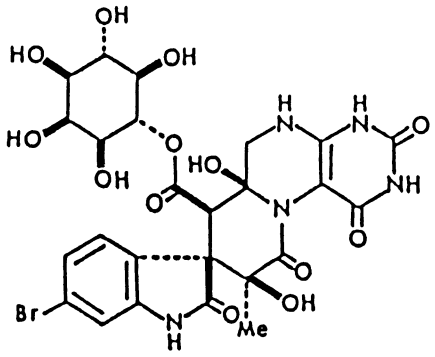
CHEMISTRY LETTERS, pp. 703-706, 1989.

A New Approach in the Construction of the Pentacyclic Ring System of Neosurugatoxin

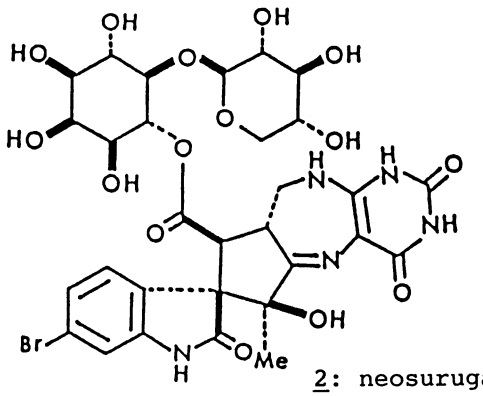
Kunisuke OKADA,* Yasushi MIZUNO, Hideo TANINO, Hisae KAKOI, and Shoji INOUE
Faculty of Pharmacy, Meijo University, Tenpaku, Nagoya 468

Details on a second synthetic procedure of neosurugatoxin framework are described using a Diels-Alder adduct obtained from 6-bromo-3-ethoxycarbonylmethylene-2-oxoindoline and 1,3-pentadiene.

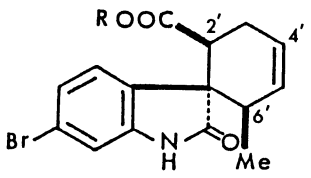
In the preceding paper,[1] we reported the preparation and properties of a Diels-Alder adduct obtained from 3-methoxycarbonylmethylene-2-oxoindolines and unsymmetrical dienes, as a part of our work on the synthesis of naturally occurring 3-spiro-2-oxoindoline derivatives such as surugatoxin 1[2] or neosurugatoxin 2.[3] In this paper, a successful application of this type of Diels-Alder adduct for the synthesis of methylsulfonylethyl ester of the aglycone of neosurugatoxin 19[3] is described. 6-Bromo-2-oxoindoline-3-spiro-1'-(methylthioethyl 6'-methyl-4'-cyclohexene-2'-carboxylate) 5,[4] prepared from the $C_{6'}$-β-methyl isomer of the Diels-Alder adduct 3[5] by the usual ester exchange reaction via the carboxylic acid 4 was converted into the spiro-cyclopentene derivative 10 by the following sequence: (1) the methylthioethyl group of 5 was oxidized with mCPBA (2.8 equiv., CH_2Cl_2, rt, 30 min) to give a methylsulfonylethyl ester derivative 6 (93%, mp 171 °C); (2) ozonization of 6 in CH_2Cl_2-MeOH (10:1) at -66 °C was followed by cleavage with a large excess of $P(OEt)_3$ at -20 °C for 30 min and then recyclization of the resulting dialdehyde under the Knoevenagel condition (piperidine-AcOH(1:10) in THF-benzene, 50 °C, 3 h) gave the spiro-cyclopentene aldehyde 7 (mp 183 °C) in 62% overall yield; (3) reduction of 7 with $NaBH_4$, followed by treatment with MsCl/TEA in THF, gave an unstable mesylate 8 (mp 59-61 °C) in 83% yield; and (4) reaction of 8 with sodium azide in DMF (5 °C, 1 h) produced the azide 9 (91%, mp 133 °C), which was



