Synthesis of *myo*-Inositol Derivatives Required for the Total Synthesis of Surugatoxin, Prosurugatoxin, and Neosurugatoxin

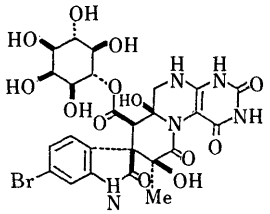
Kunisuke OKADA,* Kiyomatsu HASHIZUME, Hideo TANINO, Hisae KAKOI, and Shoji INOUE

Faculty of Pharmacy, Meijo University, Tenpaku, Nagoya 468 Japan. *Received September 29, 1988*

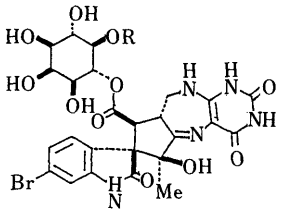
Two *myo*-inositol derivatives (4) and (5), required for the total synthesis of surugatoxin, prosurugatoxin, and neosurugatoxin, were prepared. Synthesis of (±)-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-1-*O*-methoxymethyl-*myo*-inositol (4) was achieved from (±)-1-*O*-benzoyl-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-*myo*-inositol (6) in 4 steps, and (−)-2,3-*O*-cyclohexylidene-1,4-di-*O*-methoxymethyl-5-*O*-[2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl]-*myo*-inositol (5) was synthesized from (±)-1-*O*-benzoyl-2,3-*O*-cyclohexylidene-5,6-*O*-isopropylidene-*myo*-inositol (12) in 7 steps.

Keywords 1,2,3,4,5-penta-*O*-substituted *myo*-inositol derivative; 2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-1-*O*-methoxymethyl-*myo*-inositol; 2,3-*O*-cyclohexylidene-1,4-di-*O*-methoxymethyl-5-*O*-[2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl]-*myo*-inositol; surugatoxin; prosurugatoxin; neosurugatoxin

The Japanese ivory shell (*Babylonia japonica*) harvested from the Ganyudo area in Suruga Bay was the cause of an outbreak of food poisoning in 1965. Afterwards, Kosuge and his co-workers carried out the isolations and structure determinations of the causative agents, surugatoxin (**1**),[1] prosurugatoxin (**2**),[2] and neosurugatoxin (**3**),[3] all of which contain an ester linkage between a *myo*-inositol derivative and a new type of pentacyclic heterocycle.



1 : surugatoxin



2 : prosurugatoxin R=H

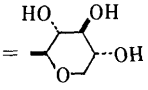
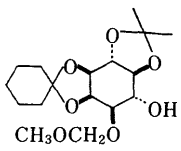
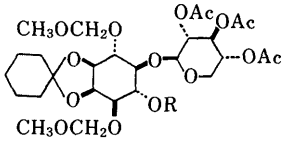
3 : neosurugatoxin R= 

Chart 1

In connection with our synthetic studies on these pharmacologically interesting metabolites, showing mydriasis-evoking and anti-nicotinic activities,[4] we required (±)-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-1-*O*-methoxymethyl-*myo*-inositol (**4**) for surugatoxin[5] and prosurugatoxin[6] synthesis and (−)-2,3-*O*-cyclohexylidene-1,4-di-*O*-methoxymethyl-5-*O*-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)-*myo*-inositol (**5**) for neosurugatoxin[7] synthesis. This paper describes the synthesis of **4** and **5**, both of which were successfully utilized in the synthesis of these toxic metabolites.



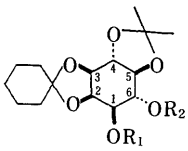
4



5a,b : R=H
23a,b : R=CH_2Ph

Chart 2

Treatment of the known (±)-1-*O*-benzoyl-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-*myo*-inositol (**6**)[8] with sodium hydride and benzyl bromide in dimethylformamide (DMF) produced a mixture of **7** and **8**, which was, without any purification, hydrolyzed with 1 N potassium hydroxide in methanol at room temperature for 2 h to give two mono-*O*-benzylated *myo*-inositol derivatives (**9** and **10**) in 46.7% and 40.6% yields based on **6**, respectively. The hydroxy group at C_1 in **9** was then protected with a methoxymethyl group in the usual manner to give **11** in 89.0% yield. Removal of the benzyl group at C_6 in **11** gave, upon crystallization from hexane, the desired (±)-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-1-*O*-methoxymethyl-*myo*-inositol (**4**) in 90.3% yield.



