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Synthetic Approaches to Anatoxin-a

Howard L. Mansell

Wyeth Research (U.K.) Ltd., Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH

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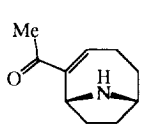
1. INTRODUCTION

Anatoxin-*a* (**1**) is a potent neurotoxin present in the filamentous freshwater blue-green microalga *Anabaena flos-aquae*, and has been responsible for the fatal poisoning of wildlife in North America. Anatoxin-*a* has also been known as Very Fast Death Factor, and has caused death by respiratory paralysis with an LD_{50} (intraperitoneal, mouse) of 0.2 mg kg^{-1}.[1]



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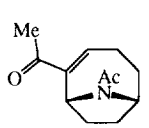


2

The isolation of anatoxin-*a* (**1**) was originally reported in 1977, and the structure was confirmed by X-ray crystallographic analysis of the *N*-acetyl derivative **2**.[2,3] The spectral and physical properties of anatoxin-*a* have been investigated thoroughly.[4] Recent computational studies suggested that owing to intramolecular electrostatic interactions, the most stable conformation of the protonated form was the chair *s-trans* enone (Figure 1).[5] However, molecular mechanics have shown that the hydrochloride salt conformer with minimum energy was the *s-cis* enone.[6]

Figure 1 *s*-cis *s*-trans

Anatoxin-*a* (**1**) is a potent and stereospecific agonist at nicotinic acetylcholine receptors.[7] Owing to its importance as a pharmacological probe, and to the fact that anatoxin-*a* was until recently the only naturally occurring alkaloid which contains the 9-azabicyclo[4.2.1]nonane skeleton, it has attracted much synthetic interest. A number of synthetic approaches to anatoxin-*a* and its analogues have been devised, and a discussion of these synthetic approaches from acyclic or commercially available cyclic starting materials in approximate chronological order is presented in this review.

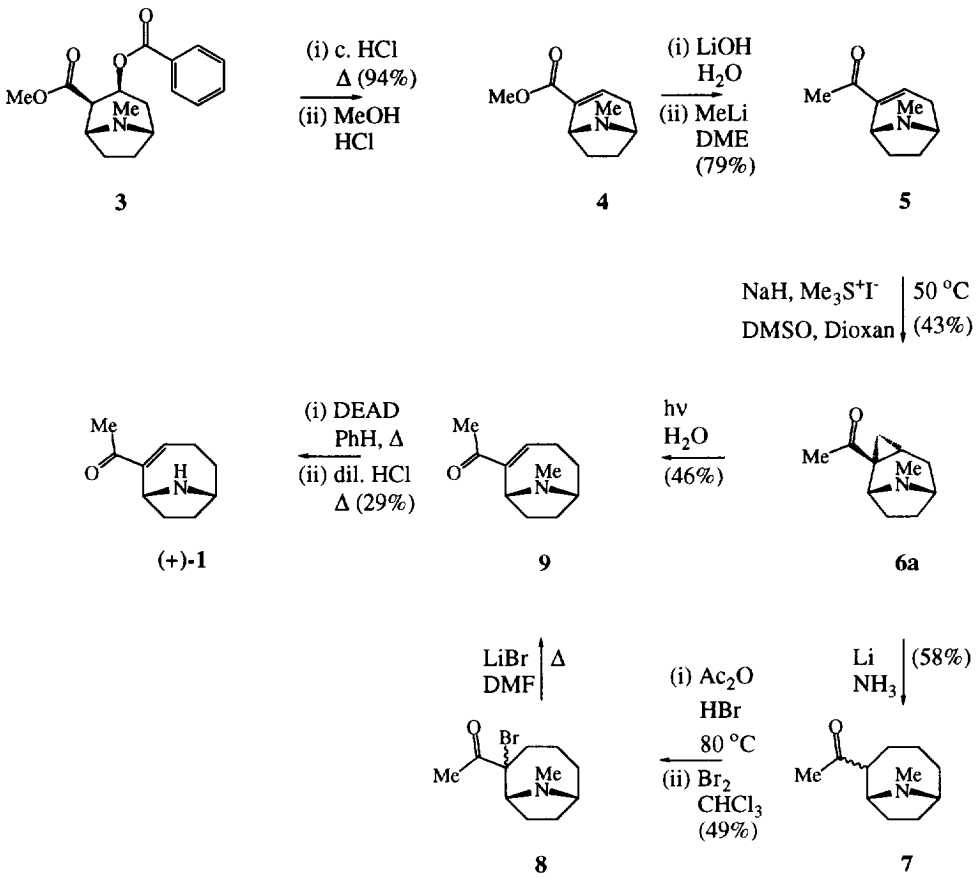
2. RING EXPANSION OF TROPANES

The majority of the early syntheses of anatoxin-*a* (**1**) afforded the natural product as the racemate. However, the earliest synthesis was asymmetric and started with cocaine (**3**) (Scheme 1). This synthesis came from the Edwards group, which also reported the isolation of anatoxin-*a*.[8]

(-)-Cocaine (**3**) was hydrolysed with concentrated hydrochloric acid with the loss of benzoic acid and methanol to give anhydroecgonine, which was reesterified with dry methanol and anhydrous hydrogen chloride to give anhydroecgonone methyl ester (**4**). The enone **5** was obtained from the hydrochloride salt of the ester **4** in two steps by treatment with two equivalents of lithium hydroxide, and then methylation of the intermediate lithium salt of anhydroecgonine with methyllithium in ethylene glycol dimethyl ether.

Treatment of the enone **5** with trimethylsulfoxonium iodide and sodium hydride gave rise to the formation of two cyclopropanes (70%) as a 65:35 mixture of *endo* **6a** and *exo* **6b** diastereomers, which were separated by chromatography. When the ring expansion of the mixture of cyclopropanes was attempted, differences were observed between the reactivity of the *endo* and *exo* diastereomers.

The *endo* cyclopropane **6a** was treated with lithium in liquid ammonia to afford the ketone **7** as a 1:2 mixture of diastereomers. When this reaction was carried out with the *exo* cyclopropane, reduction of the carbonyl function was observed and the alcohol **10** was formed (Scheme 2).

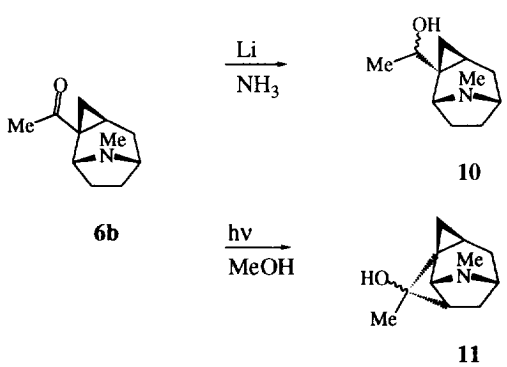


3 **4** **5**

(+)-1 **9** **6a**

8 **7**

Scheme 1



6b **10** **11**

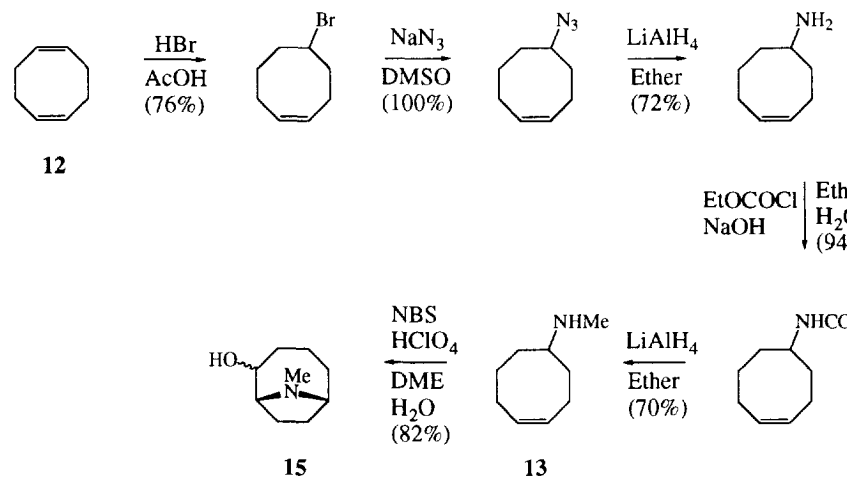
Scheme 2

Alternatively, the photochemical irradiation of the *endo* cyclopropane **6a** gave the enone *N*-methylanatoxin-*a* (**9**). The photolysis of the *exo* cyclopropane **6b** produced an epimeric mixture of alcohols **11**, which had arisen from the formation of a bond between the ethano bridge and the carbon atom of the carbonyl function, and the *exo* cyclopropane ring was preserved.

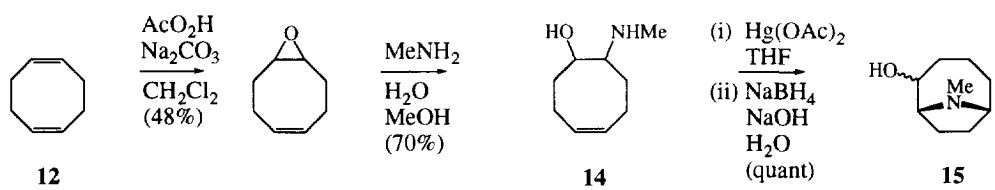
The bicyclic ketone **7** was converted to *N*-methylanatoxin-*a* (**9**) *via* a three step sequence which involved enol acetate formation, bromination and dehydrobromination. Subsequent demethylation of *N*-methylanatoxin-*a* to natural anatoxin-*a* (**1**) {hydrochloride salt: $[\alpha]_D$ +36° (c 0.85 in EtOH)} was achieved by treatment with diethyl azodicarboxylate and hydrolysis with acid. Although the demethylation of *N*-methylanatoxin-*a* by treatment with 2,2,2-trichloroethyl chloroformate was originally reported to be troublesome, success with this demethylation reaction was subsequently claimed by Chinese workers.[8,9]

3. CYCLISATION OF CYCLOOCTANES

The first total synthesis of racemic anatoxin-*a* (**1**) was also achieved by the Edwards group, and proceeded *via* the two 4-cyclooctenylamines **13** and **14**, which are readily accessible from 1,5-cyclooctadiene (**12**).[10-12]



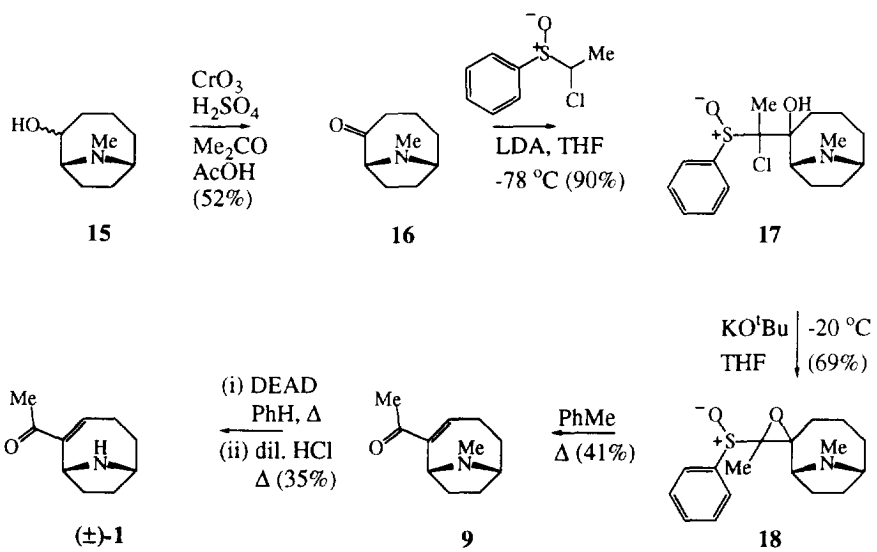
Scheme 3



Scheme 4

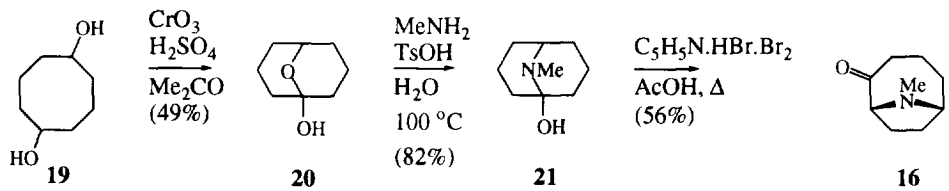
The sequential addition of hypobromous acid, prepared from perchloric acid and *N*-bromosuccinimide, to the methylamine **13** and treatment with base afforded an epimeric mixture of alcohols **15** (Scheme 3).[13] Alternatively, an epimeric mixture of alcohols **15** was prepared from the 4-cyclooctenol **14** by treatment with mercury (II) acetate and demercuration with alkaline sodium borohydride (Scheme 4).[14] In each cyclisation reaction, small amounts (*c.* 5%) of the structurally isomeric bicyclo[3.3.1]nonanols were also formed, but this material was removed during the purification of the bicyclic ketone **16** produced by oxidation of the epimeric mixture of alcohols **15** with Jones reagent (Scheme 5).

The bicyclic ketone **16** was elaborated to *N*-methylanatoxin-*a* (**9**) in three steps. Initial treatment with chloroethyl phenyl sulfoxide (prepared in three steps from thiophenol) and lithium diisopropylamide yielded the adduct **17**. When this adduct was treated with potassium *tert*-butoxide, the epoxide **18** was formed, and this underwent loss of the elements of benzenesulfenic acid to furnish *N*-methylanatoxin-*a*.



