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An efficient synthesis of (+)-Anatoxin-a.[1]

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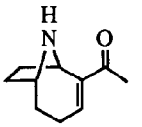
Abstract: *An efficient synthesis (38 % overall yield in 8 steps starting from* **2***) of the potent neurotoxin (+)-anatoxin-a is described. The key step involves the stereoselective addition of 5-hexenylcopper to the chiral N-acyliminium ion* **2a**.

Anatoxin-a (**1**), isolated from the blue-green freshwater alga *Anabaena Flos aquae*, is one of the most powerful agonists of the nicotinic acetylcholine receptor known today. Of particular interest is the large difference in receptor binding affinities observed for the two enantiomers, the naturally occurring (+)-enantiomer being about 100 times more powerful.



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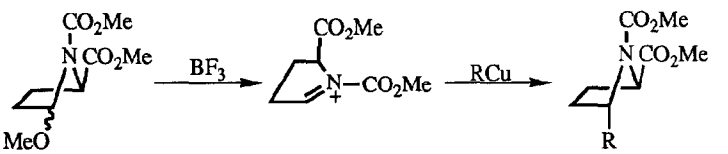
The relative rigidity of the homotropane system makes **1** a suitable starting point for structure-activity studies of the nicotinic acetylcholine receptor. Synthetic approaches towards **1** are numerous[2], however, syntheses of enantiomerically pure (+)-**1** have mainly been carried out by the Rapoport group.[3-5]

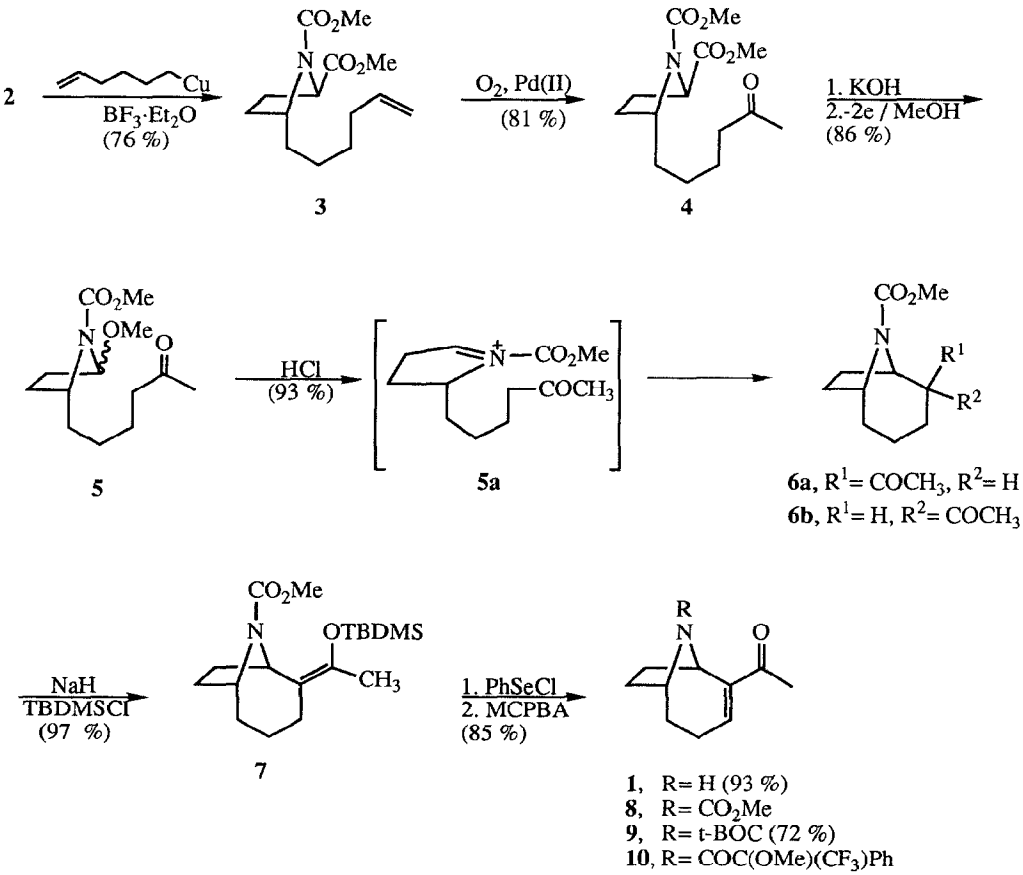
In our synthesis of (+)-**1**, we have utilized the highly selective *trans* addition of alkylcopper reagents to



