Pergamon

Tetrahedron, Vol. 52, No. 35, pp. 11637-11642, 1996
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0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00645-X

Tandem Reactions of Anions: A Short and Efficient Route to ±Anatoxin-*a*.

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Abstract: A new route to anatoxin-*a* (1) is reported which involves an anionically induced small ring opening / ring closure / ring opening cascade. The azabicyclo[4.2.1]nonane ring system of anatoxin-*a* is hence formed in one synthetic operation.
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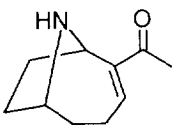
Anatoxin-*a* (**1**) has been isolated from strains of Anabaena flos aqua, a freshwater blue-green algae responsible for the death of livestock, waterfowl and fish[1] The structure of anatoxin-*a* (**1**) was determined by X-ray analysis[2] and spectroscopy[3] and was found to be a derivatised 9-azabicyclo[4.2.1] nonane. The LD_{50} intraperitoneal (IP) mouse for purified anatoxin is 200μgkg^{-1} body mass, with a survival time of 4-7 min.[4] Anatoxin-*a* (**1**) mimics the neurotransmitter acetylcholine and acts as a potent agonist for the nicotinic acetylcholine receptor (nAChR).[5] The combination of biological potency and its unique structure has led to numerous racemic[6] and chiral[7] syntheses of anatoxin-*a* over the past twenty years. We now report in full our total synthesis of anatoxin-*a* which is short and efficient and relies on a tandem methyllithium induced β-lactam ring opening-intramolecular cyclisation to furnish the anatoxin skeleton. (Scheme 1)



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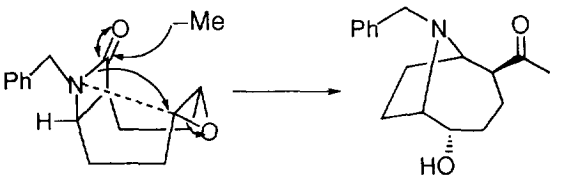
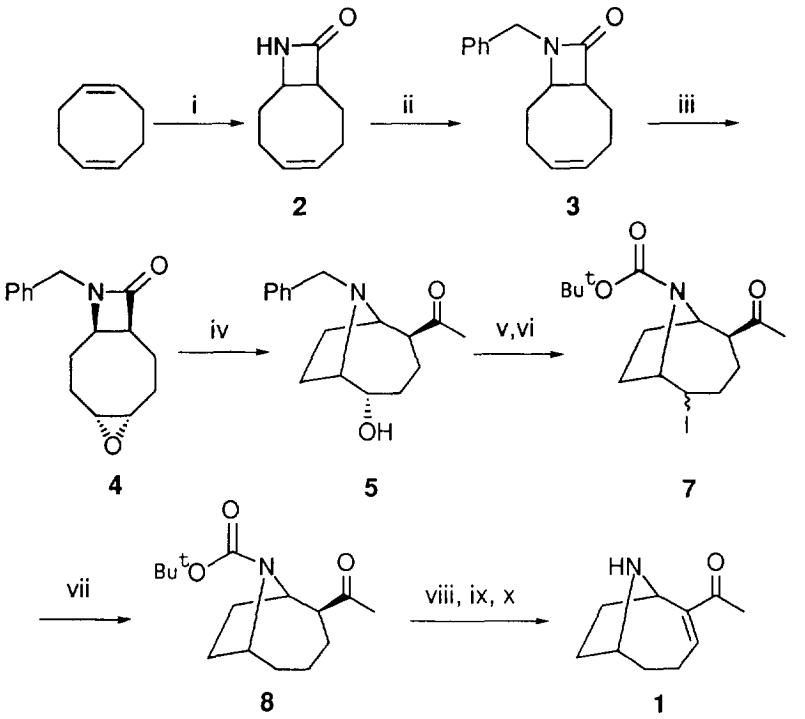


Scheme 1

An advantage of our synthetic route is that gramme quantities of precursors for the construction of anatoxin analogues can be prepared. The readily available starting materials for our synthesis of anatoxin-*a* (**1**) were cyclooctadiene and chlorosulphonyl isocyanate.[8] Careful addition of the isocyanate to a solution of cyclooctadiene in dichloromethane containing sodium carbonate was required to prevent a violent exotherm. After hydrolysis of the intermediate sulphonyl chloride the β-lactam (**2**) was isolated in 48% yield.