15 **16** **17** **18** (±)-**1** **9**

Scheme 5

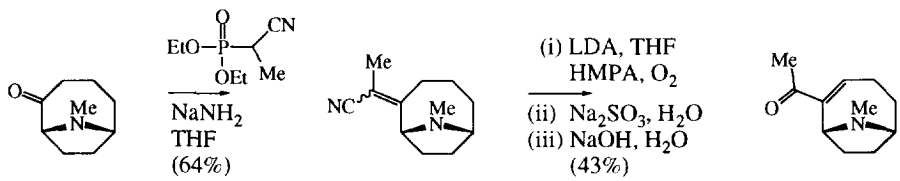


19 **20** **21** **16**

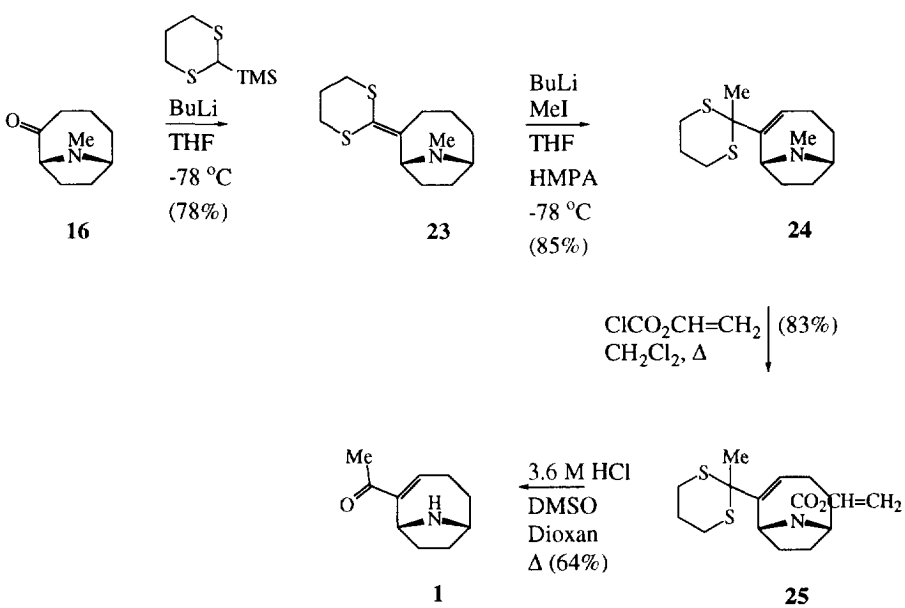
Scheme 6

The bicyclic ketone **16** has also been prepared from 1,5-cyclooctanediol (**19**) by the sequence shown in Scheme 6.[15] Thus, 1,5-cyclooctanediol underwent oxidation with chromic acid to afford the hemiketal **20**, and this gave the amino alcohol **21** when treated with hot aqueous methylamine and subsequently hydrolysed with sulfuric acid.[16] This amino alcohol underwent bromination with pyridinium bromide perbromide in hot acetic acid to yield the bicyclic ketone **16**. The purification of this ketone was reported to be easier if the bromination reaction was carried out with freshly prepared trimethylammonium perbromide hydrobromide.[17]

The bicyclic ketone **16** was also elaborated to *N*-methylanatoxin-*a* (**9**) *via* the enonitrile **22** (Scheme 7). This enonitrile was prepared as a 3:2 mixture of *Z* and *E* isomers from the ketone **16** by treatment with diethyl (1-cyanoethyl)phosphonate,[18] and underwent oxidation with lithium diisopropylamide and oxygen to give an intermediate hydroperoxide. This hydroperoxide was subjected to sequential reduction with sodium sulfite and hydrolysis with sodium hydroxide to give *N*-methylanatoxin-*a*.



Scheme 7

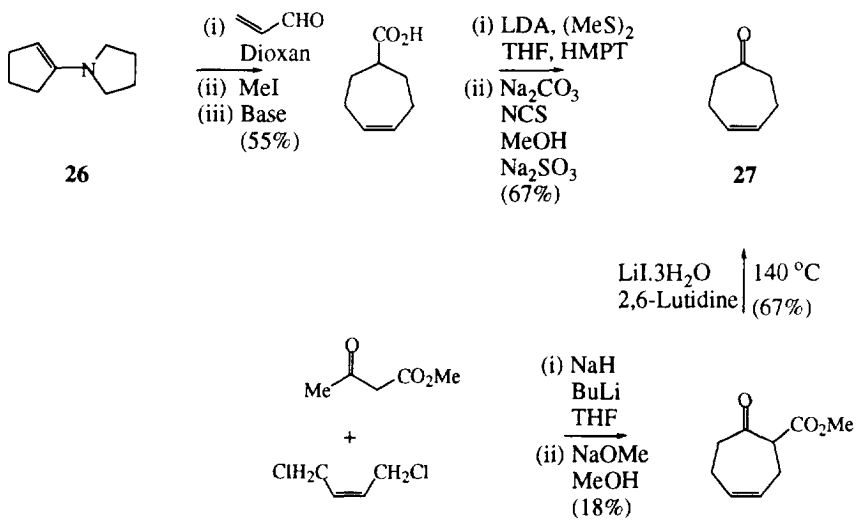


Scheme 8

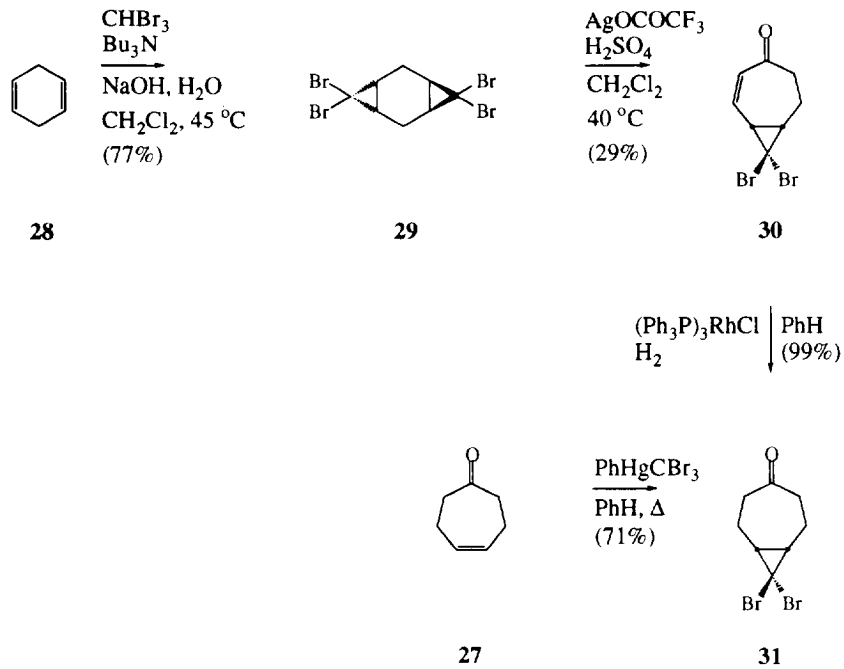
In Stjernlof's synthesis (Scheme 8), anatoxin-*a* (**1**) was prepared from the bicyclic ketone **16** using [1,3]dithiane chemistry.[19] The ketone **16** was treated with 2-(trimethylsilyl)[1,3]dithiane and butyllithium to give the ketene dithioketal **23**. The methyl group on the side chain of anatoxin-*a* was introduced by treatment of this dithioketal with butyllithium and iodomethane, and this resulted in both methylation at C-2 of the dithiane group and isomerisation of the C=C bond to furnish the enone dithioketal **24**. Anatoxin-*a* was obtained from this dithioketal *via* the vinyl carbamate **25** by sequential treatment with vinyl chloroformate and hydrolysis with acid. Classical diastereomeric salt resolution of the bicyclic ketone **16** with (-)- and (+)-dibenzoyltartaric acids prior to elaboration to the final target facilitated the synthesis of anatoxin-*a* (**1**) as a single enantiomer.[17]

For the synthesis of an appropriately substituted cyclooctane derivative, Danheiser's strategy employed the chemistry of dibromocyclopropanes (Scheme 10).[20] The bicyclo[5.1.0]octanone **31** was prepared by the treatment of 4-cycloheptenone (**27**) with the Seyferth reagent phenyl(tribromomethyl)mercury.[21] 4-Cycloheptenone was obtained either from 1-pyrrolidino-1-cyclopentene (**26**) or from alicyclic precursors (Scheme 9).[22,23]

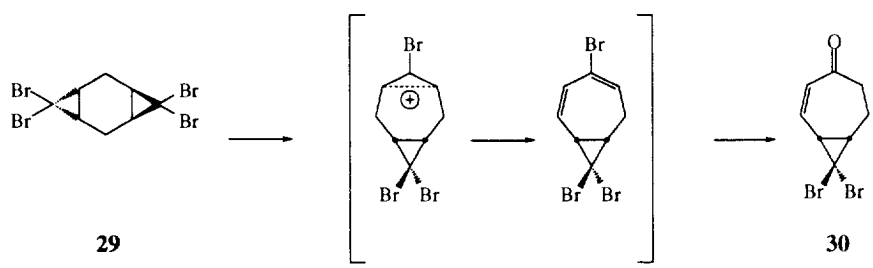
Alternatively, the more readily available 1,4-cyclohexadiene (**28**) underwent a phase transfer catalysed reaction with bromoform to furnish the tetrabromotricyclooctane **29**. This tetrabromotricyclooctane underwent an acid mediated, two phase ring expansion to produce the enone **30**, and the mechanism of this ring expansion is depicted in Scheme 11. The enone **30** was hydrogenated with Wilkinson's catalyst to give the bicyclo[5.1.0]octanone **31**.



Scheme 9

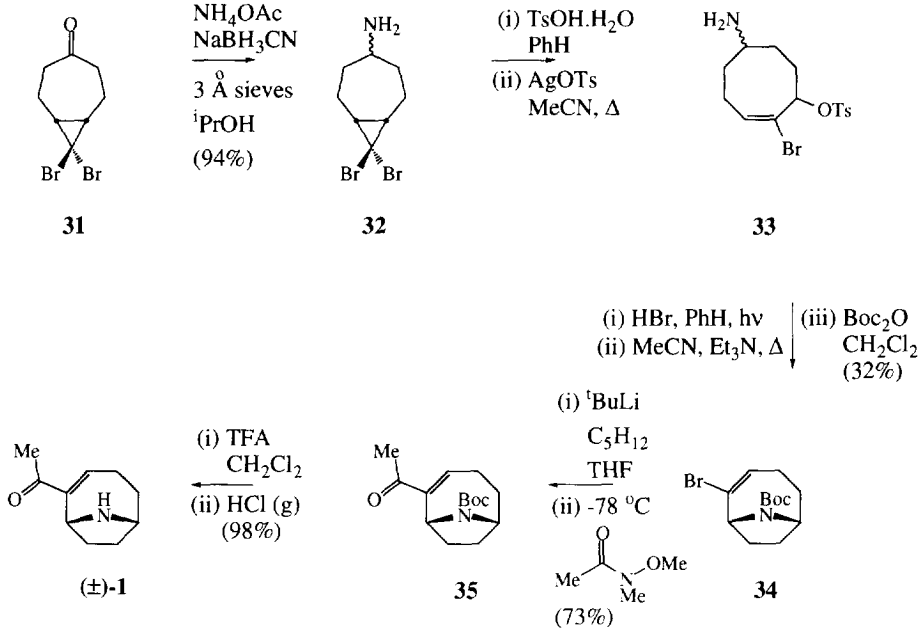


Scheme 10



Scheme 11

Reductive amination of the bicyclo[5.1.0]octanone **31** with ammonium acetate and sodium cyanoborohydride gave the primary amine **32** as a 5:2 mixture of diastereomers (Scheme 12). This mixture of primary amine diastereomers was heated with silver tosylate to give a mixture of 4-cyclooctenylamines **33**. Cyclisation of this mixture of 4-cyclooctenylamines to the bicyclic vinyl bromide **34** was achieved *via* a three step sequence which involved: photochemical isomerisation of the hydrobromide salts; prolonged heating with triethylamine; and treatment with di-*tert*-butyl dicarbonate (Boc_2O).



Scheme 12

The vinyl bromide **34** was treated with *N*-methoxy-*N*-methylacetamide and *tert*-butyllithium to provide *N*-*t*-Boc-anatoxin-*a* (**35**), and the hydrochloride salt of racemic anatoxin-*a* (**1**) was obtained from this by sequential treatment with trifluoroacetic acid and hydrogen chloride gas.

4. CYCLISATION OF IMINIUM SALTS

4.1 *Alkyl iminium salts*

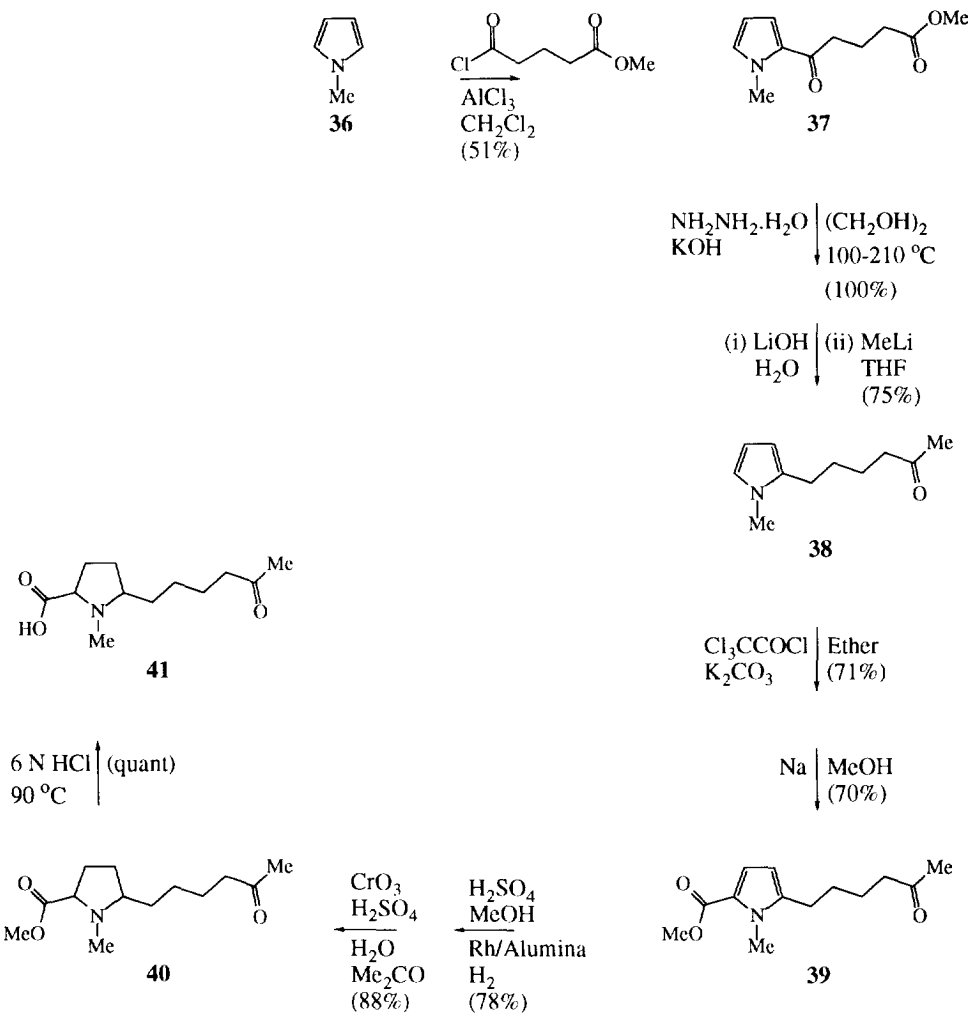
The contribution of the Rapoport group to the asymmetric synthesis and generation of structure activity information of anatoxin-*a* (**1**) and its analogues has been considerable.[24,25] Their first synthesis *via* iminium salts of advanced precursors of anatoxin-*a* afforded racemic products.[26]

The iminium salt **42** was formed when the substituted pyrrolidine-2-carboxylic acid **41** was decarbonylated using phosphorus oxychloride (Scheme 14).[27] This iminium salt was cyclised in refluxing methanol to furnish the bicyclic ketone **7** as a single diastereomer.

