on the direct azidolysis of methyl 2,3,5-tri-*O*-mesyl-D-xylofuranoside (**6**), we could obtain the compound **3** as expected, thus accomplishing a new route to the synthesis of streptolidine from D-xylose.



Z=$C_6H_5CH_2OCO$, Ms=CH_3SO_2

a: R^1=H, R^2=OCH_3

b: R^1=OCH_3, R^2=H

Results and Discussion

D-Xylose was treated with hydrogen chloride in methanol and then with mesyl chloride in pyridine to afford a mixture of tri-*O*-mesyl-α and β-D-xylofuranoside (**6a** and **6b**), in which the β-anomer (**6b**) exists predominantly. When the mixture[5] was treated with sodium azide in *N*,*N*-dimethylformamide (DMF) at 100 °C for 2 h and then at 140 °C for 2 h, four azido compounds were formed, which were isolated by column chromatography.

In the NMR spectra (100 MHz) of these compounds, most of the signals of the individual protons were well separated from each other, and could be assigned with the aid of decoupling experiments. They are given in Table 1. The data indicate the number of the remaining mesyloxy groups, the positions of substituents as well as the anomeric configuration in each compound. The main syrupy product (**7**) (37% of the starting mixture) retaining two unchanged mesyl groups was found to be 5-monoazide since only the signals of C-5 protons shifted considerably into higher field. The product is probably a mixture of anomers, being rich in β-form (**7b**) contaminated with a minor amount of α-form (**7a**). The assignment of the monoazide structure was supported by the formation of monobenzamido derivative on hydrogenation of **7** followed by benzoylation. The other two products (**8a** and **8b**, 3.4 and 27%, respectively, of the starting mixture), both being diazides, were assigned to anomers of 3,5-diazide, because the chemical shift values of C-3 and C-5 protons indicate undoubtedly the location of the azide groups on these carbon atoms. The anomeric configurations were determined on the basis of coupling constants. Thus, $J_{1,2}$ value of **8a** (4.5 Hz) shows cis relation of C-1 and C-2 protons, while that of **8b** (0 Hz) shows trans relation, indicating the structure of metyl 3,5-diazido-3,5-dideoxy-2-*O*-mesyl-α- and β-D-ribofuranoside for **8a** and **8b**, respectively.

The fourth product (**9a**) obtained in only a very small amount (0.75% of starting mixture) showed no NMR signal of the mesyl group. On catalytic hydrogenation followed by benzyloxycarbonylation, it afforded tris(benzyloxycarbonylamino) derivative (**10a**) which was differentiated from methyl 2,3,5-tris(benzyloxycarbonylamino)-2,3,5-trideoxy-β-D-arabinofuranoside (**10b**) prepared from D-ribose.[1]

Table 1. Chemical shifts and coupling constants of protons in mesyl and azide derivatives[a]

	H-1	H-2	H-3	H-4	H_2-5	OCH_3	OMs
6b	5.10	5.10 (J=2)	5.28 dd (J=2, 6)	4.74 q (J=6)	4.41 d (J=6)	3.44	3.08 (3H) 3.14 (3H) 3.16 (3H)
7		5.1——5.3		4.53	≈3.55 d	3.50	3.20 (6H)
8a	5.04 d (J=4.5)	4.90 dd (J=4.5, 7.5)	3.88 dd (J=7.5, 5)	4.05 m	3.36 dd(1H) 3.55 dd(1H)	3.38	3.10 (3H)
8b	4.96 s	4.91 d (J=4)	≈4.05	≈4.05	≈3.3 dd(1H) 3.50 dd(1H)	3.33	3.06 (3H)
9a	4.90 d (J=3)	3.93 dd (J=3, 5.5)	3.72 dd (J=5.5, 7)	4.06 m	≈3.4 dd(1H) ≈3.6 dd(1H)	3.40	—

a) Measured on Varian XL-100 spectrometer in $CDCl_3$. The chemical shifts and the coupling constants were recorded in δ values and Hz.

