SYNTHESIS OF (±)-PROSURUGATOXIN AND RING TRANSFORMATION OF PROSURUGATOXIN INTO SURUGATOXIN[1]

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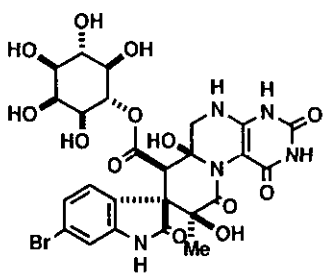
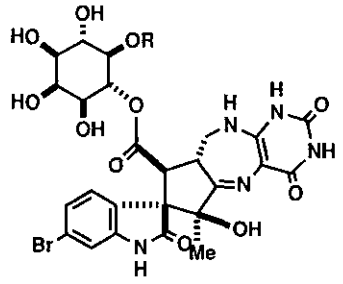
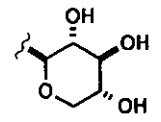
Abstract-Synthetic identification of prosurugatoxin and a possible mechanism for the ring transformation of prosurugatoxin into surugatoxin are presented.

The Japanese ivory shell, Babylonia japonica, commonly eaten in Japan, has been found in some cases to be poisonous. There were 26 such cases in and around Fuji City, Shizuoka Prefecture, in 1965. A study group, Kosuge et al., isolated surugatoxin, thought to be a causative agent, from mid-gut gland of the relevant shellfish. Its structure was determined as 1 by X-ray analysis in 1972.[2] In 1981, the Kosuge group reported the toxic substance not to be surugatoxin, but neosurugatoxin, isolated from



Surugatoxin 1



R = 

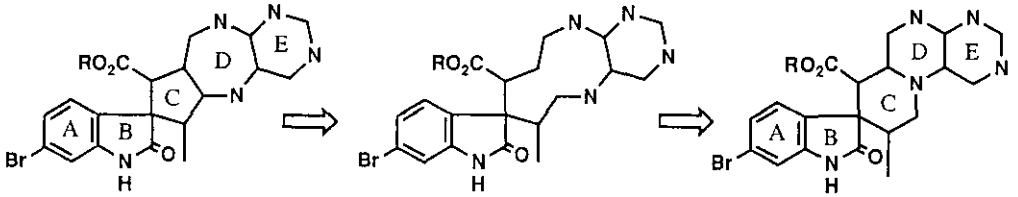
Neosurugatoxin 2

R = H

Prosurugatoxin 3

Figure 1

the same ivory shell and to have structure **2** as shown in Figure 1, based on the results of X-ray analysis.[3] This toxin accounts for half of the total toxicity of the shell. In 1985, the Kosuge group isolated a new toxic component from the same shellfish, accounting for the other half of the toxicity. It was designated as prosurugatoxin[4] since it gradually converted into surugatoxin (**1**) in dilute acetic acid solution. This interesting skeletal conversion suggests cleavage of the C/D ring in the prosurugatoxin framework first to give a ten-membered intermediate followed by ring closure to form the pentacyclic surugatoxin framework as outlined below:



