Second Approach to the Construction of a Pentacyclic Ring System for Neosurugatoxin[1)]

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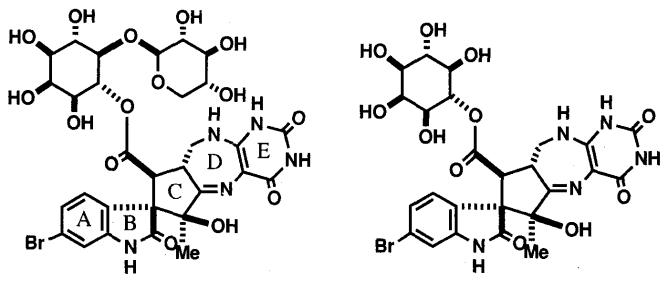
The Diels–Alder adduct obtained from (*E*)-6-bromo-3-ethoxycarbonylmethylene-2-oxoindoline and *trans*-1,3-pentadiene was successfully transformed into the diacetate of the aglycone of neosurugatoxin, which is the key intermediate in our first total synthesis of neosurugatoxin in 16 steps.

Keywords spiro-6-bromo-2-oxoindoline derivative; (*E*)-6-bromo-3-ethoxycarbonylmethylene-2-oxoindoline; Diels–Alder adduct; *trans*-1,3-pentadiene; neosurugatoxin; marine toxin; neosurugatoxin formal synthesis; 2-(methylthio)ethyl 6′-bromo-1′,2′-dihydro-6-methyl-2′-oxospiro[4-cyclohexene-1,3′-[3*H*]indole]-2-carboxylate

The Japanese ivory shell (*Babylonia japonica*) harvested from the Ganyuudo area in Suruga Bay in Japan was the cause of an outbreak of food poisoning in 1965.[2)] Afterwards, Professor Kosuge and his co-workers isolated two causative metabolites and succeeded in the structure elucidation of these materials, named neosurugatoxin (**1**)[3)] and prosurugatoxin (**2**).[4)] Both compounds, which possess a new and quite unusual pentacyclic framework, have an extremely high affinity for central and peripheral nicotinic receptors as compared to classical nicotinic receptor antagonists[5)] such as hexamethonium. Thus, it is desirable to develop an efficient synthetic approach to this unique ring system with the aim of obtaining useful pharmacological tools for the study of nicotinic receptors. We completed the first total synthesis of neosurugatoxin (**1**) in 1986.[6)] The crucial problems in the synthesis of **1** were the development of a methodology for the construction of the unique pentacyclic framework and the introduction of four consecutive asymmetric carbons in the five-membered ring C.



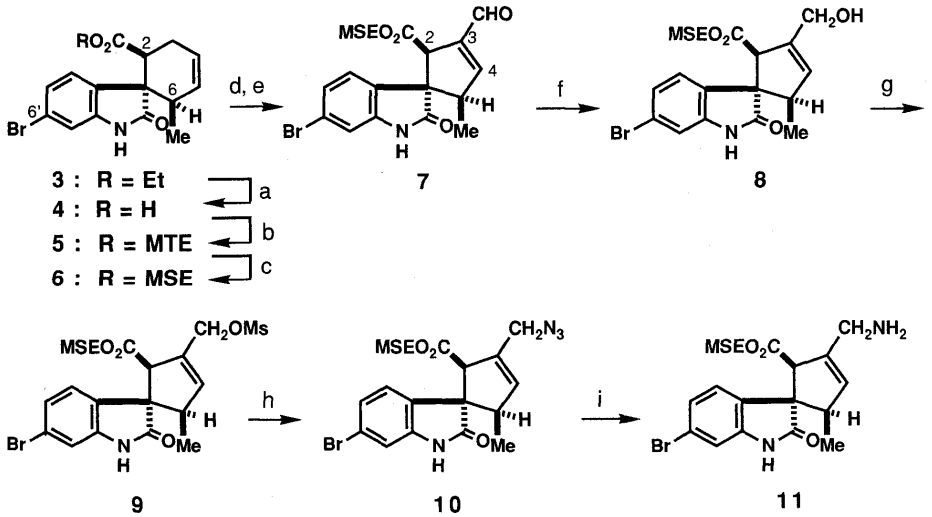
neosurugatoxin (1) prosurugatoxin (2)

Chart 1

We described, in the preliminary communication,[7)] the synthesis and structural features of the Diels–Alder adduct prepared from (*E*)-3-methoxycarbonylmethylene-2-oxoindoline and *trans*-1,3-pentadiene and concluded that the adduct was a promising material for the synthesis of **1** and **2**. The analogous spiro-6-bromo-2-oxoindoline derivative (**5**) has now been synthesized and successfully transformed into **21**, the key intermediate in our first synthesis of neosurugatoxin.[6)] This paper deals with the second formal synthesis of neosurugatoxin starting from **5**.

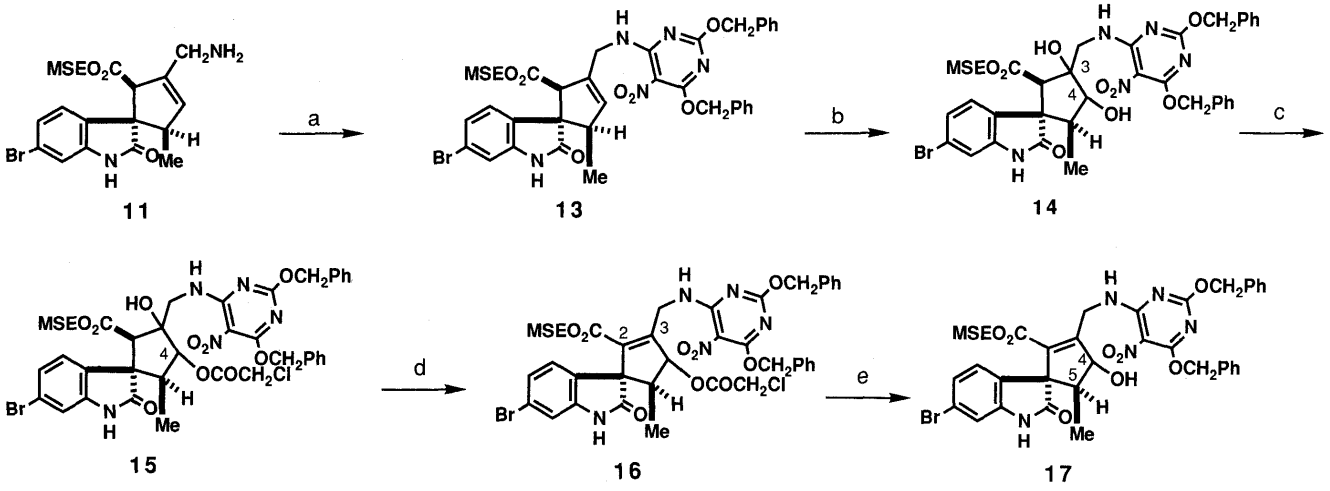
Results and Discussion

The starting material (**5**), prepared from the Diels–Alder adduct (**3**) *via* the carboxylic acid (**4**), was converted into the corresponding methylsulfonylethyl (MSE) ester (**6**) by treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at room temperature for 30 min. Ozonization of **6** in dichloromethane–methanol (10 : 1 v/v) at −60 °C