Scheme 2 *Reagents and conditions*: i, chlorosulfonyl isocyanate (1 equiv.), anhydrous Na_2CO_3 (0.15 equiv.), CH_2Cl_2, 0 °C for 2 h and then overnight at room temp., then aqueous Na_2SO_3 and Na_2HPO_4; ii, 1:1 mixture of a 50% solution of NaOH; CH_2Cl_2, Bu_4NHSO_4 (0.1 equiv.), benzyl bromide (1.2 equiv.); iii, MCPBA (1.2 equiv.), CH_2Cl_2, room temp. 24 h; iv, methyllithium (1.4 M, in ether, 1 equiv.), THF, -25 °C, 1 h; v, H_2, 10% Pd/C, MeOH, Boc_2O (2 equiv.)[7d]; vi, Ph_3P (1.25 equiv), I_2 (1.3 equiv.), imidazole (4 equiv.), CH_2Cl_2, RT, 1h.; vii, Bu_3SnH (1.2 equiv.), AIBN (0.1 equiv.), toluene, reflux, 30 min.; viii, NaH (3 equiv.), THF, cat. MeOH, room temp., 7 h, then TBDMSCl (3 equiv.), Et_3N, THF, -15 °C then room temp. overnight[7d]; ix, $Pd(OAc)_2$, MeCN, room temp., 48 h[7b]; or PhSeCl, THF, -78 °C, 2 h, MCPBA, 0 °C[7d]; x, TFA, CH_2Cl_2, 1h.[7b]

Scheme 2

Although alkylation of the β-lactam (2) with benzyl bromide was achieved using sodium hydride as the base, in the presence of 18-crown-6 ether (60%), alkylation of (2) under phase-transfer conditions proved to be the most efficient method (95%).[9] Treatment of the benzyl protected β-lactam (3) with metachloroperoxybenzoic acid provided the epoxide (4) in 84% yield as a white solid. The relative anti relationship between the epoxide and β-lactam moieties in (4) provides the correct geometry for the key carbon nitrogen bond forming reaction to take place (Scheme 1). The lack of amide resonance in the β-lactam ring allows nucleophilic attack to take place on the carbonyl group.[10] Thus we reasoned that the β-lactam in (4) could be opened with methyllithium, allowing a tandem ring opening-ring closure sequence to take place. To our delight we found that the desired cyclisation could be achieved using methyllithium at -25 °C. At lower temperatures methyllithium can act as a base and hence various competing reactions

were observed at temperatures lower than 25 °C. Dropwise addition of methyllithium to the epoxide (**4**) at -25°C in tetrahydrofuran gave the bicyclic alcohol (**5**) in 40% yield. Dehydration of the alcohol (**5**) was attempted but without success; the methyl ketone was cleaved and fragmentation of the bicyclic framework was observed. To overcome this we carried out an *in situ* debenzylation / BOC protection sequence on (**5**) using the method of Rapoport.[7b] The resulting alcohol (**6**)was treated with iodine in the presence of triphenylphosphine and imidazole to give the iodide (**7**). Reduction of (**7**) with tri-n-butyltin hydride in boiling toluene gave BOC protected dihydroanatoxin (**8**). The total synthesis of anatoxin-*a* (**1**) was completed using the method of Rapoport.[7b,d]

Experimental Section

General Methods. Reactions were conducted in flame-dried glassware, under a dry argon atmosphere except when noted otherwise. Solvents and reagents were freshly distilled as follows: Tetrahydrofuran (THF) was distilled from sodium / benzophenone; dichloromethane, toluene, and triethylamine were distilled from CaH_2. 1,5-Cyclooctadiene and benzyl bromide were distilled under reduced pressure and stored over molecular sieves. Melting points (electrothemal apparatus, open capillary) are uncorrected. NMR spectra were recorded in $CDCl_3$ and chemical shifts are recorded in parts per million (δ) downfield from Me_4Si (^1H) or relative to $CDCl_3$ at 77.0 ppm (^{13}C). ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad), coupling constant(s) in hertz (Hz), number of protons. In cases where DEPT experiments were undertaken with ^{13}C NMR acquisitions, the carbon multiplicities are listed as (0) quaternary; (1) methine; (2) methylene; (3) methyl. Both ^1H and ^{13}C NMR spectra of many of the Boc-protected intermediates are complicated by the presence of carbamate rotamers.

