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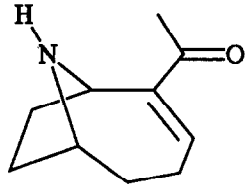
# A Short and Enantioselective Synthesis of (+)-Anatoxin-a

**Peter Somfai* and Jens Åhman**

Organic Chemistry 2, Chemical Center
Lund Institute of Technology, P. O. B. 124
S-221 00 Lund, Sweden

**Abstract:** A short and enantioselective total synthesis of the neurotoxic alkaloid (+)-Anatoxin-a (**1**) from the L-pyroglutamic acid derivative **2** is described. The key step involves an intramolecular cyclisation of an N-tosyl iminium ion derived from the corresponding α-methoxy sulfonamide.

(+)-Anatoxin-a (**1**), also known as Very Fast Death Factor (VFDF), is a powerful neurotoxin isolated from the fresh-water blue-green algae *Anabaena flos-aqua*[1]. Due to its unusual structure coupled with its interesting biological activity, Anatoxin-a (**1**) has attracted the interest of organic chemists, resulting in a number of elegant total syntheses[2,3]. Of these, however, only two have yielded the target alkaloid in optically active form[3]. Herein we would like to report a short and efficient route to (+)-Anatoxin-a (**1**) starting from the N-tosyl lactam **2**, easily prepared from L-glutamic acid[4]. The key step in our approach consists of an intramolecular cyclisation of an N-tosyl iminium ion, derived from an α-methoxy sulfonamide, to set up the desired bicyclic ring system[5].

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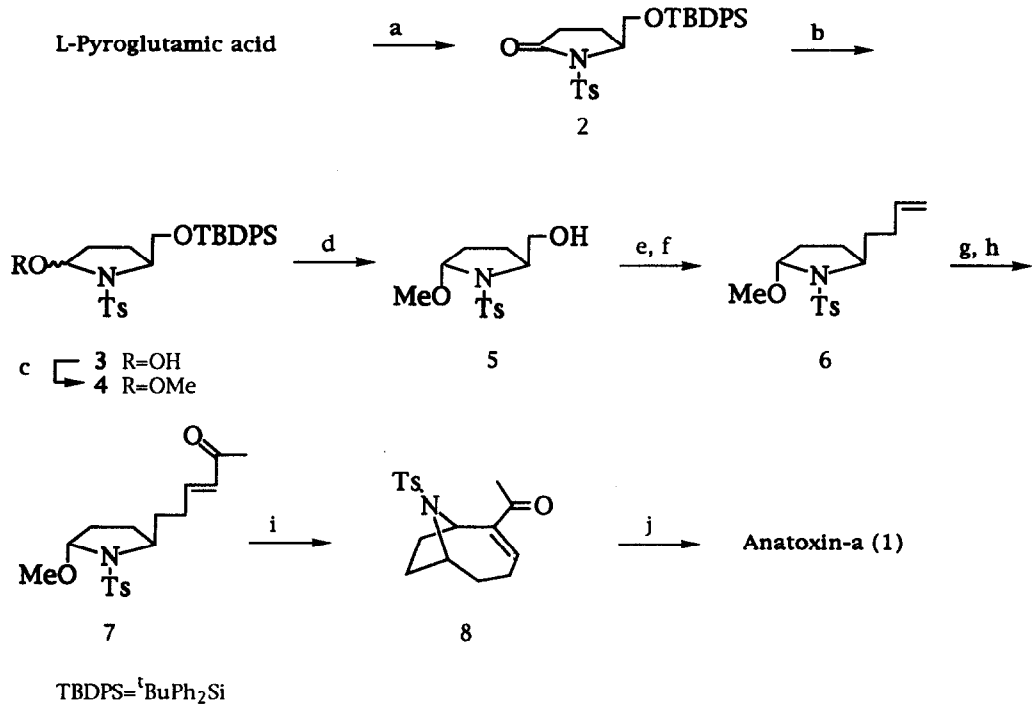
Our synthesis starts with a DIBAL reduction of the N-tosyl lactam **2**[4] to yield α-hydroxy sulfonamide **3** as an inseparable 4/1 mixture of isomers, Scheme 1. Acid catalyzed conversion of amide **3** into α-methoxy sulfonamide **4** (19/1 mixture of isomers) followed by removal of the silyl protecting group afforded the crystalline alcohol **5**. Recrystallisation of this material then furnished the pure 2,5-substituted pyrrolidine derivative **5** as a single isomer[6,7](72% overall yield from **2**).



