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TOTAL SYNTHESIS OF NEOSURUGATOXIN

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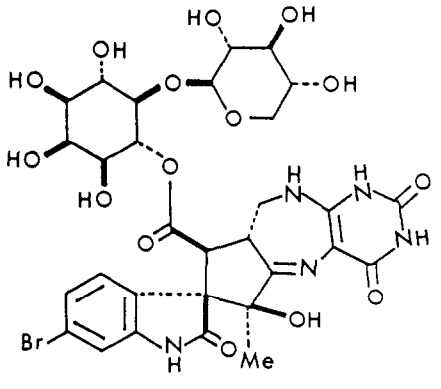
Summary: Total synthesis of neosurugatoxin, having a strong affinity for nicotinic receptors, is described.

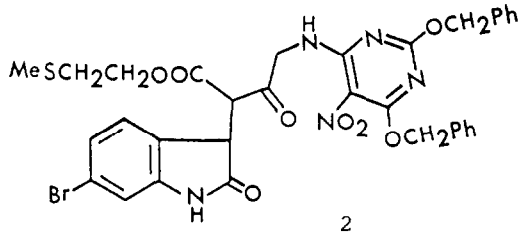
Neosurugatoxin 1, isolated from the toxic Japanese ivory shell (Babylonia japonica) by Kosuge et al.[1] in 1981, is the causative agent of intoxication resulting from ingestion of the toxic shell. This toxin evoked mydriasis in mice at a minimum dose of 3 ng/g and at a concentration of 1×10^{-9} g/ml, inhibited the contractile response of isolated guinea pig ileum to 3×10^{-5} g/ml of nicotine.[1] Recently, it was also demonstrated that the high affinity constant of neosurugatoxin for nicotinic receptors in the rat forebrain as well as in the guinea pig ileum is at least three orders of magnitude greater than that of commercial hexamethonium.[2]

We now report the total synthesis of this new marine toxin 1 starting from synthon 2 successfully utilized in surugatoxin synthesis.[3]

Our synthetic procedure described in this paper involves (i) the stepwise synthesis of aglycone 3 from 2, (ii) esterification of 3 with the optically active xylopyranosyl-myo-inositol derivative 9, and (iii) stereocontrol of the four asymmetric carbons by thermodynamic equilibration of 11.



1 : neosurugatoxin



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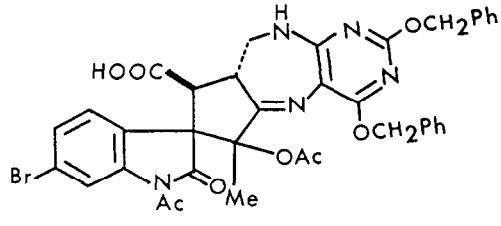
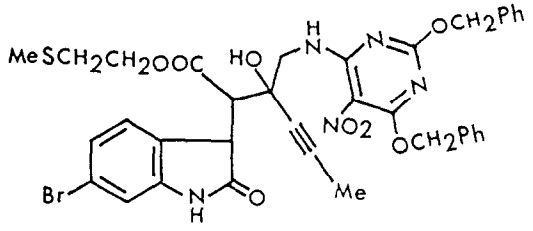