2 **2a**

the chiral *N*-acyliminium ion **2a**. We have shown, that reaction of **2a** with organocopper reagents occurs with a much higher degree of stereoselectivity than with ordinary π-nucleophiles, e. g. allyltrimethylsilane.[6] Using a suitable nucleophile, the selective trans addition to **2a** would create the necessary *R* stereochemistry for the transformation of the adduct into (+)-anatoxin-a. Consequently, reaction of the α-methoxylated carbamate **2** (available in 100 g quantities from L-proline *via* *N*-acylation, esterification and anodic methoxylation[6,7]) with hexenylcopper[8] in the presence of $BF_3{\cdot}Et_2O$ gave the trans alkylated product **3** (cis:trans 3:97, 76 % yield). Oxidation of **3** under Wacker conditions[9] then gave the methyl ketone **4** (Scheme). The next stage of the synthesis involves formation of the *N*-acyliminium ion **5a** followed by an intramolecular cyclization leading to the homotropane ring system in **6**. Thus, hydrolysis (KOH, MeOH) of

Scheme.



4 followed by anodic decarboxylation[10] gave the corresponding α-methoxylated pyrrolidine **5** as a 1:1 mixture of diastereomers. Treatment of **5** with various Lewis acids commonly used to form *N*-acyliminium ions from the corresponding α-alkoxy amide or carbamate ($TiCl_4$, $AlCl_3$ or $BF_3{\cdot}Et_2O$) only gave unreacted starting material or unidentifiable oligomers. However, on treatment of **5** with HCl in MeOH,[2b,11] a clean reaction occurred and the dihydroanatoxin-a derivative **6** was isolated as a mixture of isomers (1:1, separable by chromatography).

The introduction of the α,β unsaturated moiety into **6** was performed using Rapoport's methodology.[3] Thus, **6** was converted into the enol ether **7** on treatment with sodium hydride-TBDMSCl. Only one stereoisomer could be detected and this is assumed to be the Z-isomer in analogy with Rapoport's results. Reaction of **7** with PhSeCl followed by oxidation with MCPBA gave *N*-methoxycarbonylanatoxin-a **8**. (+)-Anatoxin-a was obtained from **8** by treatment with TMSI.[12] Spectral data were identical to the reported literature values; the optical rotation of our material ($[\alpha]_D^{25}$ +39.8 (c 0.676, abs. EtOH)) was in agreement with the reported literature values ($[\alpha]_D^{24}$ +43.2 (c 0.676, abs. EtOH)[3], $[\alpha]_D^{20}$ +37.0 (c 1.0 methanol)[4]). The optical purity of our material was checked indirectly by conversion of (+)-**1** into the corresponding t-BOC derivative **9** which in all respects was identical to the material prepared by Rapoport[3] ($[\alpha]_D^{25}$ -46.8 (c 0.839, CH_2Cl_2), lit. $[\alpha]_D^{24}$ -47.2 (c 0.839, CH_2Cl_2)).

A more direct examination of the optical purity of our material was performed by conversion of (+)-**1** into the corresponding Mosher amide **10**.[13] ^1H NMR and HPLC analysis of **10** revealed the presence of 3 % of (-)-**1** corresponding to an enantiomeric purity of 94 %. This is probably due to the contamination of **3** with the corresponding *cis* compound which ultimately ends up as (-)-**1**.

In conclusion, we have reported an efficient 8-step synthesis of (+)-anatoxin-a in 38 % overall yield starting from **2**. The highly stereoselective addition of alkylcopper reagents to the *N*-acyliminium ion **2a** was used as the key step to control the absolute stereochemistry of the final product.