1: surugatoxin



2: neosurugatoxin

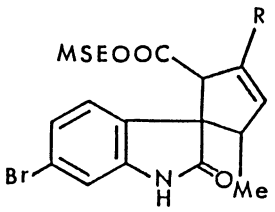


3: R = CH_2CH_3

4: R = H

5: R = $CH_2CH_2SCH_3$

6: R = $CH_2CH_2SO_2CH_3$

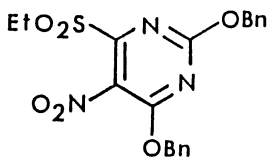


7: R = CHO

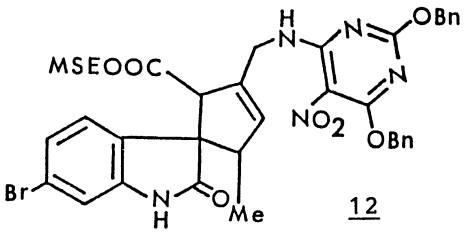
8: R = CH_2OMs

9: R = CH_2N_3

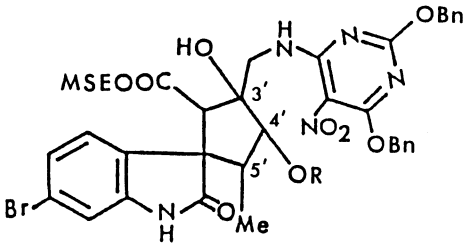
10: R = CH_2NH_2



11

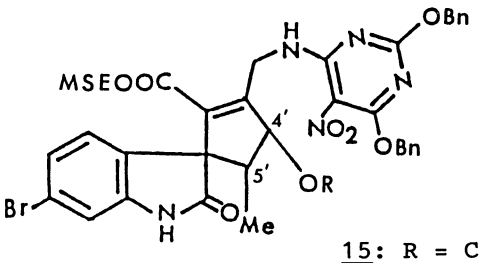


12



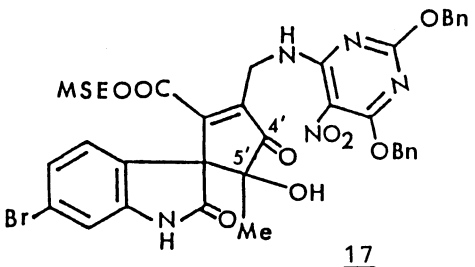
13: R = H

14: R = $COCH_2Cl$

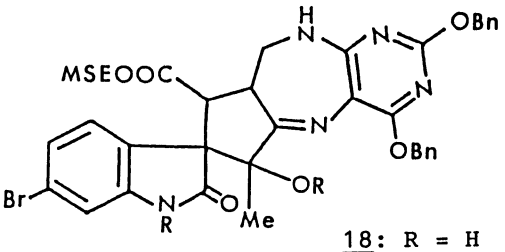


15: R = $COCH_2Cl$

16: R = H



17



18: R = H

19: R = Ac

subsequently reduced with Zn-AcOH in CH_2Cl_2 to give the corresponding amine 10.

Since the resulting amine 10 was markedly unstable, it was immediately reacted (without purification) with 2,4-dibenzyloxy-6-ethylsulfonyl-5-nitropyrimidine 11, to give the 6-aminopyrimidine derivative 12 in 51% overall yield from 9. The double bond in 12 was oxidized with OsO_4 in pyridine (rt, 3 h) to form the osmate, which was then cleaved into 3',4'-diol 13 in the usual manner (10% aq. $NaHSO_3$-pyridine=1:8, rt, overnight). Partial acylation of 13 with monochloroacetic anhydride-pyridine (5 °C, 1 h) gave the 4'-monochloroacetate 14 in high yield. The remaining tertiary hydroxyl group at $C_{3'}$ was eliminated with thionyl chloride-pyridine at 0 °C to yield the α,β-unsaturated ester derivative 15. Selective removal of the chloroacetyl protecting group at $C_{4'}$ occurred in a quantitative yield when 15 was treated with thiourea (1.1 equiv.) in MeOH under reflux for 3 h. The resulting 4'-hydroxy derivative 16 was then subjected to selenium oxidation in an attempt to form an acyloin moiety at the $C_{4'}$-$C_{5'}$ position of 16. When a mixture of 16 (332 mg) and $(phSeO)_2O$ (1 g, ca. 3.5 equiv.) in dioxane (60 ml) was heated at 80 °C for 2 h, the oxidation proceeded stepwise (as judged by TLC) to form the $C_{4'}$-ketone[6] first followed by α-hydroxylation to the desired acyloin. After extractive work up, the product was purified on a silica gel column (CH_2Cl_2-MeOH=20:1) to give 307 mg (91%) of 17. Compound 17 was easily epimerized in organic solvents such as CH_2Cl_2 and MeOH at room temperature, to form a 1:1 mixture of $C_{5'}$-epimers. Therefore, derivation of the stable single product neosurugatoxin analog 19 was achieved by the following steps. Reduction of a mixture of the $C_{5'}$-epimers of 17 with Zn-AcoH in CH_2Cl_2-MeOH (10:1) at room temperature was followed by treatment with a catalytic amount of CSA in CH_2Cl_2 (rt, 10 min), resulting in ring closure and formation of the neosurugatoxin framework. Without separation, the resulting four isomeric mixtures of the cyclized products 18 were subsequently treated with Ac_2O (large exess)-DMAP (6.0 equiv) in THF (rt, 1.5 h), to give a single diacatate 19 in 72% yield. 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-NMR spectrum of 19[7] were identical to those of the key intermediate reported in our first synthesis of neosurugatoxin.[3]