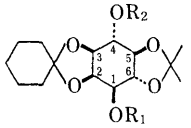
6 : R_1=COPh, R_2=H
7 : R_1=COPh, R_2=CH_2Ph
8 : R_1=CH_2Ph, R_2=COPh
9 : R_1=H, R_2=CH_2Ph
10 : R_1=CH_2Ph, R_2=H
11 : R_1=CH_2OCH_3, R_2=CH_2Ph

Chart 3

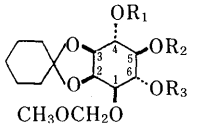
Synthesis of **5** was developed starting from the known (±)-1-*O*-benzoyl-2,3-*O*-cyclohexylidene-5,6-*O*-isopropylidene-*myo*-inositol (**12**).[8] The benzoyl group in **12** was removed by treatment with 1 N potassium hydroxide in methanol at room temperature for 2 h to give a diol **13** in 72.8% yield, and this was further converted into the 1,4-di-*O*-methoxymethyl derivative (**14**) in the usual manner in 96.0% yield. The isopropylidene group in **14** was then selectively removed by treatment with 1% trifluoroacetic acid in dichloromethane at room temperature for 30 min, giving **15** in 91.3% yield. Selective benzylation of the resulting 2,3-*O*-cyclohexylidene-1,4-di-*O*-methoxymethyl-*myo*-inositol (**15**) at C_6 was next examined. When the solution of **15** in DMF was treated with 1 molar eq of sodium hydride and 1.2 molar eq of benzyl bromide at room temperature for 1 h, the desired 6-*O*-benzyl derivative **16** was obtained in 35.7% yield, after separation by silica gel chromatography, together with the undesired 5-*O*-benzyl

derivative (**17**), 5,6-*O*-dibenzyl derivative (**18**), and starting material in 21.4%, 6.4%, and 28.9% yields, respectively. De-*O*-benzylation of **17** and **18** in a usual manner easily regenerated **15** in high yield. The structure of **16** was determined as follows: compound **16** together with **20** and **21** was also obtained from **11**, the final intermediate for **4**, by removal of the acetonide group followed by selective methoxymethylation. Now, the coupling reaction of **16** with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**22**)[9] was achieved under the following conditions. Silver triflate[10] (3.3 molar eq) and 1,1,3,3-tetramethylurea (5.0 molar eq) were successively added to a solution of **16** and the freshly crystallized bromide **22** (3.0 molar eq) in dry dichloromethane under a nitrogen atmosphere at room temperature. After stirring for 3 h in the dark, the resulting reaction mixture was separated by preparative thin-layer chromatography (TLC) to give the diastereomeric products **23a** and **23b** in 33.2% and 38.9% yields, respectively.

The stereochemistry of the glycosidic bonds in **23a** and **23b** was assigned as the desired β-configuration on the basis of the ^{13}C-^{1}H coupling constants[11] (**24a**, 162.35 Hz; **24b**, 160.85 Hz) between $^{13}C_1$ and $^{1}H_1$ of the xylopyranoside moiety. Thus, hydrogenolysis of each isomer **23a** and **23b** gave the desired β-D-xylopyranosyl-[1,5]-*myo*-inositol derivative (**5a**) and the unnatural diastereoisomer (**5b**), respectively. The stereochemistry of those products was characterized by careful comparison of the proton nuclear magnetic resonance (^{1}H-NMR) spectra between the final product synthesized from **5a** or **5b** and natural neosurugatoxin.