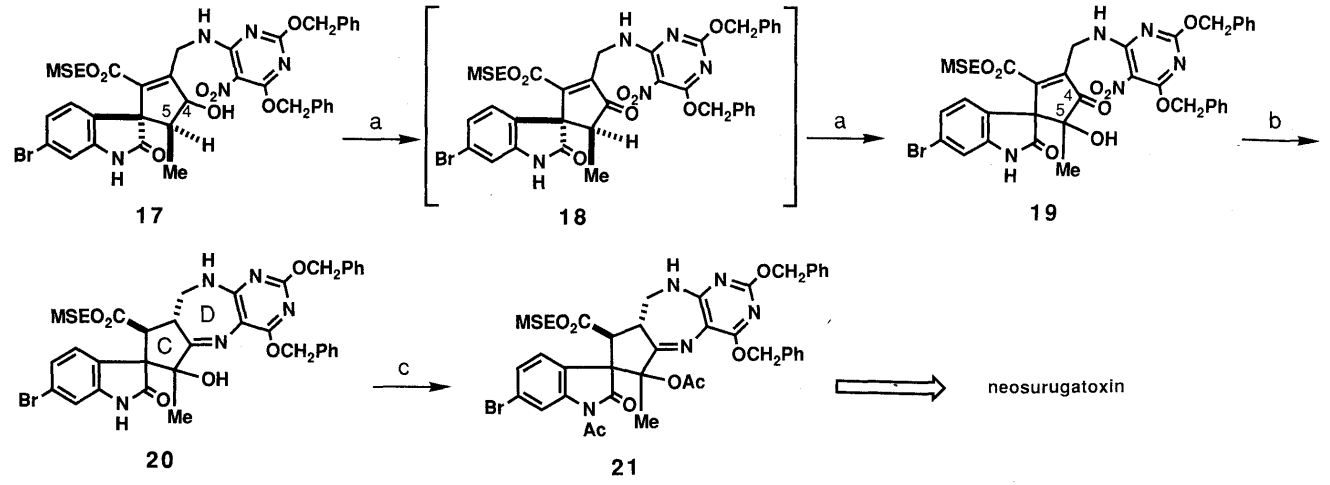
a: 10% KOH aq. b: $MeSCH_2CH_2OH$/picryl chloride c: *m*-CPBA d: 1) O_3, 2) $P(OEt)_3$ e: piperidine/AcOH f: $NaBH_4$ g: MsCl/py h: NaN_3 i: Zn/AcOH

Chart 2



a: 4-(ethylsulfonyl)-5-nitro-2,6-bis(phenylmethoxy)-pyrimidine (**12**)/$NaHCO_3$
b: 1) OsO_4/py, 2) $NaHCO_3$ c: $(ClCH_2CO)_2O$/py d: $SOCl_2$/py e: thiourea

Chart 3



a: $(PhSeO)_2O$ b: 1) Zn/AcOH, 2) CSA c: Ac_2O/DMAP

Chart 4

was followed by reductive cleavage using a large excess of triethyl phosphite at −20 °C for 30 min, and then cyclization of the resulting dialdehyde under the Knoevenagel condition (piperidine–acetic acid (1 : 10 v/v) in tetrahydrofuran (THF)–benzene, 50°C, 3 h) gave the desired aldehyde (**7**) as a single product in 62% overall yield as shown in Chart 2.

Reduction of **7** with sodium borohydride in methanol gave the alcohol (**8**) in 88% yield. This alcohol (**8**) was then converted into the mesylate (**9**) in 83% yield by treatment with methanesulfonyl chloride (MsCl) and triethylamine (TEA) in THF at room temperature for 1 h and successive treatment of **9** with sodium azide in dimethylformamide (DMF) at 5 °C for 1 h produced the corresponding azide (**10**) in 91% yield. Reduction of the azide group in **10** with zinc powder and acetic acid in dichloromethane gave the desired primary amine derivative (**11**).

Since the amine (**11**) thus obtained was very unstable, it was immediately reacted with 4-(ethylsulfonyl)-5-nitro-2,6-bis(phenylmethoxy)pyrimidine (**12**),[8] a protected form of the uracil moiety in neosurugatoxin, to give the desired 4-amino-5-nitropyrimidine derivative (**13**) in 51% overall yield from **10**. The double bond in **13** was oxidized with osmium tetroxide (OsO_4) in pyridine (room temperature, 3 h) to form the corresponding osmate, which was then cleaved in the usual manner (10% aqueous $NaHSO_3$: pyridine = 1 : 8 v/v, room temperature, overnight), giving the desired 3,4-diol (**14**). Selective acylation of the hydroxyl group at C_4 in **14** with monochloroacetic anhydride in pyridine at 5 °C for 1 h gave the 4-monochloroacetate (**15**) in 91% yield. The remaining tertiary hydroxyl group at C_3 was then eliminated by treatment with thionyl chloride in pyridine at 0 °C for 30 min to yield the α,β-unsaturated ester (**16**). Removal of the chloroacetyl protecting group was achieved in a quantitative yield, when **16** was treated with thiourea (1.1 molar eq) in methanol under reflux for 3 h (Chart 3).

The resulting 2,3-unsaturated 4-hydroxy derivative (**17**) was then subjected to selenium oxidation in an attempt to form an acyloin at the C_4–C_5 position of **17**. Namely, when a mixture of **17** and benzeneseleninic anhydride (3.5 molar

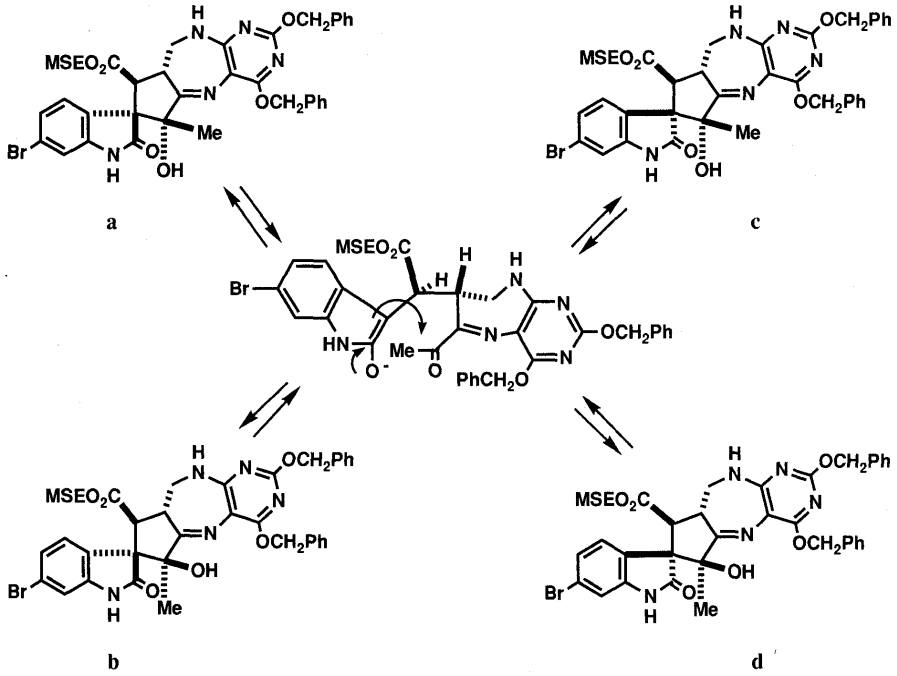


Chart 5

eq) in dioxane was heated at 80 °C for 2 h, the oxidation proceeded stepwise (as judged by thin layer chromatography (TLC)) to form the C_4-ketone (**18**) first and subsequent α-hydroxylation of the ketone gave the desired acyloin (**19**) in 91% overall yield. Compound **19** thus obtained incorporates all the elements necessary to construct the neosurugatoxin framework and it was one of the intermediates of our first neosurugatoxin synthesis.[6] However, the identification of **19** was difficult, since it was easily epimerized in organic solvents such as dichloromethane or methanol at room temperature, to form a 1 : 1 mixture of C_5-epimers. Therefore, **19** was converted into a stable single compound (**21**) as shown in Chart 4.

