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TOTAL SYNTHESIS OF (±)-SURUGATOXIN

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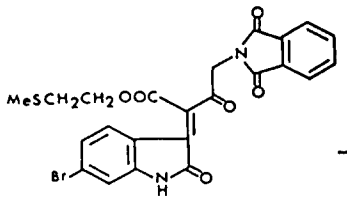
Summary: Total synthesis of surugatoxin 1, isolated from the toxic Japanese ivory shell (Babylonia japonica), was achieved from 6-bromoisatin by stepwise ring construction involving two key steps: the stereospecific cyclization (9 → 10) and hydration (17 → 1).

In the preceding paper,[1] we established an efficient method for the construction of the pentacyclic framework leading to the ethyl ester of the debromo-aglycone of surugatoxin. In this paper, the successful application of this method to the total synthesis of surugatoxin 1 was described.

According to the synthetic procedure developed by the model experiment as reported previously,[1] we prepared the methylthioethyl ester of the pentacyclic derivative 10 by the sequence;(1) condensation of 6-bromoisatin with 2'-methylthioethyl 4-phthalimidoacetoacetate[2] (AcOH-piperidine (4:1) in dry benzene, reflux, 5 h) to give 2 (81%, mp 228°C (decomp)); (2) reduction of the conjugated double bond in 2 (aqueous $Na_2S_2O_4$, EtOH, reflux, 10 min) to give 3 (92%, mp 200-201°C (decomp)); (3) removal of the phthalimido group in 3 ((i) 6.6 equiv of hydrazine hydrate, THF-MeOH (7:3), -15°C, 30 min, (ii) 17 equiv of c-HCl, -15 to 0°C, 2 h, (iii) filtration of the precipitates of hydrazine hydrochloride and phthalhydrazide) to give a solution of the amino-ketone hydrochloride 4; (4) coupling of 4 with 2,6-dibenzyloxy-4-ethylsulfonyl-5-nitropyrimidine ($NaHCO_3$ (large excess), THF-MeOH (7:3), room temperature, 2 h) to give 5 (36% yield from 3, mp 178-179°C (decomp)); (5) reductive cyclization of 5 (Zn powder, AcOH-THF (5:1), 0°C, 10 min) to give 6[3] (94%, mp 166-167°C, ^{1}H-NMR(DMSO-d_6): δ 4.27 (1H, s), 4.47 (2H, s); (6) oxidative acetyla-



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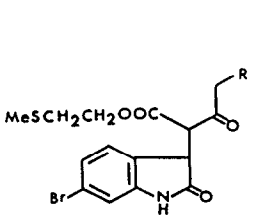
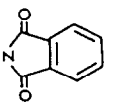


3 R = 

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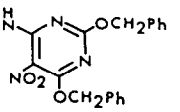
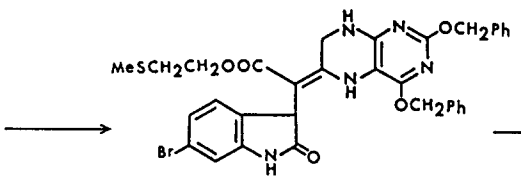
5 R = 



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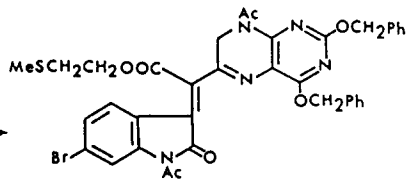

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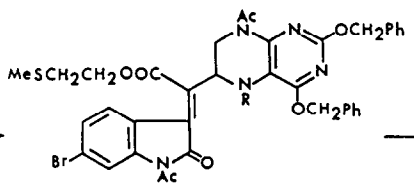
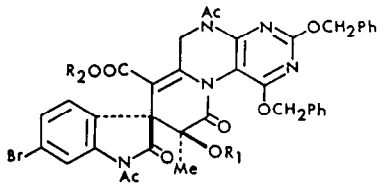


8 R = H

9 R = COCOMe

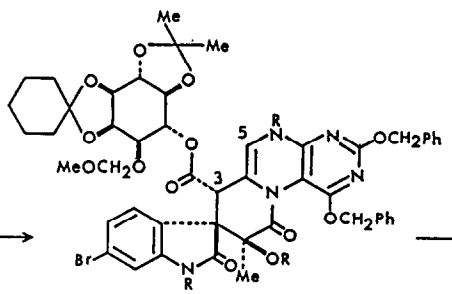


10 R_1 = H R_2 = CH_2CH_2SMe

11 R_1 = Ac R_2 = CH_2CH_2SMe

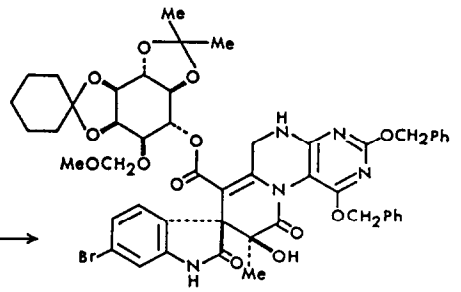
12 R_1 = Ac R_2 = $CH_2CH_2SO_2Me$

13 R_1 = Ac R_2 = H



14 R = Ac

15 R = H



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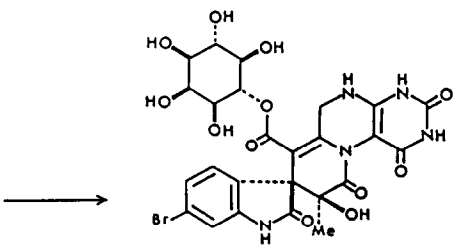