The coupling constant value of $J_{1,2}$=0 Hz in **10a** indicated trans relation of C-1 and C-2 protons. NMR data (Table 1) confirmed the structure of **9a** to be the triazide of the desired configuration, *i.e.*, methyl 2,3,5-triazido-2,3,5-trideoxy-α-D-arabinofuranoside.

The exclusive formation of triazide (**9a**) of α-glycoside structure may suggest that azidolysis of C-2 mesyloxy group proceeds only from the methyl α-glycoside (**6a**) but not from the β-anomer (**6b**) in the starting mixture. In fact, no trace of a triazide was detected when the pure β-glycoside of monomesyl diazide (**8b**) was treated with sodium azide in DMF or HMPA at 140 °C; whereas its α-anomer (**8a**) could be readily converted into the triazide (**9a**) in DMF at 140 °C.

Great differences in the reactivity of 2-sulfonate between both anomers have been observed by Miljković *et al.*[3] but only in pyranoside systems. They reported that S_N2 type substitution of C-2 mesyloxy groups with a charged nucleophile occurs in methyl β-gluco- and β-mannopyranoside but not in the corresponding α-anomers. In our experiments, however, the substitution reaction of the 2-mesyloxy group occurs only in the α-furanoside. The apparent discrepancy in the reactivity of each anomer of the furanoside and the pyranoside is not surprising since steric situations in the two ring systems differ a great deal.

The exhaustive azidolysis of D-xylose derivative might be utilized as a new direct method leading to the 2,3,5-triaminopentose derivative of desired stereochemistry. Attempts were next made to anomerize the β-glycofuranosides, the main product in Fischer's glycosidation reaction of xylose, to the α-furanoside derivative which can be used as the starting material for the triazide (**9a**). When β-diazide (**8b**) was heated in methanol containing dry hydrogen chloride, anomerization took place giving 16% of α-diazide (**8a**) and 61% of unchanged **8b** which were separated from each other by column chromatography. Use of titanium tetrachloride in methylene chloride gave a similar result. On the other hand, no anomerization occurred on the β-anomer of the trimesylate (**6b**) under similar conditions.

The α-diazide (**8a**) thus obtained was converted into the triazide (**9a**) in 38% yield by heating with sodium azide in DMF at 140 °C for 4 h. This condition seemed to be optimal, since higher temperature caused decomposition of the materials resulting in loss of the yield. In order to increase the yield of triazide, effect of "crown ether"[6] on the substitution reaction was examined. Addition of 18-crown-6 to the reaction mixture did not improve the reaction. In other solvents such as acetonitrile, benzene, dioxane, toluene, and *o*-xylene, **8a** did not react with sodium azide at all even on addition of 18-crown-6.

After the triazide (**9a**) was converted into the tris(benzyloxycarbonylamino) derivative (**10a**) as described above, the glycoside linkage was hydrolyzed with *p*-toluenesulfonic acid in aqueous dioxane. Comparison of mps, IR and NMR spectra showed that the hydrolysis product was identical with 2,3,5-tris(benzyloxycarbonylamino)-2,3,5-trideoxy-D-arabinofuranose (**3**) previously prepared from D-ribose.[1] Since the conversion of **3** into streptolidine had been performed through oxidation, deprotection and guanidination successively,[1] it is now established that streptolidine was formally synthesized also from D-xylose by an alternative and improved method.

Experimental

All melting points are uncorrected. Silica gel 60 (0.063—0.200mm, Merck) was used for column chromatography. TLC and preparative TLC were performed on Silica gel G and H, Merck, respectively.