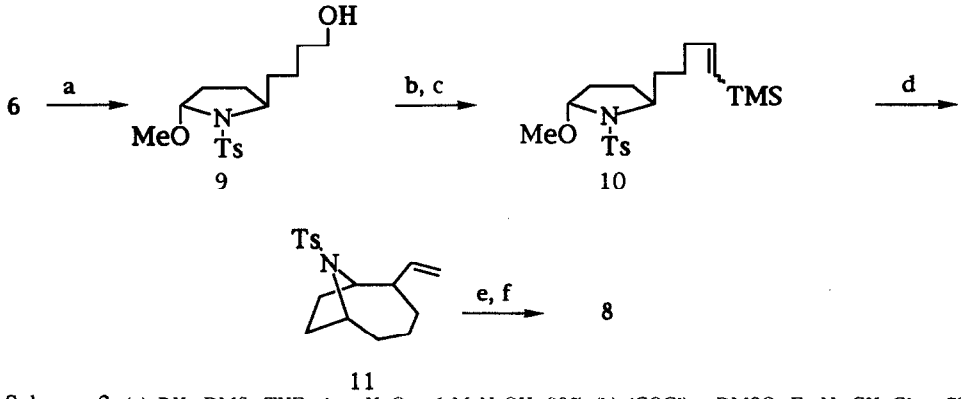

Scheme 1. (a) see ref. 4 (b) DIBAL, $CH_2Cl_2$, -78°C, 92% (c) MeOH, $HC(OMe)_3$, PPTS, 87% (d) $Bu_4NF$, THF, 96% (e) ClC(S)OPh, BuLi, THF, -78°C (f) Allyltributyltin, hv, toluene, 76% (two steps) (g) $O_3$, $CH_2Cl_2$, -78°C, then $Me_2S$, 87% (h) $(MeO)_2P(O)CH_2C(O)CH_3$, NaH, THF 79%, (i) MeOH, HCl, $CH_2Cl_2$, then DBU, toluene, reflux, 67% (j) Na(Hg), $Na_2PO_4$, MeOH, -40°C, 10 min, 76%.

Treating alcohol **5** with BuLi followed by addition of phenyl chlorothionoformate resulted in a clean conversion to the corresponding thionocarbonate which, due to its instability was processed immediately in the subsequent allylation, using the Keck protocol[8], to furnish alkene **6**[7]. Ozonolysis of compound **6** then gave the corresponding aldehyde which was converted into enone **7** through reaction with dimethyl (2-oxopropyl) phosphonate (79%, two steps, E/Z=10/1), thus completing the synthesis of our first cyclisation precursor.

Exposure of enone **7** to the cyclisation conditions developed by Hiemstra and Speckamp[2d] (saturated solution of HCl in MeOH, $CH_2Cl_2$ at -78°C) yielded N-tosyl Anatoxin-a (**8**) along with the corresponding saturated β-chloroketone. Treating the product with DBU in refluxing toluene[2d] cleanly effected the desired elimination affording pure **8**[7] in 67% yield (two steps). Finally, removal of the nitrogen protecting group (Na(Hg), $Na_2HPO_4$, MeOH, -40°C, 10 min., 76%) afforded (+)-Anatoxin-a (**1**), its hydrochloric acid salt having spectral and physical data in excellent accord with the literature values[9].

An alternative route from alkene **6** to N-tosyl Anatoxin-a (**8**) was also investigated as depicted in Scheme 2. Thus, hydroboration/oxidation of alkene **6** gave alcohol **9**. Swern oxidation of this material gave the corresponding aldehyde which was reacted with (2-tri-methylsilylethylidene)triphenylphosphorane[10] to yield allyl silane **10** as a mixture of isomers (E/Z=7/1). Slow addition of this material to a solution of $TiCl_4$

(0.2 eq.) in $CH_2Cl_2$ at -78°C smoothly effected the desired cyclisation affording the bicyclic alkene **11**[7] in 76% yield[11,12]. Although this material proved to be a single isomer ($^1H$ NMR) it was not possible to determine the stereochemistry of the newly created stereocenter. Wacker oxidation[13] of **11** gave the corresponding methyl ketone which was converted into N-tosyl Anatoxin-a (**8**) by the method developed by Rapaport and coworkers[3b,c] (KH, TMSCl, THF, then $Pd(OAc)_2$, $Et_3N$, $CH_3CN$, 50%).




Scheme 2. (a) $BH_3$-DMS, THF, then $H_2O_2$, 6 M NaOH, 90% (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78°C (c) $Ph_3PCHCH_2SiMe_3$, THF, 64% (two steps) (d) $TiCl_4$ $CH_2Cl_2$, -78°C, 76% (e) $PdCl_2$, CuCl, $O_2$ DMF/$H_2O$, 71% (f) KH, TMSCl, then $Pd(OAc)_2$, $Et_3N$, $CH_3CN$, 50%.