3

Preparation of aglycone 3 was accomplished as follows: (1) addition of propynylmagnesium bromide (10 equiv in THF, -60°C) to the carbonyl carbon of nitro-ketone 2 gave an acetylenic alcohol 4 as a mixture of inseparable diastereoisomers in 21% yield (corrected yield, 80%); (2) treatment of 4 with mCPBA (2.2 equiv, CH_2Cl_2, 5°C) followed by acetylation with AcCl-pyridine (-15°C, 30 min) afforded methylsulfonylethyl ester of the 2-acetoxyindole derivative 5 (mp 75°C, 83% yield from 4); (3) the α-diketone directed oxidation of the acetylene moiety of 5 using OsO_4 (4 equiv) in THF-ether-pyridine solution (45:30:1, -15°C and then 0°C, overnight) gave an unstable osmium ester complex which was allowed to react with a solution of $NaHSO_3$-H_2O-pyridine=1:15:20, rt, 2 hr) to give the spirooxindole derivative 6 (57% from 5);[4] (4) dehydration ($SOCl_2$-pyridine, -15°C, 10 min) followed by reduction (Zn-AcOH in MeOH-CH_2Cl_2 (1:10), rt, 10 min) and treatment with a catalytic amount of CSA in CH_2Cl_2 (rt, 10 min) resulted in the formation of the neosurugatoxin framework to give four isomeric mixtures of 7 (82%). Without separation, the mixtures were subsequently acetylated with Ac_2O (large-excess)-DMAP (6.0 equiv) in THF (rt, 1.5 hr) to form a single diacetate 8[5] (mp 120°C, 72%); and (5) removal of the ester protecting group by means of $NaHCO_3$-Na_2CO_3 buffer (0.1 M, pH 10.2)-acetone (1:5, rt, 3 hr) gave the desired carboxylic acid 3 (mp 154-155°C, 95%).

Esterification of the aglycone diacetate 3 with a highly sterically hindered alcohol 9[6] ($[\alpha]_D^{20}$=-85° ($CHCl_3$; c, 1.00)) was effected via the agency of picryl chloride in pyridine (rt, 2hr).[3] The resulting diastereomeric mixture of 10 (12%, 10a:10b=7:9) was separated by repeated silica gel TLC (i:CH_2Cl_2-MeOH=100:3, ii:AcOEt-benzene=3:5; a less polar isomer, 10a;[7] a more polar isomer, 10b). The stereochemistry of these esters were unknown at this stage; however, 10a was found to be the one desired since it was transformed to natural neosurugatoxin 1 by the following experiments. Removal of all acetyl groups in 10a with 0.1 N KOH-MeOH under nitrogen atmosphere followed by heating the deacetylated product 11 in MeOH containing a small amount of AcONa resulted in the formation of an equilibrium mixture of four stereoisomeric neosurugatoxin derivatives (11a-d, separated by silica gel TLC, MeOH-CH_2Cl_2=1:10, Rf values and yields : 11a, 0.64 (64%); 11b, 0.57 (18%); 11c, 0.43 (5%); and 11d, 0.40 (8%)). Among them, the chemical shift of the C_1-methyl in 11b (^{1}H-NMR($CDCl_3$): δ 1.35 ppm)[8] was consistent with that of neosurugatoxin. Consequently, the recovered unnatural three isomers 11a,c,d were combined and submitted again to the above equilibration (total yield of 11b for five runs, 76% (corrected)). Finally, exposure of 11b in 90% TFA (rt, 1 hr) resulted in removal of all protecting groups to give the desired neosurugatoxin 1 (77%). Chromatographical (TLC, HPLC) and spectral (400 MHz ^{1}H-NMR, SIMS, UV) properties in addition to the biological activity (mydriasis in mice) of the synthetic neosurugatoxin 1 were completely identical with those of natural neosurugatoxin.[1]



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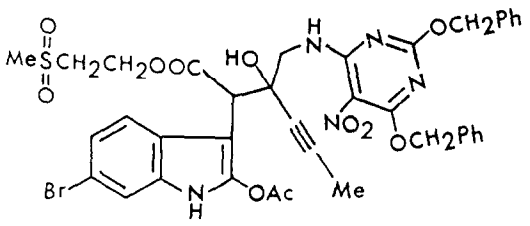

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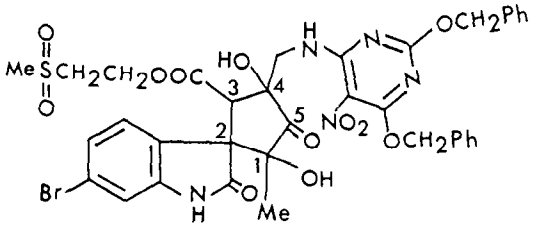

