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Total Synthesis of Neosurugatoxin[1]

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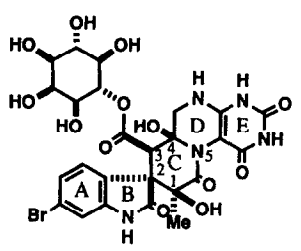
Abstract: Total synthesis of neosurugatoxin 2, having a strong affinity for nicotinic receptors, in described.

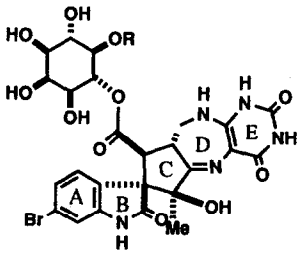
INTRODUCTION

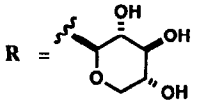
In 1981, Kosuge et al. reported that the substance which had caused the food poisoning due to shellfish (Babylonia japonica) was not surugatoxin 1 as described previously,[2] but neosurugatoxin, having structure 2 in Chart 1, on the basis of an X-ray analysis.[3] In 1985, another toxic substance was isolated from the mid-gut gland of the same toxic shellfish.[4] The latter toxic substance was called prosurugatoxin because it gave rise to surugatoxin 1 gradually in a diluted acetic acid solution at room temperature and this toxin accounts for half the total toxicity of the shell. Their possible chemical structures are listed in Chart 1. Both neosurugatoxin 2 and prosurugatoxin 3 evoke mydriasis in mice like atropine.[3,4] With the activity to evoke mydriasis in mice, compound 2 is 10 times as potent as atropine. Both substances are tightly bound to nicotinic receptors in the ganglia.[5,6] A high affinity constant of 2 for nicotinic receptors in a rat's forebrain as well as in a guinea pig's ileum was reported at least three orders of magnitude grater than that of commercial hexamethonium or mecamylamine.[5] Only a very small amount of these two compounds are available from the toxic shellfish, although they are interesting. So we attempted to synthesize these natural products. This paper deals with the first synthesis of neosurugatoxin 2.

Surugatoxin 1 and neosurugatoxin 2, sharing ring A, B, and E, are



Surugatoxin 1





Neosurugatoxin 2

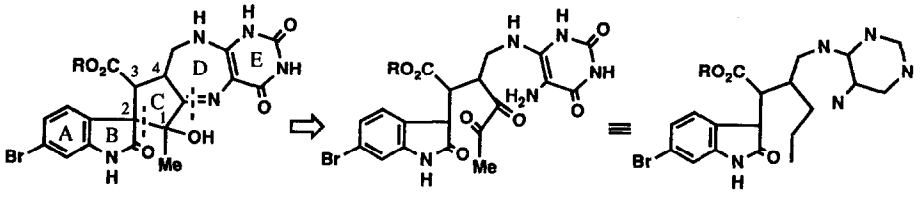
R = H

Prosurugatoxin 3

Chart 1

compounds having a pentacyclic ring system in the molecule. Compounds 1 and 2 differ from each other in rings C and D. With compound 1, rings C and D both consist of six atoms. In contrast, rings C and D have five and seven atoms, respectively, in compound 2, which is, as a consequence, structurally less stable. Using our knowledge obtained through the surugatoxin synthesis,[7] we planned to design a synthesis for neosurugatoxin.

From the standpoint of retrosynthesis, if compound 2 undergoes ring opening as marked by the broken lines in Scheme 1, the resultant α-diketone 2', an imaginary compound, corresponds to the skeletal form [VII] resulting from the addition of the three carbon unit to [III] in Scheme 2.



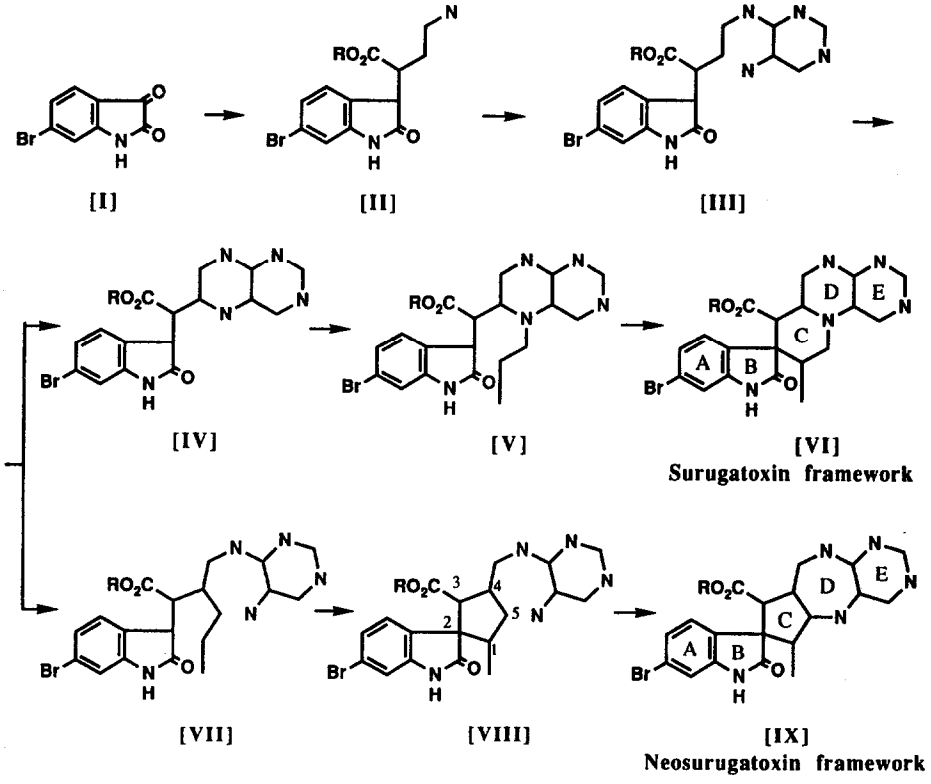
2 2' [VII]

R = xylopyranosyl-*myo*-inositol

Scheme 1

As reported previously,[8] the basic skeleton of surugatoxin [VI] was constructed from [I] via [III], [IV], and [V] according to the outline given in Scheme 2. If the same conception can be applied to the synthesis of neosurugatoxin 2 starting from [III], three carbon unit corresponding to α-diketone moiety in 2' is first to be introduced into [III] to form [VII]. Then, cyclization to form ring C followed by formation of ring D

may give rise to the desired neosurugatoxin framework [IX]. We regarded this route as a relatively simple procedure for the pentacyclic ring construction. The stereochemistry of the synthesis is as follows.