3-Azabicyclo[6.2.0]dec-7-ene-2-one (2). A 250 mL three-necked, round-bottomed flask was equipped with an argon inlet adaptor, glass stopper, and rubber septum. The flask was charged with 1,5-cyclooctadiene (42.5 mL, 346 mmol), anhydrous Na_2CO_3 (5.5 g, 0.15 mol%), and dichloromethane (15 mL) and cooled to 0 °C. Chlorosulfonyl isocyanate (30 mL, 345 mmol) was added dropwise to the stirred reaction mixture over 20 min. Stirring was continued at 0 °C for a further 2 h and then the reaction mixture was allowed to warm to room temperature overnight. The resultant thick brown liquid was diluted with further dichloromethane (30 mL) and added dropwise to a 2-L conical flask containing a vigorously stirred, two phase mixture of, Na_2SO_3 (126 g) and Na_2HPO_4 (141 g) in H_2O (600 mL), underlayed with chloroform (500 mL). The organic layer was separated and the aqueous phase extracted with chloroform (2 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield an off-white solid. Purification using column chromatography (EtOAc) provided the β-lactam as a white solid (25 g, 48%): mp 112-113 °C (Et_2O / hexane); TLC (EtOAc) R_f 0.31; IR (nujol mull) 3197, 1731, 1704, 1646; ^1H NMR δ 1.87-2.10 (m, 6H), 2.35-2.48 (m, 2H), 3.27-3.34 (m, 1H), 3.81-3.87 (m, 1H), 5.65-5.74 (m, 2H), 6.20 (br, 1H); ^{13}C NMR δ 22.6 (2), 23.8 (2), 24.3 (2), 30.7 (2), 53.3 (1), 54.0 (1), 130.4 (1), 131.0 (1), 171.5 (0); HRMS, *m/z* calcd for $C_9H_{13}NO$ (M^+) 151.0997, found 151.0996; Anal. calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found C, 71.33; H, 8.67; N, 9.15.

3-Benzyl-3-azabicyclo[6.2.0]dec-7-ene-2-one (3). A 1-L round-bottomed flask was charged with β-lactam **2** (20 g, 132 mmol), tetrabutylammonium hydrogen sulfate (4.5 g, 10 mol%), benzyl bromide (18.8 mL, 159 mmol), and dichloromethane (200 mL). The reaction mixture was cooled to 0 °C and a 50% aqueous solution of NaOH (200 mL) was added cautiously with vigorous stirring. The reaction mixture was allowed to warm to room temperature and vigorous stirring was maintained for 3 h. After this time, the reaction mixture was diluted with H_2O (500 mL) and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. Purification using column chromatography (Et_2O) provided the benzylated β-lactam as a white solid (30.3 g, 95%): mp 64-65 °C (Et_2O / hexane); TLC (Et_2O) R_f 0.43; IR (nujol mull) 1759, 1732, 1653; ^1H NMR δ 1.68-1.80 (m, 1H), 1.91-2.18 (m, 5H),

2.28-2.46 (m, 2H), 3.25-3.32 (m, 1H), 3.62-3.68 (m, 1H), 4.07 (d, J =15.4 Hz, 1H), 4.55 (d, J =15.4 Hz, 1H), 5.60-5.72 (m, 2H), 7.23-7.38 (m, 5H); ^{13}C NMR δ 22.3 (2), 24.0 (2), 24.3 (2), 27.9 (2), 43.9 (2), 53.6 (1), 56.5 (1), 127.6 (1), 128.1 (1), 128.7 (1), 130.3 (1), 131.1 (1), 136.2 (0), 170.2 (0); HRMS, *m/z* calcd for $C_{16}H_{19}NO$ (M^+) 241.1467, found 241.1490; Anal. calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found C, 79.57; H, 8.03; N, 5.78.