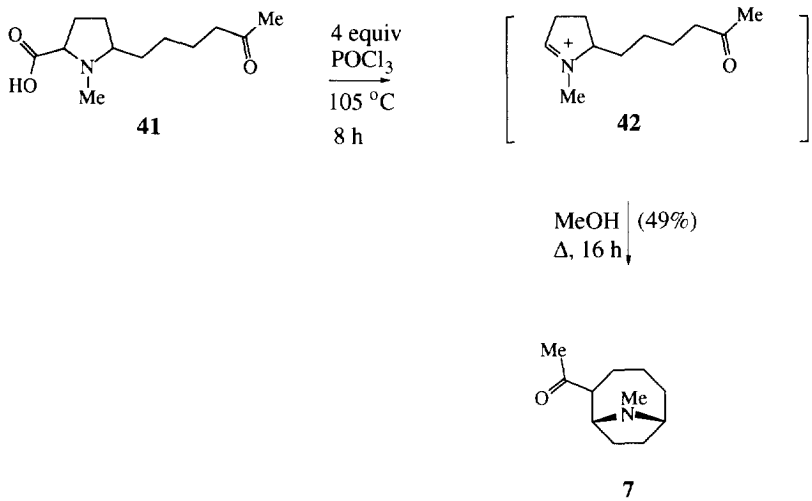
Once the iminium salt **42** had been generated, it was liable to undergo two fates: either reversible cyclisation to the ketone **7** or irreversible polymerisation. In the case of the iminium salt **42**, the formation of the ketone **7** was favoured by the position of equilibrium for cyclisation, no decomposition of this ketone was observed in acid at 20 °C, and the rate of polymerisation of the cyclised ketone **7** under basic conditions was slow.

However, this study also showed that for the intramolecular reaction of iminium salts with carbon nucleophiles of the malonic ester type **43** (Scheme 15), cyclisation in anhydrous methanol was not favoured (yield 2%), the diester **44** underwent steady decomposition to the iminium salt **43** in aqueous acid, and the rate of polymerisation of the diester **44** at alkaline pH was rapid. The yield of diester **44** was raised to 24% if the cyclisation of the iminium salt **43** was carried out in water at pH 9.8 and at 0→20 °C with minimal contact time.

The differences of both the positions of equilibrium of cyclisation and the stabilities of the products **7** and **44** were attributed to the steric strain of the product. The products of cyclisation **7** and **44** were purified by Kugelrohr distillation.

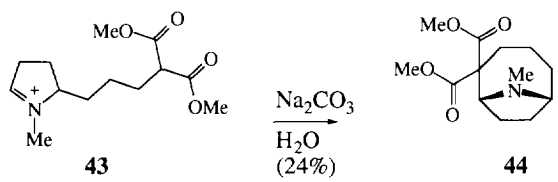


Scheme 13



41 **42** **7**

Scheme 14



43 **44**

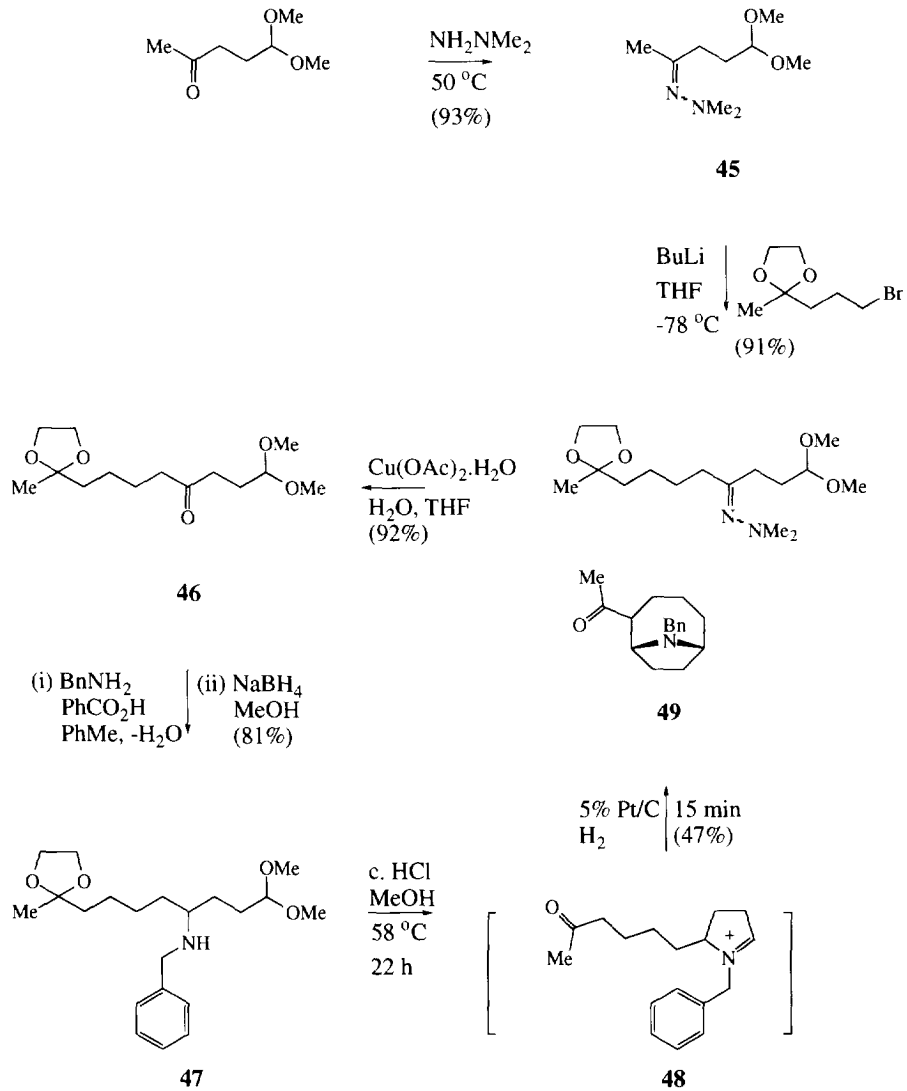
Scheme 15

The iminium salt precursor **41** was constructed from 1-methylpyrrole (**36**) (Scheme 13). 1-Methylpyrrole was acylated with methyl glutaryl chloride to produce the ketoester **37**, and the methyl ketone **38** reacted with trichloroacetyl chloride to afford the ketoester **39**.[28] The carboxylic acid **41** was prepared from the ketoester **39** *via* a three step sequence which involved: hydrogenation over rhodium on alumina; reoxidation of the intermediate secondary alcohol with Jones reagent; and acid hydrolysis of the pyrrolidine ester **40**.

In another approach to the synthesis of racemic precursors to anatoxin-*a* (**1**), Rapoport reported the synthesis of the ketone **49** from acyclic starting materials (Scheme 16).[29] Thus, 5,5-dimethoxy-2-pentanone, 1,1-dimethylhydrazone (**45**) underwent a butyllithium mediated alkylation at -78 °C to furnish, following regeneration of the carbonyl function, the ketone **46**. This ketone was subjected to reductive amination with benzylamine to furnish the iminium salt precursor **47**. This precursor was heated under reflux in methanol with concentrated hydrochloric acid and then hydrogenated over platinum on carbon to give the ketone **49** as the major product, although significant amounts (34%) of the uncyclised pyrrolidine side product, which had arisen by reduction of the uncyclised iminium salt **48**, were also isolated. This hydrogenation step was employed to prevent the reversal of equilibrium arising from the polymerisation of the iminium salt which is encouraged by

the formation of the basic product. The ketone **49** was obtained as a 30:70 mixture of α and β diastereomers, and was purified by MPLC.

The yields of the ketones **7** and **49**, from the cyclic and acyclic iminium salt precursors **41** and **47** respectively are of similar magnitude (47-49%).

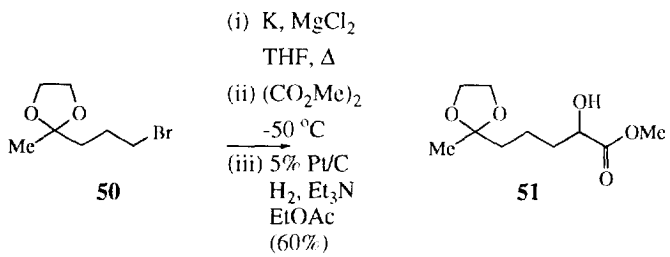


Scheme 16

Subsequent reports by Rapoport and coworkers dealt with the asymmetric synthesis of anatoxin-*a* (**1**) and its analogues. The first asymmetric synthesis of the enantiomers of anatoxin-*a* by this group appeared in 1984, and the results of some related optimisation studies were published shortly afterwards.[4,30] The protocol established by this group has also been applied to the synthesis of various hydroxyl analogues and carboxylic acid derivatives related to anatoxin-*a*.[31,32] More recently, this group has reported the synthesis of conformationally constrained ring fused analogues.[6] Rapoport and his group have also achieved the synthesis of both of the enantiomers of anatoxin-*a* from a single chiral starting material.[33]

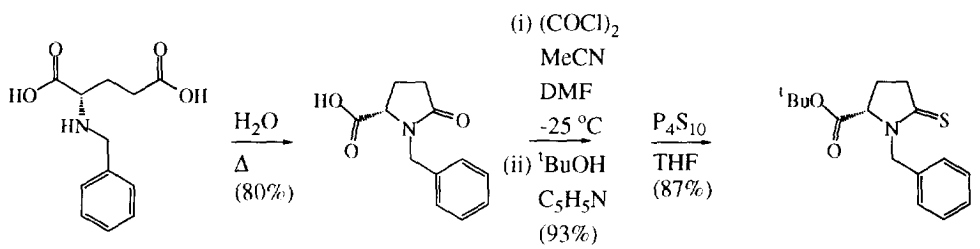
Thus, for this enantiodivergent synthesis of (+)- and (-)-anatoxin-*a* (**1**) (Scheme 19), the thiolactam **53** reacted with the triflate derivative of the alcohol **51** in the presence of triphenylphosphine and 1-methylpiperidine to furnish the vinylogous *O*-methyl carbamate **56** *via* the extrusion of sulfur.[34] This vinylogous carbamate was hydrogenated stereospecifically and in a *cis* fashion and rebenzylated, and the diester **57** was obtained as a 4:1 mixture of epimers.[33]

The alcohol precursor **51** of this triflate was obtained from 5-bromo-2-pentanone ethylene ketal (**50**) in two steps (Scheme 17) by means of a Grignard reaction with dimethyl oxalate and hydrogenation of the intermediate keto ester. The thiolactam **53** was prepared from *N*-benzyl-L-glutamic acid (**52**) in three steps as shown in Scheme 18.[30]



