# A Short and Efficient Route to (±)-Anatoxin-*a*

**Philip J. Parsons,* Nicholas P. Camp, J. Mark Underwood and in part Darren M. Harvey**

*Department of Chemistry, University of Reading, Reading, Berkshire, UK RG6 2AD*

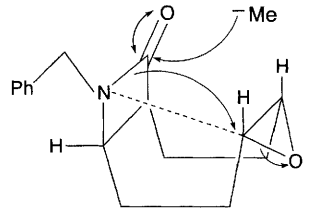
A new route to Anatoxin-*a* **1** is reported which involves a tandem methyllithium mediated ring opening/intramolecular cyclisation as a key step to provide the required 2-acetyl-9-azabicyclo [4.2.1] nonane ring structure in one synthetic operation.

Certain strains of *Anabaena flos aqua*, a freshwater blue–green algae, produce an alkaloidal neurotoxin that has proved fatal to livestock, waterfowl and fish.[1] This toxin was identified by X-ray crystallography[2] and spectroscopy[3] as a secondary amine containing the 9-azabicyclo[4.2.1]nonane ring structure and was named anatoxin-*a* **1** or 'Very Fast Death Factor' (VFDF).[4] The $LD_{50}$ intraperitoneal (IP) mouse for purified toxin is 200 μg $kg^{-1}$ body mass, with a survival time of 4–7 min.[5] Anatoxin-*a* mimics the neurotransmitter acetylcholine and acts as a potent agonist for the nicotinic acetylcholine receptor (nAChR).[6] Such powerful biological activity coupled with its unique ring structure has led to numerous racemic[7] and chiral[8] syntheses of this molecule over the last twenty years. Construction of the aforementioned ring system and introduction of the methyl ketone at the correct oxidation level have proved to be the major challenges in this regard. We wish to report a short and efficient route to anatoxin-*a* which allows access to a variety of analogues.

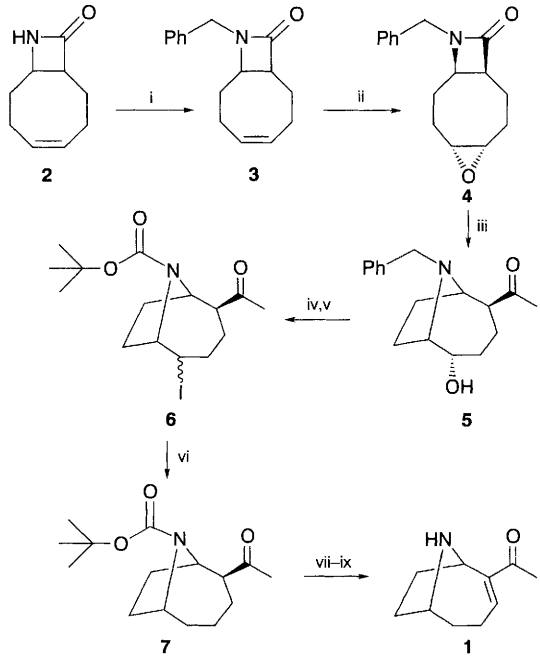
The key step in our approach involves a tandem methyllithium induced β-lactam ring opening–intramolecular cyclisation, to afford the desired ring structure, complete with methyl ketone in one synthetic operation. Transformation of the resultant alcohol **5** to Boc-dihydroanatoxin-*a* **7** was easily achieved and the synthesis was completed using methods developed by Rapoport and coworkers.[8b,d] The advantage of our route stems from the accessibility of multigram quantities of the relatively simple precursors and an early entry into the 2-acetyl-9-azabicyclo [4.2.1] nonane ring system.

The β-lactam **2** was prepared by careful addition of chlorosulfonyl isocyanate to 1,5-cyclooctadiene in dichloromethane (DCM) containing anhydrous sodium carbonate at 0 °C and hydrolysis of the chlorosulfonyl β-lactam intermediate. Removal of the polymeric side products by work up and flash silica chromatography afforded the β-lactam **2** as a white solid in 48% yield. Alkylation to provide the benzyl protected β-lactam **3** could be achieved in 60% yield by treatment of **2** with sodium hydride (1.1 equiv.) in THF followed by addition of benzyl bromide in the presence of a catalytic amount of 18-crown-6 ether. In our hands the alkylation of **2** under phase transfer conditions proved to be the most efficient method, affording **3** as a white solid in excellent yield (95%). Treatment of the benzyl protected β-lactam **3** with MCPBA in DCM provided the racemic epoxide **4** in 84% yield, as a white solid. X-ray crystallography[9] confirmed the relative anti-relationship of the β-lactam to the epoxide, and was attributed to the reaction of the peroxyacid with the least hindered face of the double bond. This relationship provides the correct geometry necessary for the key nitrogen–carbon bond formation in the cyclisation step (Scheme 1). Due to the strain of the four-membered ring and lack of amide type resonance, we reasoned that the β-lactam carbonyl should have considerable electrophilic nature and thus be prone to nucleophilic attack. If the β-lactam could be opened with methyllithium we were confident that the nitrogen–carbon bond formation would occur.