Scheme 2

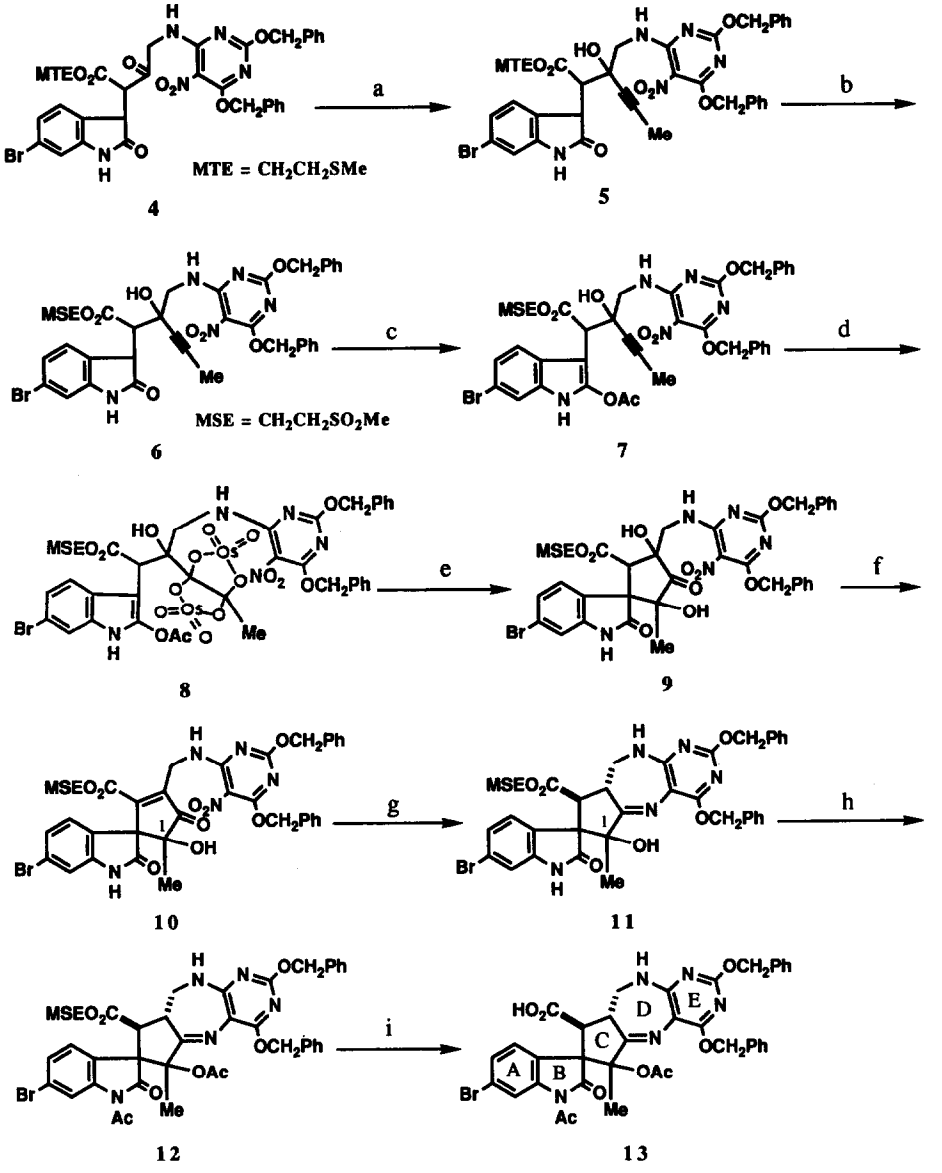
Neosurugatoxin **2** possess four consecutive asymmetric carbon atoms in ring C. Like C1 and C2 carbon atoms in surugatoxin **1**, those atoms in **2** are also involved in variable stereoisomerism. Therefore, we expect that initial introduction of two hydrogen atoms to C3 and C4 in the trans-position in [VIII] may allow us to adjust the stereochemistry of ring C to obtain the desired stereochemistry at the final stage of the synthesis. Based on the above view, intermediate nitroketone **4** used in the surugatoxin synthesis[7] was chosen as the starting material because it is a compound corresponding to the skeletal form [III] and the following experiments were undertaken.

RESULTS AND DISCUSSION

As described above, nitroketone **4** having ring A, B, and E was used as

the starting material. Compound **4** requires a unit containing three carbon atoms to form rings C and D. If the three carbon unit to be attached to the carbon atom in the carbonyl group in **4** had a methyl group at one end and an acetylenic carbon at the other end, the unit may give rise to α-diketone under mild conditions. Our preliminary experiments revealed that the carbonyl group in nitroketone **4**, the substrate, has a poorly reactive carbonyl carbon atom for nucleophilic attacks.[9] We examined a nucleophilic addition using a large excess amount of the acetylene Grignard reagent. Thus, to nitroketone **4**, that was dissolved in a THF solution, MeC≡CMgBr (over ten times the equivalent weight) was substantially added, and the mixture was reacted at -60 °C for 30 min. The corrected yield of Grignard adduct **5** was 80% when the reaction was quenched while a considerable amount of the starting material still remained in the reaction mixture.

To protect the substrate from osmium tetroxide (OsO_4) oxidation, used for oxidizing the propyne unit to α-diketone, the methylthioethyl (MTE) ester group in **5** was treated with m-CPBA to give methylsulfonylethyl (MSE) ester **6**. However, C2 and C3 in the oxindole moiety in **6** still remained to be protected from OsO_4. Protection for the C2 and C3 in the oxindole unit could be removed in a neutral or weak acidic solution because compound **6** has a MSE group sensitive to the bases. Therefore, we planned to convert the oxindole unit into a 2-acetoxyindole form. Compound **6**, however, has four sites which may undergo acetylation. Selective acetylation to obtain monoacetate **7**, an enol acetate form, was succeeded when to a solution of **6** in pyridine was added 30 equivalents of acetyl chloride at -18 °C and the reaction was quenched after 10 min. This reaction had a 95% yield and product **7** could be separately obtained as a single product. Oxidation of **7** with 4 equivalents of OsO_4 in THF-ether-pyridine resulted in precipitation of pyridinium complex of diosmate **8**. We expected that the resultant diosmate **8** may undergo cyclization to form ring C simultaneously with the formation of α-diketone when it undergoes hydrolysis of the acetate. Therefore, diosmate **8** was dissolved in pyridine and the solution was treated with aqueous $NaHSO_3$: $NaHSO_3$ was used for the hydrolysis of the diosmate as well as the acetate protective group and pyridine for the cyclization of the resulting α-diketone to form the ring C. The mixture was stirred for 1 h at room temperature. As expected, the three reactions occurred successively yielding spirooxyindole **9** in 58% yield based on monoacetate **7**. Although the cyclization product was a mixture of interconvertible two diastereomers, it was submitted to the subsequent reaction without separation. If dehydration of compound **9** leads to a conjugated enone unit in the molecule, the reduction of the resultant



