# Neurotoxic Alkaloids: Synthesis of (±)-Anatoxin-a

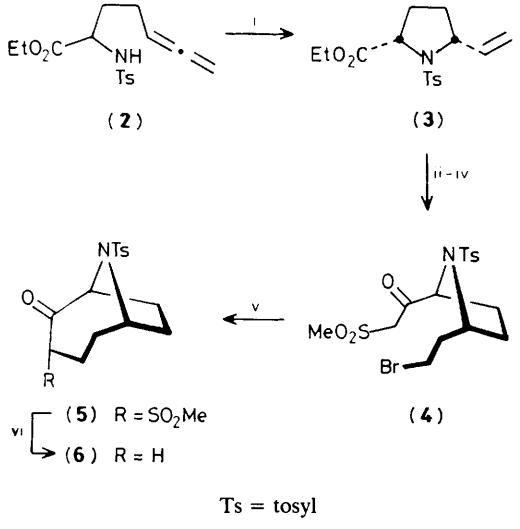
**Peter Vernon and Timothy Gallagher***

*School of Chemistry, University of Bath, Bath BA2 7AY, U.K.*

A synthesis of (±)-anatoxin-a (**1**), *via* the bicyclic ketone (**6**), is described.

The application of naturally occurring toxins to the identification and classification of different neuronal receptors is a process that offers considerable potential in the study of neurotransmission pathways.[1] The alga exotoxin, anatoxin-a (**1**), provides a good example of such a probe as this structurally unusual alkaloid is the most potent agonist known for the nicotinic acetylcholine receptor (nAChR).[2] This potency, together with the inaccessibility of anatoxin-a from natural sources, and the need for analogues to establish the structural features of this and other related receptor sites, has resulted in considerable synthetic interest in anatoxin-a.[3] We now report our preliminary studies in this area, which have led to a synthesis of racemic anatoxin-a (**1**). Our initial target was the bicyclic ketone (**6**), which was prepared as shown in Scheme 1.

The synthesis and stereoselective cyclisation of the allenic amino ester (**2**) to give the *cis*-2,5-disubstituted pyrrolidine (**3**) has been described.[4] Selective manipulation of both the ethoxycarbonyl and vinyl substituents of (**3**) led, in three steps [47% overall yield from (**3**)], to bromide (**4**)† [m.p. 123—123.5 °C (ethyl acetate–hexane), $\delta_H$ 4.59 (1H, d, *J* 15 Hz), 4.36 (1H, d, *J* 15 Hz), 4.08 (1H, t, *J* 8 Hz), 3.40 (1H, m), 3.14 (3H, s), 2.51 (1H, m), 2.15 (1H, m), 2.04 (1H, m), 1.80 (1H, m), 1.65—1.52 (2H, m)]. Treatment of (**4**) with NaH in dimethyl sulphoxide (DMSO) effected intramolecular alkylation[5] to give bicyclic ketosulphone (**5**) [m.p. 215 °C (methanol), $\delta_H$ 4.56 (1H, dd, *J* 12, 2 Hz), 4.53 (1H, m), 4.45 (1H, dd, *J* 10, 2 Hz), 3.06 (3H, s), 2.65 (1H, dtd, *J* 14, 4, 1.5 Hz), 2.27 (1H, tt, *J* 14, 4 Hz), 2.00—1.54, (6H, m)] which was then reduced, using Al/Hg, to ketone (**6**) [m.p. 155 °C (ethyl acetate–hexane), $\delta_H$ 4.53 (1H, m), 4.32 (1H, dd, *J* 10, 2 Hz), 3.05 (1H, td, *J* 14, 2 Hz), 2.32 (1H, dd, *J* 14, 6 Hz), 1.93—1.50 (7H, m)] in 76% yield from bromide (**4**). This ketone, which represents a key synthetic intermediate in our approach to (±)-anatoxin-a, is available in 6 steps (36% overall yield) from amino ester (**2**).

