Studies on the Synthesis of Batrachotoxin

Philip Magnus,* Theophilus Leapheart, and Clive Walker

Department of Chemistry, Indiana University, Bloomington, Indiana 47405, U.S.A.

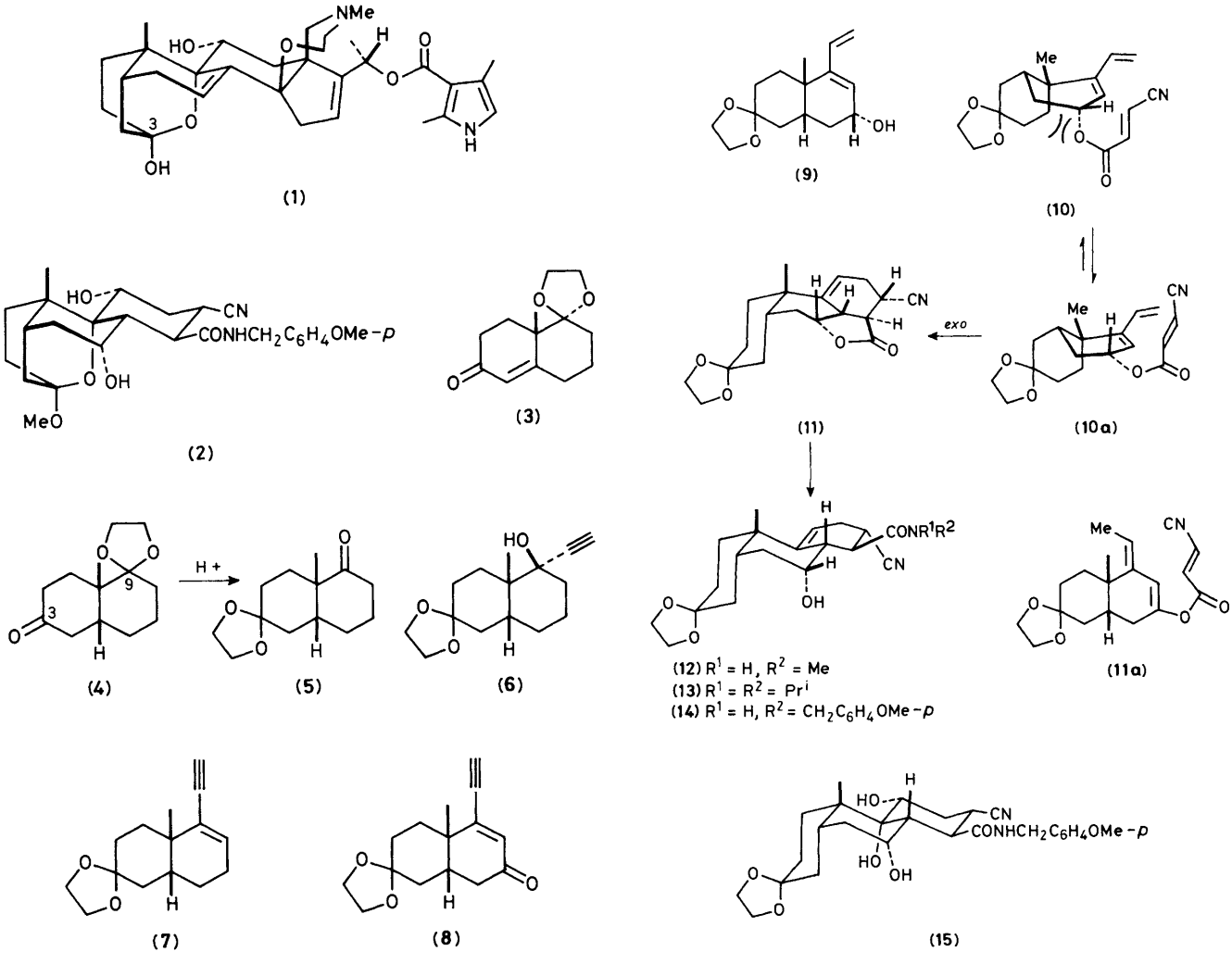
The readily synthesised diene (**10a**) on heating gave the strained lactone (**11**), which was further modified into the acetal (**2**) containing the so-called oxygen triad of batrachotoxin.