*Methyl 2,3,5-Tri-O-mesyl-α- and β-D-xylofuranoside (**6a** and **6b**).* A mixture of D-xylose (20.0 g, 0.133 mol) in methanol (500 ml) containing dry HCl (0.5 wt%) was stirred at room temperature overnight. After neutralization with Ag_2CO_3, the mixture was filtered and the solvent was evaporated *in vacuo* to a syrupy residue. To an ice-cooled solution of this residue in pyridine (200 ml) was added mesyl chloride (50 ml, 0.64 mol) dropwise with stirring. The mixture was stirred in an ice bath for 5 h, allowed to stand at room temperature overnight and then evaporated *in vacuo*. The residue was taken up in CH_2Cl_2, washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. Recrystallization from ethyl acetate–hexane afforded a mixture of **6a** and **6b** yield, 35.8 g (68%). The proportion of **6a** to **6b** was determined by preparative TLC on silica gel (benzene–ethyl acetate 1 : 2). From 108.0 mg of the mixture, 9.4 mg of **6a** and 96.4 mg of **6b** were obtained, indicating a ratio

of 9 : 91.

Repeated recrystallization of this mixture from ethyl acetate–benzene afforded pure **6b**; mp 111—112 °C; $[\alpha]_D^{17}$ −18.6° (*c* 1.83, ethyl acetate); NMR, see Table 1.

Found: C, 27.41; H, 4.55; S, 23.89%. Calcd for $C_9H_{18}O_{11}S_3$: C, 27.13; H, 4.55; S, 24.14%.

From the mother liquor of **6b**, the anomer **6a** was isolated by column chromatography on silica gel (benzene–ethyl acetate), and recrystallized from benzene–ethyl acetate; mp 132 °C; $[\alpha]_D^{17}$ +10.8° (*c* 1.97, ethyl acetate).

Found: C, 27.05; H, 4.59; S, 23.87%.

*Azidolysis of a Mixture of **6a** and **6b**.* A mixture of **6a** and **6b** described above (10.0 g, 25.2 mmol) was heated with NaN_3 (11.5 g, 178 mmol) in DMF (150 ml) at 100—110 °C (bath temp) for 2 h, then at 135—140 °C (bath temp) for 2 h. After the mixture had been cooled, the precipitate was filtered off and the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2, washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was subjected to column chromatography on silica gel. A mixture of hexane–ethyl acetate (4 : 1) eluted **9a**, **8b**, **8a**, and **7** in this order.

i) *Methyl 5-Azido-5-deoxy-2,3-di-O-mesyl-α- and β-D-xylofuranoside (**7a** and **7b**)*: Yield, 3.19 g (37%); syrup; NMR see Table 1. This product was hydrogenated in methanol–tetrahydrofuran in the presence of HCl and Pd on charcoal, and then treated with benzoyl chloride and triethylamine to afford monobenzamido derivative; mp 146—147 °C.

Found: C, 42.06; H, 5.03; N, 3.22; S, 15.19%. Calcd for $C_{15}H_{21}O_9NS_2$: C, 42.54; H, 5.00; N, 3.31; S, 15.14%.

ii) *Methyl 3,5-Diazido-3,5-dideoxy-2-O-mesyl-α-D-ribofuranoside (**8a**)*: Yield, 250 mg (3.4% of the starting anomeric mixture, 38% of **6a**); syrup; NMR, see Table 1. This compound was characterized by conversion into crystalline dibenzamido derivative in a similar manner to that described in (i); mp 210 °C; $[\alpha]_D^{19}$ +82.4 °C (*c* 2.08, $CHCl_3$).

Found: C, 55.96; H, 5.36; N, 6.22; S, 7.18%. Calcd for $C_{21}H_{24}O_7N_2S$: C, 56.24; H, 5.39; N, 6.25; S, 7.15%.

iii) *Methyl 3,5-Diazido-3,5-dideoxy-2-O-mesyl-β-D-ribofuranoside (**8b**)*: Yield, 1.98 g (27% of the mixture, 30% of **6b**); mp 59—60 °C; $[\alpha]_D^{14}$ +72.8° (*c* 1.51, ethyl acetate); NMR, see Table 1.

