A Concise Asymmetric Synthesis of (−)-Anatoxin-a using an Enantioselective Enolisation Strategy

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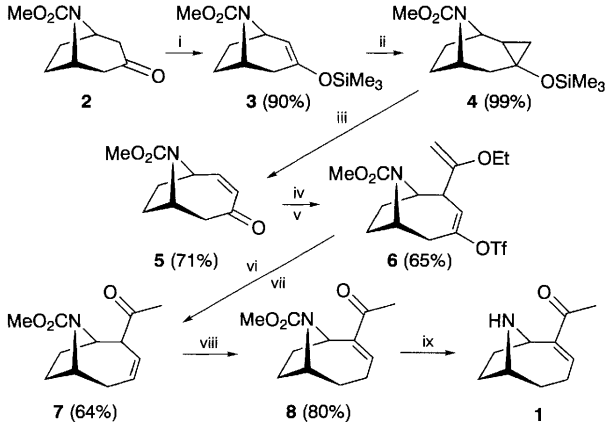
The unnatural enantiomer of anatoxin-a is prepared in enantiomerically pure form by a concise route involving enantioselective enolisation of a tropinone derivative by a chiral lithium amide base as the key step.

The unique homotropane alkaloid (+)-anatoxin-a **1** has been the subject of extensive synthetic studies, primarily owing to interest in its extremely potent activity as an agonist of the acetylcholine receptor.[1] Herein we describe a new total synthesis of this target in enantiomerically pure form, which relies on an enantioselective enolisation reaction of a readily available tropinone derivative by a chiral lithium amide base.[2]

We initially established a new route to racemic anatoxin-a as shown in Scheme 1. Formation of enol silane **3** by enolisation of azabicyclic ketone **2** and quenching the reaction mixture with Me_3SiCl proceeded straightforwardly under standard conditions. With the expectation that the use of a chiral lithium amide base would provide this enol silane in enantiomerically enriched form, and thus enable enantioselective access to subsequent intermediates, we next examined the key ring-expansion step to form the homotropane skeleton. Cyclopropanation of the enol silane **3** using Et_2Zn–CH_2I_2 in Et_2O proved very low yielding,[3] the desired trimethylsilyloxycyclopropane **4** being more efficiently prepared using modified conditions as described by Denmark and Edwards.[4] Effective ring expansion, using the method of Saegusa *et al.*, was accomplished by reaction of **4** with $FeCl_3$ in DMF and treating the crude reaction mixture with mild base.[5]

With homotropane enone **5** in hand, we required a concise reaction sequence which would allow introduction of the required ketonic side chain and the subsequent functional group manipulation required to furnish anatoxin-a. The reaction of higher order cyanocuprates with **5** was readily accomplished, the reagent formed by metallation of ethyl vinyl ether allowing introduction of the desired methyl ketone in masked form.[6] When cuprate addition was combined with electrophilic quench on oxygen, using the triflimide reagent of Comins and Dehghani,[7] the enol triflate derivative **6** was isolated in 65% yield. This sensitive intermediate was then subjected to palladium-catalysed hydrogenolysis of the enol triflate function,[8] and the crude product given an acidic work-up to effect hydrolysis of the vinyl ether side chain, thus affording the deconjugated anatoxin derivative **7**. Isomerisation to the desired α,β-unsaturated ketone proved less facile than expected, thus exposure of **7** to neutral alumina provided the expected product **8** contaminated with substantial amounts of by-products.[9] In contrast, the $RhCl_3$-mediated isomerisation proved clean and high-yielding,[10] completing a formal total synthesis of racemic anatoxin-a.