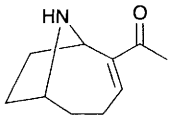
Temperature studies were undertaken and the desired cyclisation was observed at temperatures ranging between −25 and 0 °C. Various competing side reactions were observed, including elimination and over addition products, due to the basic nature of methyllithium and the generation of a more electophilic methyl ketone carbonyl during the course of the cyclisation. At −78 °C no cyclisation product and only elimination products were observed due to the enhanced basic properties of methyllithium at this temperature. Dropwise addition of methyllithium (1 equiv.) to the epoxide **4** in THF at −25 °C and reaction at this temperature for 1 h provided alcohol **5**† in 40% yield after purification. Several attempts to dehydrate the alcohol **5** failed and fragmentation of the methyl ketone was




Scheme 1




**Scheme 2** *Reagents and conditions*: i, 1 : 1 mixture of a 50% solution of NaOH; $CH_2Cl_2$, $Bu_4NHSO_4$ (0.1 equiv.), benzyl bromide (1.2 equiv.); ii, MCPBA (1.2 equiv.), $CH_2Cl_2$, room temp. 24 h; iii, methyllithium (1.4 mol $dm^{-3}$, in ether, 1 equiv.), THF, −25 °C, 1 h; iv, $H_2$, 10% Pd/C, MeOH, $Boc_2O$ (2 equiv.);[8d] v, $Ph_3P$ (1.25 equiv.), $I_2$ (1.3 equiv.), imidazole (4 equiv.), $CH_2Cl_2$, room temp., 1 h; vi, $Bu_3SnH$ (1.2 equiv.), AIBN (0.1 equiv.), toluene, reflux, 30 min.; vii, NaH (3 equiv.), THF, cat. MeOH, room temp., 7 h, then TBDMSCl (3 equiv.), $Et_3N$, THF, −15 °C then room temp. overnight;[8d] viii, $Pd(OAc)_2$, MeCN, room temp., 48 h;[8b] or PhSeCl, THF, −78 °C, 2 h, MCPBA, 0 °C;[8d] ix, TFA, $CH_2Cl_2$, 1 h[8b]




Anatoxin-a 1

observed. Possible reactions at the bridgehead tertiary amine were proposed and provided a possible explanation for the observed fragmentation. To overcome this difficulty we carried out an *in situ* debenzylation/Boc protection in 84% yield using the method of Rapoport.[8d] Dehydration with Burgess' salt, phosphorus pentoxide and various xanthate esters still proved fruitless. However, the alcohol could be cleanly converted to the iodide **6** in 85% yield using triphenylphosphine, iodine and imidazole in DCM at room temp. Reduction of the iodide **6** was achieved by treatment with tri-n-butyltin hydride (1.1 equiv.) and AIBN in refluxing toluene. Removal of the tri-n-butyltin iodide by treatment with potassium fluoride and flash silica chromatography provided Boc-dihydroanatoxin-*a* **7** in 86% yield as a colourless oil. The total synthesis was completed as shown in Scheme 2, using the method of Rapoport to provide Anatoxin-*a* **1**.[8b,d]

Thus, we have demonstrated a new approach to anatoxin-*a* which involves a novel and specific intramolecular ring cyclisation step which allows easy access to a range of analogues on a multigram scale.

All new compounds and literature analogues possess satisfactory analytical purity and identical spectra and high resolution mass spectra to those previously reported.

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## Footnote

† *Selected spectroscopic data* for compound **5**: $C_{17}H_{24}NO_2$ requires 274.1807 $(M + H)^+$, found 274.1807. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 21.44 ($CH_2$), 22.54 ($CH_2$), 27.20 ($CH_3$), 31.06 ($CH_2$), 33.75 ($CH_2$), 61.46 ($CH_2$), 61.55 (CH), 62.81 (CH), 68.35 (CH), 73.53 (CH), 126.98, 128.10, 128.60 (aromatic CH), 140.51 (quat. aromatic) and 210.81 (CO).

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