Reduction of a mixture of **19** with zinc powder and acetic acid in dichloromethane–methanol (10 : 1 v/v) at room temperature was followed by treatment with a catalytic amount of camphorsulfonic acid (CSA) in dichloromethane at room temperature for 10 min, resulting in ring closure and the formation of a neosurugatoxin framework as a mixture of four stereoisomers of **20**.[6] This result may be due to ring-chain tautomerism as shown in Chart 5.

The resulting mixture of four isomers was treated with an excess of acetic anhydride and dimethylaminopyridine (DMAP, 6.0 molar eq) in THF at room temperature for 1.5 h to yield a single diacetate (**21**) in 72% yield. The *Rf* values by TLC in three solvent systems, the melting point (mp 120 °C), the mixed melting point with an authentic sample, and the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum of this product indicated it to be identical with the key intermediate in our first synthesis of neosurugatoxin.[6]

Experimental

All melting points are uncorrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. ^{1}H-NMR spectra reported herein were recorded on a JEOL JNM GX-270 spectrometer with Me_4Si as an internal standard. The following abbreviations are used: br = broad, d = doublet, dd = double doublets, ddd = double double doublets, m = multiplet, q = quartet, s = singlet, t = triplet. For column chromatography, silica gel (Kanto Chemical, over 100 mesh) was used. TLC was performed on Kiselgel 60F_{254} plates (Art. 5744, Merck).

Ethyl 6′-Bromo-1′,2′-dihydro-6-methyl-2′-oxospiro[4-cyclohexene-1,3′-[3*H*]indole]-2-carboxylate (3) *trans*-1,3-Pentadiene (4 ml, 40.1 mmol) was added to a suspension of (*E*)-6-bromo-3-ethoxycarbonylmethylene-2-oxoindoline[9] (500 mg, 1.69 mmol) in toluene (50 ml) in a sealed tube, and the mixture was heated in an oil bath at 130 °C for 3 h. After cooling to room temperature, the reaction mixture was filtered through Hyflo Super-Cel, which was washed with CH_2Cl_2 (100 ml). The organic solution was concentrated under reduced pressure and the residual oil was purified on a silica gel column (50 g, AcOEt : hexane = 1 : 1 v/v) to give the adduct **3** (553 mg, 90%), mp 188—189 °C (from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.60 (3H, d, J = 7.4 Hz, $-CHC\underline{H}_3$), 1.08 (3H, t, J = 7.2 Hz, $-OCH_2C\underline{H}_3$), 2.52—2.88 (3H, m, $=CHC\underline{H}_2-$ and $-C\underline{H}CH_3$), 3.31 (1H, m, $-OCOC\underline{H}-$), 3.94 (2H, m, $-COOC\underline{H}_2-$), 5.56 (1H, dd, J = 1.7, 10.1 Hz, $=C\underline{H}-$), 5.88 (1H, m, $=C\underline{H}-$), 6.99 (1H, d, J = 8.4 Hz, arom.-H), 7.05 (1H, dd, J = 1.8, 8.4 Hz, arom.-H), 7.11 (1H, d, J = 1.8 Hz, arom.-H), 9.35 (1H, br s, –NH–). *Anal.* Calcd for $C_{17}H_{18}BrNO_3$: C, 56.06; H, 4.98; N, 3.85. Found: C, 56.06; H, 4.93; N, 3.83.

6′-Bromo-1′,2′-dihydro-6-methyl-2′-oxospiro[4-cyclohexene-1,3′-[3*H*]-indole]-2-carboxylic Acid (4) A solution of the ethyl ester (**3**) (1 g, 2.75 mmol) in dioxane (10 ml) was treated with 8 ml of 10% aqueous KOH and the mixture was heated at 100 °C for 1 h, then cooled at 0 °C in an ice bath and neutralized with 1 N HCl. The solvent was removed under reduced pressure to give crystalline precipitates, which were collected by filtration, washed with water and air dried. Recrystallization of the crude product from AcOEt gave the pure carboxylic acid (**4**) (870 mg, 94%), mp 270—271 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.57 (3H, d, J = 7.4 Hz, $-CHC\underline{H}_3$), 2.50—2.87 (3H, m, $=CHC\underline{H}_2-$ and $-C\underline{H}CH_3$), 3.29 (1H, m, $-OCOC\underline{H}-$), 5.54 (1H, dd, J = 2.0, 10.1 Hz, $=C\underline{H}-$), 5.89 (1H, m, $=C\underline{H}-$), 6.99 (1H, d, J = 8.0 Hz, arom.-H), 7.04 (1H, d, J = 2.0 Hz, arom.-H), 7.08 (1H, dd, J = 2.0, 8.0 Hz, arom.-H), 9.45 (1H, br s, –NH–). *Anal.* Calcd for $C_{15}H_{14}BrNO_3$: C, 53.59; H, 4.20; N, 4.17. Found: C, 53.50; H, 4.18; N, 4.20.

2-(Methylthio)ethyl 6′-Bromo-1′,2′-dihydro-6-methyl-2′-oxospiro[4-cyclohexene-1,3′-[3*H*]indole]-2-carboxylate (5) Picryl chloride (957 mg, 3.87 mmol) was added in small portions to a stirred solution of the carboxylic acid (**4**) (1 g, 2.98 mmol) in dry pyridine (12 ml), and then 2-(methylthio) ethanol (285 μl, 3.22 mmol) was added dropwise, under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h, then concentrated under reduced pressure. The dried residue was dissolved in CH_2Cl_2 and the solution was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, and then dried. The organic solvent was

removed under reduced pressure and the residue was crystallized from a mixture of hexane–AcOEt (2 : 1 v/v). Recrystallization of the crude product from MeOH gave a pure methylthioethyl ester (MTE ester) derivative (**5**) (1.12 g, 92%), mp 146—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.60 (3H, d, J=7.4 Hz, –CHC$\underline{H}_3$), 2.05 (3H, s, –SC$\underline{H}_3$), 2.54 (2H, t, J=7.0 Hz, –SC$\underline{H}_2$–), 2.59—2.70 (2H, m, =CHC$\underline{H}_2$–), 2.71 (1H, m, –C$\underline{H}$CH$_3$), 3.37 (1H, dd, J=6.5, 11.4 Hz, –OCOC$\underline{H}$–), 4.07 (2H, t, J=7.0 Hz, –COOC$\underline{H}_2$–), 5.56 (1H, dd, J=2.0, 10.1 Hz, =C$\underline{H}$–), 5.78 (1H, m, =C$\underline{H}$–), 7.00 (1H, d, J=7.7 Hz, arom.-H), 7.08 (1H, d, J=1.7 Hz, arom.-H). 7.09 (1H, dd, J=1.7, 7.7 Hz, arom.-H), 8.41 (1H, br s, –NH–). *Anal.* Calcd for $C_{18}H_{20}BrNO_3S$: C, 52.69; H, 4.91; N, 3.41. Found: C, 52.66; H, 4.85; N, 3.45.

