A Concise Route to Racemic Anatoxin a from Cycloocta-1,5-diene

by **Tse-Lok Ho***[1]) and **Elvira Zinurova**

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan, Republic of China (e-mail: tlho@cc.nctu.edu.tw)

The synthesis of racemic anatoxin a (**1a**) from cycloocta-1,5-diene *via* its 1:1 cycloadduct with *N*-chlorosulfonyl isocyanate is described. The *N*-unsubstituted β-lactam **2b** was converted to a β-amino ester **3** which was then submitted to a Pd-catalyzed cyclization to afford the conjugated ester **4a**. The *N*-tosyl derivative **4b** was then elaborated into *N*-tosylanatoxin a (**1b**) *via* a *Weinreb* amide.

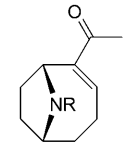
We are very interested in developing synthetic routes to various natural products on the basis of symmetry considerations [1]. In the area of alkaloids, we have accomplished work on tacamonine [2], cryptolepine and cryptotackiene [3], nicotyrine [4], eburnamonine [5], and tangutorine [6]. Simultaneously with the research on nicotyrine, a route to anatoxin a (**1a**), the poisonous metabolite of *Anabaena flos-aquae* (LYNGB.) DE BREB., previously known as the 'very fast death factor' [7], was pursued. Anatoxin a has attracted enormous attention of synthetic chemists [8] because it possesses potent activity as a nicotinic agonist (mimics the neurotransmitter acetylcholine) and the novel 9-azabicyclo[4.2.1]nonane skeleton.

The symmetrical precursor we chose for the synthesis is cycloocta-1,5-diene. This inexpensive hydrocarbon contains all C-atoms of the target molecule except for the acetyl side chain. Accordingly, it requires only the introduction of the missing C-atoms and a secondary amino group across the existing ring. The known 1:1 adduct **2a** of cycloocta-1,5-diene and *N*-chlorosulfonyl isocyanate [9] serves our purpose well as it has the same β-amino carbonyl substructure as the alkaloid while a remote C=C bond is present for inducing a transannular heterocyclization. Actually, the same cycloadduct served as the first intermediate in our approach to nicotyrine.

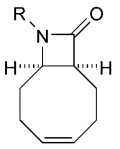
Following the conversion of **2a** to **2b**, a ring-opening methanolysis afforded the β-amino ester **3**. We believe epimerization had taken place during this transformation (*vide infra*). On treatment of **3** with $PdCl_2/CuCl_2/HCl$ in MeOH, we obtained the bicyclic ester **4a** besides the tricyclic lactone **5** [10] in a single step. The *N*-tosyl derivative **4b** of the main product from the reaction shows spectral data which are identical with those reported in [8e]. Therefore, our access to **4b** represents a formal synthesis of racemic anatoxin a (**1a**).

---

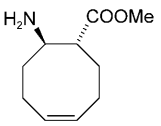
[1]) Present address: Shanghai Institute of Organic Chemistry (c/o Prof. X. L. Hou, Organometallic Division), Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China.



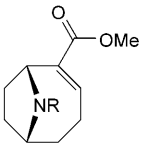
1a R = H
1b R = SO_2Tol



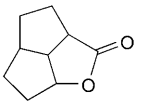
2a R = SO_2Cl
2b R = H



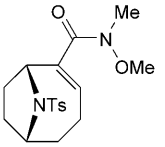
3



4a R = H
4b R = SO_2Tol



5

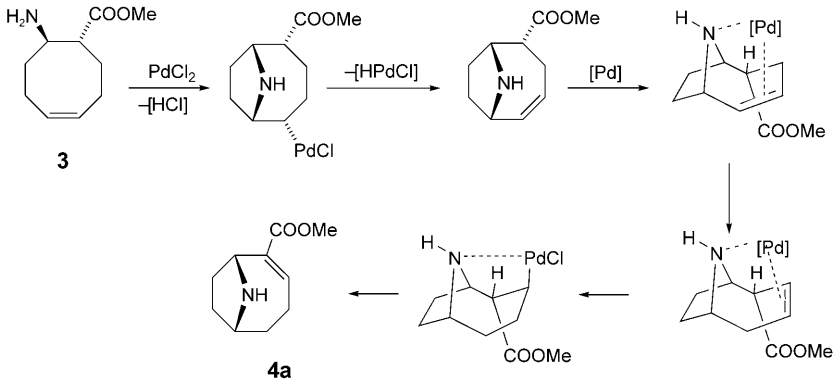


6

We also saponified **4b** to furnish the corresponding carboxylic acid and derivatized it into a *Weinreb* amide **6** in 80% yield employing 2-chloro-2,6-dimethoxy-1,3,5-triazine as activating agent [11]. Reaction of **6** with MeLi provided *N*-tosylanatoxin a (**1b**) [8e] which is also a synthetic intermediate of anatoxin a (**1a**).