12 : R_1=COPh, R_2=H
13 : R_1=H, R_2=H
14 : R_1=CH_2OCH_3, R_2=CH_2OCH_3



15 : R_1=CH_2OCH_3, R_2=H, R_3=H
16 : R_1=CH_2OCH_3, R_2=H, R_3=CH_2Ph
17 : R_1=CH_2OCH_3, R_2=CH_2Ph, R_3=H
18 : R_1=CH_2OCH_3, R_2=CH_2Ph, R_3=CH_2Ph
19 : R_1=H, R_2=H, R_3=CH_2Ph
20 : R_1=H, R_2=CH_2OCH_3, R_3=CH_2Ph
21 : R_1=CH_2OCH_3, R_2=CH_2OCH_3, R_3=CH_2Ph

Chart 4

Experimental

All melting points are uncorrected. Unless otherwise noted, the organic solutions obtained after extractions were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a Hitachi M-80 mass spectrometer and JNM FX-100 NMR spectrometer with Me_4Si as an internal standard. The following abbreviations are used: br=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet. Optical rotations were measured on a JASCO DIP-181 polarimeter. For column chromatography, silica gel (Kanto Chemical, over 100 mesh) was used. TLC was performed on Kieselgel $60F_{254}$ plates (Art. 5744, Merck).

(±)-6-*O*-Benzyl-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-*myo*-inositol (9) and (±)-1-*O*-Benzyl-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-*myo*-inositol (10) A cold solution of **6** (2.02 g, 5 mmol) in DMF (20 ml) was treated with NaH (50% in mineral oil, 288 mg, 6 mmol) and the mixture was stirred at 0 °C under a nitrogen atmosphere for 30 min. To this, benzyl bromide (0.712 ml, 6 mmol) was added dropwise at 0 °C and the mixture was stirred for a further 2 h at room temperature. After dilution of the mixture with EtOAc (300 ml), the whole was washed with water (twice) and brine, then the organic layer was dried. Removal of the solvent under reduced pressure gave an oil (a mixture of mainly **7** and **8**), which was treated with 1 N KOH in MeOH (50 ml) at room temperature for 2 h. The solvent was evaporated off and the residual syrup was dissolved in CH_2Cl_2 (200 ml). This solution was washed with water (twice) and brine, then the organic layer was dried and concentrated. The residue was chromatographed on a silica gel column (CH_2Cl_2 : MeOH = 100 : 1) to give **9** (0.911 g, 46.7%) as an oil from the first eluate. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (6H, s), 1.24—1.88 (10H, m), 2.64 (1H, br s, –OH), 3.57 (1H, dd, J=10, 8 Hz), 3.94 (1H, dd, J=8, 2 Hz), 4.02—4.56 (4H, m), 4.66 (1H, d, J=12 Hz), 4.81 (1H, d, J=12 Hz), 7.36 (5H, s). High-resolution MS Found: m/z 390.2007; $C_{22}H_{30}O_6$ requires 390.2040 (M^+). The second eluate gave **10** (0.791 mg, 40.6%), which was crystallized from ether, mp 135—136 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, s), 1.24—1.88 (10H, m), 2.83 (1H, br s, –OH), 3.27 (1H, t, J=9 Hz), 3.55 (1H, dd, J=7, 4 Hz), 3.77 (1H, dd, J=9, 8 Hz), 4.07 (1H, dd, J=9, 7 Hz), 4.18 (1H, dd, J=8, 5 Hz), 4.39 (1H, dd, J=5, 4 Hz), 4.64 (1H, d, J=12 Hz), 4.78 (1H, d, J=12 Hz), 7.34 (5H, s). *Anal.* Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.54; H, 7.98.

(±)-6-*O*-Benzyl-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-1-*O*-methoxymethyl-*myo*-inositol (11) A cold solution of **9** (851 mg, 2.18 mmol) in DMF (10 ml) was treated with NaH (50% in mineral oil, 126 mg, 2.62 mmol) and the mixture was stirred at 0 °C for 30 min under a nitrogen atmosphere. To this, chloromethyl methyl ether (0.198 ml, 2.62 mmol) was added dropwise at 0 °C and the mixture was stirred for a further 3 h at room temperature. After dilution of the mixture with EtOAc (100 ml), the whole was washed successively with water (twice), saturated aqueous $NaHCO_3$, and brine, then the organic layer was dried. Removal of the solvent gave an oil, which was chromatographed on a silica gel column with a mixture of EtOAc–hexane (1 : 4) to give **11** (841 mg, 89.0%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (6H, s), 1.20—1.89 (10H, m), 3.35 (3H, s), 3.50 (1H, dd, J=10, 8 Hz), 3.87 (1H, dd, J=8, 4 Hz), 3.99 (1H, t, J=4 Hz), 4.04 (1H, dd, J=10, 7 Hz), 4.31 (1H, t, J=7 Hz), 4.46 (1H, dd, J=7, 4 Hz), 4.58—4.92 (4H, m), 7.32 (5H, s). High-resolution MS Found: m/z: 434.2262; $C_{24}H_{34}O_7$ requires 434.2302 (M^+).