2-(Methylsulfonyl)ethyl 6′-Bromo-1′,2′-dihydro-6-methyl-2′-oxospiro[4-cyclohexene-1,3′-[3*H*]indole]-2-carboxylate (6) *m*-Chloroperbenzoic acid (80%, 1.2 g, 5.57 mmol) was added to a stirred solution of the MTE ester (**5**) (1 g, 2.44 mmol) in CH_2CH_2 (25 ml), and the solution was stirred for 30 min at room temperature. After being diluted with CH_2Cl_2 (100 ml), the mixture was washed with 10% aqueous $Na_2S_2O_3$, water, saturated aqueous $NaHCO_3$, and brine, and then dried. The organic solvent was removed under reduced pressure to give a solid mixture, which was recrystallized from MeOH to provide the pure methylsulfonylethyl ester (MSE ester) (**6**) (1.0 g, 93%) as colorless crystals, mp 170—171 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.61 (3H, d, J=7.4 Hz, –CHC$\underline{H}_3$), 2.64 (2H, m, =CHC$\underline{H}_2$–), 2.91 (1H, m, –C$\underline{H}$CH$_3$), 2.97 (3H, s, –SO$_2$C$\underline{H}_3$), 3.20 (2H, t, J=5.7 Hz, –SO$_2$C$\underline{H}_2$–), 3.35 (1H, dd, J=7.4, 10.4 Hz, –OCOC$\underline{H}$–), 4.36 (2H, m, –COOC$\underline{H}_2$–), 5.58 (1H, dd, J=2.0, 10.1 Hz, =C$\underline{H}$–), 5.88 (1H, m, =C$\underline{H}$–), 6.99 (1H, d, J=7.7 Hz, arom.-H), 7.08—7.14 (2H, m, arom.-H), 8.24 (1H, br s, –NH–). *Anal.* Calcd for $C_{18}H_{20}BrNO_5S$: C, 48.89; H, 4.56; N, 3.17. Found: C, 48.75; H, 4.57; N, 3.21.

2-(Methylsulfonyl)ethyl 6′-Bromo-3-formyl-1′,2′-dihydro-5-methyl-2′-oxospiro[3-cyclopentene-1,3′-[3*H*]indole]-2-carboxylate (7) A stirred solution of the MSE ester (**6**) (500 mg, 1.13 mmol) in a mixture of CH_2Cl_2 (6 ml) and MeOH (60 ml) at −60 °C was bubbled with O_3/O_2 until a blue color persisted (about 5 min). The reaction mixture was purged with N_2 gas and quenched with triethyl phosphite (0.5 ml). The solution was stirred at −20 °C for 30 min, then concentrated under reduced pressure and dried completely under a high vacuum. The residue was dissolved in a mixture of dry THF (7 ml) and benzene (60 ml) containing a small amount of AcOH (0.4 ml) and piperidine (0.04 ml), and then the mixture was heated at 52 °C. The reaction mixture was stirred for 3 h, then diluted with AcOEt (100 ml) and the resulting organic solution was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine, and then dried. Evaporation of the solvent gave an oil, which was purified on a silica gel column (CH_2Cl_2 : MeOH = 100 : 7 v/v) to give the aldehyde (**7**) (320 mg, 62%), mp 182—183 °C (from MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J=7.5 Hz, –CHC$\underline{H}_3$), 2.76—3.16 (2H, m, –SO$_2$C$\underline{H}_2$–), 2.91 (3H, s, –SO$_2$C$\underline{H}_3$), 3.54 (1H, m, =CHC$\underline{H}$CH$_3$), 3.94 (1H, ddd, J=4.7, 7.7, 12.3 Hz, –COOC$\underline{H}_2$–), 4.25 (1H, ddd, J=4.7, 6.4, 12.3 Hz, –COOC$\underline{H}_2$–), 4.35 (1H, br s, –OCOC$\underline{H}$–), 6.93—6.97 (2H, m, =C$\underline{H}$– and arom.-H), 7.09—7.13 (2H, m, arom.-H), 9.81 (1H, s, –C$\underline{H}$=O). *Anal.* Calcd for $C_{18}H_{18}BrNO_6S$: C, 47.38; H, 3.98; N, 3.07. Found: C, 47.24; H, 4.03; N, 2.92.

2-(Methylsulfonyl)ethyl 6′-Bromo-1′,2′-dihydro-3-hydroxymethyl-5-methyl-2′-oxospiro[3-cyclopentene-1,3′-[3*H*]indole]-2-carboxylate (8) A solution of the aldehyde (**7**) (930 mg, 2.04 mmol) in a mixture of CH_2Cl_2 (5 ml) and MeOH (95 ml) was treated with $NaBH_4$ (40 mg, 1.06 mmol) at room temperature. The mixture was stirred for 30 min, then the reaction was quenched by addition of AcOH (about 5 ml) at 0 °C and the whole was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 ml) and the whole was washed with water, saturated aqueous $NaHCO_3$, and brine, and then dried. Evaporation of the solvent gave an amorphous solid, which was purified by crystallization from ether and further recrystallization from MeOH, giving the pure alcohol (**8**) (820 mg, 88%), mp 213—214 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, J=7.4 Hz, –CHC$\underline{H}_3$), 2.78—2.86 (1H, m, –SO$_2$C$\underline{H}_2$–), 2.92 (3H, s, –SO$_2$C$\underline{H}_3$), 2.93—3.02 (1H, m, –SO$_2$C$\underline{H}_2$–), 3.32—3.40 (1H, m, =CHC$\underline{H}$CH$_3$), 3.90 (1H, ddd, J=5.0, 6.4, 12.1 Hz, –COOC$\underline{H}_2$–), 4.19—4.26 (1H, m, –COOC$\underline{H}_2$–), 4.29 (1H, br s, –OCOC$\underline{H}$–), 4.33 (1H, br d, J=14.8 Hz, –C$\underline{H}_2$OH), 4.45 (1H, br d, J=14.8 Hz, –C$\underline{H}_2$OH), 5.78 (1H, br s, =C$\underline{H}$–), 7.05—7.11 (3H, m, arom.-H), 7.43 (1H, br s, –OH). *Anal.* Calcd for $C_{18}H_{20}BrNO_6S$: C, 47.17; H, 4.40; N, 3.06. Found: C, 46.98; H, 4.48; N, 3.06.

2-(Methylsulfonyl)ethyl 6′-Bromo-1′,2′-dihydro-5-methyl-3-[[(methylsufonyl)oxy]methyl]-2′-oxospiro[3-cyclopentene-1,3′-[3*H*]indole]-2-carboxylate (9) Triethylamine (216 μl, 1.55 mmol) and subsequently MsCl (110 μl, 1.42 mmol) were added to a solution of the alcohol (**8**) (285 mg, 0.62 mmol) in dry THF (40 ml). The mixture was stirred for 1 h at room temperature, the reaction was quenched by a dropwise addition of MeOH (100 μl), and the whole was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 ml) and the solution was washed with water, saturated aqueous $NaHCO_3$, and brine, and then dried. Evaporation of the solvent gave an oil, which was chromatographed on a silica gel column (CH_2Cl_2 : MeOH = 100 : 7 v/v), giving the mesylate (**9**) (314 mg, 94.6%), mp 59—60 °C (amorphous). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=7.4 Hz, –CHC$\underline{H}_3$), 2.77—2.89 (1H, m, –SO$_2$C$\underline{H}_2$–), 2.91 (3H, s, –SO$_2$C$\underline{H}_3$), 2.97—3.03 (1H, m, –SO$_2$C$\underline{H}_2$–), 3.06 (3H, s, –OSO$_2$C$\underline{H}_3$), 3.42 (1H, m, =CHC$\underline{H}$CH$_3$), 3.92 (1H, ddd, J=4.9, 5.4, 12.0 Hz, –COOC$\underline{H}_2$–), 4.27 (1H, ddd, J=4.9, 6.0, 12.0 Hz, –COOC$\underline{H}_2$–), 4.39 (1H, br s, –OCOC$\underline{H}$–), 5.08 (1H, br d, J=14.8 Hz, –SO$_2$OC$\underline{H}_2$–), 5.12 (1H, br d, J=14.8 Hz, –SO$_2$OC$\underline{H}_2$–), 6.01 (1H, br s, =C$\underline{H}$–), 6.99 (1H, d, J=8.0 Hz, arom.-H), 7.10 (1H, dd, J=1.7, 8.0 Hz, arom.-H), 7.13 (1H, d, J=1.7 Hz, arom.-H), 8.69 (1H, br s, –NH–). *Anal.* Calcd for $C_{19}H_{22}BrNO_8S_2$: C, 42.54; H, 4.14; N, 2.61. Found: C, 42.45; H, 4.43; N, 2.38.