In conclusion, we have developed two efficient and enantioselective routes to the neurotoxic alkaloid (+)-Anatoxin-a (**1**). The syntheses rely on the generation and intramolecular cyclisation of N-tosyl iminium ions which, in turn, are derived from the corresponding α-methoxy sulfonamides. We are currently investigating the use of similar approaches for the synthesis of other biologically significant polycyclic alkaloids.

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5. For similar approaches in the racemic series, see refs. 2d and 2f.

6. The relative stereochemistry of alcohol **5** could not be determined and is arbitrarily depicted as bieng *trans*. It should be noted that the stereochemistry of the newly created stereocenter is of no consequence for the outcome of the synthetic plan.

7. Spectroscopic data for (a) alcohol **5**: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.69 (2H, d, J=8.4, tosyl), 7.33 (2H, d, J=8.4, tosyl), 5.09 (1H, d, J=5.1), 3.77-3.56 (3H, m), 3.45 (3H, s, -OC<u>H</u>$_3$), 2.96 (1H, m, -O<u>H</u>), 2.42 (3H, s, $CH_3$-tosyl), 1.92-1.76 (3H, m), 1.13 (1H, m); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 144.1, 135.2, 129.9, 127.3 (aromatics), 93.4, 66.4, 62.6, 55.1, 32.0, 26.1, 21.5; IR (KBr) 3320, 3015, 2950, 1595, 1340, 1156 cm$^{-1}$; $[\alpha]_D$=-46.8° (c 1.09, CHCl3); mp=74-76°C
(b) alkene **6**: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2H, d, J=8.3, tosyl) 7.29 (2H, d, J=8.3, tosyl) 5.83 (1H, m) 5.09-4.94 (3H, m) 3.48 (1H, m) 3.41 (3H, s,-OC<u>H</u>$_3$) 2.41 (3H, s, $CH_3$-tosyl) 2.18-1.97 (3H, m) 1.88-1.51 (4H, m) 1.09 (1H, m); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 143.8, 138.0, 135.9, 129.9, 127.6, 114.8, 92.7, 60.5, 54.9, 36.1, 32.0, 29.9, 29.3, 21.8; IR (film) 3061, 2939, 1638, 1595, 1344, 1156 cm$^{-1}$; $[\alpha]_D$=-106.8° (c 1.39, $CHCl_3$)
(c) N-tosyl Anatoxin-a (**8**): $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.74 (2H, d, J=8.5, tosyl) 7.28 (2H, d, J=8.5, tosyl) 6.88 (1H, tr, J=5.6, vinylic) 5.22 (1H, br d, J=7.5) 4.45 (1H, m) 2.68 (1H, m) 2.43 (3H, s, $CH_3$-tosyl) 2.29 (3H, s, COC<u>H</u>$_3$) 2.19 (1H, m) 1.82-1.63 (H, m) 1.60-1.45 (H, m); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 197.5, 147.4, 143.2 (aromatic and vinylic), 137.3, 129.7, 127.0, 58.9, 56.4, 33.6, 32.0, 29.9, 25.3, 24.4, 21.5; IR (film) 3059, 2941, 1656, 1630, 1592, 1339, 1158 cm$^{-1}$; $[\alpha]_D$=-16.5° (c 1.16, $CHCl_3$)
(d) alkene **11**: $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.71 (2H, d, J=8.4, tosyl) 7.24 (2H, d, J=8.4, tosyl) 6.09 (1H, m) 5.05-4.89 (2H, m) 4.27, (1H, m) 4.09 (1H, dd, J=9.5, 2.4) 2.41 (3H, s, $CH_3$-tosyl) 2.11 (1H, m) 1.89-1.31 (10H, m); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 143.1, 142.8, 137.2, 129.6, 127.1, 112.9, 63.7, 60.2, 51.5, 36.3, 33.3, 31.9, 28.8, 21.8, 21.5; IR (KBr) 3061, 2925, 1637, 1596, 1339, 1156 cm$^{-1}$; $[\alpha]_D$=+58.5° (c 1.83, $CHCl_3$).

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9. **1**·HCl: $[\alpha]_D$=+45.9° (c 0.32, EtOH) [lit.[3a] $[\alpha]_D$=+36° (c 0.85, EtOH); lit.[3b] $[\alpha]_D$=+43.2° (c 0.676, EtOH).

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12 Other Lewis acids, e. g. $SnCl_4$, $BF_3$·$Et_2O$ and $FeCl_3$, worked equally well in this cyclisation.

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