prosurugatoxin framework surugatoxin framework

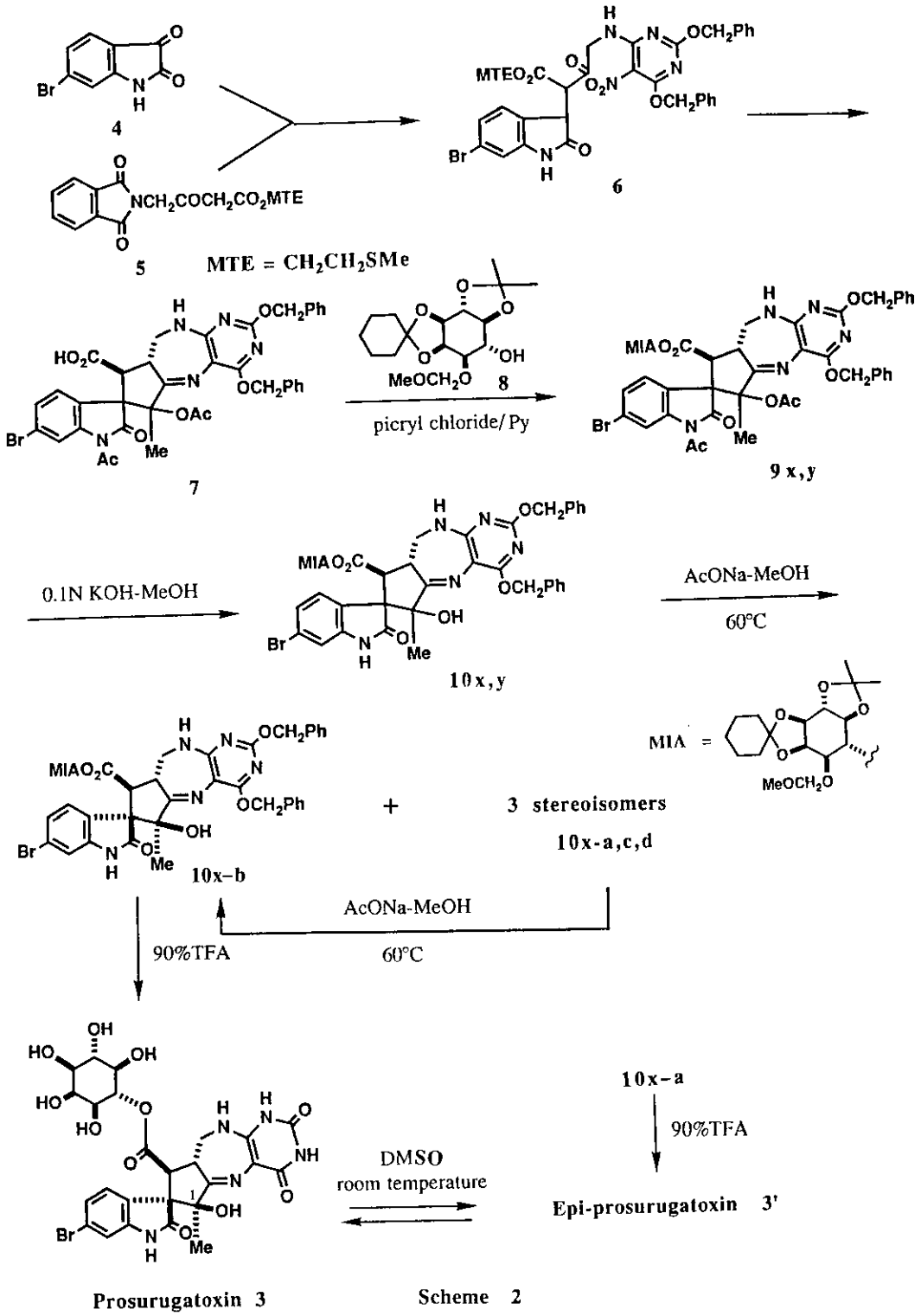
Scheme 1

Spectral data along with the conversion of this new toxin into surugatoxin (**1**), clearly indicated prosurugatoxin to differ from neosurugatoxin (**2**) in its ester unit. Its structure was thus proposed to be dexylopyranosyl neosurugatoxin shown in structure **3**.[4] To confirm the structure and ring transformation of **3** into **1**, **3** was synthesized starting from the carboxylic acid (**7**),[5] the aglycone of neosurugatoxin (**2**). This paper provides confirmation of the structure of **3** as prosurugatoxin and presents a possible mechanism for the ring transformation of **3** into surugatoxin (**1**). Aglycone (**7**) was prepared from 6-bromoisatin (**4**) and methylthioethyl 4-phthalimidoacetoacetate (**5**) in 13 steps *via* the nitro ketone (**6**), the key intermediate in both surugatoxin (**1**) and neosurugatoxin (**2**) synthesis as reported previously.[5,6] Esterification of **7** with (±)-2,3-*O*-cyclohexylidene-4,5-*O*-isopropylidene-1-*O*-methoxymethyl-*myo*-inositol (**8**),[7] used