The most potent steroidal toxins belong to the small neotropical frogs of the genus *Phyllobates*.[1] Batrachotoxin (**1**) was isolated from the skin secretions of these frogs, and is one of the most toxic substances known (LD_{50} 2 μg kg^{-1} mice).[2] Because of its extreme inaccessibility, combined with its importance as a neurochemical agent for the study of sodium ion transport in nerve and muscle, its total synthesis constitutes an important chemical and pharmacological challenge. While a detailed and very important synthetic study from Wehrli's laboratories[3] has resulted in a partial synthesis, no reports directed towards a total synthesis of batrachotoxin (**1**) or analogues that contain the oxygen-triad[4] have appeared.

This communication reports the synthesis of a highly functionalized precursor (**2**) of batrachotoxin (**1**), that is formed by an intramolecular Diels–Alder reaction that results in the most conformationally strained product.

Hydrogenation (10% Pd–C–EtOH, atmospheric pressure) of (**3**)[5] gave (**4**) (>95%), which upon treatment with a catalytic amount of *p*-$MeC_6H_4SO_2OH$ in CH_2Cl_2 gave the rearranged acetal (**5**) (77%), m.p. 74—75 °C (hexane).[6] The fortuitous migration of the acetal protection from the C-9 carbonyl group to the C-3 carbonyl group is readily explained by the proximity of the acetal at C-9 to C-3 when the octalone (**4**) is *cis*-fused. Addition of lithium acetylide–ethylenediamine complex to (**5**) gave, after recrystallization, the equatorial tertiary alcohol (**6**) (70%),[7] m.p. 110—112 °C (hexane–EtOAc), which was dehydrated using $POCl_3$–1,8-diazabicyclo[5.4.0]undec-7-ene in CH_2Cl_2 to give the enyne (**7**) (63%). Allylic oxidation of the enyne (**7**) using the Salmond procedure,[8] CrO_3–3,5-dimethylpyrazole–CH_2Cl_2 gave the enynone (**8**) (53%), m.p. 101—103 °C.

Hydrogenation of (**8**) (Lindlar catalyst), followed by $LiAlH_4$ reduction gave the dienol (**9**) (85%). Treatment of (**9**) with *E*-3-cyanoacrylic acid[9]–4-*N*,*N*-dimethylaminopyridine–CH_2Cl_2–cyclohexyl-3-(2-morpholinylethyl)carbodiimide methotoluene-*p*-sulphonate gave the required Diels–Alder



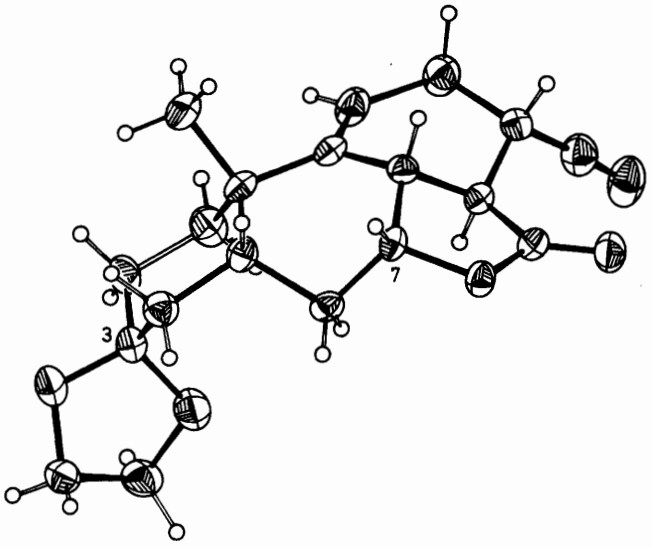


Figure 1. Molecular structure of (**11**).