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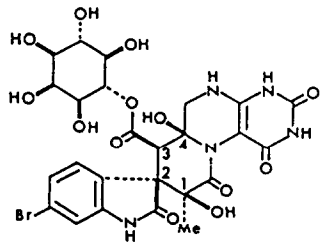

1 surugatoxin

tion of 6 to give a 5:1 inseparable stereoisomeric mixture of the dihydropteridine diacetates 7,[4] (50% combined yield, Ac_2O-pyridine (2:1), 70°C, 2 h); (7) selective reduction of 7 (6 equiv of $NaBH_3CN$, EtOAc-2N HCl, -10°C, 10 min) to give a mixture of the tetrahydropteridine derivatives 8 (82%, major: mp 175 °C, minor: mp 89-90°C); (8) acylation of 8 with pyruvoyl chloride in dry benzene at room temperature to give 9 (92%, major: mp 104-105°C, minor: mp 102-103°C); and (9) stereospecific cyclization of 9 in pyridine (room temperature, 10 h) to give the desired pentacyclic derivative 10 (85%, mp 123°C, ^{1}H-NMR (DMSO-d_6): δ 1.32 (3H, s), 3.45 (1H, br.d, J=16 Hz), 6.32 (1H, br.d, J=16 Hz) as a single product. Acetylation of the tert-hydroxy group of 10 with Ac_2O-NaOAc[5] (120°C, 1.5 h) gave 11 (78%, mp 173°C), which was then oxidized with mCPBA (2.2 equiv, CH_2Cl_2) to give 12 (97%, mp 171°C). Removal of the 2'-methylsulfonylethyl ester group in 12 (0.1M pH 10.2 $NaHCO_3$-Na_2CO_3 buffer in acetone (1:3), room temperature, 2 h) furnished the carboxylic acid 13 (61%, mp 158-159°C). Esterification of 13 with (±)-1,2-cyclohexylidene-5,6-isopropylidene-3-methoxymethyl myo-inositol[6] was effected via the agency of picryl chloride[7] in pyridine (room temperature, 1.5 h). Unexpected double bond isomerization occurred however during the esterification to give a 1:1 diastereomeric mixture of the dihydropteridine derivative 14,[8] each of which was easily separated by chromatography on silica gel (EtOAc-benzene=1:7, 55% combined yield, more polar isomer: mp 214-216°C; less polar isomer: mp 149-151 °C). The acetyl groups in 14 were removed by alkaline hydrolysis (0.1N KOH-MeOH, room temperature, 2 h) and the resulting enamine derivative 15[9] (72%, mp 188-189°C (decomp)) was converted to the desired isomer 16 (mp 214-216°C (decomp)) in 76% yield by treatment with $Pb(OAc)_4$ (1 equiv) in AcOH followed by $NaBH_3CN$ (3 equiv) in AcOH. Finally, exposure of 16 to 90% TFA (room temperature, 1 h) resulted in removal of the all protecting groups to give the dehydrated surugatoxin 17 (mp 245-250°C (decomp)). Subsequent stereospecific hydration (90% TFA, 60°C, over 7 h) afforded an equilibrium mixture of (±)-surugatoxin 1 (15%, mp > 300°C (decomp)) and 17 (71%). Although the equilibrium was unfavorable for our target compound 1, it was obtained in a reasonable yield (40%) by recycling the recovered 17. The chromatographical (TLC, HPLC) and spectral (^{1}H-NMR, ^{13}C-NMR, Mass, UV) properties of the

synthetic (±)-surugatoxin were found to be identical with those of natural surugatoxin.[10]

ACKNOWLEDGEMENT: We are indebted to Professor T. Kosuge at Shizuoka College of Pharmacy for the generous gift of natural surugatoxin.

REFERENCES AND NOTES

1) Tetrahedron Lett., preceding paper on this issue.

2) This material was prepared from ethyl 4-phthalimidoacetoacetate by trans-esterification with 2-methylthioethanol (160°C, 6 h, distillation of eluted EtOH under N_2 atmosphere).

3) Even 5 was a mixture of diastereoisomers, 6 was obtained as a sole product.

4) Assignment of E, Z stereochemistry of the double bond remains unknown.

5) A small amount of C_1-epimer of 11 was also obtained.

6) This material was prepared from the known (±)-1-O-benzoyl-2,3-cyclohexylidene-4,5-isopropylidene myo-inositol [S. Ogawa, S. Oki, H. Kunitomo, and T. Suami, Bull. Chem. Soc. Jpn., 50, 1867 (1977)] in four steps: (1) $PhCH_2Br$, NaH, DMF; (2) 2N KOH-MeOH; (3) $ClCH_2OMe$, NaH, DMF; (4) H_2, Pd-C, AcOH-dioxane.

7) S. Takimoto, J. Inanaga, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 54, 1470 (1981).

8) Since the more polar isomer of 14 afforded natural surugatoxin, further discussion described in this paper is concerned with this diastereomer (^{1}H-NMR($CDCl_3$): δ 4.56 (1H, s), 7.08 (1H, s)).

9) ^{1}H-NMR($CDCl_3$): δ 4.24 (1H, s), 5.88 (1H, d, J=6 Hz (d → s by addition of D_2O)).

10) T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, and H. Narita, Tetrahedron Lett., 2545 (1972).

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