in the synthesis of surugatoxin (**1**)[6] occurred through the action of picryl chloride[8] in pyridine (room temperature, 1 h). The diastereomeric mixture of the ester (**9**) thus obtained was separated by repeated silica gel tlc [i) MeOH-CH_2Cl_2=1:50, ii) THF-n-hexane=3:8] to give more polar isomer (**9x**) and less polar one (**9y**). As in the synthesis of neosurugatoxin,[5] **9x** gave natural prosurugatoxin (**3**) by the following procedure. Hydrolysis of **9x** with 0.1N KOH in MeOH under a nitrogen atmosphere (room temperature, 45 min) followed by heating a mixture of the resulting deacetylated products (**10x**) with excess AcONa in MeOH (60°C, 30 min) gave an equilibrium mixture of four separable stereoisomeric prosurugatoxin derivatives (**10x-a~d**). The nmr spectrum of **10x-b** was consistent with that of the natural form and thus it was collected by recycling the three recovered unnatural isomers (**10x-a**, **10x-c**, and **10x-d**) [total yield of **10x-b** for five runs, 70% (corrected)]. Treatment of **10x-b** with 90% TFA (room temperature, 45 min) provided (±)-prosurugatoxin (**3**) in 75% yield, whose structure was clearly confirmed by comparison of its chromatographical (hplc: Develosil ODS-5, 30% MeOH in H_2O) and spectral (^{1}H-nmr, sims, uv) data with those of natural prosurugatoxin (**3**).[4]

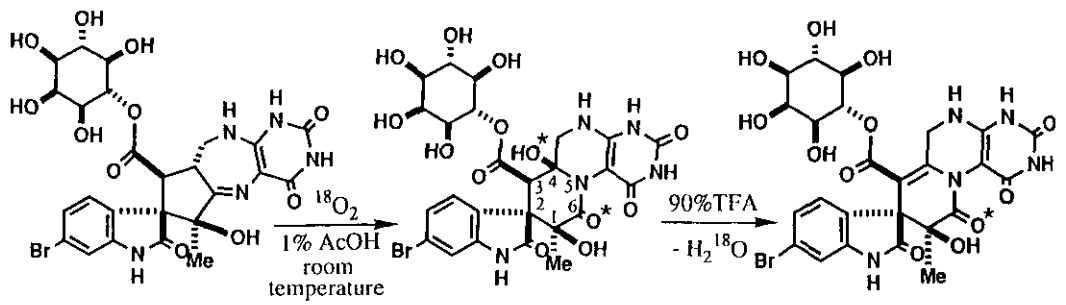
The mydriasis activity of synthetic (±)-**3** was about half that of natural prosurugatoxin (**3**) while the activity of the diastereoisomer of (±)-**3**, prepared from **9y** by the same method as for **9x**, was essentially the same as that of (±)-prosurugatoxin (**3**). Thus, mydriasis is not influenced by its stereochemical difference with the myo-inositol ester moiety in **3**.

(±)-Prosurugatoxin (**3**) thus obtained was found to be fairly unstable in DMSO at room temperature for isomerizing into a mydriasis active product, designated epi-prosurugatoxin (**3'**), possibly the C_1-epimer of (±)-**3**. Compound (**3**) gradually changed to a mydriasis inactive product[4a] on keeping a solution of **3** in 1% acetic acid for a few days at room temperature. This reaction led to the complete detoxication of **3** and the resulting product was observed to be identical with surugatoxin (**1**).