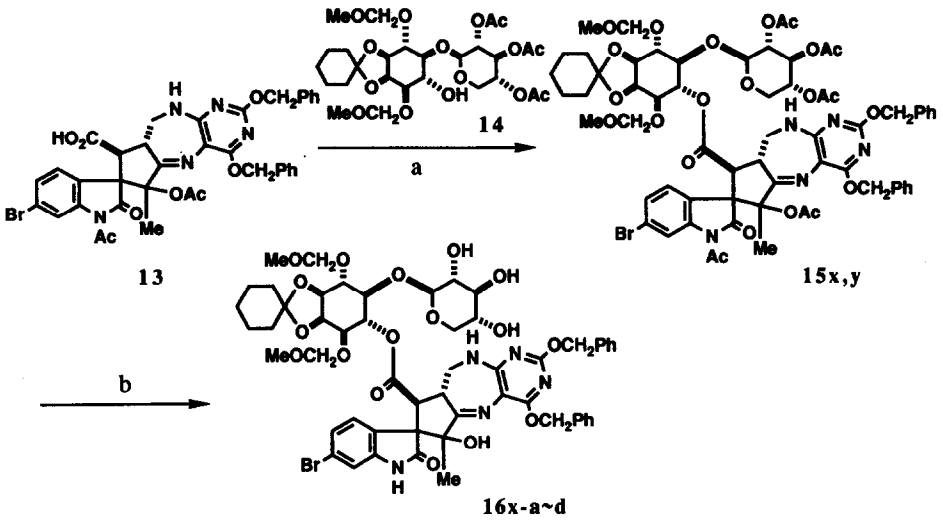
a) i) MeC≡CMgBr, ii) 20% H_2SO_4; b) *m*-CPBA, CH_2Cl_2; c) AcCl, pyridine, -18 °C; d) OsO_4, pyridine, THF; e) $NaHSO_3$, H_2O, pyridine; f) $SOCl_2$, pyridine; g) i) Zn-AcOH; ii) CSA, CH_2Cl_2; h) Ac_2O, DMAP, THF; i) pH10.2 buffer, acetone.

Scheme 3

enone with the zinc-acetic acid system may lead to hydrogenation of the conjugated double bond in trans-configuration and a simultaneous reduction in the nitro group attached to the pyrimidine moiety to an amino group, which will be linked to the carbonyl group in ring C to form ring D. Actually, dehydration ($SOCl_2$-py, -15 °C, 10 min, 73%) followed by a reduction [Zn-AcOH in MeOH-CH_2Cl_2 (1:10), rt, 10 min] and treatment with CSA in CH_2Cl_2 (rt, ca. 10 min) resulted in the formation of the neosurugatoxin framework to give **11** as a mixture of interconvertible four isomers in 93% overall yield. Although their separation was easy, each single isomer gave a mixture of four isomers when the MSE ester protection was removed under a basic condition, as was expected. To simplify the subsequent procedure for this total synthesis, it was required to convert the four isomers into a single one. Thus, mixture **11** was dissolved in THF containing 4-dimethylaminopyridine (DMAP), and to the solution, chilled in an ice bath, acetic anhydride was added. When the reaction mixture was allowed to stand at temperature ranging from 5 °C to room temperature, one of isomers of diacetate **12** was thus obtained fortunately as a single product in 72% yield. Under the same conditions as used for the synthesis of surugatoxin[7] or in the $NaHCO_3$-Na_2CO_3 solution (pH 10.2), the MSE ester protection was removed from compound **12**. Target neosurugatoxin aglycone diacetate **13** was obtained without any isomers in 98% yield.

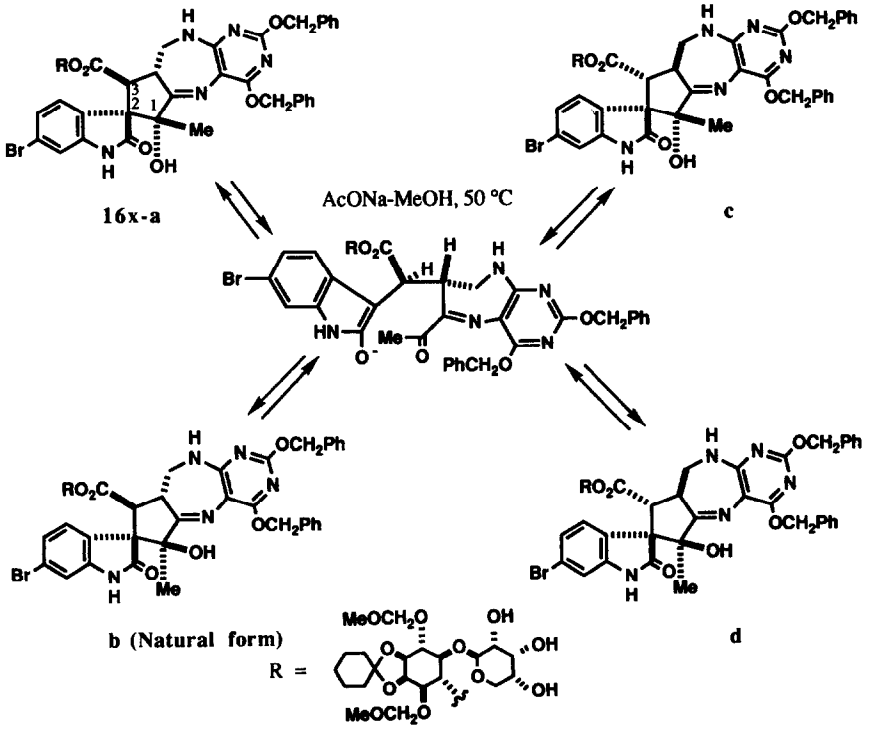
The aglycone **13** is a relatively stable carboxylic acid derivative. Compound **13** was condensed with xylopyranosyl myo-inositol-6-monool **14**[10] to give an ester under the same conditions in picryl chloride/pyridine as used for the synthesis of surugatoxin,[7] to give about a 7:9 mixture of xylopyranosyl myo-inositol esters **15x** and **15y**. The resulting diastereomers can be easily separated by thin layer chromatography (TLC) on a silica gel plate. Subsequent deacetylation of **15x** with 0.1 N KOH/MeOH led to an equilibrium mixture of four isomers [**16x-a**, **b**, **c**, and **d**] from each of **15x-a**, **b**, **c**, and **d**. The protective groups were fully removed from each of the isomers respectively with 90% TFA. Like neosurugatoxin, the product from **16x-b** alone was effective in evoking mydriasis in mice.

As mentioned above, compound **16** yields an equilibrium mixture of four isomers when treated under basic conditions. This isomerization may convert compound **16x-a**, **c**, or **d** into the same isomer having the natural structure of **16x-b**. As shown in Scheme 5, however, this isomerization for yielding an equilibrium mixture is based on the retroaldol-aldol reaction in which the C1-C2 bond in ring C is broken and then linked again. An equilibrium mixture of the four isomers was almost exclusively produced when compound **16x** (or **16y**) was heated at 50 °C with sodium acetate in



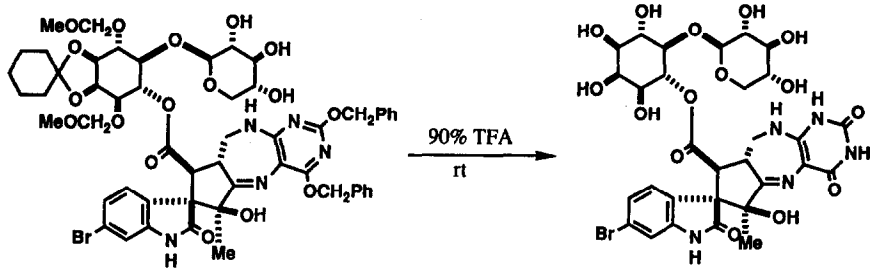
a) picryl chloride, pyridine; b) i) 0.1N KOH-MeOH; ii) AcONa, MeOH, 50 °C.