7-Epoxy-3-benzyl-3-azabicyclo[6.2.0]decan-2-one (4). A 500 mL two-necked round-bottomed flask, was charged with benzyl protected β-lactam **3** (20 g, 83 mmol), dichloromethane (200 mL), and 4 Å molecular sieves. The solution was cooled to 0 °C and MCPBA (28.6 g, 99 mmol) was added portionwise to the stirred solution over a 20 min period. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was filtered and the solid residues washed with dichloromethane (100 mL). The combined dichloromethane washings were extracted with Na_2SO_3 (1 x 100 mL), $NaHCO_3$ (2 x 100 mL), and brine (1 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a colourless oil. Trituration with cold ether (100 mL) and filtration provided the epoxide as a white solid (17.9 g, 84%): mp 117-118 °C (Et_2O / hexane); TLC (EtOAc) R_f 0.25; IR (nujol mull) 1736, 1720; ^1H NMR δ 0.80-0.96 (m, 2H), 1.25-1.35 (m, 1H), 1.50-1.60 (m, 1H), 1.89-1.98 (m, 1H), 2.08-2.27 (m, 2H), 2.37-2.46 (m, 1H), 2.98-3.07 (m, 2H) 3.25-3.31 (m, 1H), 3.53-3.60 (m, 1H), 4.12 (d, J =15.4 Hz, 1H), 4.52 (d, J =15.4 Hz, 1H), 7.22-7.37 (m, 5H); ^{13}C NMR δ 18.5 (2), 22.7 (2), 22.8 (2), 25.5 (2), 44.1 (2), 55.1 (1), 55.6 (1), 55.8 (1), 56.6 (1), 127.8 (1), 128.2 (1), 128.8 (1), 136.0 (0), 169.2 (0); HRMS, *m/z* calcd for $C_{16}H_{19}NO_2$ (M^+) 257.1416, found 257.1428; Anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.54; H, 7.45; N, 5.42.

2-Acetyl-9-benzyl-5-hydroxy-9-azabicyclo[4.2.1]nonane (5). A 500 mL three-necked, round-bottomed flask was equipped with an argon inlet adaptor, glass stopper, and rubber septum. The flask was charged with epoxide **4** (10.4 g, 40 mmol) in THF (200 mL) and cooled to -25 °C. Methyllithium (1.4 M in ether, 30 mL, 42 mmol) was added dropwise to the solution over 20 min and the resultant yellow solution was left to stir at -25 °C for 1 h. After this time, the solution was quenched with water (20 ml) and the reaction mixture poured into ether (200 mL). The organic layer was washed with H_2O (1 x 50 mL), brine (1 x 50 mL), dried over $MgSO_4$ and concentrated to afford a yellow oil. Purification using column chromatography (Et_2O) provided the alcohol as a colourless oil (4.4 g, 40%): TLC (Et_2O) R_f 0.29; IR (neat) 3400, 1703; ^1H NMR δ 1.38-1.47 (m, 1H), 1.52-1.60 (m, 1H), 1.63-1.70 (m, 1H), 1.80-1.96 (m, 4H), 1.96 (s, 3H), 2.26-2.30 (dd, J = 16.5, 7 Hz, 1H), 2.38-2.48 (m, 1H), 3.18-3.24 (m, 1H), 3.52-3.56 (d, J = 9.16 Hz, 1H), 3.64-3.78 (ABq, J = 13.2 Hz, 2H), 3.68-3.78 (m, 1H), 7.20-7.34 (m, 5H); ^{13}C NMR δ 21.4 (2), 22.5 (2), 27.2 (3), 31.1 (2), 33.8 (2), 61.5 (2), 61.6 (1), 62.8 (1), 68.3 (1), 73.5 (1), 127.0 (1), 128.1 (1), 128.6 (1), 140.5 (0), 210.8 (0); CIMS *m/z* (rel intens) 274 (MH^+, 100), 184 (MH^+ - C_6H_5CH, 31); HRMS, *m/z* calcd for $C_{17}H_{24}NO_2$ (MH^+) 274.1807, found 274.1807; Anal. calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found C, 74.34; H, 8.23; N, 4.99.