4
5
MTE = CH_2CH_2SMe
6
7
8
picryl chloride/ Py
9 x, y
0.1N KOH-MeOH
10 x, y
AcONa-MeOH
60°C
MIA =
10x-b
+
3 stereoisomers
10x-a,c,d
AcONa-MeOH
60°C
90%TFA
Prosurugatoxin 3
DMSO
room temperature
10x-a
90%TFA
Epi-prosurugatoxin 3'

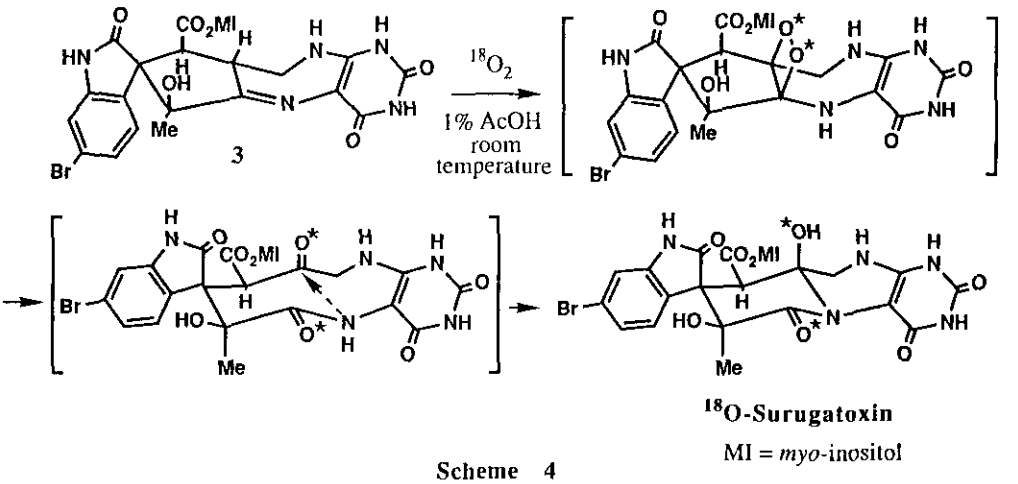
Scheme 2

When this reaction was carried out in the absence of oxygen, there was no conversion. Ring transformation thus clearly occurs through an oxidation reaction with molecular oxygen via the formation of an intermediary dioxetane ring. Clarification of the mechanism for this novel phenomenon was made as follows; a solution of (±)-3 (1 mg) in 1% acetic acid (3 ml) was introduced into a cylinder filled with $^{18}O_2$ (100 ml, 1 atom) and stirred at room temperature. After two days, the reaction mixture was separated by hplc (Develosil ODS-5, 30% MeOH in H_2O) to give surugatoxin (1) (40%), epi-prosurugatoxin (3') (7%), and recovered prosurugatoxin (3)(45%). Surugatoxin (1) was analyzed by its mass spectrum [sims: m/z 690, 688 $(M+H)^+$], which clearly indicated the presence of two atoms of ^{18}O in its molecule. The positions of these oxygens were considered to be C_4 and C_6 in **1**. Actually, the mass spectrum of the dehydrated derivative (11), readily available from ^{18}O-labeled **1** with 90% TFA, indicated the absence of the ^{18}O-containing hydroxy group at the C_4-position in 1.[6] Thus, ^{18}O-labelling experiments demonstrate this novel ring transformation of 3 into 1 to occur stereospecifically via a ten-membered lactam intermediate where it is generated in situ by the decomposition of an intermediate dioxetane formed by autoxidation of the imine moiety of 3, as shown in Scheme 4.



Prosurugatoxin **3** ^{18}*O-Surugatoxin* * = ^{18}O **11**

Scheme 3



Scheme 4

EXPERIMENTAL

Melting points were taken in capillary tubes and uncorrected. Spectra were recorded by the following instruments: uv spectra, Hitachi 323 spectrophotometer; ms spectra, Hitachi M-80B spectrometer, nmr spectra, JEOL JNM GX400 (400 MHz) and Nicolet NT 300 (300 MHz) spectrometers. Chemical shifts of nmr spectra are given in ppm from tetramethylsilane as the internal standard. Hplc separations were carried out on a JASCO Trirotar V. Preparative thin layer chromatography was conducted on a Kiselgel $60F_{254}$ (Merck, Art. 5744) or Kiselgel $60F_{254}S$ (Merck, Art. 13792) plates. Rf values are quoted for Kiselgel $60F_{254}$ (Merck, Art. 5554) plates of 0.2 mm in thickness.