Formation of **4a** and **5** in the reaction of **3** deserves some comment. As shown in the *Scheme*, we conjecture that activation of the C=C bond of **3** upon Pd^{II}-coordination is followed by an internal attack of the N-atom in analogy to that described in the methoxycarbonylative cyclization method [8d]. However, in the absence of CO, the Pd-species undergoes β-hydride elimination. Subsequently, the released low-valent Pd-atom suffers re-oxidation by $CuCl_2$ and serves to mediate migration of the C=C bond around the seven-membered heterocycle. This process, likely occurring with participation of the N-atom, results in the penultimate carbopalladium species that is well

Scheme. *Pd^{II}-Catalyzed Oxidative Cyclization*



disposed to undergo the final β-hydride elimination. Generation of the conjugated ester in this manner represents a great improvement over the previously reported methods.

Regarding the formation of lactone **5**, it is proposed that a transannular cyclization occurs after the amino group is protonated. By a sequence of deprotonation, and protonation, the carbocation center is placed at the *peri*-position close to the ester group and lactonization ensues. Since this side reaction is thought to be acid-catalyzed, we tried to carry out the Pd-catalyzed reaction without HCl. Unfortunately, the desired transformation was adversely affected.

In conclusion, we elaborated a very concise route to anatoxin a (**1a**) from cycloocta-1,5-diene. Although the same starting material had been employed by other chemists, our method is by far the shortest, because, with some insight into the mechanism of the Pd^{II}-catalyzed cyclization under oxidative conditions, we were able to preserve the C=C bond, and *via* migration, located it at the desired position. Furthermore, our present work was carried out with the same aim of achieving synthetic economy and expediency by employing a common, symmetrical intermediate for the construction of two series of molecular skeletons (*i.e.*, to nicotyrine), further examples of which are the cryptolepine/cryptotackiene [3] and the cuparene/herbertene [12] pairs.

Financial support of our work by the *National Science Council* is gratefully acknowledged.

Experimental Part

General. During workup, org. solns. were dried over anh. Na_2SO_4. Column chromatography (CC): *Merck* silica gel. IR Spectra: *Biorad-FTS*-165; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian-Unity-300* and *Bruker-DRX-300* spectrometers, $CDCl_3$ as solvent unless otherwise indicated; δ in ppm, J in Hz. EI-MS: *Trio-2000* and *Jeol-SX-120A* spectrometers; ionization potential 70 eV.

Methyl 8-Aminocyclooct-4-ene-1-carboxylate (**3**). Gaseous HCl was bubbled through a soln. of bicyclic lactam **2b** (1.0 g) in MeOH (10 ml) under reflux during 1 h. Reflux was continued for an additional 10 h with periodic addition of more gaseous HCl. The solvent was evaporated: **3**·HCl. Free base **3**: IR: 2924, 1704, 1423, 1224. ^{1}H-NMR (300 MHz): 1.56–2.08 (*m,* 8 H); 2.33 (*m*, 1 H); 2.49 (*m*, 1 H); 2.72 (*dd*, J=4.5, 1 H); 3.34 (*t*, J=6.9, 1 H); 3.61 (*s*, 3 H); 5.52 (*m*, 1 H); 5.64 (*m*, 1 H). ^{13}C-NMR (75 MHz): 24.0; 24.1; 26.4; 35.2; 46.6; 51.4; 51.7; 128.1; 131.1; 176.7. HR-MS: 183.1260 ($C_{10}H_{17}NO_2^+$, calc. 183.1262).