2-(Methylsulfonyl)ethyl 3-(Azidomethyl)-6′-bromo-1′,2′-dihydro-5-methyl-2′-oxospiro[3-cyclopentene-1,3′-[3*H*]indole]-2-carboxylate (10) Sodium azide (61 mg, 0.94 mmol) was added to a stirred solution of the mesylate (**9**) (250 mg, 0.466 mmol) in dry DMF (10 ml) at 5 °C under an N_2 atmosphere. The reaction mixture was stirred for 1 h in an ice water bath, then diluted with AcOEt (150 ml) and the solution was washed with five 20 ml portions of water and then brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was chromatographed on a silica gel column (AcOEt : CH_2Cl_2 = 1 : 2 v/v) to give the azide (**10**) (205 mg, 91%), mp 132—133 °C (from MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, J=7.4 Hz, –CHC$\underline{H}_3$), 2.76 (1H, ddd, J=5.2, 7.4, 12.8 Hz, –SO$_2$C$\underline{H}_2$–), 2.92 (3H, s, –SO$_2$C$\underline{H}_3$), 2.94 (1H, m, –SO$_2$C$\underline{H}_2$–), 3.38 (1H, m, =CHC$\underline{H}$CH$_3$), 3.87 (1H, ddd, J=5.9, 7.4, 12.1 Hz, –COOC$\underline{H}_2$–), 4.13 (1H, br d, J=15.0 Hz, –C$\underline{H}_2$N$_3$), 4.22 (1H, ddd, J=5.2, 7.4, 12.1 Hz, –COOC$\underline{H}_2$–), 4.30 (1H, br d, J=15.0 Hz, –C$\underline{H}_2$N$_3$), 4.28 (1H, br s, –OCOC$\underline{H}$–), 5.84 (1H, br s, =C$\underline{H}$–), 6.99 (1H, d, J=8.4 Hz, arom.-H), 7.08 (1H, dd, J=1.6, 8.4 Hz, arom.-H), 7.11 (1H, d, J=1.6 Hz, arom.-H). *Anal.* Calcd for $C_{18}H_{19}BrN_4O_5S$: C, 44.73; H, 3.96; N, 11.59. Found: C, 44.81; H, 3.88; N, 11.35.

2-(Methylsulfonyl)ethyl 6′-Bromo-1′-2′-dihydro-5-methyl-3-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2′-oxospiro[3-cyclopentene-1,3′-[3*H*]indole]-2-carboxylate (13) Zinc powder (2 g) was added in portions to a stirred solution of the azide (**10**) (500 mg, 1.04 mmol) in CH_2Cl_2 (10 ml) containing 1 ml of AcOH at 5 °C. After 10 min of vigorous stirring at 5 °C, the reaction mixture was filtered through Hyflo Super-Cel, which was washed with CH_2Cl_2. The combined organic solution was washed with saturated aqueous $NaHCO_3$, and brine, and then dried. Evaporation of the solvent gave a viscous oil, which was further dried under a high vacuum. The resulting residue (crude amine **11**) was dissolved in dry dioxane (30 ml). To this solution, powdered $NaHCO_3$ (100 mg) and 4-(ethylsulfonyl)-5-nitro-2,6-bis(phenylmethoxy)pyrimidine[8] (**12**, 600 mg, 1.40 mmol) were added and the mixture was stirred at room temperature overnight. After evaporation of the solvent, the residual mixture was dissolved in CH_2Cl_2 (100 ml). The CH_2Cl_2 solution was washed with saturated aqueous $NaHCO_3$, and brine, and dried. Evaporation of the solvent gave a mixture, which was separated on a silica gel column (AcOEt : CH_2Cl_2 = 2 : 1 v/v) to give **13** (418 mg, 51% from **10**), mp 127—128 °C (from MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, d, J=7.4 Hz, –CHC$\underline{H}_3$), 2.70 (1H, ddd, J=5.2, 7.4, 14.0 Hz, –SO$_2$C$\underline{H}_2$–), 2.88 (3H, s, –SO$_2$C$\underline{H}_3$), 2.91 (1H, ddd, J=5.2, 7.4, 14.0 Hz, –SO$_2$C$\underline{H}_2$–), 3.40 (1H, m, =CHC$\underline{H}$CH$_3$), 3.88 (1H, ddd, J=5.2, 7.4, 12.1 Hz, –COOC$\underline{H}_2$–), 4.22 (1H, ddd, J=5.2, 7.4, 12.1 Hz, –COOC$\underline{H}_2$–), 4.27 (1H, s, –OCOC$\underline{H}$–), 4.47 (1H, br d, J=17.0 Hz, –C$\underline{H}_2$NH–), 4.63 (1H, br d, J=17.0 Hz, –C$\underline{H}_2$NH–), 5.44 (2H, s, –C$\underline{H}_2$NH–), 5.56 (2H, s, –C$\underline{H}_2$Ph) 5.66 (1H, br s, =C$\underline{H}$–), 6.98—7.07 (3H, m, arom.-H), 7.29—7.51 (10H, m, Ph-H), 9.12 (1H, br s, –NH–). *Anal.* Calcd for $C_{36}H_{34}BrN_5O_9S$: C, 54.55; H, 4.32; N, 8.84. Found: C, 54.29; H, 4.25; N, 8.65.

2-(Methylsulfonyl)ethyl 6′-Bromo-1′,2′-dihydro-3,4-dihydroxy-5-methyl-3-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2′-oxospiro[cyclopentane-1,3′-[3*H*]indole]-2-carboxylate (14) Osmium tetroxide (250 mg, 0.98 mmol) was added to a solution of **13** (530 mg, 0.669 mmol) in pyridine (8 ml), and the mixture was stirred at room temperature for 3 h in the dark. After being diluted with pyridine (60 ml), the reaction mixture was treated with 10% aqueous sodium bisulfite (10 ml) and the whole was left to stand at room temperature overnight and then concentrated. The residual oil was diluted with CH_2Cl_2 (200 ml) and water (20 ml) and the phases were separated. The organic layer was