Esterification of the Aglycone (7)

To a solution of **7** (330 mg, 0.44 mmol) and (±)-2,3-O-cyclohexylidene-4,5-O-isopropylidene-1-O-methoxymethyl-myo-inositol (**8**) (181 mg, 0.53 mmol) in pyridine (10 ml) was added picryl chloride (195 mg, 0.79 mmol) at room temperature with stirring. After 20 min, picryl chloride (195 mg, 0.79 mmol) was added portion-wise over 20 min. After being stirred for an

additional 20 min at room temperature, the mixture was evaporated to dryness in vacuo. The residue was taken up in CH_2Cl_2. The extracts were washed with saturated aqueous $NaHCO_3$ solution twice, and dried (Na_2SO_4). The solvent was evaporated to dryness in vacuo and the residue was purified by silica gel tlc [i) MeOH-CH_2Cl_2=1:50, ii) THF-n-hexane=3:8] to give two fractions:

Fraction 1: **9x** [more polar, natural diastereomer, (54.7 mg, 11.6%)] recrystallized from Et_2O-n-hexane to colorless crystalline solid, mp 139-140°C (decomp); ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.36 (3H, s), 1.53 (3H, s), 1.20-1.74 (10H, m), 2.02 (3H, s), 2.62 (3H, s), 2.87 (1H, dd, J=10.7, 7.8 Hz), 3.33 (3H, s), 3.47 (1H, dd, J=3.7, 2.4 Hz), 3.49 (1H, ddd, J=12.0, 7.8, 1.5 Hz), 3.68 (1H, ddd, J=11.0, 7.8, 2.9 Hz), 3.73 (1H, dd, J=7.3, 3.7 Hz), 3.84 (1H, d, J=11.0 Hz), 4.01 (1H, ddd, J=12.0, 7.3, 2.9 Hz), 4.03 (1H, d, J=10.7, 7.3 Hz), 4.16 (1H, t, J=7.3 Hz), 4.57 and 4.65 (2H, d of AB, J=6.6 Hz), 4.95 (1H, dd, J=7.8, 2.4 Hz), 5.35 (2H, s), 5.41 and 5.49 (2H, d of AB, J=13.2 Hz), 5.80 (1H, br dd, J=7.3, 1.5 Hz), 6.99 (1H, d, J=8.1 Hz), 7.24-7.50 (11H, m), 8.52 (1H, d, 2.0 Hz) ppm. Anal. Calcd for $C_{54}H_{58}N_5O_{14}Br$: C, 60.00; H, 5.41; N, 6.48. Found: C, 59.93; H, 5.27; N, 6.47.

Fraction 2: **9y** [less polar, unnatural diastereomer, (99.7 mg, 21.1 %)] recrystallized from CH_2Cl_2-MeOH to colorless needles, mp 206-207°C (decomp.); ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.36 (3H, s), 1.38 (3H, s), 1.51 (3H, s), 1.50-1.72 (10H, m), 2.01 (3H, s), 2.60 (3H, s), 2.88 (1H, dd, J=10.6, 8.4 Hz), 3.36 (3H, s), 3.46 (1H, t, J=3.0 Hz), 3.51 (1H, ddd, J=12.1, 7.7, 1.5 Hz), 3.65 (1H, ddd, J=10.6, 7.7, 2.8 Hz), 3.77 (1H, dd, J=7.0, 3.0 Hz), 3.81 (1H, d, J=10.6 Hz), 4.03 (1H, dd, J=10.6, 7.0 Hz), 4.05 (1H, ddd, J=12.1, 7.3, 2.8 Hz), 4.17 (1H, t, J=7.0 Hz), 4.60 and 4.68 (2H, d of AB, J=6.6 Hz), 4.97 (1H, dd, J=8.4, 3.0 Hz), 5.35 (2H, s), 5.40 and 5.49 (2H, d of AB, J=13.2 Hz), 5.82 (1H, br dd, J=7.3, 1.5 Hz), 6.96 (1H, d, J=8.1 Hz), 7.22-7.48 (11H, m), 8.52 (1H, d, J=1.8 Hz) ppm. Anal. Calcd

for $C_{54}H_{58}N_5O_{14}Br$: C, 60.00; H, 5.41; N, 6.48. Found: 59.92; H, 5.25; N, 6.48.