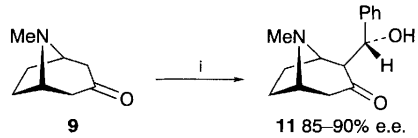


Scheme 1 *Reagents and conditions*: i, LDA, THF, Me_3SiCl; ii, Et_2Zn, ICH_2Cl, $ClCH_2CH_2Cl$; iii, $FeCl_3$, DMF, NaOAc, MeOH; iv, $[CH_2{=}C(OEt)]_2Cu(CN)Li_2$, THF, Et_2O; v, 2-triflimido-5-chloropyridine; vi, $Pd(OAc)_2(PPh_3)_2$, Bu_3N, HCO_2H, DMF; vii, HCl, MeOH; viii, $RhCl_3$, EtOH; ix, Me_3SiI, $CHCl_3$

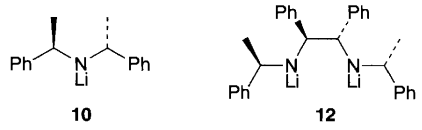
Our expectation that the above route could be used to access non-racemic anatoxin was based on our previous observation that enantioselective enolisation of tropinone **9** with the chiral lithium amide **10** furnishes products such as the aldol **11** (the sense of asymmetric induction being that required for natural anatoxin) in 85–90% e.e. (Scheme 2).[11] To our great surprise, non-racemic enone **5**, derived from the enol silane prepared using base **10**, proved to be of only 15–20% e.e.† Brief screening of other bases available in our laboratories identified the base **12** as the most effective for the desired enolisation.[12] Thus, treatment of ketone **2** with a mixture of the doubly lithiated base **12**, lithium chloride and Me_3SiCl in THF at −100 °C resulted in the formation of the desired enol silane in 84% yield and 78% e.e., as judged by conversion to the enone **5**.

Although the *racemic* enone **5** has been stored refrigerated as an oil over extended periods of time, the enantiomerically enriched product underwent extensive crystallisation on cold storage overnight. The crystalline material proved to be of >99% e.e., and was subsequently transformed into the enantiomerically pure anatoxin-a derivative **8** as described above.‡ At this point, comparison of optical rotation data with those published for **8** showed that base **12** has provided intermediates possessing the unnatural absolute configuration.§ This was confirmed by deprotection of **8** using Me_3SiI in $CHCl_3$,[13] to give unnatural (−)-anatoxin-a (isolated as the HCl salt), having spectroscopic data in accord with those for the natural product and an optical rotation of equal magnitude but opposite sign to that of the natural (+)-isomer.[14]

The synthesis described provides access to enantiomerically pure anatoxin in only seven steps from the starting ketone **2**, this being the first true asymmetric approach to this compound. Furthermore, the route proceeds *via* the versatile intermediate **5**, which should allow access to modified anatoxin analogues by the use of different 1,4-addition–electrophilic quenching combinations.[15] Although we have prepared the unnatural enantiomer of anatoxin, the natural product would be available by use of the antipode of chiral base **12**.



Scheme 2 *Reagents and conditions*: i, **10**, LiCl, THF, PhCHO



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Footnotes

† Enantiomeric excess determinations were carried out on samples of enone **5** by HPLC using a Chiralpak AD column (25 × 0.46 cm), eluting with 9 : 1 hexane–propan-2-ol containing 0.1% TFA, and employing UV detection at 254 nm.

‡ Chemical yields for the sequence employing non-racemic material are comparable to those shown in Scheme 1. Enantiomeric enrichment of the enone **5** has not yet been optimised but recrystallisation of **5** {initial $[\alpha]_D$ +19.5, (*c* 0.62, $CHCl_3$)} from Et_2O–light petroleum mixtures provides about 60% recovery of enantiomerically pure product {$[\alpha]_D$ +24.8, (*c* 0.22, $CHCl_3$}.

§ Our protected anatoxin derivative **8**, prepared using enantiomerically pure enone precursor **5** had $[\alpha]_D^{23}$ + 51.5 (*c* 1.0, MeOH), compared to $[\alpha]_D^{25}$ −40.9 (*c* 1.0, MeOH).[1b]

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