washed with 1 N HCl (twice), water, saturated aqueous $NaHCO_3$, and brine, and then dried. Evaporation of the solvent produced an oil, which was purified on a silica gel column (AcOEt : benzene = 2 : 1, v/v) to give a mixture of the stereoisomeric diols (**14**) (430 mg, 78%). A portion of this material was separated by silica gel TLC for analysis. The major isomer was crystallized from MeOH, mp 122—123 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.69 (3H, d, J=6.7 Hz, $-CHC\underline{H}_3$), 2.52 (1H, m, $-C\underline{H}CH_3$), 2.74 (1H, m, $-SO_2C\underline{H}_2-$), 2.85 (3H, s, $-SO_2C\underline{H}_3$), 2.97 (1H, m, $-SO_2C\underline{H}_2-$), 3.23 (1H, d, J=8.8 Hz, –OH), 3.82 (1H, dd, J=8.8, 11.4 Hz, $-C\underline{H}OH$), 3.91 (1H, m, $-COOC\underline{H}_2-$), 4.15 (1H, dd, J=6.1, 14.8 Hz, $-C\underline{H}_2NH-$), 4.19 (1H, dd, J=6.1, 14.8 Hz, $-C\underline{H}_2NH-$), 4.23 (1H, m, $-COOC\underline{H}_2-$), 4.74 (1H, s, $-OCOC\underline{H}-$), 5.42 (2H, s, $-C\underline{H}_2Ph$), 5.57 (2H, s, $-C\underline{H}_2Ph$), 6.83 (1H, d, J=8.7 Hz, arom.-H), 7.10 (1H, dd, J=1.7, 8.7 Hz, arom.-H), 7.11 (1H, d, J=1.7 Hz, arom.-H), 7.32—7.49 (10H, m, Ph-H), 8.21 (1H, s, –NH–), 9.18 (1H, t, J=6.1 Hz, $-CH_2N\underline{H}-$). *Anal.* Calcd for $C_{36}H_{36}BrN_5O_{11}S\cdot H_2O$: C, 52.31; H, 4.39; N, 8.47. Found: C, 52.24; H, 4.37; N, 8.11.

2-(Methylsulfonyl)ethyl 6′-Bromo-4-[(chloroacetyl)oxy]-1′,2′-dihydro-3-hydroxy-5-methyl-3-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]-amino]methyl]-2′-oxospiro-[cyclopentane-1,3′-[3*H*]indole]-2-carboxylate (15) Monochloroacetic anhydride (150 mg, 0.88 mmol) was added in portions to a solution of the diol (**14**) (207 mg, 0.251 mmol) in dry pyridine (4 ml) with stirring at 0 °C. After 1 h, the reaction mixture was diluted with a large volume of CH_2Cl_2 (100 ml) and the solution was washed with 1 N HCl (twice), saturated aqueous $NaHCO_3$, and brine, and then dried. Evaporation of the solvent gave an oil, which was purified on a silica gel column (AcOEt : CH_2Cl_2 = 2 : 1 v/v) to give the monochloroacetate (**15**) (207 mg, 91%), mp 161—162 °C (from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.66 (3H, d, J=6.7 Hz, $-CHC\underline{H}_3$), 2.82 (3H, s, $-SO_2C\underline{H}_3$), 2.76—3.05 (3H, m, $-SO_2C\underline{H}_2-$ and $-C\underline{H}CH_3$), 3.67 (1H, s, $-OCOC\underline{H}-$), 3.96 (1H, m, $-COOC\underline{H}_2-$), 4.07 (1H, d, J=14.8 Hz, $-OCOC\underline{H}_2Cl$), 4.14 (1H, d, J=14.8 Hz, $-OCOC\underline{H}_2Cl$), 4.19 (2H, d, J=6.1 Hz, $-C\underline{H}_2NH-$), 4.23 (1H, m, $-COOC\underline{H}_2-$), 5.37 (1H, d, J=9.4 Hz, $-C\underline{H}OCO-$), 5.39 (2H, s, $-C\underline{H}_2Ph$), 5.55 (2H, s, $-C\underline{H}_2Ph$), 7.12 (1H, d, J=9.1 Hz, arom.-H), 7.15 (1H, d, J=9.1 Hz, arom.-H), 7.32—7.47 (11H, m, arom.-H and Ph-H), 8.59 (1H, br s, –NH–), 9.06 (1H, t, J=6.1 Hz, $-CH_2N\underline{H}-$). *Anal.* Calcd for $C_{38}H_{37}BrClN_5O_{12}S$: C, 50.54; H, 4.13; N, 7.75. Found: C, 50.57; H, 4.10; N, 7.71.

2-(Methylsulfonyl)ethyl 6′-Bromo-4-[(chloroacetyl)oxy]-1′,2′-dihydro-5-methyl-3-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2′-oxospiro[2-cyclopentene-1,3′-[3*H*]indole]-2-carboxylate (16) Thionyl chloride (81 μl, 1.11 mmol) was added dropwise to a stirred solution of the monochloroacetate (**15**) (200 mg, 0.222 mmol) in dry pyridine (4 ml) at 0 °C under an N_2 atmosphere. After 30 min, the reaction mixture was diluted with CH_2Cl_2 (60 ml) and the resulting solution was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on a silica gel column (AcOEt : CH_2Cl_2 = 2 : 1 v/v) to give **16** (177 mg, 90% yield), mp 118—119 °C (from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, J=7.0 Hz, $-CHC\underline{H}_3$), 2.69 (3H, s, $-SO_2C\underline{H}_3$), 2.81 (1H, m, $-C\underline{H}CH_3$), 3.19 (2H, m, $-SO_2C\underline{H}_2-$), 4.09 (1H, d, J=14.8 Hz, $-COC\underline{H}_2Cl$), 4.16 (1H, d, J=14.8 Hz, $-COC\underline{H}_2Cl$), 4.44 (2H, m, $-COOC\underline{H}_2-$), 4.50 (1H, dd, J=5.4, 16.5 Hz, $-C\underline{H}_2NH-$), 5.09 (1H, dd, J=5.4, 16.5 Hz, $-C\underline{H}_2NH-$), 5.29 (1H, d, J=12.1 Hz, $-C\underline{H}_2Ph$), 5.41 (1H, d, J=12.1 Hz, $-C\underline{H}_2Ph$), 5.55 (1H, d, J=13.5 Hz, $-C\underline{H}_2Ph$), 5.60 (1H, d, J=13.5 Hz, $-C\underline{H}_2Ph$), 6.01 (1H, d, J=8.4 Hz, $-C\underline{H}OCO-$), 6.70 (1H, d, J=8.1 Hz, arom.-H), 6.80 (1H, dd, J=1.7, 8.1 Hz, arom.-H), 7.09 (1H, d, J=1.7 Hz, arom.-H), 7.34—7.50 (10H, m, Ph-H), 8.61 (1H, br s, –NH–), 9.07 (1H, t, J=5.4 Hz, $-CH_2N\underline{H}-$). *Anal.* Calcd for $C_{38}H_{35}BrClN_5O_{11}S$: C, 51.57; H, 3.99; N, 7.91. Found: C, 51.47; H, 3.94; N, 7.90.