Hydrolysis of the Ester Diacetate (9x)

A solution of **9x** (30.3 mg, 0.028 mmol) in 0.1N KOH-MeOH (4.2 ml, 15 equiv.) was kept at room temperature with stirring under a nitrogen atmosphere. After 45 min, the mixture was neutralized with AcOH and evaporated to dryness in vacuo. The residual solid was taken up in CH_2Cl_2 and purified by silica gel tlc (MeOH-CH_2Cl_2=3:97) to give a mixture of four isomers (**10x-a~d**) (24 mg, 53.3%). A mixture of diastereomers (**9y-a~d**) was obtained from **9y** by the same treatment.

Equilibration and Subsequent Separation of the myo-Inositol Ester (10x-b)

A solution of **10x-a~d** (24.0 mg, 0.024 mmol) in MeOH (24 ml) containing AcONa (40 mg, 0.49 mmol) was warmed at 60°C with stirring under a nitrogen atmosphere. After 30 min, the resulting equilibrated reaction mixture (monitored by tlc) was evaporated to dryness and the residue consisting a mixture of four isomers was separated by silica gel tlc (MeOH-CH_2Cl_2=1:20) to obtain the natural isomer (**10x-b**). The three unnatural isomers (**10x-a,c,d**) were combined and subjected to equilibration so as to separate the natural form (**10x-b**). This recycling process was repeated four times. The product obtained was further purified by tlc (AcOEt-benzene=3:2) to give the natural isomer (**10x-b**) (13.0 mg, 70% corrected yield, rf=0.64).

10x-b: ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.36 (3H, s), 1.41 (3H, s), 1.50-1.80 (10H, m), 2.93 (1H, dd, J=10.6, 8.1 Hz), 3.03 (1H, d, J=10.3 Hz), 3.26 (1H, ddd, J=12.1, 9.5, 1.0 Hz), 3.36 (3H, s), 3.46 (1H, dd, J=3.7, 2.6 Hz), 3.79 (1H, d, J=7.3, 3.7 Hz), 3.89 (2H, m), 4.02 (1H, dd, J=10.6, 7.3 Hz), 4.17 (1H, t, J=7.3 Hz), 4.24 (1H, br s), 4.63 and 4.67 (2H, d of AB, J=6.6 Hz), 5.04 (1H, dd, J=8.1, 2.6 Hz), 5.33 (2H, s), 5.40 and 5.44 (2H, d of AB, J=12.5 Hz), 5.90 (1H, br dd, J=6.6, 1.0 Hz), 7.05

(1H, d, J=1.8 Hz), 7.06 (1H, d, J=8.1 Hz), 7.20 (1H, dd, J=8.1, 1.8 Hz), 7.24-7.48 (10H, m), 8.17 (1H, s) ppm.

^{1}H-nmr (400 MHz) spectra of the three unnatural isomers (**10x-a,c,d**):