Scheme 4



Scheme 5

methanol. For the mixture of the four isomers, **16x-b** was separately obtained by TLC on a silica gel plate, and the rest of the three unnatural type isomers, **15x-a**, **c**, and **d**, were combined and then submitted to the same isomerization. This procedure was repeated to accumulate the amount of natural type isomer **16x-b**. At the final stage where all the protection was removed to give neosurugatoxin, **16x-b** dissolved in 90% TFA was allowed to stand at room temperature for 50 min and the yield was satisfactory. The resultant neosurugatoxin was the same as the natural one[3] as examined by TLC, high performance liquid chromatography coupled with IR, UV, MS, and ^{1}H NMR spectra. It was also quite identical with natural neosurugatoxin in the mydriasis activity test in mice.



16x-b **Neosurugatoxin 2**

Scheme 6

CONCLUSIONS

A synthetic route leading to biological active neosurugatoxin via the carboxylic acid **13** was established in the present study. Acid **13**, the aglycone of neosurugatoxin **2** and prosurugatoxin **3**, can be used as an intermediate for synthesizing toxins **2** and **3**[11] and various esters[12] related to them. Several esters synthesized from carboxylic acid **13** show identical pharmacological activity.[6] For example, an ethyl ester analogue which can be easily synthesized from **13** dilates the pupil in mice at a dose of 2μg. This activity is identical to that of atropine. Antinicotinic activity of the ethyl ester analogue was found to be essentially the same as that of synthetic (±)-prosurugatoxin **3** which accounts for half the activity of **2**. The activity of the cyclohexyl ester analogue was about 1/10 that of (±)-**3**. On the other hand, the activity of the debromo analogue of the natural type was about 1/100 that of **2**. All unnatural isomers of **2** or various ester analogues related to **2** were completely inactive, but could be transformed into the natural form by recycling through equilibration produced by the internal aldol-retroaldol

reaction. Shellfish toxin blocks nicotinic receptors in the ganglia as described above. This action is specific and substantially potent. Neosurugatoxin **2** is thus a natural product of interest from the standpoint of neuropharmacology and a excellent tool for studing the neurosystem. It is very difficult to obtain from natural sources.[3] The synthesis of toxin **2** and active analogues has made it possible to obtain a considerable amount of each by the present synthetic route.

EXPERIMENTAL SECTION

Melting points were taken in capillary tubes and uncorrected. Spectra were recorded on the following instruments; IR spectra, JASCO IRA-1 spectrometer; UV spectra, Hitachi 323 spectrophotometer; MS spectra, Hitachi M-80B spectrometer; NMR spectra, JEOL JNM PS100 (100 MHz), JEOL JNM FX100 (100 MHz), and JEOL JNM GX400 (400 MHz) spectrometers. Chemical shifts of NMR spectra are given in ppm from tetramethylsilane as the internal standard. HPLC separation was carried out on JASCO Trirotar II. Preparative thin-layer chromatography was conducted on a Kieselgel $60F_{254}$ (Merck, Art. 5744) or Kiselgel $60F_{254}S$ (Merck, Art. 13792) plates and column chromatographic separations were preformed on a silica gel (Kanto Chemical, Silica gel, over 100 mesh).

Reaction of Propynylmagnesium Bromide and 2-(Methylthio)ethyl 6-Bromo-2,3-dihydro-α-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]ace- tyl]-2-oxo-1H-indole-3-acetate (4). To a solution of nitroketone **4** (4.0 g) in THF (200 ml) at -60 °C was added a solution of propynylmagnesium bromide (prepared from 1.4 g of magnesium) in THF (100 ml) with vigorous stirring. After 30 min, the reaction was quenched by pouring it into 200 ml of 20% H_2SO_4 containing 100 g of crushed ice and extracted with AcOEt. The extracts were washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). Removal of the solvent *in vacuo* left an oily residue, which was dissolved in hot MeOH. After being cooled, the separated crystalline solid of unreacted **4** was filtered off, the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel (AcOEt-benzene=1:3) to fractionate Grignard adduct **5** (903 mg, 21%, corrected yield 80%) as a 1:1 inseparable mixture of diastereoisomers. An analytical sample was prepared by recrystallization from CH_2Cl_2-*n*-hexane to give a pale-yellow crystalline solid: mp 79-80 °C; IR (KBr) 3330, 1715, 1590, 1525, 1450, 1330, 1280, 1150 cm^{-1}; UV (MeOH) λ_{max} 237 (log ε 4.46), 280 (log ε 3.85), 338 (log ε 3.86) nm; ^1H NMR (100 MHz, $CDCl_3$) δ 1.79 and 1.84 (3H in total, s each), 1.95 and 2.02 (3H in total, s each), 2.28 and

2.59 (2H in total, t each, J=6 Hz), 3.48 and 3.64 (1H in total, d each, J=3 Hz), 3.80-4.40 (5H, m), 5.30 and 5.34 (2H in total, s each), 5.48 and 5.50 (2H in total, s each), 7.00-7.60 (13H, m), 8.81 and 8.86 (1H in total, s each, NH), 9.18 (1H, dd, J=8, 4 Hz, NH). Anal. Calcd for $C_{36}H_{34}BrN_5O_8S$: C, 55.67; H, 4.41; N, 9.02. Found: C, 55.56; H, 4.36; N, 8.95.

2-(Methylsulfonyl)ethyl 6-Bromo-2,3-dihydro-α-[1-hydroxy-1-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2-butynyl]-2-oxo-1H-indole-3-acetate (6). m-CPBA (80%, 368 mg, 1.71 mmol) was added to a cold solution (5 °C) of **5** (600 mg, 0.773 mmol) in CH_2Cl_2 (12 ml) with stirring. After 20 min, the reaction mixture was diluted with CH_2Cl_2, washed succcessively with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and brine, and then dried (Na_2SO_4). Removal of the solvent in vacuo left an oily product which was purified by silica gel column chromatography (AcOEt-benzene=1:1) to give **6** (565 mg, 91%) as a 1:1 mixture of diastereoisomers: mp 95-96 °C (decomp); IR (KBr) 3340, 1720, 1590, 1530, 1330, 1285, 1155, 1130 cm^{-1}; UV (MeOH) λ_{max} 237 (log ε 4.44), 279 (log ε 3.82), 336 (log ε 3.84) nm; ^1H NMR (100 MHz, $CDCl_3$) δ 1.78 and 1.84 (3H in total, s each), 2.79 and 2.85 (3H in total, s each), 2.93 and 3.21 (2H in total, t each, J=7 Hz), 3.55 and 3.63 (1H in total, d each, J=3 Hz), 3.90-4.60 (5H, m), 5.32 and 5.34 (2H in total, s each), 5.52 (2H, s), 6.90-7.60 (13H, m), 8.81 and 8.86 (1H in total, s each, NH), 9.18 (1H, br t, J=4 Hz, NH). Anal. Calcd for $C_{36}H_{34}BrN_5O_{10}S$: C, 53.47; H, 4.24; N, 8.66. Found: C, 53.31; H, 4.23; N, 8.67.

