# A Formal Asymmetric Synthesis of (+)-Anatoxin-a Using an Enantioselective Deprotonation Strategy on an Eight-Membered Ring**

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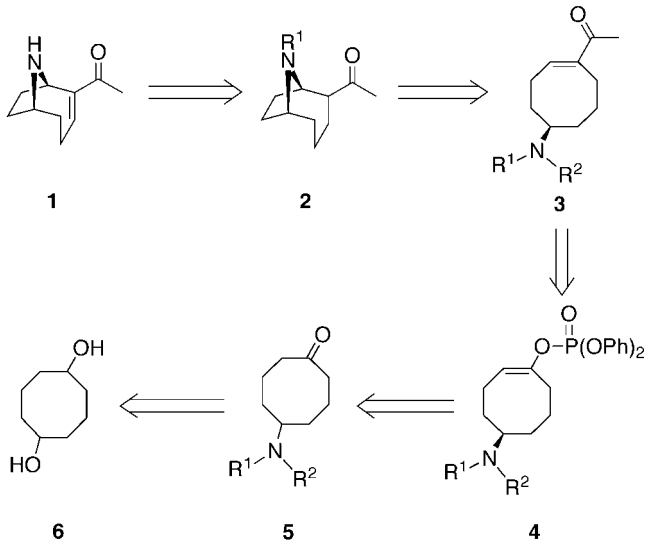
Anatoxin-a (**1**) is a low molecular weight potent neurotoxin present in toxic blooms of the filamentous freshwater blue green algae *Anabaena flos-aquae*, and has been responsible for the fatal poisoning of wildlife in North America and Europe.[1] Anatoxin-a has attracted much synthetic interest,[2] primarily because of its potent agonist activity at acetylcholine receptors,[3] but also because it contains an unusual 9-azabicyclo[4.2.1]nonane skeleton. Herein, we describe a short formal asymmetric synthesis of this natural product, which relies on an enantioselective deprotonation of a cyclooctanone by a chiral lithium amide base (Scheme 1).




Scheme 1. Retrosynthetic analysis of (+)-anatoxin-a (**1**).

The retrosynthetic analysis of (+)-anatoxin-a (**1**) is shown in Scheme 1. The azabicyclic ketone **2** has previously been transformed into **1** by Rapoport et al.,[4] and could potentially be obtained from **3** by intramolecular conjugate addition of the amine moiety. Enone **3** could be accessed through a Stille reaction from the vinyl phosphate **4**, which itself could be obtained from ketone **5**. One of the key steps in the synthesis is the enantioselective deprotonation of cyclooctanone **5**.

Desymmetrization of conformationally locked six-membered rings and bicyclic systems have been well explored over the last decade, and high levels of asymmetric induction have been achieved.[5] However, prior to the start of this work desymmetrization of medium and large rings had not been reported.[6] This is perhaps because of the commonly held belief that the greater conformational flexibility of these ring systems would result in several low-energy conformations that would lead to low enantioselectivity. However, we were encouraged by the work of Still and Allinger who showed that cyclooctanones exist in conformations having as few transannular nonbonded repulsions and high-energy torsional arrangements as possible (namely chair–boat).[7] Cyclooctanone **5** should therefore adopt conformation **A** in which the carbonyl moiety resides at the position shown (Figure 1) and the amino group occupies an equatorial position. Several

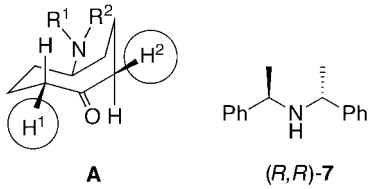



Figure 1. Conformational analysis of prochiral ketone **5** and Simpkins base **7**.

other conformations are populated at room temperature as a result of relatively small barriers to pseudorotation and ring inversion. However, at low temperature one conformation should be largely favored, which would lead to the possibility of high asymmetric induction. The enolizable protons of the low-energy conformation of cyclooctanone **5** are circled in Figure 1. By correlating the sense of asymmetric induction in the desymmetrization of 4-*tert*-butylcyclohexanone with the Simpkins base **7**[8] we predicted that Li-(*R*,*R*)-**7** would preferentially abstract $H^2$ and provide the enolate required for the synthesis of (+)-anatoxin-a.[9]

Our route to key intermediate **10** began with *cis*-1,5-cyclooctanediol (**6**), which was oxidized (PDC, $CH_2Cl_2$) to the intermediate hemiacetal (Scheme 2). Treatment of this hemiacetal with hot aqueous benzylamine gave a mixture of the hemiaminal **8** and aminal **9**. Subsequent addition of sulfuric acid converted this mixture into the required hemiaminal in high overall yield.[11] Attempted ring opening of hemiaminal **8** and protection of the amine moiety with the benzyl carbamate group using standard conditions ($PhCH_2OCOCl$, $Et_3N$, $CH_2Cl_2$) was ineffective, returning only starting material. However, the addition of catalytic quantities of $Sc(OTf)_3$ resulted in rapid protection.