10x-a (2.9 mg, 10.4 %, rf=0.75): ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.30 (3H, s), 1.34 (3H, s), 1.37 (3H, s), 1.48-1.80 (10H, m), 2.47 (1H, s), 3.02 (1H, dd, J=10.6, 8.1 Hz), 3.25 (1H, ddd, J=12.5, 8.8, 1.5 Hz), 3.37 (3H, s), 3.45 (1H, dd, J=3.7, 2.2 Hz), 3.54 (1H, d, J=10.3 Hz), 3.80 (1H, dd, J=7.3, 3.7 Hz), 3.85 (1H, ddd, J=10.3, 8.8, 2.9 Hz), 3.88 (1H, ddd, J=12.5, 7.0, 2.9 Hz), 4.03 (1H, dd, J=10.6, 7.3 Hz), 4.18 (1H, t, J=7.3 Hz), 4.63, 4.66 (2H, AB-q, J=6.6 Hz), 5.05 (1H, dd, J=8.1, 2.2 Hz), 5.35 (2H, s), 5.39, 5.49 (2H, AB-q, J=13.2 Hz), 5.86 (1H, br dd, J=7.0, 1.5 Hz), 7.04 (1H, d, J=1.8 Hz), 7.19 (1H, dd, J=8.1, 1.8 Hz), 7.24-7.46 (11H, m), 8.24 (1H, s, NH) ppm.

10x-c (9.0 mg, 32.2 %, rf=0.33): ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.18 (3H, s), 1.38 (6H, s), 1.50-1.80 (10H, m), 2.58 (1H, dd, J=3.7, 1.1 Hz), 3.25 (3H, s), 3.45 (1H, dd, J=11.0, 7.7 Hz), 3.53 (1H, ddd, J=11.4, 9.2, 1.0 Hz), 3.61 (1H, ddd, J=9.2, 9.2, 2.9 Hz), 3.77 (1H, d, J=9.2 Hz), 3.78 (1H, m), 3.93 (1H, dd, J=7.3, 3.7 Hz), 4.13 (1H, dd, J=11.0, 7.3 Hz), 4.29 (1H, t, J=7.3 Hz), 4.38, 4.54 (2H, AB-q, J=6.6 Hz), 4.42 (1H, s, OH), 4.91 (1H, dd, J=7.7, 1.1 Hz), 5.35, 5.38 (2H, AB-q, J=12.5 Hz), 5.41, 5.52 (2H, AB-q, J=13.2 Hz), 6.15 (1H, br dd, J=6.6, 1.0 Hz), 6.73 (1H, d, J=8.1 Hz), 7.13 (1H, dd, J=8.1, 1.8 Hz), 7.16 (1H, d, J=1.8 Hz), 7.22-7.48 (10H, m), 8.75 (1H, s, NH) ppm.

10x-d (3.0 mg, 10.7 %, rf=0.31): ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.39 (3H, s), 1.54 (3H, s), 1.46-1.80 (10H, m), 2.50 (1H, dd, J=3.7, 0.8 Hz), 3.25 (3H, s), 3.38 (1H, ddd, J=11.4, 8.1, 1.0 Hz), 3.40 (1H, d, J=9.9 Hz), 3.47 (1H, dd, J=11.0, 7.3 Hz), 3.67 (1H, ddd, J=9.9, 8.1, 2.9 Hz), 3.80 (1H, ddd, J=11.4, 7.0, 2.9 Hz), 3.90 (1H, dd, J=7.3, 3.7 Hz), 4.14 (1H, dd, J=11.0, 7.3 Hz), 4.31 (1H, t, J=7.3 Hz), 4.36, 4.53 (2H, AB-q, J=6.6 Hz), 4.92 (1H, dd, J=7.3, 0.8 Hz), 5.36 (2H, s), 5.42, 5.50 (2H, AB-

q, J=12.5 Hz), 5.97 (1H, br s, NH), 6.67 (1H, d, J=8.1 Hz), 7.06 (1H, d, J=1.8 Hz), 7.10 (1H, dd, J=8.1, 1.8 Hz), 7.24-7.50 (10H, m), 7.87 (1H, s, NH) ppm.

(±)-6'-Bromo-1,1',2',3,4,6,8,8aβ,9,10-decahydro-6α-hydroxy-6β-methyl-2,2',4-trioxospiro[cyclopenta[e]pyrimido[4,5-b][1,4]diazepine-7β(2H),3'-[3H]indole]-8β-carboxylic Acid 6-myo-Inositol Ester [(±)-Prosurugatoxin] (3)

A solution of **10x-b** (6.5 mg, 0.01 mmol) in 90% TFA (0.26 ml) was kept for 45 min at room temperature. The reaction mixture was evaporated to dryness in vacuo, the residue was washed with ether followed by hplc to afford the desired (±)-prosurugatoxin (3.2 mg, 75%).