2-(Methylsulfonyl)ethyl 2-(Acetyloxy)-6-bromo-α-[1-hydroxy-1-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2-butynyl]-1H-indole-3-acetate (7). To a solution of **6** (1.5 g, 1.86 mmol) in pyridine (60 ml) at -18 °C was added dropwise acetyl chloride (4 ml, 56.1 mmol, 30 equiv) with stirring. When the acetylation was completed [ca. 10 min as judged by TLC (AcOEt-benzene=1:1), single spot], the reaction was quenched by an addition of EtOH (4 ml). After 20 min, the reaction mixture was evaporated to dryness in vacuo. The solid residue was taken up in CH_2Cl_2, the solvent was washed with ice water and dried (Na_2SO_4). Removal of the solvent in vacuo essentially gave pure monoacetate **7** (1.5 g, 95%) as a single product. A sample was recrystallized from CH_2Cl_2-n-hexane to give colorless crystals: mp 74-75 °C (decomp); IR (KBr) 3340, 1780, 1740, 1590, 1530, 1455, 1290, 1170 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.85 (3H, s), 2.23 (3H, s), 2.32 (3H, s), 3.11 (2H, t, J=5 Hz), 3.84 (2H, m), 4.11 (1H, s), 4.51 (2H, m), 4.55 (1H, br s, OH), 5.10 (2H, s), 5.48 (2H, s), 6.90-7.60

(13H, m), 8.86 (1H, br t, J=4 Hz, NH), 9.09 (1H, s, NH). Anal. Calcd for $C_{38}H_{36}BrN_5O_{11}S$: C, 53.65; H, 4.27; N, 8.23. Found: C, 53.56; H, 4.18; N, 8.22.

Preparation of the Spirooxyindole Derivative: 2-(Methylsulfonyl)ethyl 6'-Bromo-1',2'-dihydro-3,5-dihydroxy-5-methyl-3-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2',4-dioxospiro[cyclopentane-1,3'-[3H]indole]-2-carboxylate (9). To a solution of **7** (500 mg, 0.588 mmol) in THF (3 ml)-ether (6 ml) containing 0.2 ml of pyridine was added dropwise a solution of 10% OsO_4 in THF (6 ml, 2.36 mmol, 4 equiv) with stirring at -15 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm up to 0 °C and was kept overnight to precipitate osmium ester complex **8**, which was then collected, washed with ether and dried. Resulting unstable **8** was dissolved in pyridine (20 ml). To this was added a solution of $NaHSO_3$ (1.0 g, 9.61 mmol) in H_2O (15 ml) with stirring at 5 °C and the mixture was gradually warmed to room temperature. After one hour at room temperature, the mixture was concentrated to one-fifth of the original volume, extracted with AcOEt, washed with water and dried (Na_2SO_4). Removal of the solvent left an oily residue which was purified through silica gel column (AcOEt-benzene=1:1) to give **9a** (200 mg, 41% from **7**) and **9b** (81 mg, 17%).

9a: mp 134-135 °C (from ether); IR (KBr) 3340, 1720, 1590, 1530, 1330, 1280, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, s), 2.81 (3H, s), 3.20 (2H, m), 3.45 (1H, s, OH), 4.14 (1H, s), 4.36 (4H, m), 5.35 and 5.42 (2H, d of AB, J=12.1 Hz), 5.52 (2H, s), 6.28 (1H, s, OH), 7.04 (1H, d, J=1.5 Hz), 7.14 (1H, dd, J=8.1, 1.5 Hz), 7.27-7.50 (11H, m), 8.37 (1H, s, NH), 9.06 (1H, t, J=6.2 Hz, NH). Anal. Calcd for $C_{36}H_{34}BrN_5O_{12}S$: C, 51.44; H, 4.08; N, 8.33. Found: C, 51.29; H, 3.97; N, 8.35.

9b: This compound is easily epimerized during recrystallization from ether. ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (3H, s), 2.81 (3H, s), 3.19 (2H, m), 3.62 (1H, s), 4.14 (1H, br s, OH), 4.36 (4H, m), 5.39 (2H, s), 5.53 (2H, s), 6.13 (1H, s, OH), 7.01 (1H, d, J=1.8 Hz), 7.02 (1H, d, J=8.1 Hz), 7.16 (1H, dd, J=8.1, 1.8 Hz), 7.28-7.50 (10H, m), 8.67 (1H, br s, NH), 9.01 (1H, t, J=6.6 Hz, NH).

2-(Methylsulfonyl)ethyl 6'-Bromo-1',2'-dihydro-5-hydroxy-5-methyl-3-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2',4-dioxospiro-2-cyclopentene-1,3'-[3H]indole]-2-carboxylate (10). A solution of **9** (500 mg, 0.595 mmol) in pyridine (5 ml) at -15 °C was treated with a solution of thionyl chloride (354 mg, 2.98 mmol) in CH_2Cl_2 (0.2 ml). After 10 min, the reaction mixture was diluted with ice water and extracted with CH_2Cl_2.

The organic layer was washed successively with water, 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine and then dried (Na_2SO_4). Removal of the solvent left an oily residue which was purified through a silica gel column (AcOEt-benzene=1:1) to give **10** (355 mg, 73%) as a mixture of interconvertible two diastereoisomers: mp 164-166 °C (from CH_2Cl_2); IR (KBr) 3360, 1730, 1585, 1530, 1450, 1300 cm^{-1}; UV (MeOH) λ_{max} 265 (log ε 4.11), 335 (log ε 3.98) nm; ^1H NMR (100 MHz, DMSO-d_6) δ 1.10 and 1.23 (3H in total, s each), 2.90 (3H, s), 3.32 (2H, s), 4.26 (2H, br t, J=5 Hz), 4.66 (2H, br s), 5.28 (2H, br s), 5.42 (2H, s), 6.01 and 6.22 (1H in total, s each, OH), 6.80-7.60 (13H, m), 9.14 (1H, br t, J=5 Hz, NH), 10.63 and 10.80 (1H in total, br s each, NH). Anal. Calcd for $C_{36}H_{32}BrN_5O_{11}S$: C, 52.56; H, 3.92; N, 8.51. Found: C, 52.30; H, 3.78; N, 8.41.

2-(Methylsulfonyl)ethyl 6'-Bromo-1',2',8,8a,9,10-hexahydro-6-hydroxy-6-methyl-2'-oxo-2,4-bis(phenylmethoxy)spiro[cyclopenta[e]pyrimido[4,5-b]-[1,4]diazepine-7(6H),3'-[3H]indole]-8-carboxylate (11): Compound having a Neosurugatoxin Framework. Zn powder (5 g) and AcOH (1.8 ml) was added to a solution of **10** (500 mg, 0.608 mmol) in 50 ml of MeOH-CH_2Cl_2 (1:10) with stirring. After 10 min at room temperature, the mixture was filtered and the unreacted Zn powder was washed with CH_2Cl_2. The filtrate and the washings were combined, washed with water and saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 ml). To this solution was added CSA (500 mg) and the mixture was stirred at room temperature. When the ring closure was completed (ca. 10 min) as judged by TLC (AcOEt-benzene=2:1), the reaction mixture was washed with water and saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). After the solvent was evaporated to dryness *in vacuo*, the residue was chromatographed on silica gel (AcOEt-benzene=2:1) to give the following four fractions.