2-Acetyl-9-(*tert*-butoxycarbonyl)-5-hydroxy-9-azabicyclo[4.2.1]nonane (6). Using a modification of the method of Rapoport,[7d] di-*tert*-butyl dicarbonate (4.8 g, 22 mmol) was added to a solution of **5** (3 g, 11 mmol) in methanol (120 mL) followed by 10% Pd / C (480 mg), and the resulting suspension was hydrogenated (balloon) for 3 h. The catalyst was filtered off and thoroughly washed with methanol (50 mL), and the combined filtrates were evaporated. The residue was diluted with Et_2O, washed with saturated $NaHCO_3$, brine and dried. Filtration and evaporation, provided a pale oil which was purified by column chromatography (Et_2O) to yield **6** as a colourless oil (2.6 g, 83%) that crystallised upon storage at 0 °C: mp 87-89 °C; TLC (EtOAc) R_f 0.34; IR (neat) 3399, 1710, 1687; ^1H NMR δ (two rotamers 4 / 1) 1.39 and 1.45 (s, 9H), 1.40-1.57 (m, 1H), 1.70-2.08 (m, 6H), 2.20 and 2.27 (s, 3H), 2.35 (dd, J = 15.7, 7.3 Hz, 1H), 2.44-2.54 (m, 1H), 3.92 and 3.98 (br, 1H), 4.18 and 4.32 (br, 1H) 4.47 and 4.49 (d, J = 9.16 Hz, 1H); ^{13}C NMR δ 20.98, 21.33 (2), 21.55, 21.92 (2), 28.08 (3), 28.35 (3), 29.65, 30.48 (2), 33.73, 35.10 (2), 54.80, 55.11 (1), 60.07, 60.27 (1), 60.47, 60.87 (1), 69.89, 71.11 (1), 80.60 (0), 153.33 (0), 208.05 (0);

CIMS *m/z* (rel intens) 284 (MH^+, 54), 245 (MH^+ - $(H_3C)_2CCH_2$ + NH_3, 27), 228 (MH^+ - $(H_3C)_2CCH_2$, 100), 184 (MH^+ - Boc, 51), 70 (24); HRMS, *m/z* calcd for $C_{15}H_{26}NO_4$ (MH^+) 284.1862, found 284.1862; Anal. calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found C, 63.51; H, 8.96; N, 4.93.

2-Acetyl-9-(*tert*-butoxycarbonyl)-5-iodo-9-azabicyclo[4.2.1]nonane (7). A solution of alcohol **6** (1g, 3.5 mmol) in dichloromethane (10 mL) was added to a mixture of triphenylphosphine (1.16 g, 4.4 mmol, 125 mol%), imidazole (960 mg, 14.1 mmol, 400 mol%), and iodine (1.16 g, 4.6 mmol, 130 mol%) in dichloromethane (30 mL). The resulting mixture was allowed to stir at room temperature for 1 h and then washed with 10% Na_2CO_3 (30 mL), $NaSO_3$ (30 mL), and brine (30 mL). The separate aqueous layers were back extracted with dichloromethane (30 mL) and the combined organic phase was dried, and filtered through a 2" pad of silica. Elution with Et_2O and evaporation provided the iodide as a colourless oil (1.2 g, 86%) that crystallised upon storage at 0 °C: mp 84-86 °C; TLC (Et_2O / hexane, 1/1) R_f 0.23; IR ($CDCL_3$) 1710, 1687; ^1H NMR δ (two rotamers 5 / 6) 1.40-1.69 (m, 2H), 1.44 and 1.45 (s, 9H), 1.88-2.30 (m, 5H), 2.21 and 2.24 (s, 3H), 2.47-2.53 (m, 2H), 4.26, 4.36, 4.48, 4.71 and 4.83 (m, 3H); ^{13}C NMR δ 20.27, 20.82, 22.36 (2), 27.86, 27.92 (3), 28.21 (3), 30.18, 30.68 (1), 31.24, 32.29, 32.80, 33.46 (2), 44.98, 46.22, 49.88, 51.16, 51.25, 52.00 (1), 80.35 (0), 153.59, 153.68 (0), 208.09, 208.58 (0); EIMS *m/z* (rel intens) 393 (M^+, 4), 320 (M^+ - $(H_3C)_2CCH_2$ - H_2O, 11), 292 (M^+ - Boc, 8), 266 (M^+ - I, 18), 250 (21), 210 (7), 166 (100), 122 (12), 82 (14), 57 (60); HRMS, *m/z* calcd for $C_{15}H_{24}INO_3$ (M^+) 393.0800, found 393.0802; Anal. calcd for $C_{15}H_{24}INO_3$: C, 45.81; H, 6.15; N, 3.56. Found C, 45.81; H, 6.18; N, 3.55.