2-(Methylsulfonyl)ethyl 6′-Bromo-1′,2′,-dihydro-4-hydroxy-5-methyl-3-[[[5-nitro-2,6-bis(phenylmethoxy)-4-pyrimidinyl]amino]methyl]-2′-oxospiro[2-cyclopentene-1,3′-[3*H*]indole]-2-carboxylate (17) Thiourea (25 mg, 0.328 mmol) was added to a stirred solution of **16** (260 mg, 0.294 mmol) in a mixture of CH_2Cl_2–MeOH (1 : 10 v/v, 11 ml), and the mixture was heated at 80 °C for 3 h. After cooling, the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (50 ml). The solution was washed with saturated aqueous $NaHCO_3$, and brine, and then dried. Evaporation of the solvent gave a solid, which was purified on a silica gel column (CH_2Cl_2 : MeOH = 100 : 5 v/v) to give the alcohol (**17**) (224 mg, 94.3%), mp 157—158 °C (from Et_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, J=7.1 Hz, $-CHC\underline{H}_3$), 2.61 (1H, m, $-C\underline{H}CH_3$), 2.82 (3H, s, $-SO_2C\underline{H}_3$), 3.24 (2H, m, $-SO_2C\underline{H}_2-$), 4.45 (2H, m, $-COOC\underline{H}_2-$), 4.58—4.66 (2H, m, $-C\underline{H}OH$ and $-C\underline{H}_2NH-$), 4.88 (1H, dd, J=5.7, 11.4 Hz, $-C\underline{H}_2NH-$), 5.07 (1H, br d, J=7.1 Hz, –OH), 5.37 (1H, d, J=12.1 Hz, $-C\underline{H}_2Ph$), 5.44 (1H, d, J=12.1 Hz, $-C\underline{H}_2Ph$), 5.55 (2H, s, $-C\underline{H}_2Ph$), 6.63 (1H, d, J=7.7 Hz, arom.-H), 7.04 (1H, dd, J=1.7, 7.7 Hz, arom.-H), 7.08 (1H, d, J=1.7 Hz, arom.-H), 7.33—7.48 (10H, m, Ph-H), 8.50 (1H, br s, –NH–), 9.35 (1H, t, J=5.7 Hz, $-CH_2N\underline{H}-$). *Anal.* Calcd for $C_{36}H_{34}BrN_5O_{10}S$: C, 53.46; H, 4.24; N, 8.66. Found: C, 53.21; H, 4.29; N, 8.71.

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′-[3*H*]indole]-2-carboxylate (19) Benzeneseleninic anhydride (1 g, 2.78 mmol) was added to a stirred solution of **17** (332 mg, 0.410 mmol) in dioxane (60 ml) and the mixture was heated at 80 °C for 2 h. After cooling, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (80 ml) and the solution was washed with saturated aqueous $NaHCO_3$ and brine, and then dried. Evaporation of the solvent left a residual oil, which was separated by chromatography on a silica gel column (CH_2Cl_2 : MeOH = 100 : 5 v/v), affording an inseparable stereoisomeric mixture (1 : 1) of **19** (307 mg, 91%) as an amorphous solid, mp 164—166 °C (from CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ: 1.26 and 1.32 (each 1.5H, s, $-C(OH)C\underline{H}_3$), 2.89 and 2.90 (each 1.5H, s, $-SO_2C\underline{H}_3$), 3.12—3.27 (2H, m, $-SO_2C\underline{H}_2-$), 4.45 and 4.51 (each 1H, t, J=5.7 Hz, $-COOC\underline{H}_2-$), 4.66 and 4.80 (each 0.5H, dd, J=5.4, 15.5 Hz, $-C\underline{H}_2NH-$), 4.80 and 4.91 (each 0.5 H, dd, J=5.4, 15.5 Hz, $-C\underline{H}_2NH-$), 5.38 (1H, d, J=12.4 Hz, $-C\underline{H}_2Ph$), 5.45 (1H, d, J=12.4 Hz, $-C\underline{H}_2Ph$), 5.52 (2H, s, $-C\underline{H}_2Ph$), 6.83 and 6.86 (each 0.5H, d, J=8.1 Hz, arom.-H), 7.09 and 7.12 (each 0.5H, dd, J=1.7, 8.1 Hz, arom.-H), 7.15 and 7.16 (each 0.5H, d, J=1.7 Hz, arom.-H), 7.29—7.52 (10H, m, Ph-H), 8.13 and 8.43 (each 0.5H, br s, –NH–), 9.34 and 9.40 (each 0.5H, t, J=5.4 Hz, $-CH_2N\underline{H}-$). *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(6*H*),3′-[3*H*]indole]-8-carboxylate (20) Zinc powder (1 g) was added in portions to a stirred solution of the stereoisomeric mixture of **19** (100 mg, 0.122 mmol) in a mixture of CH_2Cl_2–MeOH (10 : 1 v/v, 10 ml) containing a small amount of AcOH (0.35 ml). After vigorous stirring at room temperature for 10 min, the reaction mixture was filtered through Hyflo Super-Cel, which was washed with CH_2Cl_2 (20 ml). The combined solution was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 ml) containing 100 mg of CSA. The mixture was stirred for 10 min, then diluted with CH_2Cl_2 (50 ml), and the solution was washed with water, saturated aqueous $NaHCO_3$, and brine, and then dried. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (AcOEt : benzene = 2 : 1 v/v), yielding a mixture of four stereoisomers of **20** (83 mg, 88%). A portion of the mixture was separated by repeated silica gel TLC (AcOEt : benzene = 2 : 1 v/v, CH_2Cl_2 : MeOH = 100 : 3 v/v) to give the following four isomers.

Isomer 1 (43%): mp 207—208 °C (from MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.02 (3H, s, $-C(OH)C\underline{H}_3$), 2.87 (3H, s, $-SO_2C\underline{H}_3$), 3.27 (3H, m, $-SO_2C\underline{H}_2-$, $-C\underline{H}=N-$ and $-C\underline{H}_2NH-$), 3.38 (1H, m, $-SO_2C\underline{H}_2-$), 3.71 (1H, d, J=9.2 Hz, $-OCOC\underline{H}-$), 3.90 (1H, dd, J=7.1, 9.2 Hz, $-C\underline{H}_2NH-$), 4.21 (1H, ddd, J=4.8, 7.0, 11.7 Hz, $-COOC\underline{H}_2-$), 4.33 (1H, ddd, J=4.8, 7.0, 11.7 Hz, $-COOC\underline{H}_2-$), 5.30 (2H, s, $-C\underline{H}_2Ph$), 5.34 (1H, d, J=13.6 Hz, $-C\underline{H}_2Ph$), 5.39 (1H, d, J=13.6 Hz, $-C\underline{H}_2Ph$), 5.74 (1H, s, –OH), 6.98 (1H, d, J=1.8 Hz, arom.-H), 7.13 (1H, dd, J=1.8, 8.1 Hz, arom.-H), 7.25—7.50 (11H, m, arom.-H and Ph-H), 7.70 (1H, d, J=7.1 Hz, $-CH_2N\underline{H}-$), 10.58 (1H, s, –NH–). *Anal.* Calcd for $C_{36}H_{34}BrN_5O_8S\cdot 1/2H_2O$: C, 55.04; H, 4.49; N, 8.91. Found: C, 55.25; H, 4.27; N, 8.96.

Isomer 2 (6%): mp 214—215 °C (from MeOH, dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, s, $-C(OH)C\underline{H}_3$), 2.89 (3H, s, $-SO_2C\underline{H}_3$), 3.17 (1H, ddd, J=1.5, 8.8, 12.5 Hz, $-C\underline{H}_2NH-$), 3.28 (1H, m, $-SO_2C\underline{H}_2-$), 3.39 (2H, m, $-SO_2C\underline{H}_2-$ and $-C\underline{H}C=N-$), 3.61 (1H, d, J=9.9 Hz, $-OCOC\underline{H}-$), 3.81 (1H, ddd, J=2.6, 6.6, 12.5 Hz, $-C\underline{H}_2NH-$), 4.21 (1H, ddd, J=4.8, 7.0, 12.1 Hz, $-COOC\underline{H}_2-$), 4.32 (1H, ddd, J=4.8, 7.0, 12.1 Hz, $-COOC\underline{H}_2-$), 5.03 (1H, s, –OH), 5.28 (2H, s, $-C\underline{H}_2Ph$), 5.38 (1H, d, J=13.2 Hz, $-C\underline{H}_2Ph$), 5.45 (1H, d, J=13.2 Hz, $-C\underline{H}_2Ph$), 6.94 (1H, d, J=1.8 Hz, arom.-H), 7.15 (1H, dd, J=1.8, 8.1 Hz, arom.-H), 7.25 (1H, d, J=8.1 Hz, arom.-H), 7.25 (1H, d, J=8.1 Hz, arom.-H), 7.26—7.50 (10H, m, Ph-H), 7.61 (1H, dd, J=1.5, 6.6 Hz, $-CH_2N\underline{H}-$), 10.33 (1H, s, –NH–).