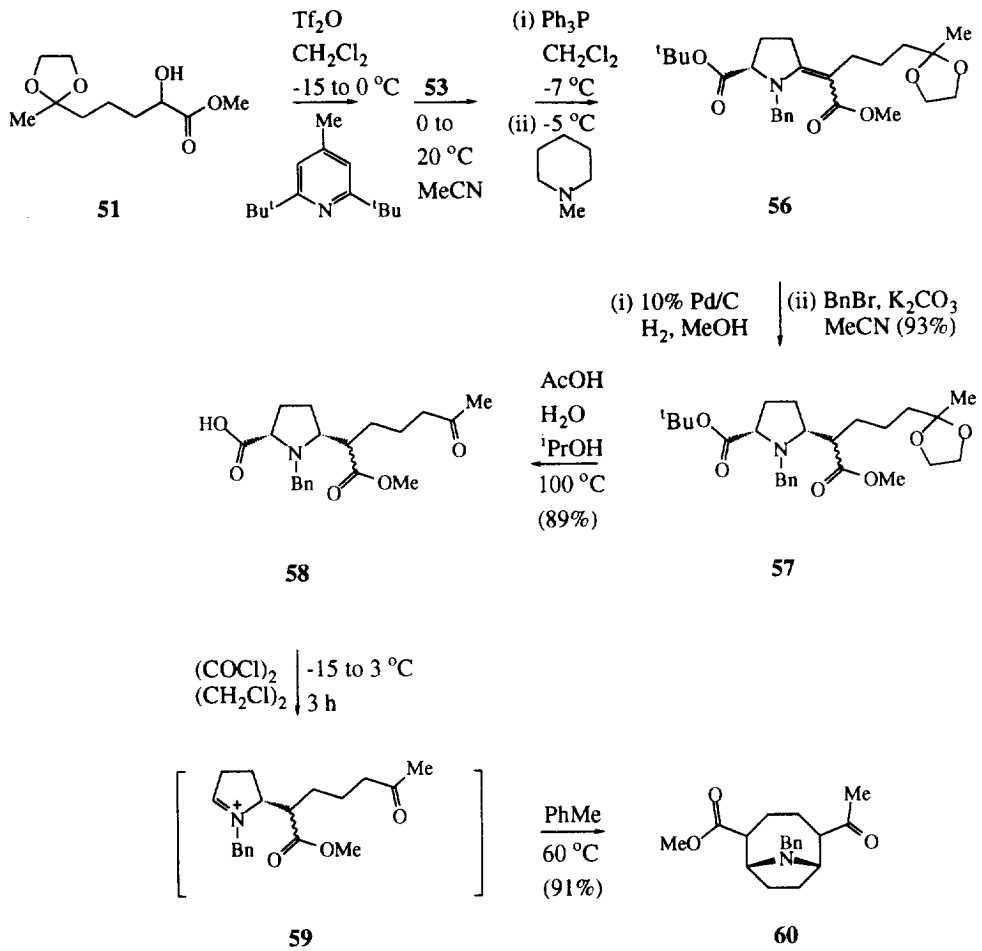
50 **51**

Scheme 17



52 **53**

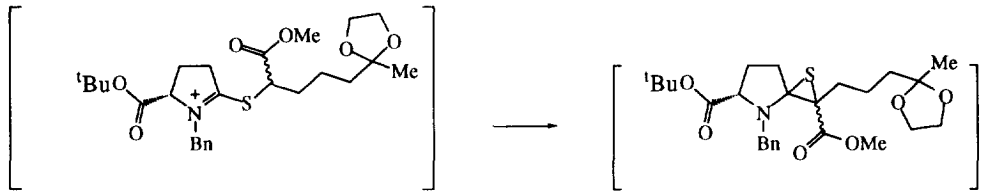
Scheme 18



Scheme 19

The major issues for this sulfur extrusion reaction were the correct choice of base to maximise regioselectivity, and the use of careful temperature control to minimise racemisation of the pyrrolidine ring at C-2.[4,35] The mechanism of formation of the vinylogous carbamate **56** is likely to involve the intermediacy of the thioiminium salt **54** and the formation of the spiroepisulfide **55** (Scheme 20).[34,36,37]

The diester **57** was hydrolysed with aqueous acid to furnish the iminium salt precursor, a chromatographically resolvable 2:7 mixture of two keto acids **58**, and cyclisation of these keto acids was effected with oxalyl chloride, which permitted the generation of the intermediate iminium salt **59** below 0 °C. The cyclisation of these keto acids produced the anatoxin-*a* precursor **60** as two distinct pairs of isomers diastereomeric at C-2 and C-5.



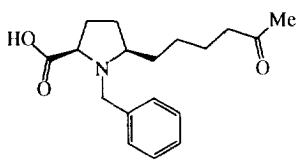
54 55

Scheme 20

Rapoport's original asymmetric synthesis of (+)-anatoxin-*a* (**1**) featured the formation of an iminium salt from the proline derivative **61**, and this iminium salt was cyclised with phosphorus oxychloride.[30] The cyclisation of the ketone **61** was subsequently improved with the substitution of phosphorus oxychloride with oxalyl chloride. Oxalyl chloride afforded gaseous side products during the generation of the iminium salt, and cyclisation in non-polar solvents, which were more likely to displace the equilibrium for cyclisation in the direction of the product.[31] During this study, attempts to effect the cyclisation of the enone **62** under these conditions were unsuccessful.

During the study of the synthesis of the carboxylic acid derivatives related to anatoxin-*a* (**1**), both the aldehyde **63** and the dimethyl acetal **64** proved to be resistant to cyclisation.[32] However, in the enantiodivergent synthesis of (+)- and (-)-anatoxin-*a*, the high yields achieved for the cyclisation of the keto acid **58** to the keto ester **60** suggested that cyclisation was enhanced by the presence of substituents on the side chain at C-5 of the pyrrolidine ring.[33]

Prior to elaboration to anatoxin-*a* (**1**) and its derivatives, the Rapoport group converted the products of the iminium salt cyclisations **49** and **60** to the corresponding *N*-*tert*-butyl carbamate derivatives. This deprotection and reprotection sequence was achieved most effectively when the hydrogenolysis of the *N*-benzyl group was carried out in the presence of Boc_2O (yield: 98%).[31]



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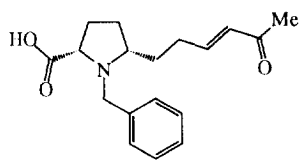

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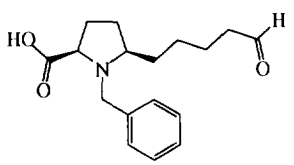

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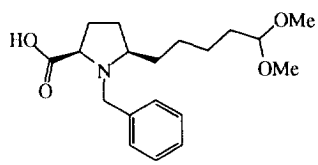
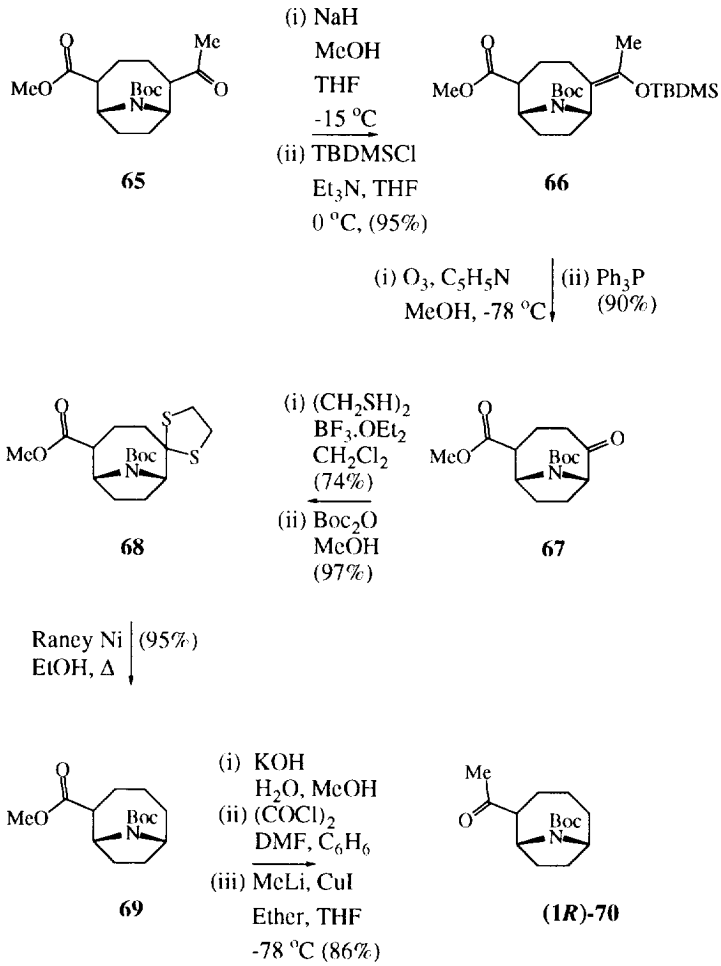


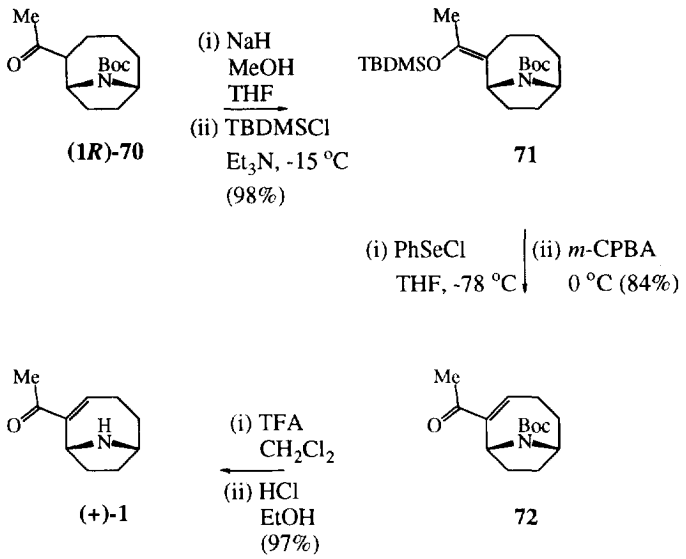
64

Thus the carbamate **65**, as a mixture of diastereomers, was elaborated to the ketone **(1*R*)-70** with the series of transformations shown in Scheme 21. The cyclic ketone **67** was prepared from the mixture of carbamates **65** by ozonolysis of the thermodynamically more stable silyl enol ether **66** formed by treatment of the latter with sodium hydride and *tert*-butyldimethylsilyl chloride. The deoxygenation of the ketone **67** was achieved *via* desulfurisation of the [1,3]dithiolane derivative **68**. The ketone **(1*R*)-70** was obtained from the product of desulfurisation **69** *via* hydrolysis of the ester functionality and treatment of the acid chloride derivative with lithium dimethylcuprate.



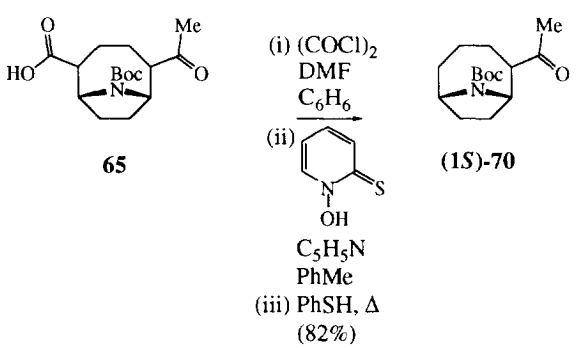
Scheme 21

The unsaturation present in anatoxin-*a* was introduced into the ketone **(1*R*)-70** by sequential treatment of the thermodynamically more stable silyl enol ether with phenylselenenyl chloride and *meta*-chloro peroxybenzoic acid, and this gave the enone **72** (Scheme 22).[31] The carbamate function of the enone **72** was removed by hydrolysis to give natural anatoxin-*a* (**1**) {hydrochloride salt: $[\alpha]_D^{24}$ +43.2° (c 0.676 in EtOH)}.[30]



Scheme 22

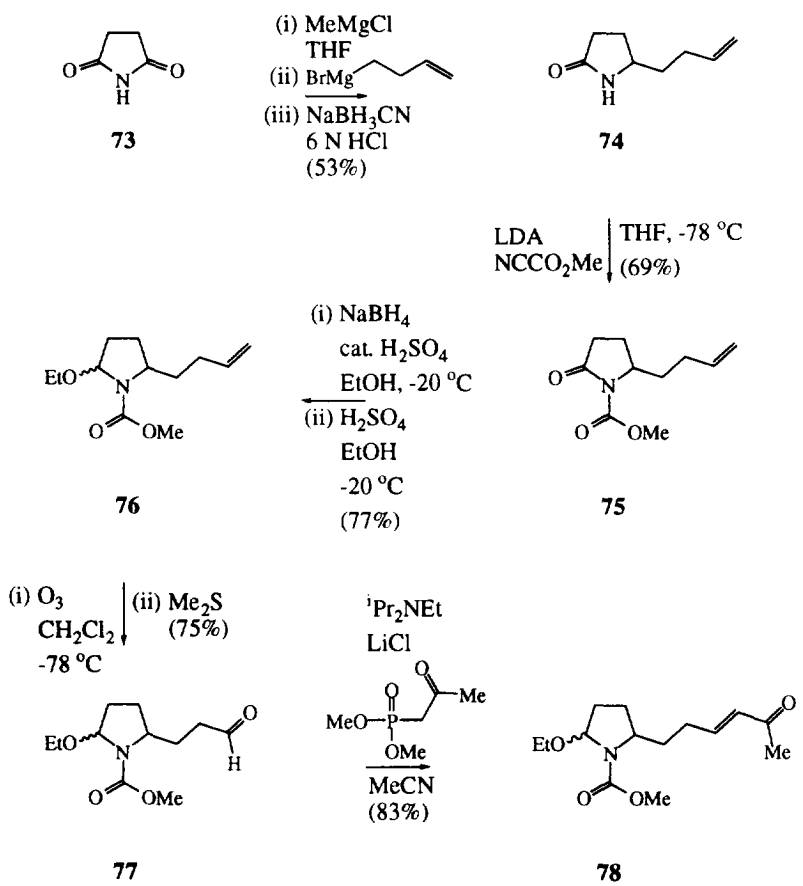
The carbamate **65** was also converted to unnatural (-)-anatoxin-*a* (**1**) *via* the ketone **(1*S*)-70** by means of the decarboxylation transformation shown in Scheme 23.[33]



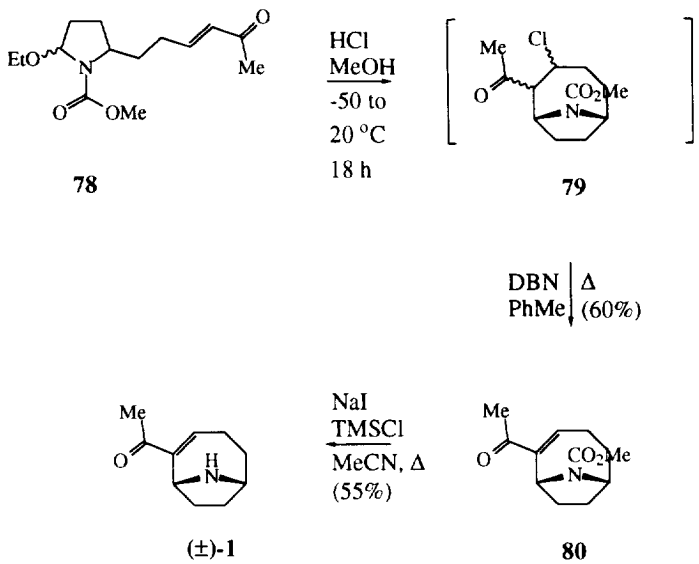
Scheme 23

4.2 Acyl iminium salts

The investigation by Rapoport and coworkers of the synthesis *via* alkyl iminium salts of anatoxin-*a* (**1**) and its analogues would appear to be exhaustive. However, other types of iminium salt have been employed elsewhere for the synthesis of anatoxin-*a*. For example, although the enone **62** failed to undergo an acid catalysed cyclisation after decarbonylation with phosphorus oxychloride, Speckamp found that the cyclisation of the enone **78** could be achieved and the 9-azabicyclo[4.2.1]non-2-ene **80** was formed (Scheme 25).[30,38] The success observed for the cyclisation of the enone **78** was probably afforded by the enhanced electrophilicity of the intermediate acyl iminium salt in comparison to the alkyl iminium salts mentioned previously.[39] Although the product of Speckamp's synthesis was a racemate, the use of acyl iminium salts also reduced number of nitrogen protection and deprotection steps which were otherwise required.