Methyl 9-Azabicyclo[4.2.1]non-2-ene-2-carboxylate (**4a**). A soln. of **3** (183 mg, 1 mmol) in MeOH (1 ml) was added to a MeOH soln. (10 ml) consisting of $PdCl_2$ (0.005M), $CuCl_2$ (0.01M), NaCl (0.1M), and HCl (0.2M) and heated at 60° for 6 h. The cooled mixture was washed with CH_2Cl_2 to remove **5** (48%) which was identified spectroscopically and by X-ray diffraction. The aq. phase was basified with NaOH and extracted with CH_2Cl_2 (3×). The combined extract was dried and evaporated, and the crude product subjected to CC(AcOEt/hexane 4:6): **4a** (40%). IR: 3452, 2934, 1704, 1334. ^{1}H-NMR (300 MHz): 2.02–2.53 (*m*, 8 H); 3.63 (*s*, 3 H); 3.88 (*m*, 1 H); 4.58 (*s*, 1 H); 6.30 (*s*, 1 H); 6.98 (*s*, 1 H). ^{13}C-NMR (75 MHz): 24.0; 28.3; 30.9; 31.9; 51.7; 54.7; 57.1; 139.2; 143.3; 166.8. HR-MS: 181.1020 ($C_{10}H_{15}NO_2$, calc. 181.1021).

Methyl 9-[(4-Methylphenyl)sulfonyl]-9-azabicyclo[4.2.1]non-2-ene-2-carboxylate (**4b**). A soln. of **4a** (300 mg, 1.66 mmol) in pyridine (1.0 ml) was treated with TsCl (315 mg, 1.66 mmol). After standing at r.t. for 8 h, the mixture was diluted with CH_2Cl_2 and washed with 1N HCl and H_2O. The org. soln. was dried, and evaporated and the residue chromatographed: **4b** (268 mg, 80%). M.p. 136–137°. IR: 2954, 1703, 1440, 1339, 1238, 1163. ^{1}H-NMR (300 MHz): 1.48–1.74 (*m*, 5 H); 2.06 (*m*, 1 H); 2.26 (*m*, 1 H); 2.36 (*s*, 3 H); 2.51 (*m*, 1 H); 3.68 (*s,* 3 H); 4.38 (*s*, 1 H); 5.08 (*d*, J=6.0, 1H); 6.96 (*t*, J=6.0, 1H); 7.22, 7.68 (*AA′BB′*, J=8.4, 2 H each). ^{13}C-NMR (75 MHz): 21.4; 23.9; 29.7; 32.0; 33.4; 51.9; 57.9; 58.6; 126.9; 129.6; 137.1; 142.6; 143.2; 144.4; 166.4. HR-MS: 335.1188 ($C_{17}H_{21}NO_4S^+$; calc. 335.1189).

N-*Methoxy*-N-*methyl-9-[(4-methylphenyl)sulfonyl]-9-azabicyclo[4.2.1]non-2-ene-2-carboxamide* (**6**). A soln. of **4b** (400 mg, 1.19 mmol) and 30% NaOH (2.4 mmol) in THF (5 ml) was stirred at r.t. for 5 h.

Acidification with 10% HCl soln. was followed by extraction with CH_2Cl_2. The crude acid obtained from the org. extracts was redissolved in THF (3 ml) and treated with 2-chloro-4,6-dimethoxy[1,3,5]triazine (248 mg, 1.41 mmol) and 4-methylmorpholine (360 mg, 3.57 mmol) while stirring at r.t. After 1 h, *N,O*-dimethylhydroxylamine·HCl (116 mg, 1.19 mmol) was added, and the reaction was allowed to proceed for 9 h after which H_2O and CH_2Cl_2 were added. The aq. phase was extracted once more with CH_2Cl_2, the combined org. soln. washed with sat. Na_2CO_3 soln. and 1N HCl, dried, and evaporated, and the residue subjected to (AcOEt/hexane 4:6): **6** (290 mg, 80%). IR: 2929, 1654, 1339, 1160. ^{1}H-NMR (300 MHz): 1.56–2.04 (*m*, 8 H); 2.39 (*s*, 3 H); 3.25 (*s*, 3 H); 3.66 (*s*, 3 H); 4.42 (*m*, 1 H); 4.70 (*t*, *J* = 5.4, 1 H); 6.18 (*t*, *J* = 6.0, 1 H); 7.25, 7.71 (*AA′BB′*, *J* = 8.4, 2 H each). ^{13}C-NMR (75 MHz): 21.5; 23.9; 29.1; 32.9; 33.0; 33.7; 59.4; 59.5; 61.2; 126.9; 129.7; 134.5; 137.3; 141.9; 143.3; 170.0. HR-MS: 364.1452 ($C_{18}H_{24}N_2O_4S^+$; calc. 364.1451).