Fraction 1: colorless leaflets (from MeOH) of **11a** (204 mg, 43%); mp 207-208 °C (decomp); IR (KBr) 3460, 3380, 1705, 1575, 1420, 1345, 1115 cm^{-1}; UV (MeOH) λ_{max} 271 (log ε 4.07), 287 (log ε 4.06), 313 (log ε 3.97) nm; ^1H NMR (400 MHz, DMSO-d_6) δ 1.02 (3H, s), 2.87 (3H, s), 3.27 (3H, m), 3.38 (1H, m), 3.71 (1H, d, J=9.2 Hz), 3.90 (1H, dd, J=9.2, 7.1 Hz), 4.21 (1H, ddd, J=11.7, 7.0, 4.8 Hz), 4.33 (1H, ddd, J=11.7, 7.0, 4.8 Hz), 5.30 (2H, s), 5.34 and 5.39 (2H, d of AB, J=13.6 Hz), 5.74 (1H, s, OH), 6.98 (1H, d, J=1.8 Hz), 7.13 (1H, dd, J=8.1, 1.8 Hz), 7.25-7.50 (11H, m), 7.70 (1H, d, J=7.1 Hz, NH), 10.58 (1H, s, NH). Anal. Calcd for $C_{36}H_{34}BrN_5O_8S.1/2H_2O$: C, 55.04, H, 4.49; N, 8.91. Found: C, 55.25; H, 4.27; N, 8.96.

Fraction 2: colorless leaflets (from MeOH) of **11b** (27 mg, 6 %); mp 214-215 °C (decomp); IR (KBr) 3370, 1740, 1720, 1580, 1415, 1345, 1130 cm^{-1}; ^1H

NMR (400 MHz, DMSO-$\underline{d}_6$) δ 1.28 (3H, s), 2.89 (3H, s), 3.17 (1H, ddd, $\underline{J}$=12.5, 8.8, 1.5 Hz), 3.28 (1H, m), 3.39 (2H, m), 3.61 (1H, d, $\underline{J}$=9.9 Hz), 3.81 (1H, ddd, $\underline{J}$=12.5, 6.6, 2.6 Hz), 4.21 (1H, ddd, $\underline{J}$=12.1, 7.0, 4.8 Hz), 4.32 (1H, ddd, $\underline{J}$=12.1, 7.0, 4.8 Hz), 5.03 (1H, s, OH), 5.28 (2H, s), 5.38 and 5.45 (2H, d of AB, $\underline{J}$=13.2 Hz), 6.94 (1H, d, $\underline{J}$=1.8 Hz), 7.15 (1H, dd, $\underline{J}$=8.1, 1.8 Hz), 7.25 (1H, d, $\underline{J}$=8.1 Hz), 7.26-7.50 (10H, m), 7.61 (1H, dd, $\underline{J}$=6.6, 1.5 Hz, NH), 10.33 (1H, s, NH).

Fraction 3: colorless leaflets (from MeOH) of **11c** (169 mg, 36%); mp 200-201 °C (decomp); IR (KBr) 3380, 3240, 1720, 1605, 1580, 1415, 1345, 1130 cm^{-1}; UV (MeOH) λ_{max} 270 (log ε 4.04), 287 (log ε 3.99), 316 (log ε 3.94) nm; ^{1}Hm NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, s), 2.89 (1H, m), 2.92 (3H, s), 3.11 (1H, ddd, $\underline{J}$=14.4, 7.7, 4.4 Hz), 3.54 (2H, m), 3.77 (1H, d, $\underline{J}$=9.2 Hz), 3.81 (1H, m), 4.10 (1H, ddd, $\underline{J}$=12.1, 7.7, 4.4 Hz), 4.41 (1H, s, OH), 4.43 (1H, m), 5.37 (2H, s), 5.42 and 5.51 (2H, d of AB, $\underline{J}$=13.5 Hz), 5.84 (1H, br s, NH), 6.69 (1H, d, $\underline{J}$=8.1 Hz), 7.11 (1H, dd, $\underline{J}$=8.1, 1.8 Hz), 7.15 (1H, d, $\underline{J}$=1.8 Hz), 7.22-7.50 (10H, m), 8.16 (1H, s, NH). Anal. Calcd for $C_{36}H_{34}BrN_5O_8S.H_2O$: C, 54.41; H, 4.57; N, 8.81. Found: C, 54.57; H, 4.29; N, 8.82.

Fraction 4: colorless crystals (from MeOH) of **11d** (36 mg, 8%); mp 189-190 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, s), 2.90 (1H, m), 2.93 (3H, s), 3.06 (1H, ddd, $\underline{J}$=14.3, 7.7, 4.4 Hz), 3.37 (1H, d, $\underline{J}$=9.9 Hz), 3.38 (1H, dd, $\underline{J}$=11.7, 8.4 Hz), 3.59 (1H, ddd, $\underline{J}$=9.9, 8.4, 2.9 Hz), 3.86 (1H, ddd, $\underline{J}$=11.7, 7.5, 2.9 Hz), 4.11 (1H, ddd, $\underline{J}$=12.1, 7.7, 4.4 Hz), 4.42 (1H, ddd, $\underline{J}$=12.1, 7.7, 4.4 Hz), 5.39 (2H, s), 5.44 and 5.50 (2H, d of AB, $\underline{J}$=12.8 Hz), 6.57 (1H, br s, NH), 6.64 (1H, d, $\underline{J}$=8.1 Hz), 7.06 (1H, dd, $\underline{J}$=8.1, 1.8 Hz), 7.08 (1H, d, $\underline{J}$=1.8 Hz), 7.29-7.48 (10H, m), 8.15 (1H, s, NH).

2-(Methylsulfonyl)ethyl 1'-Acetyl-6-(acetyloxy)-6'-bromo-1',2',8,8a,9,-10-hexahydro-6-methyl-2'-oxo-2,4-bis(phenylmethoxy)spiro[cyclopenta[e]-pyrimido[4,5-b][1,4]diazepine-7(6H),3'-[3H]indole]-8-carboxylate (12). Compound **11** (300 mg, 0.387 mmol, a mixture of 4 isomers) was dissolved in THF (12 ml) and cooled to 5° C, DMAP (300 mg, 2.46 mmol) was then added followed by the dropwise addition of Ac_2O (12 ml) with stirring. The mixture was gradually warmed to room temperature requiring 1.5 h and the mixture was evaporated to dryness. The residue was treated with water and the insoluble portion was collected, washed with water and dried. The crude product was purified through a silica gel column (AcOEt-benzene=3:1) to give diacetate **12** which was recrystallized from MeOH to give a colorless crystalline solid (239 mg, 72%): mp 120 °C; IR (KBr) 3390, 1740, 1580, 1415, 1345, 1165 cm^{-1}; UV (MeOH) λ_{max} 239 (log ε 4.52), 263 (log ε

4.12), 281 (log ε 3.98), 324 (log ε 3.96) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (3H, s), 2.01 (3H, s), 2.61 (3H, s), 2.86 (3H, s), 3.19 (2H, m), 3.49 (1H, ddd, J=11.7, 8.1, 1.8 Hz), 3.56 (1H, ddd, J=10.3, 8.1, 2.6 Hz), 3.86 (1H, d, J=10.3 Hz), 4.20 (1H, ddd, J=11.7, 7.7, 2.6 Hz), 4.40 (1H, ddd, J=11.7, 7.0, 4.8 Hz), 4.56 (1H, ddd, J=11.7, 7.0, 4.8 Hz), 5.36 (2H, s), 5.41 and 5.50 (2H, d of AB, J=13.2 Hz), 6.20 (1H, br m, NH), 6.95 (1H, d, J=8.4 Hz), 7.24-7.50 (11H, m), 8.52 (1H, d, J=1.8 Hz). Anal. Calcd for $C_{40}H_{38}BrN_5O_{10}S$: C, 55.82; H, 4.45; N, 8.14. Found: C, 55.89; H, 4.23; N, 8.34.