Isomer 3 (36%): mp 200—201 °C (from MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, s, $-C(OH)C\underline{H}_3$), 2.89 (1H, m, $-SO_2C\underline{H}_2-$), 2.92 (3H, s, $-SO_2C\underline{H}_3$), 3.11 (1H, ddd, J=4.4, 7.7, 14.7 Hz, $-SO_2C\underline{H}_2-$), 3.54 (2H, m, $-C\underline{H}C=N-$ and $-C\underline{H}_2NH-$), 3.77 (1H, d, J=9.2 Hz, $-OCOC\underline{H}-$), 3.81 (1H, m, $-C\underline{H}_2NH-$), 4.10 (1H, m, $-COOC\underline{H}_2-$), 4.43 (1H, m, $-COOC\underline{H}_2-$), 4.41 (1H, s, –OH), 5.37 (2H, s, $-C\underline{H}_2Ph$), 5.42 (1H, d, J=13.5 Hz, $-C\underline{H}_2Ph$),

5.51 (1H, d, J=13.5 Hz, –C$\underline{H}_2$Ph), 5.84 (1H, br s, –CH$_2$N$\underline{H}$–), 6.69 (1H, d, J=8.1 Hz, arom.-H), 7.11 (1H, dd, J=1.8, 8.1 Hz, arom.-H), 7.15 (1H, d, J=1.8 Hz, arom.-H), 7.22—7.50 (10H, m, Ph-H), 8.16 (1H, s, –NH–). *Anal.* Calcd for $C_{36}H_{34}BrN_5O_8S \cdot H_2O$: C, 54.41; H, 4.57; N, 8.81. Found: C, 54.57; H, 4.29; N, 8.82.

Isomer 4 (8%): mp 189—190 °C (from MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.53 (3H, s, –C(OH)C$\underline{H}_3$), 2.90 (1H, m, –SO$_2$C$\underline{H}_2$–), 3.06 (1H, ddd, J=4.4, 7.7, 14.3 Hz, –SO$_2$C$\underline{H}_2$–), 2.93 (3H, s, –SO$_2$C$\underline{H}_3$), 3.37 (1H, d, J=9.9 Hz, –OCOC$\underline{H}$–), 3.38 (1H, dd, J=8.4, 11.7 Hz, –C$\underline{H}_2$NH–), 3.59 (1H, ddd, J=2.9, 8.4, 9.9 Hz, –C$\underline{H}$C=N–), 3.86 (1H, ddd, J=2.9, 7.5, 11.7 Hz, –C$\underline{H}_2$NH–), 4.11 (1H, ddd, J=4.4. 7.7, 12.1 Hz, –COOC$\underline{H}_2$–), 4.42 (1H, ddd, J=4.4, 7.7, 12.1 Hz, –COOC$\underline{H}_2$–), 5.39 (2H, s, –C$\underline{H}_2$Ph), 5.44 (1H, d, J=12.8 Hz, –C$\underline{H}_2$Ph), 5.50 (1H, d, J=12.8 Hz, –C$\underline{H}_2$Ph), 6.57 (1H, br s, –CH$_2$N$\underline{H}$–), 6.64 (1H, d, J=8.1 Hz, arom.-H), 7.06 (1H, dd, J=1.8, 8.1 Hz, arom.-H), 7.08 (1H, d, J=1.8 Hz, arom.-H), 7.29—7.48 (10H, m, Ph-H), 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(6*H*),3′-[3*H*]indole]-8-carboxylate (21) A stirred solution of the stereoisomeric mixture of **20** (410 mg, 0.528 mmol) in dry THF (15 ml) was treated dropwise with DMAP (386.5 mg, 3.168 mmol) and Ac_2O (12 ml) at 5 °C. After 5 min, the mixture was allowed to warm to room temperature over a period of 1.5 h. The solvent was removed under reduced pressure and the residue was washed with water and then dried. The crude product was further purified by silica gel column chromatography (AcOEt : benzene = 3 : 1 v/v) to give the pure diacetate (**21**) (347 mg, 76%), mp 120 °C (from MeOH). IR (KBr): 3390, 1740, 1580, 1415, 1345, 1165 cm^{-1}. UV λ_{max}^{MeOH} (nm) (log ε): 239 (4.52), 263 (4.12), 281 (3.98), 324 (3.96). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s, –C(OAc)C$\underline{H}_3$), 2.01 (3H, s, –OCOC$\underline{H}_3$), 2.61 (3H, s, –SO$_2$C$\underline{H}_3$), 2.86 (3H, s, –NCOC$\underline{H}_3$), 3.19 (2H, m, –SO$_2$C$\underline{H}_2$–), 3.49 (1H, ddd, J=1.8, 8.1, 11.7 Hz, –C$\underline{H}_2$NH–), 3.56 (1H, ddd, J=2.6, 8.1, 10.3 Hz, –C$\underline{H}$C=N–), 3.86 (1H, d, J=10.3 Hz, –OCOC$\underline{H}$–), 4.20 (1H, ddd, J=2.6, 7.7, 11.7 Hz, –C$\underline{H}_2$NH–), 4.40 (1H, ddd, J=4.8, 7.0; 11.7 Hz, –COOC$\underline{H}_2$–), 4.56 (1H, ddd, J=4.8, 7.0, 11.7 Hz, –COOC$\underline{H}_2$–), 5.36 (2H, s, –C$\underline{H}_2$Ph), 5.41 (1H, d, J=13.2 Hz, –C$\underline{H}_2$Ph), 5.50 (1H, d, J=13.2 Hz, –C$\underline{H}_2$Ph), 6.20 (1H, br m, –NH–), 6.95 (1H, d, J=8.4 Hz, arom.-H), 7.24—7.50 (11H, m, arom.-H and Ph-H), 8.52 (1H, d, J=1.8 Hz, arom.-H). *Anal.* Calcd for $C_{40}H_{38}BrN_5O_{10}S$: C, 55.82; H, 4.45; N, 8.14. Found: C, 55.77; H, 4.29; N, 8.30.

Acknowledgments The authors are very grateful to Prof. T. Kosuge and Prof. K. Tsuji for generous gifts of natural neosurugatoxin and its spectral data. The authors also wish to express their gratitude to Miss T. Sakai for the elemental analyses and Mr. K. Masuda for the MS measurements.

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9) Synthesized from 6-bromoisatine and ethoxycarbonylmethylene triphenylphosphorane. Yellow needles, mp 226—227 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.0 Hz), 4.33 (2H, q, J=7.0 Hz), 6.90 (1H, s), 7.03 (1H, d, J=2.0 Hz), 7.16 (1H, dd, J=2.0, 8.4 Hz), 8.39 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.40; H, 3.23; N, 4.73.