Scheme 24



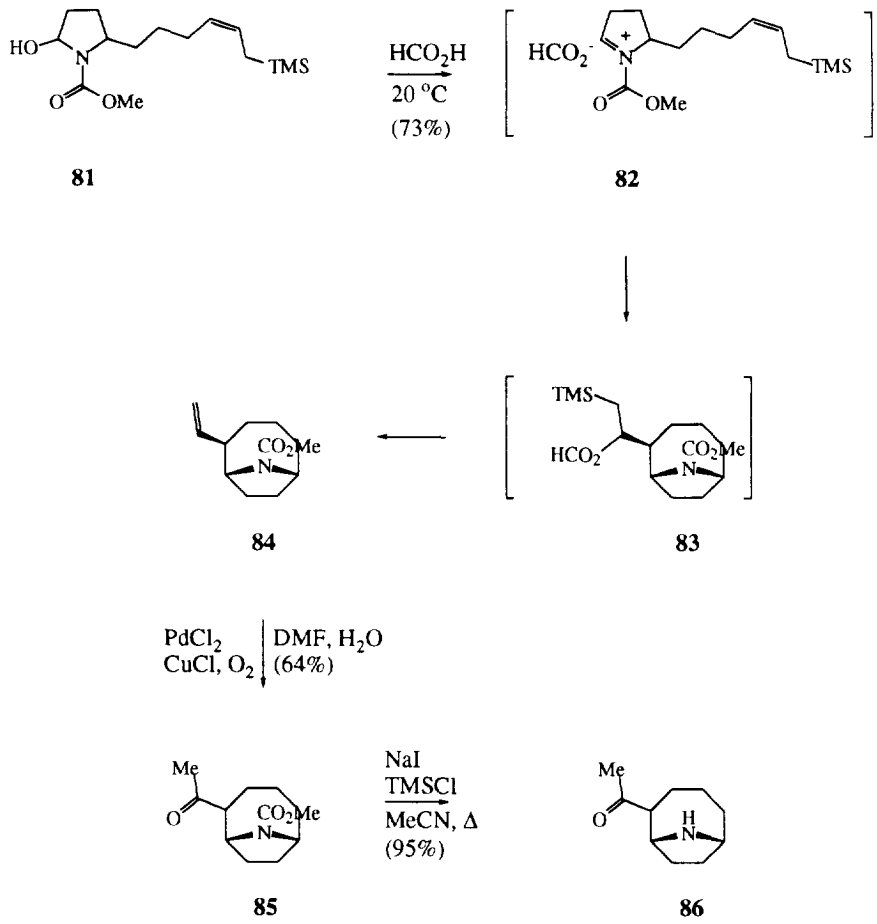
Scheme 25

The synthesis of the enone **78** is shown in Scheme 24. The 5-alkyl-2-pyrrolidinone **74** was prepared in two steps by the addition of the Grignard reagent derived from 4-bromo-1-butene to the magnesium salt of succinimide (**73**), and the intermediate acyl iminium salt formed following acidification and dehydration was reduced with sodium cyanoborohydride. The carbamate derivative **75** was reduced with sodium borohydride and subjected to sulfuric acid catalysed ethanolysis to afford the 2-ethoxypyrrolidine **76**, and this was elaborated to the enone **78** in two steps by ozonolysis and treatment of the intermediate aldehyde **77** with dimethyl (2-oxopropyl)phosphonate.[40,41]

The formation of the acyl iminium salt from the enone **78** and cyclisation to the bicyclic enone **80** were achieved by dissolution in methanol saturated with hydrogen chloride at -50 °C, and the intermediate β-chloroketone **79** was dehydrochlorinated with 1,5-diazabicyclo[4.3.0]non-5-ene in toluene at reflux. The carbamate functionality of the cyclised enone **80** was removed with iodotrimethylsilane to give racemic anatoxin-*a* (**1**).

Speckamp also achieved the synthesis of racemic anatoxin-*a* (**1**) with allylsilane derivatives (Scheme 26).[42] Thus, dissolution of the allylsilane **81** in formic acid at room temperature resulted in cyclisation to the bicyclic alkene **84**, and this was isolated as a 19:1 mixture of isomers.

The mechanism of cyclisation probably involves the initial formation of the formate iminium salt **82**.[43] The β-effect of silicon leaves the β carbon atom vulnerable to attack by formate ion and permits the existence of a nucleophilic centre γ to silicon. Thus cyclisation to the formate ester **83** is observed, and this undergoes loss of trimethylsilyl formate to give the vinyl compound **84**.



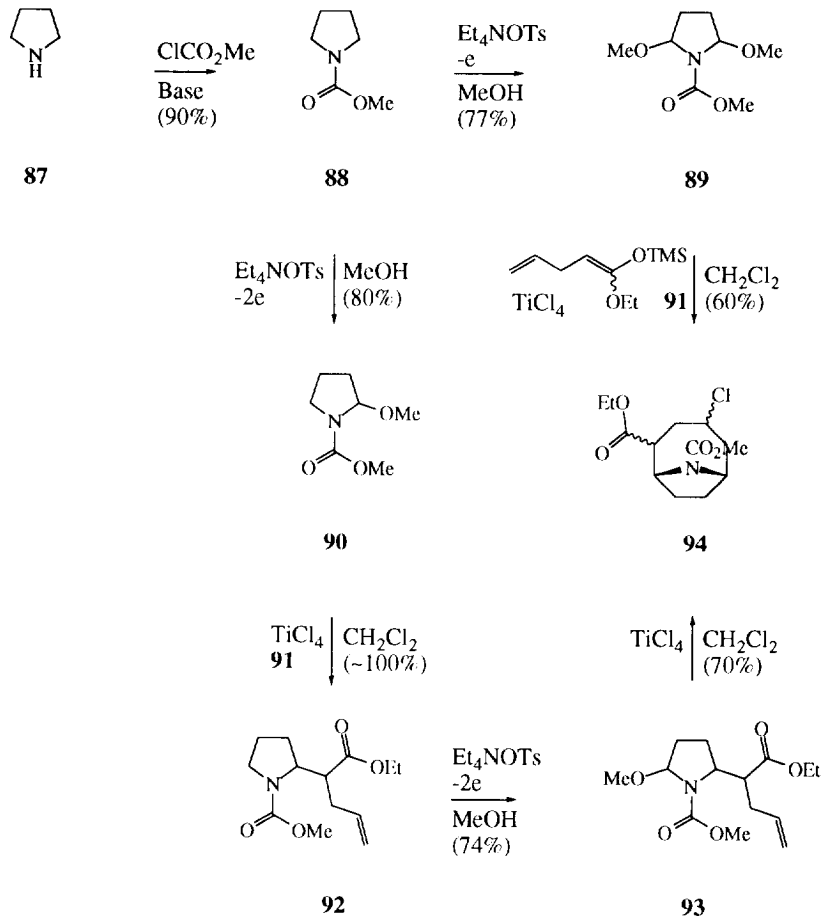
Scheme 26

The oxidation of the vinyl group of the product of cyclisation **84** with molecular oxygen, copper (I) chloride, and catalytic amounts of palladium (II) acetate gave the bicyclic ketone **85** as a 1:1 mixture of diastereomers.[44] The deprotected analogue **86** was also obtained as a mixture of diastereomers (4:1), and may be dehydrogenated *via* reprotection as the *tert*-butyl carbamate **70** (Scheme 22).

Shono and coworkers described a one step construction of the 9-azabicyclo[4.2.1]nonane skeleton from the simple pyrrolidine precursor **88**, and the likely intermediates here are also acyl iminium salts (Scheme 27).[45] The stepwise mechanism postulated for this annelation reaction was supported by the successful cyclisation of the proposed intermediate **92** under the same reaction conditions.

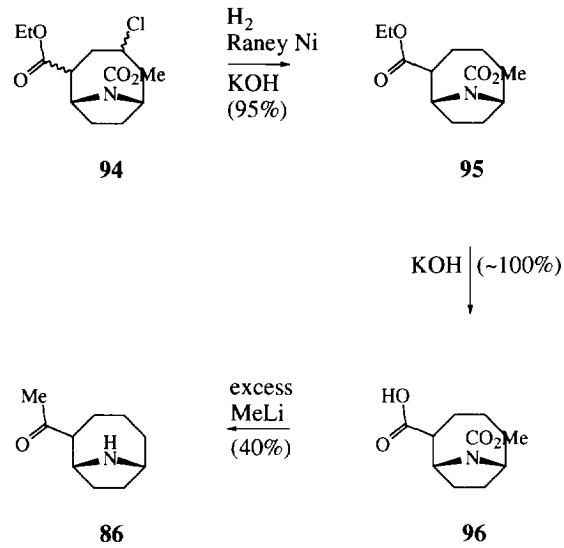
Thus the carbamate **88**, which is readily available from pyrrolidine (**87**), was subjected to anodic dimethoxylation to produce the 2,5-dimethoxypyrrolidine **89**, and this reacted with titanium (IV) chloride and the silyl ketene acetal **91** to furnish the γ-chloro ester **94**.[46]

The stepwise approach to the bicyclic ester **94** involved the reaction of the monomethoxy pyrrolidine **90** with the silyl ketene acetal **91** to yield the ester **92**, and this ester underwent anodic methoxylation to afford the cyclisation precursor **93**.[47,48] The two reactions of the silyl ketene acetal **91** were both efficient, and represent the earliest use of a Lewis acid for C-C bond formation in the construction of precursors to anatoxin-*a* (**1**).[49,50]



Scheme 27

The γ-chloro ester **94** was then elaborated to the anatoxin-*a* precursor **86** (Scheme 28). The ester **94** underwent hydrogenolysis over Raney nickel, and the dechlorinated ester **95** was hydrolysed with base to give the carboxylic acid **96**. When this carboxylic acid was treated with methyllithium, the methyl carbamate moiety was cleaved and a methyl ketone was also formed. The resultant secondary amine **86** was subsequently reprotected as the *tert*-butyl carbamate **70** by treatment with Boc_2O.

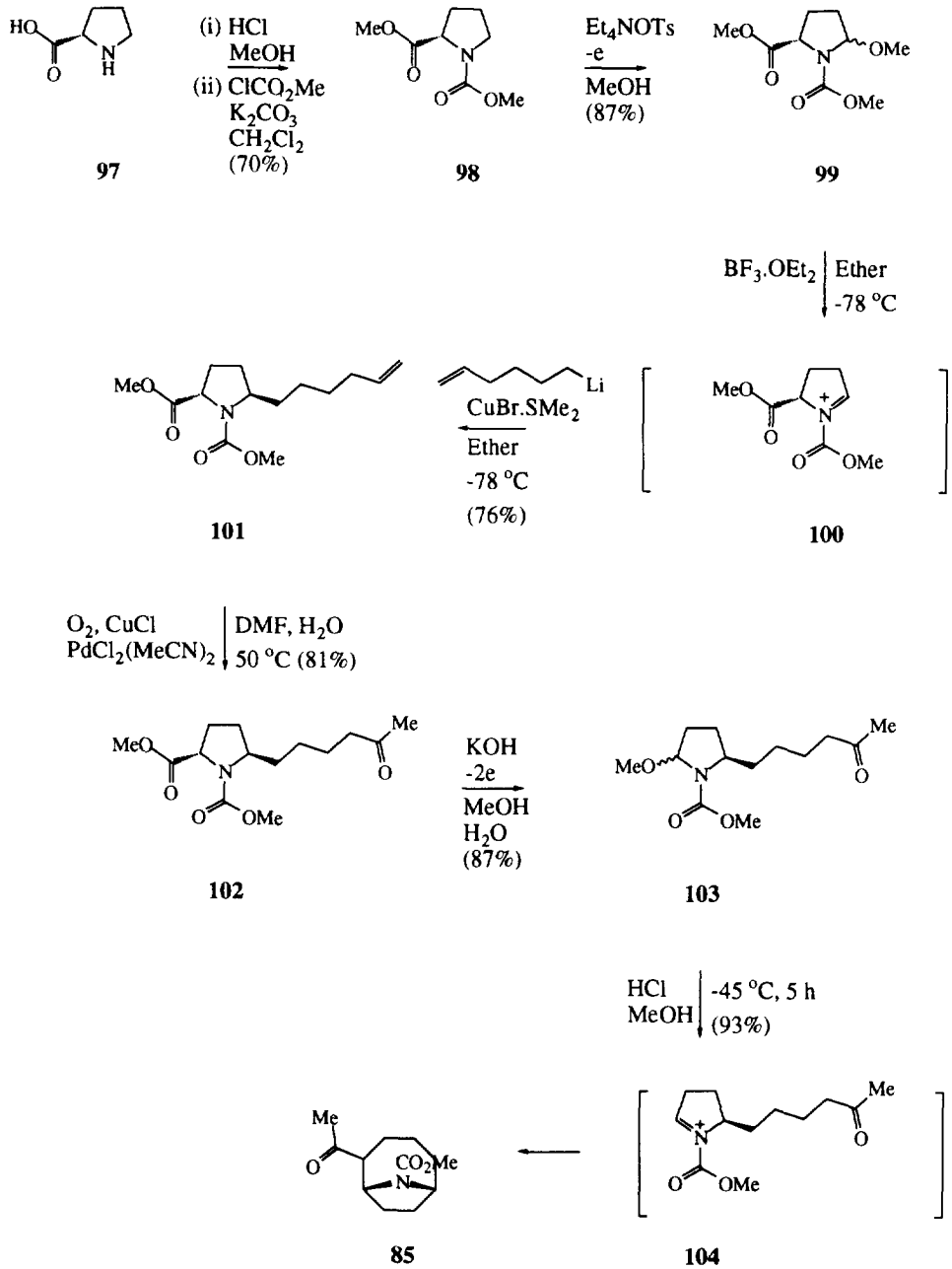


Scheme 28

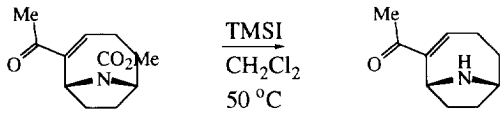
Skrinjar's synthesis of (+)-anatoxin-*a* (**1**) utilised the intermediacy of acyl iminium salts for the formation of C-C bonds at both C-2 and C-5 of substituted pyrrolidine precursors (Scheme 29).[49] The first C-C bond forming reaction was the stereoselective addition in a *trans* fashion of 5-hexenylcopper to the acyl iminium salt **100**, formed by the treatment of the 5-methoxyproline ester **99** with boron trifluoride etherate in ether, furnishing the terminal alkene **101**.[51] The ester **99** was obtained by anodic methoxylation of the ester **98**, prepared in two steps from L-proline (**97**).[46]