(±)-2,3-*O*-Cyclohexylidene-4,5-*O*-isopropylidene-1-*O*-methoxymethyl-*myo*-inositol (4) A mixture of **11** (520 mg, 1.2 mmol) and 10% Pd–C (520 mg) in EtOAc–MeOH–H_2O–AcOH (13 : 3 : 3 : 1, v/v, 10 ml) was stirred at room temperature for 2 h under atmospheric pressure of hydrogen. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a crude product, which was recrystallized from hexane, giving 372 mg of **4** as fine needles (90.3%), mp 76—77 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (6H, s), 1.40—1.84 (10H, m), 3.28 (1H, t, J=10 Hz), 3.42 (3H, s), 3.61 (1H, dd, J=7, 5 Hz), 3.73 (1H, dd, J=10, 8 Hz), 4.03 (1H, dd, J=10, 7 Hz), 4.22 (1H, dd, J=8, 5 Hz), 4.50 (1H, t, J=5 Hz), 4.78 (2H, s). *Anal.* Calcd for $C_{17}H_{28}O_7$: C, 59.28; H, 8.19. Found: C, 59.17; H, 8.50.

(±)-2,3-*O*-Cyclohexylidene-5,6-*O*-isopropylidene-*myo*-inositol (13) A solution of **12** (2.02 g, 5 mmol) in 1 N KOH in MeOH (50 ml) was allowed to stand at room temperature for 2 h, then the solvent was removed under reduced pressure. The residual oil was dissolved in 200 ml of CH_2Cl_2 and the solution was washed with water (twice) and brine, then the organic layer was dried and concentrated. The residue was purified on a silica gel column (CH_2Cl_2 : MeOH = 10 : 1) to give **13** (1.09 g, 72.8%), mp 172 °C (from Et_2O, fine needles). ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, s), 1.46 (3H, s), 1.24—1.85 (10H, m), 2.50 (1H, d, J=9 Hz, –OH), 2.78 (1H, d, J=3 Hz, –OH), 3.30 (1H, dd, J=10, 9 Hz), 3.72—4.20 (4H, m), 4.46 (1H, t, J=5 Hz). *Anal.* Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.72; H, 8.33.

(±)-2,3-*O*-Cyclohexylidene-1,4-di-*O*-methoxymethyl-5,6-*O*-isopropylidene-*myo*-inositol (14) A cold solution of **13** (1.99 g, 6.63 mmol) in DMF (30 ml) was treated with NaH (50% in mineral oil, 760 mg, 14.6 mmol) and the mixture was stirred at 0 °C for 30 min under a nitrogen atmosphere. To this, methoxymethyl chloride (1.10 ml, 14.6 mmol) was added dropwise at 0 °C and the mixture was stirred for a further 3 h at room temperature. After dilution of the mixture with EtOAc (300 ml), the whole was washed with water (twice) and brine, then the organic layer was dried. Removal of the solvent gave a syrup, which was purified on a silica gel column (EtOAc : benzene = 1 : 3) to give **14** (2.48 g, 96.0%), mp 102—103 °C (from

EtOH, needles). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (6H, s), 1.20—1.90 (10H, m), 3.20—3.40 (1H, m), 3.42 (6H, s), 3.82—4.16 (4H, m), 4.51 (1H, dd, J=5, 2 Hz), 4.73 (1H, d, J=8 Hz), 4.75 (1H, d, J=6 Hz), 4.87 (1H, d, J=6 Hz), 4.91 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{19}H_{32}O_8 \cdot 1/2EtOH$: C, 58.45; H, 8.64. Found: C, 58.53; H, 8.64.