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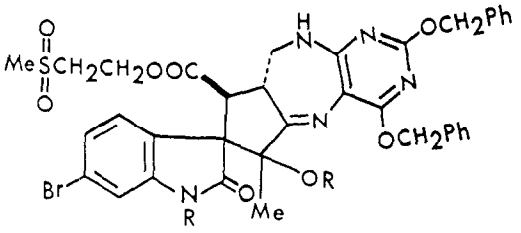
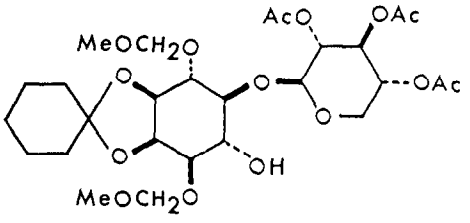


7 : R = H

8 : R = Ac



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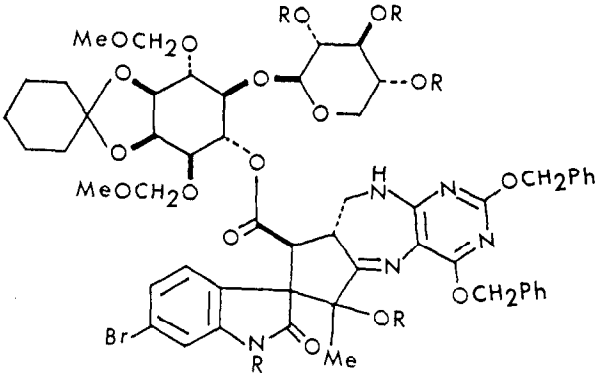
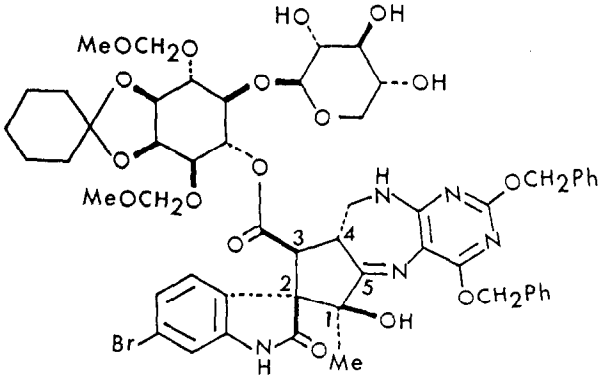


10 : R = Ac

11a-d : R = H



11b

Acknowledgements: We are indebted to Professors T. Kosuge and K. Tsuji for their kind gift of natural neosurugatoxin and helpful discussions.

References and Notes:

1) a: T. Kosuge, K. Tsuji, K. Hirai, K. Yamaguchi, T. Okamoto, and Y. Iitaka, Tetrahedron Lett., 22, 3417 (1981), b: T. Kosuge, K. Tsuji, and K. Hirai, Chem. Pharm. Bull., 30, 3255 (1982).

2) E. Hayashi, M. Isogai, Y. Kagawa, N. Takayanagi, and S. Yamada, J. Neurochem., 42, 1491 (1984).

3) S. Inoue, K. Okada, H. Tanino, K. Hashizume, and H. Kakoi, Tetrahedron Lett., 25, 4407 (1984).

4) The resulting single reaction product was partially isomerized during purification on silica gel TLC to give a small amount of C_1-methyl isomer. Since each isomer of 6 gave the same four isomeric mixtures of 7, we used the mixture for the subsequent three steps without separation.

5) PMR (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, m), 4.56(1H, m), 5.36(2H, s), 5.41 and 5.50(2H, d of AB, J=13.2 Hz), 6.20(1H, br s), 6.95(1H, d, J=8.4 Hz), 7.24-7.50(1H, m), 8.52(1H, d, J=1.8 Hz).

6) This compound was prepared from 6-O-benzyl-2,3-O-cyclohexylidene-1,2-di-O-methoxymethyl-myo-inositol and 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide. Unpublished results.

7) PMR data of a diastereomer of natural form 10a (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), 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).

8) PMR (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 s), 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), 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).

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