Found: C, 28.75; H, 4.21; N, 28.43; S, 10.90%. Calcd for $C_7H_{12}O_5N_6S$: C, 28.77; H, 4.11; N, 28.77; S, 10.96%.

iv) *Methyl* 2,3,5-*Triazido*-2,3,5-*trideoxy-α-D-arabinofuranoside (**9a**)*: Yield, 45 mg (0.75% of the mixture, 8.4% of **6a**); syrup; $[\alpha]_D^{20}$ +195.0° (*c* 2.26, $CHCl_3$); NMR, see Table 1. This compound was hydrogenated in ethanol in the presence of Pd black and HCl. The product was treated with benzyloxycarbonyl chloride and triethylamine to afford methyl 2,3,5-tris(benzyloxycarbonylamino)-2,3,5-trideoxy-α-D-arabinofuranoside (**10a**); mp 204—205 °C; $[\alpha]_D^{21}$ +32.0° (*c* 0.75, $CHCl_3$). NMR: δ 4.78 (1H s, H-1), 5.03 (6H s, $C_6H_5C\underline{H}_2$), 7.25 (15H, aromatic H).

Found: C, 63.93; H, 6.04; N, 7.50%. Calcd for $C_{30}H_{33}O_8N_3$: C, 63.93; H, 5.90; N, 7.46%.

*Attempts at Azidolysis of **8b**.* A stirred mixture of **8b** (15 mg, 0.05 mmol) and NaN_3 (16 mg, 0.25 mmol) in HMPA (3 ml) was heated and the product was tested by TLC. No reaction occurred at 145 °C (bath temp). When the mixture was heated over 155 °C (bath temp), **8b** decomposed completely, no definite spots on TLC being detected. A similar result was obtained using DMF as solvent.

*Preparation of **8a** by Anomerization of **8b**. With HCl in Methanol*: A solution of **8b** (452 mg) in methanol (50 ml) containing dry HCl (23 wt%) was heated under reflux for 6 h. After the mixture had been cooled, the solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (4 : 1) afforded **8b** (274 mg, 61%) and then **8a** (74 mg, 16%).

With $TiCl_4$ in CH_2Cl_2: To a solution of **8b** (520 mg) in CH_2Cl_2 (90 ml) was added $TiCl_4$ (0.25 ml) in CH_2Cl_2 (10 ml) and the mixture was stirred at room temperature for 1 h. On addition of ice, the mixture was stirred until the CH_2Cl_2 layer became clear. The CH_2Cl_2 layer was washed with aq $NaHCO_3$ solution and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed as above to give **8b** (308 mg, 59%) and **8a** (80 mg, 15%). Prolonged reaction time caused decomposition of the material.

*Triazide (**9a**) from **8a**.* A mixture of **8a** (155 mg, 0.53 mmol) and NaN_3 (240 mg, 3.7 mmol) in DMF (15 ml) was heated at 140—150 °C (bath temp) with stirring for 4 h and then treated as usual. The product (**9a**) was isolated by preparative TLC on silica gel (hexane–ethyl acetate 2 : 1); yield, 48 mg (38%).

*Examination of the Effect of 18-Crown-6 on Azidolysis of **8a**. In DMF*: A mixture of **8a** (1.0 g, 3.4 mmol), NaN_3 (0.88 g, 13.5 mmol), and 18-crown-6 (90 mg, 0.34 mmol) in DMF (100 ml) was heated at 130 °C (bath temp) with stirring for 18 h. By the usual work-up and chromatography, **9a** (0.23 g, 28%) and unchanged **8a** (0.06 g, 6%) were obtained. Without addition of 18-crown-6, but otherwise under the same conditions, the situation did not change; **9a** (0.23 g, 28%) and **8a** (0.06 g, 6%).

In Other Solvents: Mixtures of **8a** (25—50 mg) and NaN_3 (4 mol equivalent) in various solvents (acetonitrile, dioxane, benzene, toluene, or *o*-xylene) were heated under reflux in the presence of 18-crown-6 (1—2 mol equivalent). TLC examination indicated that **9a** was never formed in any of the solvents employed.