1'-Acetyl-6-(acetyloxy)-6'-bromo-1',2',8,8a,9,10-hexahydro-6-methyl-2'-oxo-2,4-bis(phenylmethoxy)spiro[cyclopenta[e]pyrimido[4,5-b][1,4]-diazepine-7(6H),3'-[3H]indole]-8-carboxylic Acid (13): Neosurugatoxin Aglycone Diacetate. $NaHCO_3$-Na_2CO_3 buffer (pH 10.2, 20 ml) was added dropwise to a solution of **12** (200 mg, 0.233 mmol) in acetone (100 ml) at 5 °C with stirring and the mixture was warmed to room temperature. After 3 h at room temperature, the reaction mixture was cooled to 5 °C and quenched by neutralization with AcOH. Acetone was removed *in vacuo*, separated crystals were collected by filtration and washed with water. The filtrate and the washings were combined and extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4) and then evaporated. The residue was purified by silica gel TLC (MeOH-benzene=1:10) to give a single product which was combined with the first crop of the crystalline solid. Recrystallization from MeOH gave a colorless crystalline solid of **13** (171 mg, 98%): mp 154-155 °C (decomp); IR (KBr) 3400, 1750, 1720, 1580, 1410, 1345, 1165 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 (3H, s), 2.04 (3H, s), 2.53 (3H, s), 3.25 (1H, ddd, J=10.3, 8.4, 2.2 Hz), 3.33 (1H, ddd, J=12.1, 8.4, 1.0 Hz), 3.89 (1H, d, J=10.3 Hz), 4.01 (1H, ddd, J=12.1, 7.0, 2.2 Hz), 5.31 (2H, s), 5.38 and 5.42 (2H, d of AB, J=12.8 Hz), 7.24-7.50 (11H, m), 7.53 (1H, dd, J=8.1, 1.8 Hz), 7.98 (1H, br dd, J=7.0, 1.0 Hz, NH), 8.31 (1H, d, J=1.8 Hz). Anal. Calcd for $C_{37}H_{32}BrN_5O_8 \cdot 1/2H_2O$: C, 58.20; H, 4.36; N, 9.17. Found: C, 57.96; H, 4.24; N, 9.22.

Esterification of the aglycone (13). Picryl chloride (66 mg, 0.267 mmol, 2 equiv) was added portion wise to a solution of **13** (100 mg, 0.133 mmol) and 1,2-O-cyclohexylidene-3,6-bis-O-(methoxymethyl)-5-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-D-*myo*-inositol **14** (96 mg, 0.158 mmol, 1.2 equiv) in pyridine (5 ml) at 15 °C under a nitrogen atmosphere. To the mixture was added an additional picryl chloride (three times in each 66 mg) over an 1.5 h at room temperature. After being stirred for an additional 30 min, the mixture was evaporated to dryness *in vacuo*. The residue was

taken up in CH_2Cl_2, the extracts were washed with saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was evaporated to dryness in vacuo and the residue was chromatographed on silica gel (MeOH-CH_2Cl_2=3:97) to give the following two fractions.

Fraction 1: **15x** (an isomer of natural form: 9.7 mg, 5.4%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.31-1.74 (10H, m), 1.53 (3H, s), 1.88 (3H, s), 1.96 (3H, s), 1.99 (3H, s), 2.03 (3H, s), 2.69 (3H, s), 3.14 (1H, dd, J=11.7, 9.7 Hz), 3.35 (3H, s), 3.40 (3H, s), 3.48 (1H, dd, J=9.0, 8.8 Hz), 3.58 (1H, ddd, J=11.7, 7.0, 1.5 Hz), 3.72 (1H, dd, J=8.8, 3.9 Hz), 3.76 (1H, dd, J=9.0, 6.8 Hz), 3.82 (1H, ddd, J=11.0, 7.0, 2.7 Hz), 3.85 (1H, d, J=11.0 Hz), 3.91 (1H, dd, J=11.7, 5.4 Hz), 3.98 (1H, dd, J=6.8, 5.6 Hz), 4.11 (1H, ddd, J=11.7, 7.3, 2.7 Hz), 4.25 (1H, dd, J=5.6, 3.9 Hz), 4.57 (1H, d, J=7.3 Hz), 4.58 and 4.63 (2H, d of AB, J=7.1 Hz), 4.69 and 4.72 (2H, d of AB, J=6.4 Hz), 4.93 (1H, ddd, J=9.7, 9.0, 5.4 Hz), 4.94 (1H, dd, J=9.0, 7.3 Hz), 5.07 (1H, t, J=9.0 Hz), 5.11 (1H, t, J=8.8 Hz), 5.31 and 5.38 (2H, d of AB, J=12.5 Hz), 5.46 (2H, s), 5.81 (1H, br s, NH), 6.89 (1H, d, J=8.0 Hz), 7.26-7.39 (7H, m), 7.43 (2H, dd, J=8.0, 1.7 Hz), 7.47 (2H, dd, J=8.0, 1.7 Hz), 8.53 (1H, d, J=1.7 Hz); MS (FAB): m/z 1344, 1342 $(M+H)^+$; HRMS (FAB) Found: m/z 1344.3910. Calcd for $C_{64}H_{73}BrN_5O_{22}$: 1344.3907.

Fraction 2: **15y** (an isomer of unnatural form: 12.0 mg, 6.7%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.25-1.80 (10H, m), 1.49 (3H, s), 1.97 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.07 (3H, s), 2.62 (3H, s), 3.33 (1H, dd, J=11.7, 8.8 Hz), 3.37 (3H, s), 3.38 (3H, s), 3.46 (1H, dd, J=9.0, 8.5 Hz), 3.54 (1H, ddd, J=10.7, 8.1, 2.5 Hz), 3.60 (1H, ddd, J=11.7, 8.1, 1.5 Hz), 3.74 (1H, dd, J=9.0, 6.4 Hz), 3.77 (1H, dd, J=8.5, 3.7 Hz), 3.96 (1H, d, J=10.7 Hz), 3.97 (1H, t, J=6.4 Hz), 4.05 (1H, dd, J=11.7, 4.9 Hz), 4.18 (2H, m), 4.50 (1H, dd, J=8.3, 6.9 Hz), 4.60 (1H, d, J=6.9 Hz), 4.61 and 4.68 (2H, d of AB, J=6.4 Hz), 4.65 and 4.69 (2H, d of AB, J=6.4 Hz), 5.01 (1H, ddd, J=8.5, 8.3, 4.9 Hz), 5.06 (1H, t, J=8.3 Hz), 5.21 (1H, t, J=8.5 Hz), 5.38 (2H, s), 5.41 and 5.51 (2H, d of AB, J=13.2 Hz), 7.02 (1H, d, J=8.0 Hz), 7.26-7.45 (10H, m), 7.47 (1H, dd, J=8.0, 1.7 Hz), 8.54 (1H, d, J=1.7 Hz).