The alkene **101** was then oxidised under Wacker conditions to give the methyl ketone **102**.[44] This ketone was then subjected to anodic decarboxylation to produce the aminal **103**.[52] The aminal **103** was cyclised *via* the iminium salt **104** by treatment with methanol saturated with hydrogen chloride at -45 °C to furnish the bicyclic ketone **85** as a 1:1 mixture of diastereomers, conditions similar to Speckamp's for the cyclisation of the enone **78**.[38] Attempts to effect the cyclisation of the aminal **103** under conditions of Lewis acid catalysis were unsuccessful.

The bicyclic ketone **85** was dehydrogenated to the enone **80** {$[\alpha]_D^{25}$ -40.9° (c 1.0 in MeOH) with Rapoport's methodology (Scheme 22).[31] The deprotection of the enone **80** to natural anatoxin-*a* (**1**) {free base: $[\alpha]_D^{25}$ +39.8° (c 0.676 in EtOH)} is shown in Scheme 30.[49]


(i) HCl
MeOH
(ii) ClCO2Me
K2CO3
CH2Cl2
(70%)
Et4NOTs
-e
MeOH
(87%)
97
98
99
BF3.OEt2
Ether
-78 °C
CuBr.SMe2
Ether
-78 °C
(76%)
101
100
O2, CuCl
PdCl2(MeCN)2
DMF, H2O
50 °C (81%)
KOH
-2e
MeOH
H2O
(87%)
102
103
HCl
MeOH
-45 °C, 5 h
(93%)
85
104

Scheme 29



80 **(+)-1**

Scheme 30

4.3 Sulfonyl iminium salts

Somfai achieved a synthesis of (+)-anatoxin-*a* (**1**) *via* a tosyl iminium salt.[50] As with Speckamp's synthesis (Scheme 25), the source of nucleophilic carbon for the cyclisation step was an enone.[38] Thus, when the enone **111** (Scheme 31) was dissolved in methanol saturated with hydrogen chloride at -78 °C, the tosyl iminium salt was formed and cyclisation was observed. The intermediate β-chloro ketone was dehydrochlorinated by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene to yield the bicyclic ketone **112**.

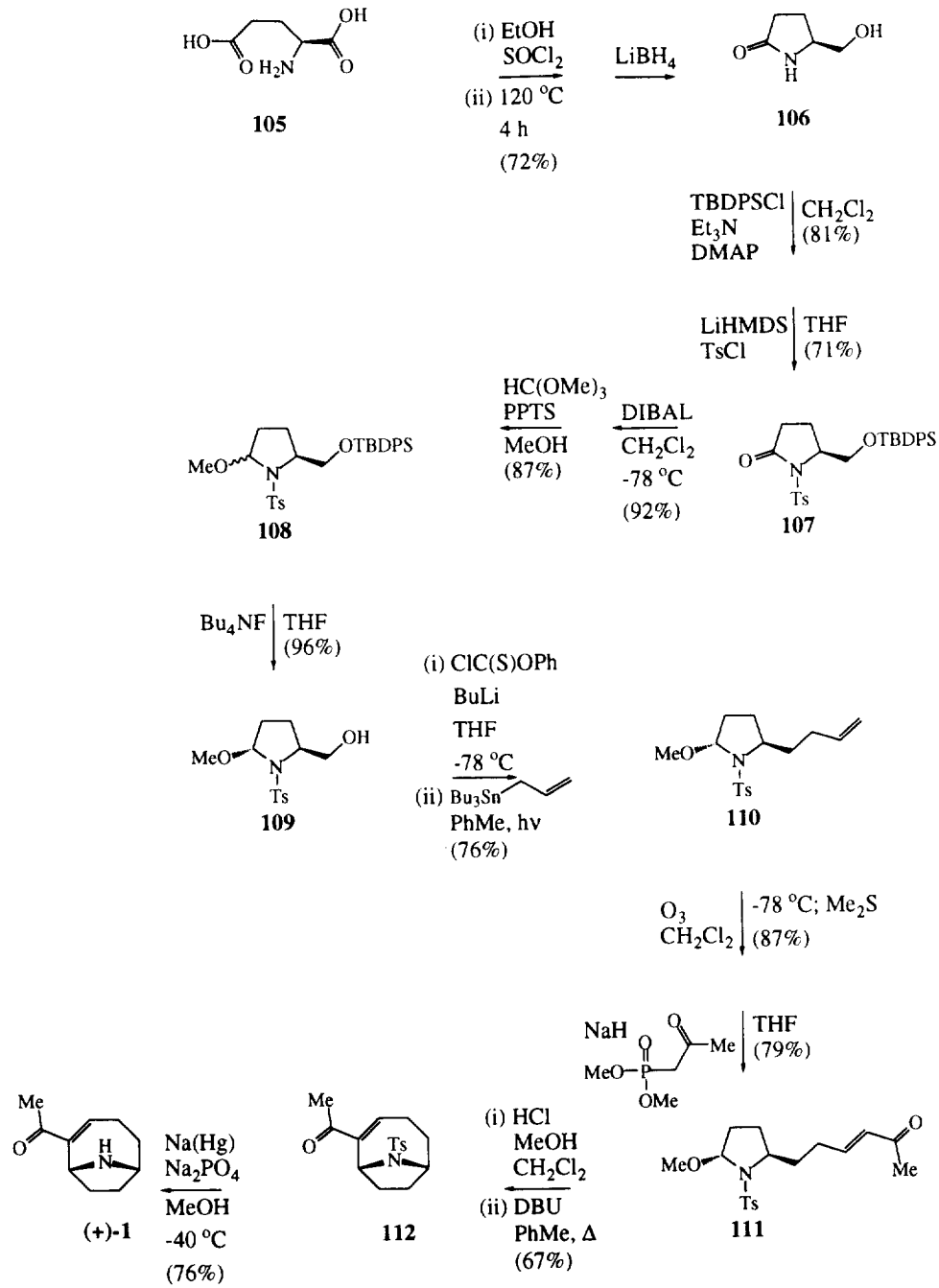
The enone **111** was obtained from L-glutamic acid (**105**) *via* a long sequence. L-Glutamic acid was converted to the diethyl ester and cylised thermally to give ethyl pyroglutamate, and the ester functionality was reduced with lithium borohydride to afford the alcohol **106**.[53] This alcohol was protected sequentially on both oxygen and nitrogen to give the silyl ether **107**.[54] The carbonyl group of **107** was then reduced, and the intermediate aminol was *O*-methylated to create the aminal functionality for the generation of the tosyl iminium salt.

The side chain of the enone **111** was next constructed. The silyl ether **108** was desilylated, and the product was recrystallised to afford the alcohol **109** as a single diastereomer. This alcohol was elaborated to the terminal alkene **110** *via* photochemical allylation of the intermediate *O*-phenylthiocarbonate derivative with allyltributyltin.[55] The alkene **110** was subjected to ozonolysis, and the intermediate aldehyde reacted with dimethyl (2-oxopropyl)phosphonate to furnish the enone **111**.[41] The desulfonation of the bicyclic ketone **112** to (+)-anatoxin-*a* (**1**) was achieved with sodium amalgam.

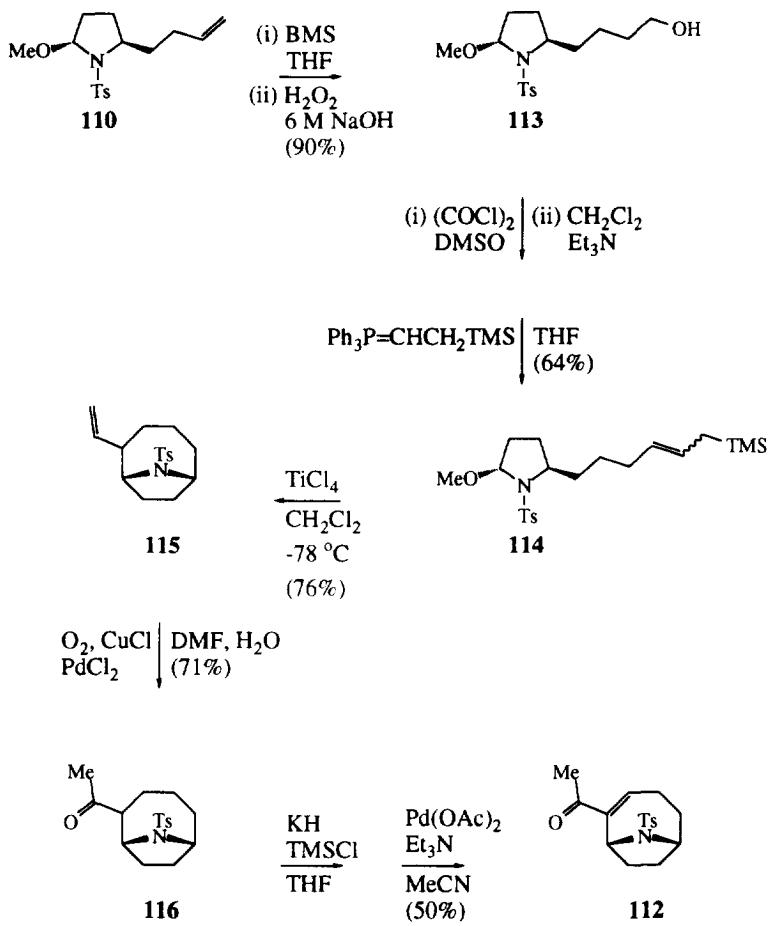
As an alternative route for the conversion of the monocyclic alkene **110** to (+)-anatoxin-*a* (**1**), the cyclisation of the allylsilane **114** to the bicyclic alkene **115** was also investigated (Scheme 32).[50] When the allylsilane **114** was added to a solution of 0.2 equivalents of titanium (IV) chloride in dichloromethane at -78 °C, an efficient cyclisation reaction took place, and the alkene **115** was isolated as a single diastereomer whose stereochemistry was not determined. The cyclisation of an allylsilane **81** with formic acid was described in Scheme 26.[42]

For the preparation of the allylsilane **114**, the alkene **110** was subjected to hydroboration and oxidation to produce the alcohol **113**. A Swern oxidation of this alcohol afforded an intermediate aldehyde, and the allylsilane **114** was obtained by the reaction of this aldehyde with (2-trimethylsilyl)ethylidene triphenylphosphorane.[56]

A Wacker oxidation of the cyclised alkene **115** gave the bicyclic ketone **116**.[44] The enone **112** was obtained from this ketone by dehydrosilylation of the thermodynamically more stable silyl enol ether derivative with palladium (II) acetate.[57]


105
(i) EtOH
SOCl2
(ii) 120 °C
4 h
(72%)
LiBH4
106
TBDPSCl
Et3N
DMAP
CH2Cl2
(81%)
LiHMDS
TsCl
THF
(71%)
HC(OMe)3
PPTS
MeOH
(87%)
DIBAL
CH2Cl2
-78 °C
(92%)
108
107
Bu4NF
THF
(96%)
(i) ClC(S)OPh
BuLi
THF
-78 °C
(ii) Bu3Sn
PhMe, hv
(76%)
109
110
O3
CH2Cl2
-78 °C; Me2S
(87%)
NaH
THF
(79%)
Na(Hg)
Na2PO4
MeOH
-40 °C
(76%)
(+)-1
112
(i) HCl
MeOH
CH2Cl2
(ii) DBU
PhMe, Δ
(67%)
111