(±)-2,3-*O*-Cyclohexylidene-1,4-di-*O*-methoxymethyl-*myo*-inositol (15) A solution of **14** (2.48 g, 6.39 mmol) in 1% trifluoroacetic acid in CH_2Cl_2 (50 ml) was allowed to stand at room temperature for 30 min. After dilution of the mixture with 100 ml of CH_2Cl_2, the whole was washed with water, saturated aqueous $NaHCO_3$ (twice), and brine, then the organic layer was dried and concentrated. The residue was purified on a silica gel column (CH_2Cl_2 : MeOH = 100 : 5) to give **15** (2.03 g, 91.3%), mp 114 °C (from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.89 (10H, m), 3.45 (6H, s), 3.22—3.89 (4H, m), 4.05 (1H, dd, J=7, 5 Hz), 4.47 (1H, t, J=5 Hz), 4.81 (1H, d, J=8 Hz), 4.84 (2H, s), 4.90 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{16}H_{28}O_8 \cdot 1/4H_2O$: C, 54.45; H, 8.14. Found: C, 54.25; H, 8.30.

Selective Benzylation of 15 A cold solution of **15** (2.03 g, 5.83 mmol) in DMF (30 ml) was treated with NaH (50% in mineral oil, 280 mg, 5.83 mmol) and the mixture was stirred at 0 °C for 30 min under a nitrogen atmosphere. To this, benzyl bromide (0.832 ml, 7.0 mmol) was added dropwise at 0 °C and the mixture was stirred for a further 1 h at room temperature. After dilution of the mixture with EtOAc (400 ml), the whole was washed with water (twice) and brine, then the organic layer was dried and concentrated. The residual viscous oil was separated on a column of silica gel (EtOAc : benzene = 1 : 3) to give **16** (913 mg, 35.7%), **17** (547 mg, 21.4%), and **18** (198 mg, 6.4%).

(±)-6-*O*-Benzyl-2,3-*O*-cyclohexylidene-1,4-di-*O*-methoxymethyl-*myo*-inositol (**16**): mp 80—81 °C (from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.90 (10H, m), 3.21 (1H, s, –OH), 3.39 (3H, s), 3.35—3.50 (1H, m), 3.43 (3H, s), 3.62—3.91 (3H, m), 4.04 (1H, dd, J=7, 4 Hz), 4.42 (1H, dd, J=6, 4 Hz), 4.79 (4H, s), 4.81 (2H, s), 7.28 (5H, s). *Anal.* Calcd for $C_{23}H_{34}O_8$: C, 62.99; H, 7.82. Found: C, 62.83; H, 8.05.

(±)-5-*O*-Benzyl-2,3-*O*-cyclohexylidene-1,4-di-*O*-methoxymethyl-*myo*-inositol (**17**): an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.92 (10H, m), 2.94 (1H, br s, –OH), 3.27 (1H, t, J=9 Hz), 3.44 (3H, s), 3.48 (3H, s), 3.67 (1H, dd, J=9, 4 Hz), 3.86 (1H, dd, J=9, 7 Hz), 3.94 (1H, t, J=9 Hz), 4.11 (1H, dd, J=7, 5 Hz), 4.48 (1H, dd, J=5, 4 Hz), 4.84 (2H, s), 4.87 (4H, s), 7.40 (5H, s). High-resolution MS Found: m/z 438.2249; $C_{23}H_{34}O_8$ requires 438.2251 (M^+).

(±)-5,6-Di-*O*-benzyl-2,3-*O*-cyclohexylidene-1,4-di-*O*-methoxymethyl-*myo*-inositol (**18**): mp 67—68 °C (from hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.88 (10H, m), 3.35 (3H, s), 3.38 (3H, s), 3.39 (1H, m), 3.75—4.15 (4H, m), 4.40 (1H, dd, J=5, 2 Hz), 4.75 (4H, s), 4.80 (4H, s), 7.24 (10H, s). *Anal.* Calcd for $C_{30}H_{40}O_8$: C, 68.16; H, 7.63. Found: C, 67.97; H, 7.88.