Hydrolysis of the Ester Diacetate: 1'-Acetyl-6-(acetyloxy)-6'-bromo-1',2',8,8a,9,10-hexahyrdo-6-methyl-2'-oxo-2,4-bis(phenylmethoxy)spiro-[cyclopenta[e]pyrimido[4,5-b][1,4]diazepine-7(6H),3'-[3H]indole]-8-carboxylic Acid 4-[1,2-O-Cyclohexylidene-3,6-bis-O-(methoxymethyl)-5-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)]-D-myo-inositol Ester (15). A solution of **15x** (23.7 mg, 0.0177 mmol) in 0.1 N KOH-MeOH (1.77 ml, 0.177 mmol) was kept at room temperature with stirring under a nitrogen atmosphere. After 30 min, the reaction 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=1:10) to afford a mixture of four isomers **16x-a~d** (10.1 mg, 51%). Similarly, a mixture of diastereoisomers **16y-a~d** was obtained from **15y** by the same treatment.

Equilibration followed by Separation of [6S-(6β,7α,8β,8aβ)]-6'-Bromo-1',2',8,8a,9,10-hexahydro-6-hydroxy-6-methyl-2'-oxo-2,4-bis(phenylmethoxy)spiro[cyclopenta[e]pyrimido[4,5-b][1,4]diazepine-7(6H),3'-[3H]indole]-8-carboxylic Acid 4-[1,2-O-Cyclohexylidene-3,6-bis-O-(methoxymethyl)-5-O-β-D-xylopyranosyl]-D-myo-inositol Ester (16x-b). A solution of **16x-a~d** (12.0 mg, 0.0106 mmol) in MeOH (24 ml) containing AcONa (24 mg, 0.29 mmol) was warmed to 50 °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 of a mixture of four isomers, was separated by silica gel TLC (MeOH-CH_2Cl_2=1:10) to obtain the natural form. The unnatural three isomers **16x-a, c, d** were combined and submitted to the equilibration to isolate the natural form **16x-b.** This recycling was repeated four times to give 5.2 mg of **16x-b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.70 (10H, m), 1.35 (3H, s), 2.98 (2H, m), 3.20-3.45 (4H, m), 3.33 (3H, s), 3.34 (3H, s), 3.59 (1H, t, J=9.5 Hz), 3.65 (1H, dd, J=11.4, 4.6 Hz), 3.78 (1H, br m), 3.82 (1H, dd, J=9.5, 7.0 Hz), 3.98 (3H, m), 4.32 (1H, br dd, J=4.9, 4.4 Hz), 4.36 (1H, d, J=7.3 Hz), 4.64 (2H, s), 4.71 and 4.75 (2H, d of AB, J=6.4 Hz), 5.17 (1H, br t, J=9.5 Hz), 5.22 and 5.30 (2H, d of AB, J=12.5 Hz), 5.41 and 5.50 (2H, d of AB, J=12.5 Hz), 6.43 (1H, br s, NH), 6.89 (1H, d, J=1.8 Hz), 6.92 (1H, d, J=8.1 Hz), 7.14 (1H, dd, J=8.1, 1.8 Hz), 7.20-7.40 (10H, m), 9.00 (1H, br s, NH); MS (FAB): m/z 1134, 1132 $(M+H)^+$; HRMS (FAB) Found: m/z 1132.3380. Calcd for $C_{54}H_{63}BrN_5O_{17}$: 1132.3399.

[6S-(6β,7α,8β,8aβ)]-6'-Bromo-1,1',2',3,4,6,8,8a,9,10-decahydro-6-hydroxy-6-methyl-2,2',4-trioxospiro[cyclopenta[e]pyrimido[4,5-b][1,4]- diazepine-7(2H),3'-[3H]indole]-8-carboxylic Acid 4-(5-O-β-D-Xylopyranosyl)-D-myo-inositol Ester (Neosurugatoxin) (2). A solution of **16x-b** (2.6 mg, 0.0023 mmol) in 90% TFA (0.26 ml) was kept for 50 min at room temperature. The reaction mixture was dried up in vacuo, the residue was washed with ether and then submitted to HPLC to give 1.4 mg (77%) of **2.** TLC: Rf=0.33 (silica gel, MeOH-H_2O=7:3); HPLC: 25.0 min [column: Nomura Chemical Co., LTD, Develosil Packed Column ODS-5, 10x250 mm, solvent: 30% MeOH in H_2O, flow rate: 2 ml/min]; colorless prisms; mp 331-335 °C (decomp); IR (KBr) 3300, 1700, 1600, 1380, 1030 cm^{-1}; UV (H_2O) λ_{max} 220 (log ε 4.65), 282 (log ε 4.18), 310_{sh} (log ε 3.96), 325_{sh} (log ε 3.80) nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (3H, s), 2.90-2.98 (2H, m), 2.99-3.08 (2H, m), 3.53-3.62

(2H, m), 3.69 (1H, s), 3.96 (1H, d, J=12.0 Hz), 4.18 (1H, d, J=7.2 Hz), 4.36 (1H, d, J=6.8 Hz), 4.62 (1H, d, J=6.0 Hz), 4.77 (1H, d, J=3.2 Hz), 4.83 (1H, t, J=9.5 Hz), 4.95 (1H, d, J=8.0 Hz), 4.96 (1H, s), 5.14 (1H, br s), 5.27 (1H, br s), 5.60 (1H, br s), 6.66 (1H, br s), 6.88 (1H, s), 7.10 (2H, s), 10.12 (1H, br s), 10.18 (1H, s), 10.53 (1H, br s); (400 MHz, D_2O, DOH=4.65 ppm) δ 1.24 (3H, s), 2.98 (1H, t, J=11.0 Hz), 3.06 (1H, t, J=9.1 Hz), 3.11 (1H, t, J=9.1 Hz), 3.20-3.28 (3H, m), 3.34 (1H, t, J=5.4 Hz), 3.38 (2H, t, J=9.0 Hz), 3.52 (1H, dd, J=11.0, 4.5 Hz), 3.59 (1H, t, J=10 Hz), 3.65 (1H, td, J=9.0, 1.8 Hz), 3.77-3.86 (2H, m), 4.32 (1H, d, J=7.2 Hz), 7.03 (1H, d, J=1.8 Hz), 7.05 (1H, d, J=7.9 Hz), 7.12 (1H, dd, J=7.9, 1.8 Hz); MS (SIMS): m/z 786, 784 $(M+H)^+$.

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