Hplc: T_R=23.6 min (column: Nomura Chemical Co., LTD, Develosil Packed Column ODS-5, 10x250 mm, solvent: 30 % MeOH in H_2O, flow rate: 2 ml/min); uv (H_2O) λ_{max} 219 (log ε 4.65), 280 (log ε 4.20), 309_{sh} (log ε 3.99), 325_{sh} (log ε 3.87) nm; ^{1}H-nmr (300 MHz, D_2O, DOH=4.65 ppm) δ 1.37 (3H, s), 2.85 (1H, t, J=11.5 Hz), 3.20-3.33 (1H, m), 3.23 (1H, dd, J=11.5. 3.5 Hz), 3.28 (1H, dd, J=11.5, 3.5 Hz), 3.41 (1H, t, J=11.5 Hz), 3.57 (2H, br s), 3.80-3.90 (2H, m), 4.81 (1H, t, J=11.5 Hz), 7.13 (1H, d, J=1.8 Hz), 7.19 (1H, d, J=8.0 Hz), 7.24 (1H, dd, J=8.0, 1.8 Hz) ppm; ms (sims): m/z 654, 652 $(M+H)^+$.

Ring Transformation of Prosurugatoxin (3) into Surugatoxin (1)

A solution of **3** (1 mg) in a oxygen saturated 1% AcOH (3 ml) was kept at room temperature for 2 days and the reaction mixture was then evaporated to dryness in vacuo. The residue was washed with ether and subjected to hplc (Develosil ODS-5, 30% MeOH in H_2O, flow rate: 2ml/min) to give three fractions:

Fraction 1 (40%): t_R=8.2 min; this compound was characterized as (±)-surugatoxin (**1**).[2]

Fraction 2 (7%): t_R=18.9 min; this compound was characterized as epi-prosurugatoxin (**3'**).

The epimerization of (±)-**3** was also observed when a solution of (±)-**3** in DMSO was kept for several hours at room temperature followed by the usual work-up. Epi-prosurugatoxin (**3'**) obtained by both experiments was identical with a specimen prepared from **10x-a** by treatment of **10x-a** with 90% TFA.

^{1}H-nmr (300 MHz, D_2O, DOH=4.65 ppm) δ 1.09 (3H, s), 2.93 (1H, t, J=9.6 Hz), 3.26 (1H, dd, J=9.6, 3.1 Hz), 3.25-3.35 (2H, m), 3.46 (1H, t, J=9.6 Hz), 3.40-3.53 (1H, m), 3.79 (1H, d, J=10.5 Hz), 3.85 (1H, t, J=3.1 Hz), 3.93 (1H, dd, J=13.1, 2.6 Hz), 4.81 (1H, t, J=9.6 Hz), 7.17 (1H, d, J=1.8 Hz), 7.22 (1H, dd, J=8.1, 1.8 Hz), 7.27 (1H, d, J=8.1 Hz) ppm.

Fraction 3 (45%): t_R=23.6 min, recovered (±)-**3**.

Preparation of ^{18}O-Containing Surugatoxin

The same transformation of **3** [1 mg in 1% AcOH (3 ml)] into **1** was carried out in a sealed tube containing 100 ml of $^{18}O_2$.

Dehydration of ^{18}O-Containing Surugatoxin

A solution of a small amount of ^{18}O-containing surugatoxin (~0.3 mg) in 90% TFA was heated at 60°C. After 7 h, the mixture was dried in vacuo and the residue was purified by silica gel preparative tlc (AcOEt-MeOH-acetone-H_2O=3:1:1:1) to give a product (**11**) corresponding to the 3,4-dehydrated surugatoxin reported previously.[6]

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