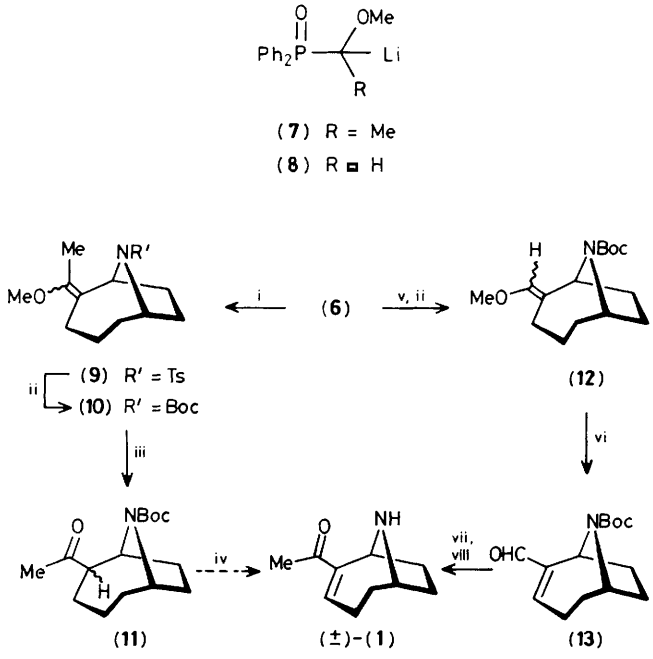



**Scheme 1.** *Reagents and conditions:* i, $AgBF_4$ (0.1 equiv.), $CH_2Cl_2$, 24 h; ii, $B_2H_6$, tetrahydrofuran (THF), then $H_2O_2$, NaOH; iii, $Me_2SO_2$–$Bu^nLi$(4 equiv.), THF, −10 °C, 20 min; iv, $PPh_3$, $Br_2$, THF, 0 °C → room temp., 10 min; v, NaH, DMSO, 40 °C, 2 h; vi, Al/Hg, aqueous THF, 60 °C, 4 h.

† All new compounds gave satisfactory spectral, microanalytical, and/or accurate mass data. $^1$H N.m.r. (400 MHz, $CDCl_3$) signals due to $-SO_2Tol$ have not been included.

The final phase of the synthesis, the homologation of a bicyclic ketone to anatoxin-a, is a problem which has been addressed by other groups.[3a,i] Because of this, we chose to examine the viability of an alternative solution involving the use of either of the lithiated methoxymethyl phosphine oxides (**7**) or (**8**)[6] (Scheme 2).

Reaction of ketone (**6**) with (**7**) gave the expected enol ethers (**9**), as a mixture of isomers. Reductive cleavage ($Na/NH_3$) of the *N*-arylsulphonyl residue followed by re-protection of the resulting secondary amine proceeded smoothly to give the *N*-t-butoxycarbonyl (Boc) enol ethers (**10**). A formal synthesis of (±)-anatoxin-a (**1**) was then accomplished by conversion of (**10**), using NaI–$Me_3SiCl$ in MeCN,[7] into (±)-*N*-Boc dihydroanatoxin-a (**11**) [30% yield from (**6**)], obtained as a 2:5 mixture of α- and β-epimers. Spectral data ($^1$H n.m.r. and i.r.) for this material matched




**Scheme 2.** *Reagents and conditions:* i, (**7**), dimethoxyethane (DME), −78 °C, 5 min, then NaH, room temp., 10 h; ii, $Na/NH_3$, −78 °C, 15 min, then $Boc_2O$, MeOH, 10 h; iii, $Me_3SiCl$–NaI, MeCN, 5 min; iv, ref. 3d; v, (**8**), DME, −78 °C, 5 min, then NaH, THF, room temp., 10 h; vi, PhSeCl, $CH_2Cl_2$, −30 °C, 5 min, then MCPBA, −78 °C, 10 min; vii, MeMgI, diethyl ether, −78 °C → −40 °C, followed by pyridinium chlorochromate, sodium acetate, $CH_2Cl_2$, 30 min; viii, conc. HCl, ethyl acetate, 2 h.

that previously described by Rapoport who has reported the conversion of (**11**) into anatoxin-a (**1**) in three steps.[3d]

Alternatively, condensation of ketone (**6**) with anion (**8**) gave, after an analogous reduction–reprotection sequence, the *N*-Boc enol ethers (**12**) [82% from (**6**)]. Using the procedure described by Nicolaou,[8] (**12**) was treated with PhSeCl followed by oxidation [*m*-chloroperoxybenzoic acid (MCPBA)] to give the α,β-unsaturated aldehyde(**13**) which was isolated in 45% yield. This aldehyde was converted into (±)-anatoxin-a (**1**) in three steps, though as yet only in 21% yield. Spectral and t.l.c. data for this material, isolated as the hydrochloride salt, was in agreement with that previously reported.

Although neither of the routes to anatoxin-a from ketone (**6**) shown in Scheme 2 have yet been optimised, other methods for this overall conversion are currently being evaluated. We would also wish to dispense with the need to switch the nitrogen protecting group in the later stages of the synthesis. Although the *N*-Boc analogues of (**2**) and (**3**) have been prepared,[4] the yields obtained are lower and problems were also encountered with this protecting group in subsequent steps. An alternative solution to this problem is being sought.

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