*Methyl 2,3,5-Tris(benzyloxycarbonylamino)-2,3,5-trideoxy-α-D-arabinofuranoside (**10a**).* The triazide (**9a**) (300 mg, 1.25 mmol) was dissolved in ethanol (30 ml) and hydrogenated in the presence of Pd black catalyst. After the catalyst had been removed, the mixture was cooled in an ice bath. Triethylamine (0.71 ml, 5.0 mmol) and benzyloxycarbonyl chloride (0.73 ml, 5.0 mmol) were added and the mixture was stirred overnight. Triethylamine (0.36 ml) and benzyloxycarbonyl chloride (0.37 ml) were again added and stirring was continued for further 4 h. The mixture was concentrated *in vacuo*, water was added and the crystalline substance was collected by filtration; yield, 580 mg (83%). Recrystallization was effected from $CHCl_3$; mp 171—173 °C.

Found: C, 62.63; H, 6.03; N, 7.54%. Calcd for $C_{30}H_{33}O_8N_3 \cdot 1/2H_2O$: C, 62.92; H, 5.99; N, 7.34%.

An anhydrous crystals of the same compound showed mp 204—205 °C.

*2,3,5-Tris(benzyloxycarbonylamino)-2,3,5-trideoxy-D-arabinofuranose (**3**).* To a solution of **10a** (600 mg) in dioxane (30 ml) was added 2 M aq solution of *p*-toluenesulfonic acid (30 ml). The mixture was heated under reflux for 1.5 h, concentrated *in vacuo*, and then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was subjected to a silica gel column. A mixture of $CHCl_3$–ethyl acetate (3 : 1) eluted first unchanged **10a** (197 mg, 30%) and then **3** (177 mg, 30%). The latter was recrystallized from $CHCl_3$; mp 208—210 °C. Its IR and NMR spectra were identical with those of the sample prepared from D-ribose.[1]

References

1) S. Kusumoto, S. Tsuji, and T. Shiba, *Tetrahedron Lett.*, **1974**, 1417; *Bull. Chem. Soc. Jpn.*, **47**, 2690 (1974). Goto

and Ohgi also reported independently a similar synthesis starting from D-ribose: T. Goto and T. Ohgi, *Tetrahedron Lett.*, **1974**, 1413.

2) Isolation: a) H. E. Carter, R. K. Clark, P. Kohn, J. M. Rothrock, W. R. Taylor, C. A. West, G. B. Whitfield, and H. G. Jackson, *J. Am. Chem. Soc.*, **76**, 566 (1954); b) K. Nakanishi, T. Ito, and Y. Hirata, *ibid.*, **76**, 2845 (1954); c) H. Brockmann and H. Musso, *Chem. Ber.*, **88**, 648 (1955); Structure determination: d) H. E. Carter, C. C. Sweeley, E. E. van Tamelen, J. R. Dyer, and H. A. Whaley, *J. Am. Chem. Soc.*, **83**, 4296 (1961); e) B. W. Bycroft and T. J. King, *J. Chem. Soc., Chem. Commun.*, **1972**, 652.

3) M. Miljkovic, M. Gligorijević, and D. Glisin, *J. Org. Chem.*, **39**, 3223 (1974).

4) M. Nakajima, H. Shibata, K. Kitahara, S. Takahashi, and A. Hasegawa, *Tetrahedron Lett.*, **1968**, 2271.

5) The ratio of α- to β-anomer was 9 : 91 (see Experimental). Although each anomer could be separated by means of column chromatography, the procedure was time-consuming and the azidolysis was thus carried out using the mixture.

6) a) C. J. Pederson, *J. Am. Chem. Soc.*, **89**, 7017 (1967); b) G. W. Gokel and H. O. Durst, *Synthesis*, **1976**, 168.