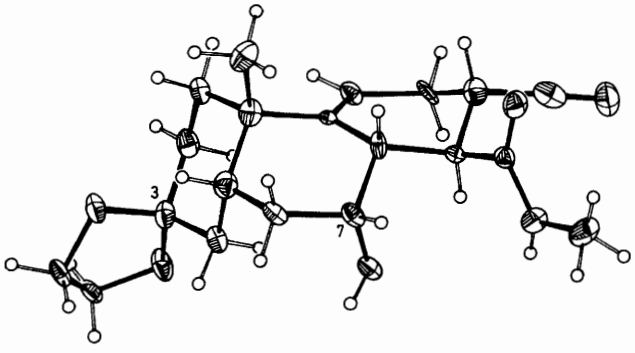


Figure 2. Molecular structure of (**12**).

precursor (**10**) (79%). When (**10**) was heated in benzene in a sealed tube (freshly silylated by treatment with hexamethyldisilazane) at 110 °C for 48 h the strained lactone (**11**) (55%) was isolated, m.p. 177—178 °C, ^{1}H n.m.r. (360 MHz) δ 5.49 (1H, m), 4.80—4.70 (1H, m), 4.0—3.90 (4H, m), 3.1—2.98 (1H, m), 2.85—2.6 (2H, m), 2.5 (1H, dd, *J* 7, 11.6 Hz), 2.1—2.0 (1H, m), 1.9—1.4 (8H, m), 1.14 (3H, s). Failure to treat the sealed tube with hexamethyldisilazane resulted in the exclusive formation of the acid-catalysed rearrangement product (**11a**).[10] The stereochemistry of (**11**) was proven by single crystal *X*-ray crystallography, Figure 1.†

† *Crystal data:* for (**11**): $C_{19}H_{23}NO_4$, M = 329.40, triclinic, space group $P\bar{1}$, a = 11.402(3), b = 14.912(5), c = 10.426(2) Å, α = 99.19(2), β = 90.37(2), γ = 111.64(2)°, U = 1622.54 Å^3, Z = 4, D_c = 1.348 g cm^{-3}, μ(Mo-K_α) = 0.881 cm^{-1}, 4253 unique reflections, 3537 with $F > 3\sigma(F)$, $6 < \theta < 45°$, $R(F)$ = 0.0457, $R_w(F)$ = 0.0454.

Crystal data for (**12**): $C_{20}H_{28}N_2O_4$, M = 360.45, orthorhombic, space group $P2_12_12_1$, a = 12.895(3), b = 11.190(3), c = 12.790(3) Å, U = 1845.54 Å^3, Z = 4, D_c = 1.297 g cm^{-3}, μ(Mo-K_α) = 0.844 cm^{-1}, 1402 unique reflections, 1118 with $F > 3\sigma(F)$, $6 < \theta < 45°$, $R(F)$ = 0.457, $R_w(F)$ = 0.0454.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

The B-ring is forced into a boat conformation to accommodate the strained *trans*-fusion between the C-ring and the lactone ring. The stereochemical outcome of the intramolecular Diels–Alder reaction (**10a**) → (**11**) is typical of an *exo*-transition state leading to a *trans*-fused hydrindanone.[11] When the lactone (**11**) was treated with $LiNPr^i_2$ the amide (**13**) was formed, demonstrating the extreme strain present in (**11**). The *N*-methylamide (**12**) gave crystals suitable for single crystal *X*-ray crystallography, Figure 2. The B-ring in (**12**) has now adopted a chair conformation and the 7α-hydroxy group returned to the axial position.†

Treatment of the lactone (**11**) with $H_2NCH_2C_6H_4OMe$-*p*–CH_2Cl_2 gave (**14**) (95%), which was directly hydroxylated using *N*-methylmorpholine *N*-oxide–OsO_4–aqueous acetone[12] to give the diol (**15**) (31%). Brief exposure of (**15**) to MeOH–HCl gave the acetal (**2**) (43%), confirming the stereochemistry of the diol (**15**).

In summary, the highly stereospecific intramolecular Diels–Alder reaction (**10a**) → (**11**) and subsequent conversion into the acetal (**2**), that contains the crucial oxygen triad, provides a viable route to the ABC-rings of batrachotoxin (**1**).

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