N-*Tosylanatoxin a* (= *1-{(1*RS,*6*RS*)-9-[(4-Methylphenyl)sulfonyl]-9-azabicyclo[4.2.1]non-2-en-1-yl}ethanone*; **1b**). To a stirred soln. of **6** (250 mg, 0.72 mmol) in THF (2 ml) was added 1.6M MeLi in Et_2O, (1.1 ml) at r.t. After 2 h, the reaction was quenched with H_2O, and the product was extracted into CH_2Cl_2. Drying, evaporation, and CC (AcOEt/hexane 2:8) afforded **1b** (106 mg, 46%). IR: 2930, 1659, 1340, 1157, 1093. ^{1}H-NMR (300 MHz): 1.23–1.62 (*m*, 7 H); 2.26 (*s*, 3 H); 2.39 (*s*, 3 H); 2.62 (*m*, 1 H); 4.43 (*m*, 1 H); 5.18 (*d*, *J* = 7.8, 1 H); 6.86 (*t*, *J* = 6.0, 1 H); 7.25, 7.70 (*AA′BB′*, *J* = 8.4, 2 H each). ^{13}C-NMR (75 MHz): 21.5; 24.4; 25.4; 29.8; 31.9; 33.6; 56.4; 58.8; 126.9; 129.7; 137.2; 143.3; 147.4; 197.5. HR-MS 319.1236 ($C_{17}H_{21}NO_3S^+$; calc. 319.1238).

REFERENCES

[1] T.-L. Ho, 'Symmetry, A Basis for Synthesis Design', John Wiley & Sons, New York, 1995.
[2] T.-L. Ho, C.-Y. Su, *Tetrahedron* **2001**, *57,* 507; T.-L. Ho, E. Gorobets, *Tetrahedron* **2002**, *58,* 4969.
[3] T.-L. Ho, D.-G. Jou, *Helv. Chim. Acta* **2002**, *85,* 3823.
[4] T.-L. Ho, E. Kuzakov, *Helv. Chim. Acta* **2004**, *87,* 2712.
[5] T.-L. Ho, C.-K. Chen, *Helv. Chim. Acta* **2005**, *88*, 2764.
[6] T.-L. Ho, C.-K. Chen, *Helv. Chim. Acta* **2006**, *89*, 122.
[7] C. S. Huber, *Acta Crystallogr., Sect. B* **1972**, *28*, 2577.
[8] a) H. L. Mansell, *Tetrahedron* **1996**, *52,* 6025 and ref. cit. therein; b) N. J. Newcombe, N. S. Simpkins, *Chem. Commun.* **1995**, 831; c) J. R. Ferguson, K. W. Lumbard, F. Scheinmann, A. V. Stachulski, P. Stjernlof, S. Sundell, *Tetrahedron Lett.* **1995**, *36,* 8867; d) C.-Y. Oh, K.-S. Kim, W.-H. Ham, *Tetrahedron Lett.* **1998**, *39,* 2133; e) B. M. Trost, J. D. Oslob, *J. Am. Chem. Soc.* **1999**, *121,* 3057; f) V. K. Aggarwal, P. S. Humphries, A. Fenwick, *Angew. Chem., Int. Ed.* **1999**, *38,* 1985; g) P. J. Parsons, N. P. Camp, N. Edwards, I. R. Sumoreeah, *Tetrahedron* **2000**, *56,* 309; h) T. Wegge, S. Schwarz, G. Seitz, *Tetrahedron: Asymmetry* **2000**, *11,* 1405.
[9] R. Graf, *Chem. Ber.* **1956**, *89,* 1071; H. Bestian, H. Biener, K. Clauss, H. Heyn, *Liebigs Ann. Chem.* **1968**, *718,* 94.
[10] C. W. Bird, H. I. Butler, E. C. J. Coffee, L. M. James, B. W. C. Schmidl, *Tetrahedron* **1989**, *45,* 5655.
[11] L. De Luca, G. Giacomelli, M. Taddei, *J. Org. Chem.* **2001**, *66,* 2534.
[12] T.-L. Ho, M.-H. Chang, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2479.

Received July 5, 2005