Transformation of 11 into 16 The acetonide group in **11** (600 mg, 1.38 mmol) was removed by the same procedure as in the case of **14** to give **19** in 92.0% yield. The resulting diol **19** (500 mg, 1.27 mmol) was treated with NaH (50% in mineral oil, 60.9 mg, 1.27 mmol) in DMF (10 ml) at 0 °C for 30 min under a nitrogen atmosphere. Chloromethyl methyl ether (0.115 ml, 1.52 mmol) was added dropwise to the above mixture at 0 °C and the whole was stirred for 2 h at room temperature. After dilution with EtOAc (100 ml), the reaction mixture was washed with water (twice), saturated aqueous $NaHCO_3$, and brine, then the organic layer was dried and concentrated. The residue was separated on a silica gel column (EtOAc : benzene = 1 : 3) to give **16** (193.4 mg, 34.8%), **20** (126.7 mg, 22.8%), and **21** (36.7 mg, 6.0%).

(±)-6-*O*-Benzyl-2,3-*O*-cyclohexylidene-1,5-di-*O*-methoxymethyl-*myo*-inositol (**20**): an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.90 (10H, m), 3.16—3.36 (1H, m), 3.42 (6H, s), 3.50 (1H, s, –OH), 3.64—3.88 (3H, m), 4.00 (1H, dd, J=7, 6 Hz), 4.42 (1H, dd, J=6, 3 Hz), 4.75 (4H, s), 4.79 (2H, s), 7.28 (5H, s). High-resolution MS Found: m/z 438.2278; $C_{23}H_{34}O_8$ requires 438.2252 (M^+).

(±)-6-*O*-Benzyl-2,3-*O*-cyclohexylidene-1,4,5-tri-*O*-methoxymethyl-*myo*-inositol (**21**): mp 52—53 °C (from EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.88 (10H, m), 3.37 (3H, s), 3.41 (3H, s), 3.44 (3H, s), 3.51 (1H, dd, J=8, 7 Hz), 3.80—3.93 (3H, m), 4.09 (1H, t, J=6 Hz), 4.43 (1H, dd, J=5, 3 Hz), 4.75—4.89 (8H, m), 7.31 (5H, s). *Anal.* Calcd for $C_{25}H_{38}O_9$: C, 62.22; H, 7.94. Found: C, 62.15; H, 8.13.

Coupling of 16 with 2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl bromide (22) Silver triflate (343 mg, 1.33 mmol) and 1,1,3,3-tetramethylurea (0.236 ml, 1.97 mmol) were added successively to a solution of **16** (173 mg, 0.395 mmol) and freshly crystallized **22** (401.7 mg, 1.19 mmol) in dry CH_2Cl_2 (3.5 ml), and the mixture was stirred under a nitrogen atmosphere at room temperature for 3 h in the dark. The whole was diluted with CH_2Cl_2 (50 ml), and washed with saturated aqueous $NaHCO_3$ (twice) and brine, then the organic layer was dried. Removal of the solvent gave an oil, which was chromatographed on silica gel with a mixture of EtOAc–hexane (1 : 3). The eluates containing a mixture of diastereoisomers of **23** were concentrated and the residue was further separated by preparative TLC (developed three times, acetone : hexane = 1 : 3) to give **23a** (91.3 mg, 33.2%) and **23b** (106.9 mg, 38.9%).

23a: mp 86 °C (from Et_2O–hexane, needles). ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.85 (10H, m), 1.98 (6H, s), 2.01 (3H, s), 3.12 (1H, dd, J=12, 9 Hz), 3.35 (3H, s), 3.37 (3H, s), 3.62—4.18 (6H, m), 4.40 (1H, dd, J=6, 3 Hz), 4.60—5.22 (10H, m), 7.28 (5H, s). *Anal.* Calcd for $C_{34}H_{48}O_{15}$: C, 58.61; H, 6.94. Found: C, 58.46; H, 7.20.

23b: mp 54—55 °C (from hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.90 (10H, m), 1.95 (3H, s), 1.99 (6H, s), 3.20 (1H, dd, J=11, 8 Hz), 3.36 (3H, s), 3.38 (3H, s), 3.64—4.22 (6H, m), 4.37 (1H, dd, J=4, 2 Hz), 4.56—5.18 (10H, m), 7.31 (5H, s). *Anal.* Calcd for $C_{34}H_{48}O_{15} \cdot H_2O$: C, 57.13; H, 7.05. Found: C, 56.85; H, 6.83.