References

1) K. Okada, H. Sakuma, M. Kondo, and S. Inoue, Chem. Lett., 1979, 213.

2) K. Okada, H. Tanino, K. Hashizume, M. Mizuno, H. Kakoi, and S. Inoue, Tetrahedron Lett., 25, 4403 (1984); S. Inoue, K. Okada, H. Tanino, K. Hashizume, and H. Kakoi, ibid., 25, 4407 (1984).

3) S. Inoue, K. Okada, H. Tanino, and H. Kakoi, Tetrahedron Lett., 27, 5225 (1986).

4) Mp 147 °C, ^{1}H-NMR ($CDCl_3$) δ: 0.60 (3H, d, J=7.4 Hz), 2.05 (3H, s), 2.54 (2H, t, J=7.0 Hz), 2.59-2.87 (3H, m), 3.37 (1H, dd, J=6.5, 11.6 Hz), 4.07 (2H, t, J=7.0 Hz), 5.56 (1H, dd, J=2.0, 10.1 Hz), 5.78 (1H, m), 6.98-7.12 (3H, m), 8.41 (1H, s, NH).

5) The β-methyl isomer at $C_{6'}$ of 3 was obtained from the 1:1 mixture of the adduct between 6-bromo-3-ethoxycarbonylmethylene-2-oxoindoline and 1,3-pentadiene (see Ref. 1) by chromatography on a silica gel column (EtOAc-hexane=1:1).

$C_{6'}$-β-methyl isomer: mp 188-189 °C, ^{1}H-NMR ($CDCl_3$) δ: 0.60 (3H, d, J=7.4 Hz), 1.08 (3H, t, J=7.2 Hz), 2.52-2.88 (3H, m), 3.31 (1H, m), 3.94 (2H, m), 5.56 (1H, dd, J=1.7, 10.1 Hz), 5.88 (1H, m), 7.03-7.11 (3H, m), 9.35 (1H, s, NH).

The following data were obtained for the $C_{6'}$-α-methyl isomer: mp 137-138 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7.1 Hz), 1.14 (3H, d, J=7.1 Hz), 2.34 (1H, m), 2.46 (1H, m), 2.81 (1H, m), 3.28 (1H, dd, J=6.7, 9.8 Hz), 4.00 (2H, q, J=7.1 Hz), 5.76 (1H, m), 5.87 (1H, m), 7.04 (3H, m), 8.03 (1H, s, NH).

6) The $C_{4'}$-ketone was also obtained from 16 by oxidation with PCC in CH_2Cl_2.

7) ^{1}H-NMR ($CDCl_3$) 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=1.8, 8.1, 11.7 Hz), 3.56 (1H, ddd, J=2.6, 8.1, 10.3 Hz), 3.86 (1H, d, J=10.3 Hz), 4.20 (1H, ddd, J=2.6, 7.7, 11.7 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 (11H, m), 8.52 (1H, d, J=1.8 Hz).

(Received December 21, 1988)