Scheme 31

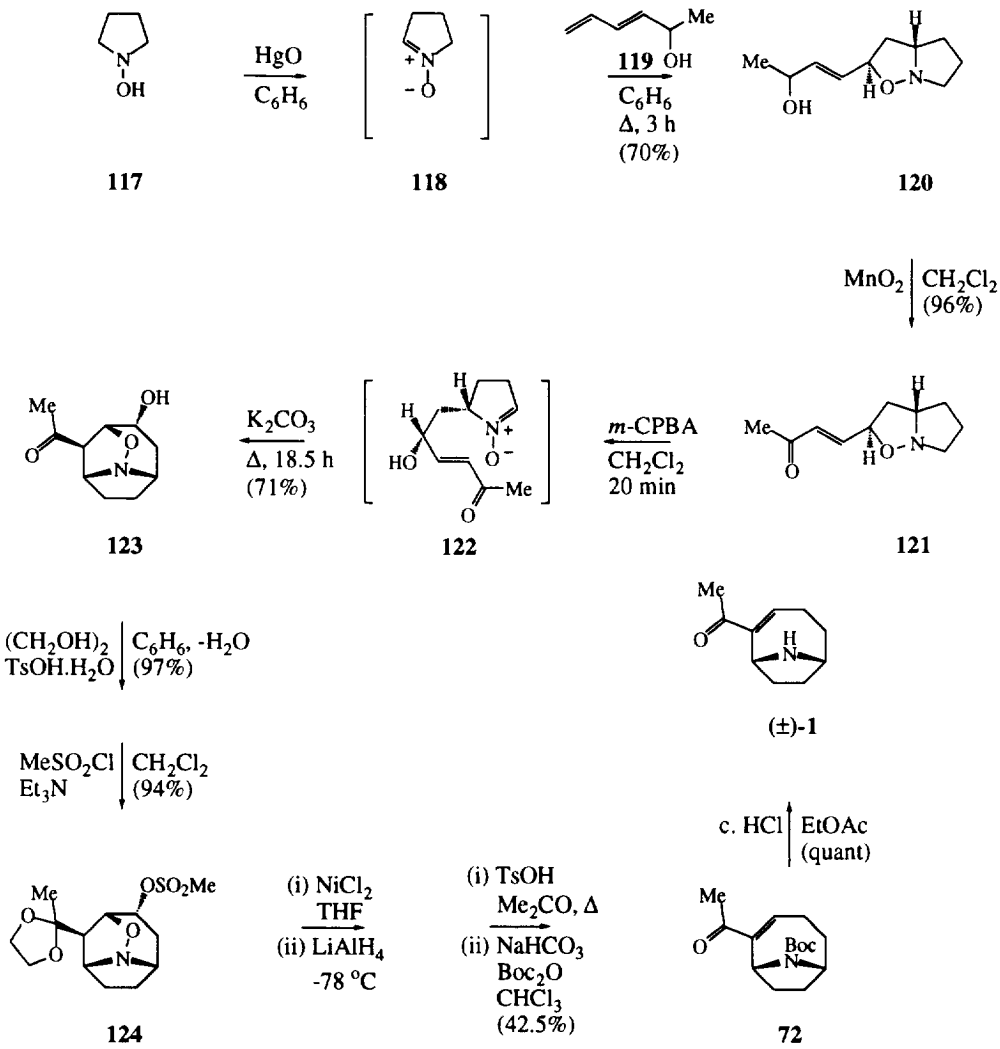


Scheme 32

5. CYCLOADDITION OF NITRONES

Tufariello and coworkers devised a synthesis of racemic anatoxin-*a* (**1**) which employed two sequential cycloadditions of a nitrone to a C=C bond.[58] Full experimental details of the nitrone approach to anatoxin-*a* were subsequently published.[59]

The nitrone **118** was formed when a solution of 1-hydroxypyrrolidine (**117**) in benzene was treated with mercury (II) oxide (Scheme 33). This nitrone underwent a cycloaddition reaction with *trans*-3,5-hexadien-2-ol (**119**) in refluxing benzene to furnish the pyrrolo[1,2-*b*]isoxazole derivative **120**. This cycloadduct underwent allylic oxidation with manganese (IV) oxide to give the enone **121**.



117 118 120

123 122 121

(±)-1

124 72

Scheme 33

When the enone **121** was treated with *meta*-chloroperoxybenzoic acid, the N-O bond of the isoxazolidine ring underwent cleavage and a second intermediate nitrone **122** was formed. This new nitrone underwent an intramolecular cycloaddition reaction across the C=C bond of the enone functionality in refluxing dichloromethane to afford the 2,7-methanopyrrolo[1,2-*b*][1,2]oxazine derivative **123**.

The stereochemistry of the pyrrolo[1,2-*b*]isoxazole **120** was assigned on the basis of previous studies by the Tufariello group, who proposed that cycloaddition reactions between nitrones and dienes occur principally *via* an *exo* transition state. The cleavage of isoxazolidine rings with *meta*-chloroperoxybenzoic acid was

reported to afford exclusively the less substituted nitrone.[60,61] During the intramolecular cycloaddition reaction of the nitrone **122**, strain requirements of the transition state were believed to favour the formation of the C-O bond at the position β rather than α to the enone group.

The tricyclic derivative **123** was then elaborated to anatoxin-*a* (**1**). The carbonyl functionality was protected as the [1,3]dioxolane derivative, and the hydroxyl group which was arose during the preparation of the second nitrone **122** was activated by formation of the mesylate derivative **124**. When this mesylate was subjected to reduction with lithium aluminium hydride and nickel (II) chloride in tetrahydrofuran at -78 °C,[62] cleavage of the N-O bond took place, and a mixture of products was formed which contained the enone **72** as the major component after deketalisation and reprotection of nitrogen as the *tert*-butyl carbamate derivative for the purposes of purification. The carbamate **72** was hydrolysed in aqueous acid to yield anatoxin-*a*.

6. ELECTROPHILIC CYCLISATION OF ALLENES

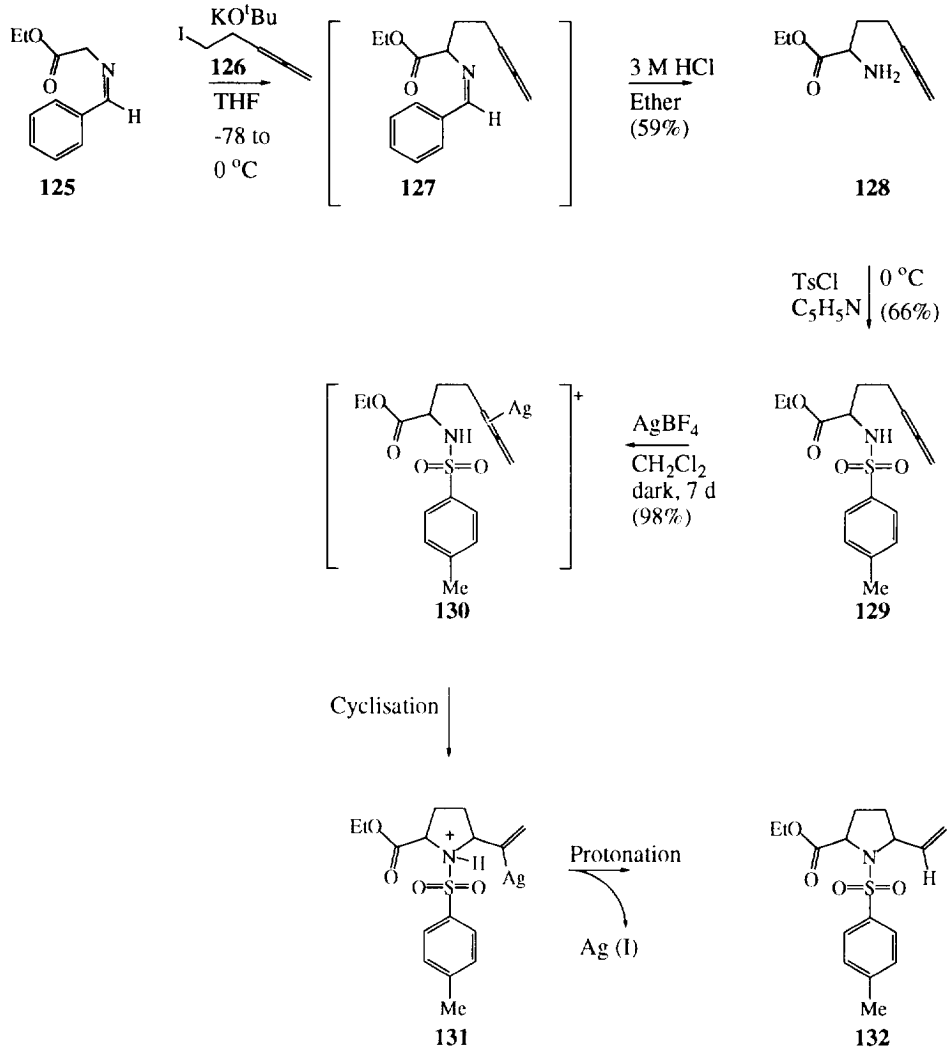
Gallagher and coworkers devised a synthesis of racemic anatoxin-*a* (**1**) by means of the stereoselective cyclisation of allenes in the presence of silver (I) salts to give *cis*-2,5-disubstituted pyrrolidines.[63] The enzymatic resolution of an early intermediate in theory enables this allene methodology to be applied to a chiral synthesis of anatoxin-*a*.[64]

Thus, ethyl *N*-benzylideneglycinate (**125**) underwent an alkylation reaction with potassium *tert*-butoxide and 1-iodopenta-3,4-diene (**126**) to give the allene **127** (Scheme 34). The benzylidene group of this allene removed by hydrolysis with acid, and the primary amine **128** was reprotected as the *p*-toluenesulfonamide to yield the cyclisation precursor **129** as the racemate.

The enzymatic resolution of the allene **129** was achieved efficiently with α-chymotrypsin I in buffered aqueous acetone. The absolute stereochemistry of the product obtained from the enzymatic resolution was verified by comparison of a sample of the carboxylic acid obtained by the ozonolysis of the chiral allene **129** with one which had been prepared from *S*-glutamic acid.

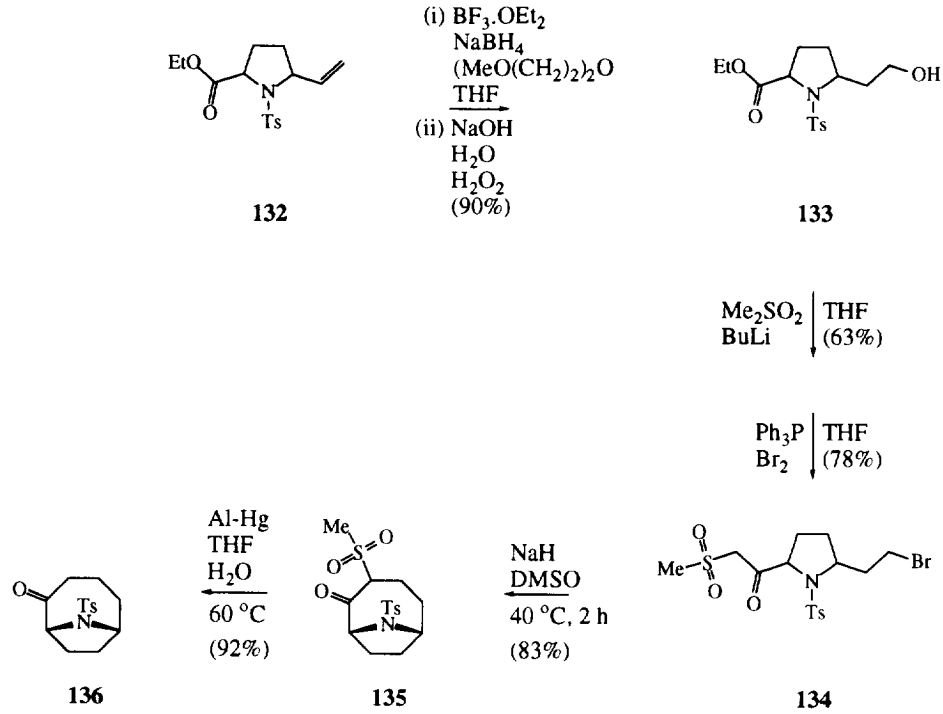
When the allene **129** was treated with 0.1 equivalents of silver tetrafluoroborate in dichloromethane at room temperature in the dark for seven days, quantitative yields of the *cis*-ethenyl pyrrolidine **132** were formed, and none of the corresponding *trans*-2,5-disubstituted pyrrolidine was observed. The *tert*-butyl carbamate, methyl carbamate, and *N*-benzyl analogues of the sulfonamide **129** also underwent cyclisation with high efficiency and selectivity. However, in the case of the primary amine **128**, cyclisation took place to give a 1:1 mixture of *cis*- and *trans*-2,5-disubstituted pyrrolidines. In addition, the electrophilic cyclisation was achieved with a range of silver (I) salts and in a variety of solvents, but no reaction was observed when cyclisation was attempted with tetrafluoroboric acid.

The mechanism of this cyclisation probably involves the reaction of the silver (I) salt with the allene **129** to form a π-complex **130**, and this undergoes cyclisation to give a vinylsilver pyrrolidinium salt **131**. The product **132** is obtained from this vinylsilver salt *via* protonation of the C-Ag bond, which results in the regeneration of Ag (I). The ionic nature of this mechanism is supported by the incorporation of deuterium into the position formally occupied by Ag when cyclisation was carried out with substrates deuterated on nitrogen.