Hydrogenolysis of 23a and 23b Hydrogenolysis of **23a** (16.3 mg) with 10% Pd–C in a mixture of EtOAc–MeOH–H_2O–AcOH (13 : 3 : 3 : 1) followed by purification by preparative TLC (CH_2Cl_2 : MeOH = 100 : 5) gave **5a** (10.1 mg, 71.2%), mp 182 °C (from CH_2Cl_2–ether). $[\alpha]_D^{22} = -85$ °C (c = 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.90 (10H, m), 2.01 (6H, s), 2.02 (3H, s), 3.30 (1H, br s, –OH), 3.39 (3H, s), 3.41 (3H, s), 3.23—4.32 (7H, m), 4.41 (1H, dd, J=5, 4 Hz), 4.68—5.37 (8H, m). *Anal.* Calcd for $C_{27}H_{42}O_{14} \cdot H_2O$: C, 53.28; H, 7.28. Found: C, 53.30; H, 7.32. The other diastereoisomer **23b** also gave **5b** in 73% yield under the same conditions described above, mp 135 °C (from CH_2Cl_2–Et_2O), $[\alpha]_D^{22} = -2.3$ °C (c = 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.88 (10H, m), 2.00 (6H, s), 2.02 (3H, s), 2.92 (1H, br s, –OH), 3.36 (3H, s), 3.40 (3H, s), 3.18—4.25 (7H, m), 4.39 (1H, dd, J=5, 4 Hz), 4.56—5.35 (8H, m). *Anal.* Calcd for $C_{27}H_{42}O_{14} \cdot H_2O$: C, 53.28; H, 7.29. Found: C, 53.29; H, 7.42.

Acknowledgements We thank Professors T. Kosuge and K. Tsuji for generous gifts of natural surugatoxin, neosurugatoxin, and prosurugatoxin. We also thank Miss T. Sakai for elemental analyses and Mr. K. Masuda for MS measurements.

References and Notes

1) T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, and H. Narita, *Tetrahedron Lett.*, **1972**, 2545.
2) T. Kosuge, K. Tsuji, K. Hirai, T. Fukuyama, H. Nukaya, and H. Ishida, *Chem. Pharm. Bull.*, **33**, 2890 (1985).
3) T. Kosuge, K. Tsuji, K. Hirai, K. Yamaguchi, T. Okamoto, and Y. Iitaka, *Tetrahedron Lett.*, **22**, 3417 (1981). T. Kosuge, K. Tsuji, and K. Hirai, *Chem. Pharm. Bull.*, **30**, 3255 (1982).
4) E. Hayashi, M. Isogai, Y. Kagawa, N. Takayanagi, and S. Yamada, *J. Neurochem.*, **42**, 1491 (1984). S. Yamada, Y. Kagawa, N. Takayanagi, K. Nakayama, K. Tsuji, T. Kosuge, E. Hayashi, K. Okada, and S. Inoue, *J. Pharmacol. Exp. Ther.*, **243**, 1153 (1987), and references cited therein.
5) S. Inoue, K. Okada, H. Tanino, K. Hashizume, and H. Kakoi, *Tetrahedron Lett.*, **25**, 4407 (1984).
6) S. Inoue, K. Okada, H. Tanino, and H. Kakoi, *Tetrahedron Lett.*, **27**, 5225 (1986).
7) S. Inoue, K. Okada, H. Tanino, and H. Kakoi, *Tetrahedron Lett.*, **29**, 1547 (1988).
8) S. Ogawa, S. Oki, H. Kunitomo, and T. Suami, *Bull. Chem. Soc. Jpn.*, **50**, 1867 (1977).
9) F. Weygand, "Methods in Carbohydrate Chemistry," Vol. I, ed. by R. L. Whistler and M. L. Wolfrom, Academic Press, Inc., New York, 1964, p. 182.
10) F. Arcamone, S. Penco, S. Redaelli, and S. Hanessian, *J. Med. Chem.*, **19**, 1424 (1976).
11) K. Bock and C. Pedersen, *J. Chem. Soc., Perkin Trans. 2*, **1974**, 293.