The key desymmetrization step required formation of enantiomerically enriched enol phosphate **11**. It had previously been shown by Simpkins and Majewski that it was possible to achieve enantioselective deprotonations utilizing lithium chloride as an external additive to enhance the enantioselectivity.[12] This was achieved by treatment of prochiral ketone **10** with the base-derived (*R*,*R*)-**7**·HCl and two equivalents of butyllithium at $-100\,^{\circ}C$.[12e] Subsequent

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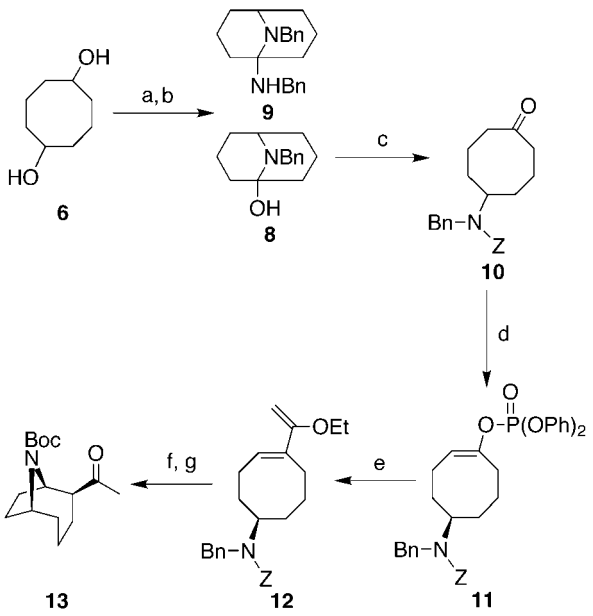


Scheme 2. Formal total synthesis of (+)-anatoxin-a (**1**). See reference [10] for abbreviations. a) PDC, $CH_2Cl_2$, 100%; b) 1. aq $PhCH_2NH_2$ (40%), *p*-TsOH (30 mol%), △; 2. $H_2SO_4$ (10%), 81% over two steps; c) $PhCH_2OCOCl$, $Sc(OTf)_3$ (5 mol%), $iPr_2NEt$, MeCN, 95%; d) (*R*,*R*)-**7**·HCl, *n*BuLi (2 equiv), $(PhO)_2POCl$, THF, −100 °C, 89%, 89% *ee*; e) $[Pd(PPh_3)_4]$, $CH_2$=CH(OEt)$SnBu_3$, LiCl, THF, △, 84%; f) 45% HBr in AcOH, 95%; g) Pd/C, $H_2$, MeOH, $(tBuCO)_2O$, 89%.

quenching of the reaction mixture with diphenyl chlorophosphate gave the enol phosphate **11** with high enantioselectivity (89% *ee*).[13]

Completion of the formal synthesis was achieved by a Stille reaction of enol phosphate[14] **11** with $CH_2$=CH(OEt)$SnBu_3$ in the presence of $[Pd(PPh_3)_4]$ and LiCl in THF, followed by a novel cascade reaction. This sequence entailed unmasking the enone moiety with concomitant nitrogen deprotection and intramolecular conjugate addition to give the required bridged azabicycle.[15] Changing the protecting group from benzyl to *tert*-butoxycarbonyl gave ketone **13**, which was identical, by $^1H$ and $^{13}C$ NMR, and IR spectroscopy and MS, to that reported by the group of Rapoport.[4] The $[\alpha]_D^{22}$ value we obtained (+47.2, $c = 0.8$ in $CH_2Cl_2$) is consistent with the production of the natural enantiomer ($[\alpha]_D^{22} = +51.9$, $c = 0.795$ in $CH_2Cl_2$).[4] Ketone **13** has been converted into (+)-anatoxin-a (**1**) by Rapoport et al. in three steps.

In conclusion, this paper describes one of the most concise and efficient routes (34% overall yield, including the final literature steps) to enantiomerically enriched (+)-anatoxin-a. Key steps in our synthesis include a highly enantioselective desymmetrization of an eight-membered ring ketone, and a novel cascade reaction to set up the 9-azabicyclo[4.2.1]nonane skeleton. Such desymmetrization reactions of medium and perhaps large ring ketones could find wide applications in synthesis.

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[10] Abbreviations: AcOH = acetic acid; Bn = benzyl; Boc = *tert*-butoxycarbonyl; *p*-TsOH = *para*-toluenesulfonic acid; PDC = pyridinium dichromate; Tf = trifluoromethanesulfonyl; THF = tetrahydrofuran; Z = benzyloxycarbonyl.
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[15] A single diastereomer at $C_2$ was formed. This observation is in keeping with a report that acid catalysis results in equilibration of the system, in favor of ketone **13**.[4]

## 2,2′-*commo*-Bis[2-ruthena-*nido*-1-($\eta^5$-pentamethylcyclopentadienyl)ruthenahexaborane(12)]: An Unusual Ruthenaborane Related to Ruthenocene and Exhibiting a Linear Triruthenium Fragment**

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The intimate connection between metallaborane chemistry and organometallic chemistry is expressed in the existence of isoelectronic pairs of compounds, for example, $[(CO)_4FeB_2H_5]^-$[1, 2] versus $[(CO)_4Fe(\eta^2\text{-}C_2H_4)]$ and $[(\eta^5\text{-}C_5H_5)CoB_4H_8]$[3] versus $[(\eta^5\text{-}C_5H_5)Co(\eta^4\text{-}C_4H_4)]$.[4–8] One of the fascinating aspects of these inorganic analogues of organo-

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