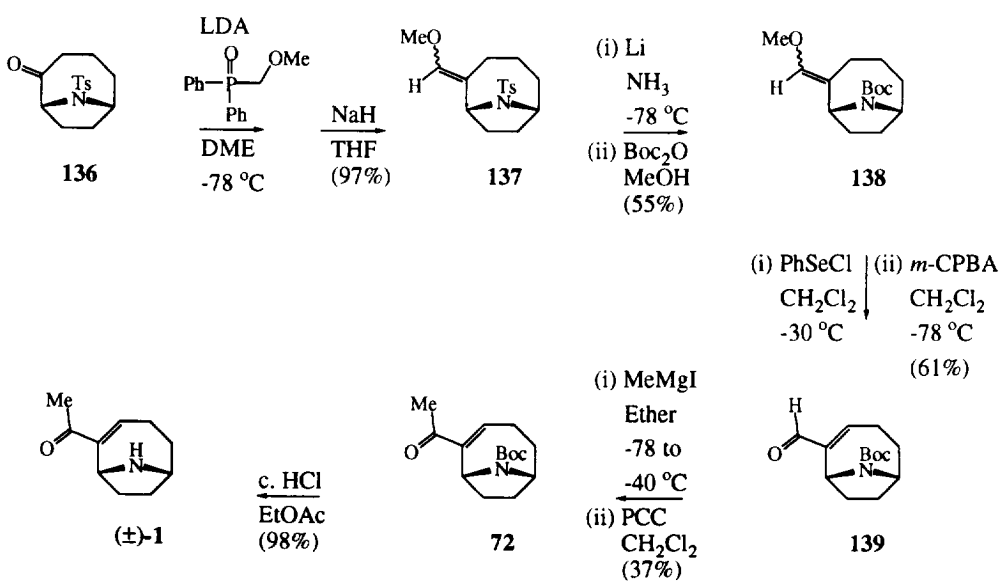


Scheme 34

The *cis*-2,5-disubstituted pyrrolidine **132** was then elaborated to the bicyclic ketone **136** (Scheme 35). Thus, the terminal alkene **132** was subjected to hydroboration and oxidation to afford the primary alcohol **133**. The carboxylate functionality of the alcohol **133** reacted with dimethyl sulfone and butyllithium to give an intermediate β-keto sulfone, and the hydroxyl function of this sulfone reacted with dibromotriphenyl phosphorane to produce the primary bromide **134**. When this primary bromide was treated with sodium hydride in dimethyl sulfoxide, cyclisation was observed, and the cyclised product **135** was desulfurised with aluminium amalgam to furnish the bicyclic ketone **136**.[65]

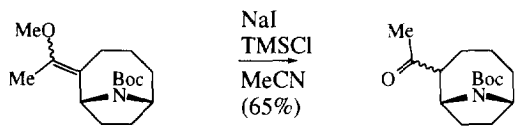


Scheme 35



Scheme 36

The homologation of the bicyclic ketone **136** to anatoxin-*a* (**1**) was achieved using carbanions stabilised by phosphine oxide derivatives. Thus, the ketone **136** reacted with 1-methoxymethyl(diphenyl)phosphine oxide, lithium diisopropylamide and sodium hydride to afford the methyl enol ether **137** (Scheme 36). This methyl enol ether was deprotected and reprotected on nitrogen as the *tert*-butyl carbamate **138**. The methyl enol ether functionality of the carbamate **138** reacted with phenylselenenyl chloride and *meta*-chloroperoxybenzoic acid, and this gave rise to dehydrogenation and regeneration of the carbonyl function to furnish the enal **139**.[66] *N*-*t*-Boc-anatoxin-*a* (**72**) was obtained from this enal *via* treatment with methylmagnesium iodide, and oxidation of the intermediate secondary alcohol with pyridinium chlorochromate.



140 (±)-**70**

Scheme 37

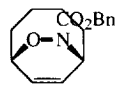
The methyl enol ether **140** was also obtained from the bicyclic ketone **136** *via* a similar series of reactions with 1-methoxyethyl(diphenyl)phosphine oxide (Scheme 37). Unlike **138**, the methyl enol ether **140** failed to undergo dehydrogenation. The carbonyl function of the methyl enol ether **140** was thus regenerated with iodotrimethylsilane to give the carbamate **70** as a 2:5 mixture of α- and β-diastereomers, and the conversion of this to anatoxin-*a* (**1**) was reported by Rapoport (Scheme 22).[31]

7. CONCLUSION

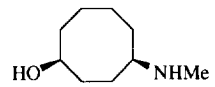
Anatoxin-*a* (**1**) is a small but structurally unusual and pharmacologically interesting molecule. It is clear from the work surveyed in this article that a diverse array of strategies has been devised for the synthesis of anatoxin-*a* and its precursors. The presence of a number of reactive functionalities has presented chemists with a demanding test of new and current synthetic methodology. Future work in this area is likely to focus on the application of the strategies outlined here to the synthesis of analogues and other natural products closely related to anatoxin-*a*.

Anatoxin-*a* (**1**) continues to inspire synthetic activity. For example, 1,3-cyclooctadiene underwent a [4+2] cycloaddition reaction with *N*-Cbz-hydroxylamine and tetramethylammonium periodate to produce the 7-oxa-8-azabicyclo[4.2.2]dec-9-ene **141**, and this was reduced with aluminium amalgam and hydrogenated to afford the 4-amino-1-cyclooctanol **142**.[67]

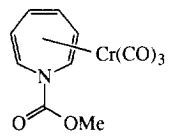
Also, the chromium tricarbonyl complex of methyl 1*H*-azepine-1-carboxylate (**143**) underwent a photochemical [6+2] cycloaddition reaction with ethyl acrylate to give the 9-azabicyclo[4.2.1]nona-2,4-diene derivative **144**.[68]



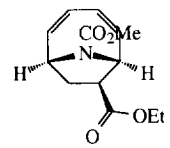
141



142



143



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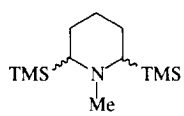
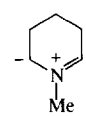


145



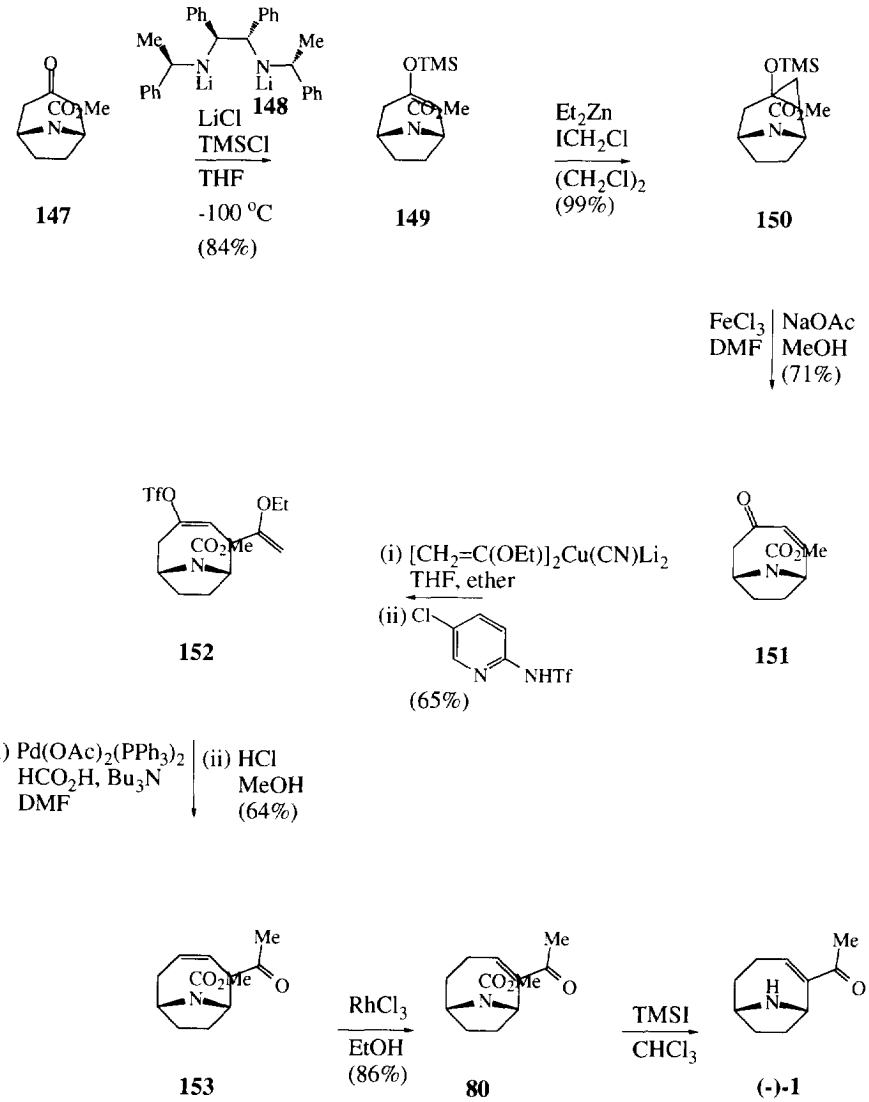
146

Tropanes have been obtained by the [3+2] cycloaddition with phenyl vinyl sulfone of the piperidine azomethine ylid **146**, prepared by treatment of the bis silyl piperidine **145** with silver (I) fluoride. The application of azomethine ylids to a synthesis of anatoxin-*a* (**1**) is an area of recent research interest.[69]

More recently, Simpkins has reported an asymmetric synthesis of unnatural (-)-anatoxin-*a* (**1**), utilising the ring expansion of tropane derivatives and employing an enantioselective deprotonation strategy (Scheme 38).[70]

Thus, the silyl enol ether **149** was obtained from tropinone, methyl carbamate (**147**) by treatment with lithium diisopropylamide and chlorotrimethylsilane in tetrahydrofuran in 90% yield. When this transformation was carried out with the chiral ethylenediamine base **148** and lithium chloride at -100 °C, substantial enantioselectivity was achieved, and this led to the formation of the enone **151** with an enantiomeric excess (e.e.) of 78%.[71] The silyl enol ether **149** was subjected to cyclopropanation with chloroiodomethane and diethylzinc to afford the silyl ether **150**.[72] This silyl ether underwent ring expansion with iron (III) chloride, and following treatment with mild base, the enone **151** was obtained.[73] The e.e. of the enantiomerically enriched enone **151** was improved to >99% by crystallisation induced by cold storage.

The enone **151** was then elaborated to (-)-anatoxin-*a*. The enone **151** underwent a conjugate addition with the higher order cuprate derived from copper (I) cyanide and two molar equivalents of 1-ethoxyvinyllithium,[74] and the adduct formed was quenched with 2-triflimido-5-chloropyridine to afford the enol ether **152**.[75] The triflate functionality of this enol ether was subjected to palladium catalysed hydrogenolysis, and an acidic work up provided the deconjugated enone **153**.[76] The isomerisation of the enone **153** was achieved with rhodium (III) chloride,[77] and the deprotection of the conjugated enone **80** with iodotrimethylsilane furnished unnatural anatoxin-*a* (**1**) {hydrochloride salt: $[\alpha]_D^{23}$ -45° (c 0.3 in EtOH)}.

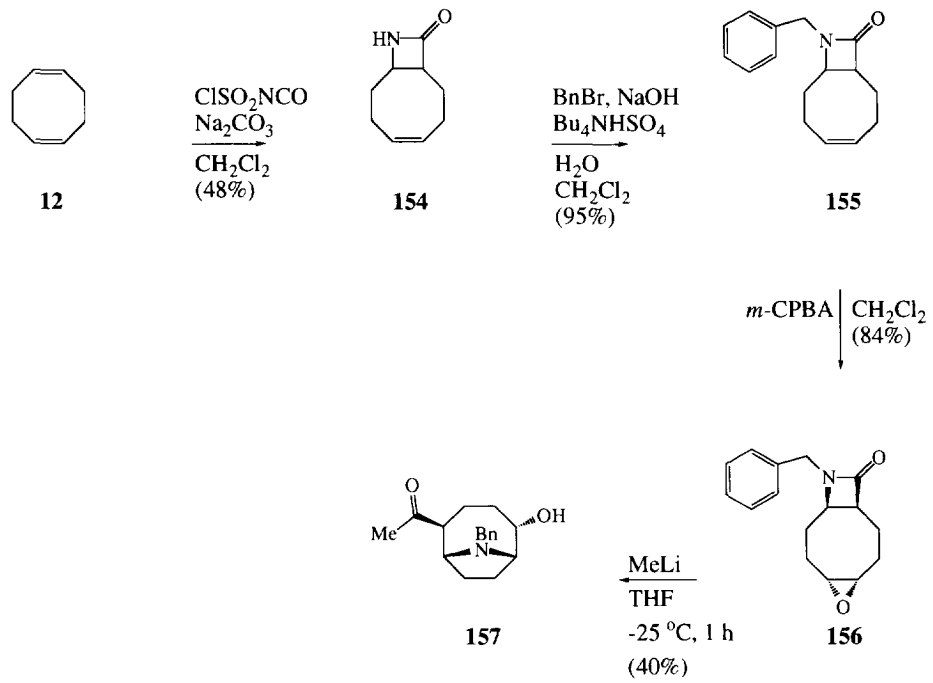


Scheme 38

The key step of Parsons' synthesis of racemic anatoxin-*a* (**1**) was a tandem methyllithium induced β-lactam ring cleavage-intramolecular cyclisation reaction.[78] Thus, treatment of the cyclooctene oxide derivative **156** with one equivalent of methyllithium at -25 °C afforded the bicyclic ketone **157** in a 40% yield (Scheme 39).

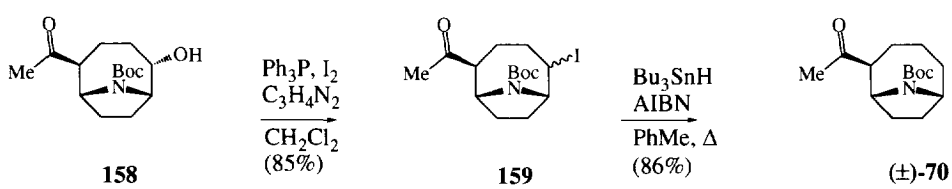
The oxirane **156** was prepared in three steps from 1,5-cyclooctadiene (**12**). The careful addition of chlorosulfonyl isocyanate to 1,5-cyclooctadiene and sodium carbonate at 0 °C gave the β-lactam **154** as a solid

in 48% yield, and this was benzylated under conditions of phase transfer catalysis. The epoxidation of the cyclooctene **155** was achieved with *meta*-chloroperoxybenzoic acid, and the anti relationship of the epoxide and lactam functionalities of **156** was confirmed with by X-ray crystallography.



12 **154** **155** **157** **156**

Scheme 39



158 **159** (±)-**70**

Scheme 40

The elaboration of the bicyclic ketone **157** to anatoxin-*a* (**1**) required the removal of the hydroxyl group arising from the intramolecular cyclisation step, and this transformation is described in Scheme 40. Thus, the alcohol **158** reacted with triphenylphosphine, iodine and imidazole to produce the iodide **159**, and this iodide was reduced with tributyltin hydride to furnish the ketone **70**. The completion of this synthesis also entails both a change of protecting group after the intramolecular cyclisation step, and the dehydrogenation and deprotection of the ketone **70**, and the conditions for these reactions were developed by the Rapoport group.[30,31]

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