2-Acetyl-9-(*tert*-butoxycarbonyl)-9-azabicyclo[4.2.1]nonane (8). A solution of AIBN (46 mg, 0.28 mmol, 10 mol%), and tri-n-butyltin hydride (0.91 mL, 3.3 mmol, 120 mol%) in toluene (10 mL) was added to a solution of the iodide **7** (1.1 g, 2.8 mmol) in toluene (15 mL), and the reaction mixture was refluxed for 30 min. After cooling, the reaction mixture was concentrated and then diluted with ethyl acetate (30 mL). Potassium fluoride dihydrate (2 g, 20 mmol) was dissolved in a minimum volume of H_2O and added to the vigorously stirred solution. After 30 min, the resultant tri-n-butyltin iodide was removed by filtration through celite, washed with ethyl acetate and the organic layer concentrated to afford a colourless oil. Purification using column chromatography (Et_2O / hexane, 3/2) provided Boc-dihydroanatoxin as a colourless oil (640 mg, 86%): TLC (Et_2O / hexane, 1/1) R_f 0.23; IR (neat) 1710, 1687; ^1H NMR δ (two rotamers 9 / 10) 1.43 and 1.45 (s, 9H), 1.47-2.30 (m, 10H), 2.21 and 2.25 (s, 3H), 2.49-2.53 (m, 1H), 4.15 and 4.32 (m, 1H), 4.45 and 4.55 (m, 1H); ^{13}C NMR δ 23.33, 23.53 (2), 27.80, 28.16 (2), 29.07, 29.24, 29.69 (3), 29.79, 29.93 (1), 34.37, 35.14, 35.43, 36.98 (2), 57.14, 57.63 (1), 62.40, 62.92 (1), 80.61, 81.51 (0), 154.62, 155.10 (0), 210.07, 211.31 (0); EIMS *m/z* (rel intens) 267 (M^+, 13), 194 (M^+ - $(H_3C)_2CCH_2$ - H_2O, 24), 167 (M^+ - Boc, 60), 149 (13), 124 (54), 96 (55), 82 (61), 57 (100); HRMS, *m/z* calcd for $C_{15}H_{25}NO_3$ (M^+) 267.1834, found 267.1829.

9-(*tert*-Butoxycarbonyl)-2-((Z)-1-(dimethyl-*tert*-butylsiloxy)ethylidene)-9-azabicyclo[4.2.1]nonane (9). This was prepared exactly according to the method of Rapoport,[7d] using (**8**) (610 mg, 2.3 mmol) to yield the silyl enol ether as a colourless oil (820 mg, 94%): ^1H NMR δ (two rotamers) 0.04, 0.09, 0.10 and 0.13 (s, 6H), 0.79 and 0.80 (s, 9H), 1.1-2.1 (m, 9H), 1.28 and 1.31 (s, 9H), 1.67 (s, 3H), 2.15 (dd, J = 14.7, 7.0 Hz, 1H), 4.11 and 4.23 (m, 1H), 4.72 and 4.76 (d, J = 8.4 Hz, 1H).

2-Acetyl-9-(*tert*-butoxycarbonyl)-9-azabicyclo[4.2.1]nonane (10). This was prepared exactly according to the method of Rapoport,[7b,d] using (**9**) (820 mg, 2.2 mmol) to yield Boc-anatoxin as a colourless oil (460 mg, 81%): ^1H NMR δ (two rotamers) 1.38 and 1.45 (s, 9H), 1.6-1.7 (m, 3H), 2.1-2.5 (m, 5H), 2.30 (s, 3H), 4.30 and 4.42 (m, 1H), 5.14 and 5.19 (m, 1H), 6.84 (t, J = 5.9 Hz, 1H). Boc-anatoxin was prepared from an authentic sample of anatoxin and gave identical TLC and ^1H NMR spectrum. Boc deprotection of (**10**) was carried out using TFA to provide anatoxin, which gave identical TLC and ^1H NMR characteristics to the authentic sample.

ACKNOWLEDGEMENTS

We thank Professor R. C. Cookson for his continued interest in this work and Tocris-Cookson Ltd for generous financial support. We thank Dr. Adrian Shell for help in the preparation of this manuscript.

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(*Received* 18 *January* 1996; *accepted* 12 *July* 1996)