Letter

Synthesis of (+)- and (−)-Anatoxin-a via Classical Diastereomeric Salt Resolution

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(+)-Anatoxin-a (**1**) (Fig. 1), the exogenic toxin from the blue–green algae *Anabaena flos-aquae* has, over the last years, been the subject of numerous chemical, pharmacological and toxicological investigations. The toxin, being one of the most potent nicotinic receptor agonists known, has found its place as a very useful ligand for receptor-binding studies. Analogues of anatoxin-a may in the future become of value for clinical use in treating disorders associated with defects in cholinergic regions of the central nervous system. Alzheimers disease, muscular dystrophy and *Myastenia gravis* are examples of disorders with such characteristics.[1]

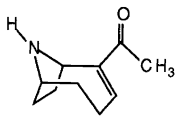

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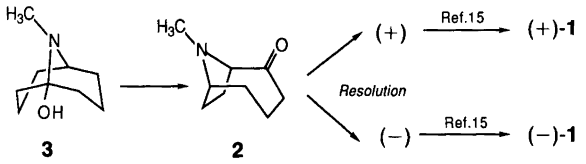
Fig. 1. Anatoxin-a (**1**).

Many synthetic approaches have been used for the preparation of anatoxin-a.[2–15] Of these, only the schemes designed by Campbell *et al.*[2] and Rapoport *et al.*[5] led to optically pure material. Thus the former group obtained (+)-**1** starting from cocaine while the latter prepared both enantiomers of **1** via a stereospecific route. Our own recently published method[15] where the bicyclic amino ketone **2** is a key intermediate, has now been updated to include the optical resolution (briefly mentioned in Ref. 16) of said ketone. In addition, we developed a slightly better modification of a very reliable method[6] for the preparation of **2** from 1,5-cyclooctadiol via the amino alcohol **3**. Thus, by using freshly prepared trimethylammonium perbromide hydrobromide instead of the corresponding pyridinium salt, time- and material-consuming purification steps to eliminate pyridine traces could be avoided.



Scheme 1. Pathway to (+)- and (−)-anatoxin-a.

The resolution of **2** was performed by fractional crystallisation of its (+)- and (−)-dibenzoyltartaric acid salts from ethanol. The progress of the resolution was followed by gas chromatography on a chiral capillary column. The column at hand did not separate the enantiomers of **2** unless they were converted into their corresponding oxime derivatives.

The optical isomers of anatoxin-a were then prepared according to our previously described method[15] from (+)- and (−)-**2**, respectively.

Experimental

NMR spectra were recorded on a JEOL FX 90 Q spectrometer operating at 90 MHz (^{1}H) or 22.5 MHz (^{13}C). Tetramethylsilane was used as an internal standard and deuteriochloroform as the solvent. Mass spectra were recorded at 70 eV using a JEOL D300 spectrometer. Gas chromatography was performed with a Hewlett-Packard HP 5830 gas chromatograph using a Chirasil-D-Val capillary column.

9-Methyl-9-azabicyclo[4.2.1]nonan-2-one (**2**). A mixture of 9-methyl-9-azabicyclo[3.3.1]nonan-1-ol (**3**, 1.0 g, 6.0 mmol) in 40 ml of acetic acid was heated at 80 °C for 3 h. Freshly prepared trimethylammonium perbromide hydrobromide (2.0 g, 6.0 mmol) was added and the temperature was kept at 80 °C for 3 h, after which the reaction was heated under reflux overnight. After being cooled, the mixture was evaporated and basified with potassium carbonate then extracted three times with diethyl ether. The organic layers were dried (magnesium sulfate), filtered and evaporated to yield 0.65 g (66 %) of the desired product. The ^{1}H NMR, ^{13}C NMR and MS data matched the data of Ref. 6.

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Resolution of compound **2**. The amino ketone **2** (10.5 g, 68.6 mmol) was dissolved in 100 ml of 99 % ethanol. To this solution, heated slowly to 40 °C, were added carefully 25.8 g (68.6 mmol) (−)-dibenzoyltartaric acid dissolved in 100 ml of 99 % ethanol. After a few min the salt precipitated. The mixture was heated to reflux and 99 % ethanol (425 ml) was added in portions until the salt had dissolved. Precipitation overnight at ambient temperature afforded a salt which, after five additional recrystallizations, on treatment with 2 M sodium hydroxide, ether extraction and drying (magnesium sulfate) gave 2.0 g of (−)-**2** with 98 % ee. Likewise a salt was formed by treatment of 6.1 g (39.3 mmol) of enriched (+)-**2** (liberated from the mother liquors) with 15.0 g (38.9 mmol) of (+)-dibenzoyltartaric acid. On recrystallisation from ethanol (three times) this salt yielded 2.0 g of (+)-**2** with 98 % ee.

The oxime samples needed for monitoring purposes were obtained by liberating **2** from salt samples with 2 M sodium hydroxide. The amino ketone was extracted into an ethereal solution which was combined with a molar excess of hydroxylamine in water (freshly prepared from an aqueous hydroxylammonium chloride solution made alkaline with 2 M sodium hydroxide). Injection of the ethereal solution into a Chirasil-D-Val capillary gas chromatography column gave a nearly baseline separation of the two enantiomers and made it possible to monitor the progress of the resolution. (+)-**2**: $[\alpha]_D^{20} = 55.0°$ (*c* 1.0, methanol). (−)-**2**: $[\alpha]_D^{20} = -52.5°$ (*c* 1.0, methanol).

*(+)- and (−)-2-Acetyl-9-azabicyclo[4.2.1]non-2-ene hydrochloride (anatoxin-a · HCl) [(+)- and (−)-***1** *· HCl].* The enantiomers of the amino ketone **2** were subjected to the synthetic route previously reported;[15] (+)- and (−)-**2** gave (+)- and (−)-**1**, respectively. Purification of their corresponding hydrochlorides was accomplished on a silica column using chloroform/methanol 10:1 as the eluant. The ^1H NMR and MS data were identical for both enantiomers and matched the data of our earlier work.[15] (+)-**1**: $[\alpha]_D^{20} = 37.0°$ (*c* 1.0, methanol) [Lit.[5] $[\alpha]_D^{24} = 43.2°$ (*c* 0.676, abs. ethanol)]. (−)-**1**: $[\alpha]_D^{20} = 39.7°$ (*c* 1.0, methanol) [Lit.[5] $[\alpha]_D^{24} = -46.3°$ (*c* 0.574, abs. ethanol)].

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