Experimental part

All chemicals used were of the highest commercial purity and were used without further purification. Petroleum ether (60-80 °C) and ethyl acetate, used for chromatography, were distilled before use. $BF_3{\cdot}Et_2O$ was distilled before use and stored under an atmosphere of argon. $CuBr{\cdot}Me_2S$ was prepared according to the method described by House.[14] Concentrations of the alkyllithium solutions were determined by titration as described by Watson and Eastham.[15] Reaction mixtures were analyzed by capillary GLC using a Varian 3400 chromatograph equipped with a Varian 4270 integrator on a 25m x 0.25mm OV 1701 column and by TLC on commercially available silica gel-aluminium foil plates. Flash chromatography was performed on TLC grade silica gel according to Taber.[16] NMR spectra were recorded in $CDCl_3$ on a Varian XL 300 machine; δ in ppm downfield from TMS as an internal standard. Optical rotations were determined on a

Perkin Elmer 241 MC instrument. Elementary analysis was preformed by Dornis und Kolbe, Mülheim, Germany. High resolution mass spectra (MS(hr)) were obtained using a Jeol SX 102 instrument.

1-Bromo-5-hexene.[17] A solution of 5-hexen-1-ol (38 g, 0.38 mol) and pyridine (2 g, 30.3 mmol) in dry ether (100 ml) was added dropwise to a solution of phosphorus tribromide (35 g, 0.13 mol) in dry ether (100 ml) at a rate which maintained the system under steady reflux. The mixture was then heated to reflux temperature for another three hours, cooled and poured on ice. The aqueous phase was extracted with ether (3x30 ml). The organic phase was washed with aqueous NaCl (50 ml) and aqueous $NaHCO_3$ (50 ml), dried and distilled. Bp. 80°C 65mmHg. Yield 47.6g (75%).

5-Hexenyllithium. A solution of 1-bromo-5-hexene (16.31 g, 100 mmol) in dry ether (100 ml) was added to a slurry of Li (1.4 g, 200 mmol) in dry ether (20 ml) under an atmosphere of argon at -40°C. After all bromohexene were added the mixture was stirred for 1h. After allowing unreacted lithium to settle, the solution was used immediately in the next step. Lithium powder, commercially available from Merck, is essential to use in order to achieve lithiation at -40°C.

(5*R*)-5-(5-Hexenyl)-1-methoxycarbonyl-*L*-proline methyl ester (3). To a suspension of $CuBr{\cdot}Me_2S$ (1.03 g, 5 mmol) in dry ether (25 ml) was added a solution of 5-hexenyllithium in ether (5 mmol) at -40 °C under an argon atmosphere. After stirring for 30 minutes, the solution was cooled to -78 °C and $BF_3{\cdot}Et_2O$ (0.52 ml, 5 mmol) was added. After 5 minutes, a solution of **2**[6] (0.54g, 2.5 mmol) in dry ether (5 ml) was added. The reaction mixture was allowed to attain room temperature and a mixture of concentrated aqueous ammonia and a saturated solution of NH_4Cl (1:1) was added. After stirring for another 30 minutes, the reaction mixture was extracted with 3 x 30 ml of CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic phase was dried, filtered, and evaporated. Purification by column chromatography (ethyl acetate:petroleum ether, 2:1) gave 0.51 g (76 %) of **3** as a colorless oil: $[\alpha]_D^{25}$ -71.2 (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, m) 4.98 (2H, m) 4.32 (1H, dd, J= 13.5, 8.6 Hz) 4.97 (1H, m) 3.70 (6H, 4s, CO_2Me) 2.20 (1H, m) 2.11-1.20 (11H, m); ^{13}C NMR (two rotamers) δ 173.3, 173.2, 155.6, 154.9, 138.8, 138.7, 114.6, 114.5, 59.5, 59.4, 58.7, 57.9, 52.5, 52.3, 52.1, 34.0, 33.7, 33.6, 33.4, 28.7, 28.7, 28.6, 28.1, 27.6, 27.2, 25.9, 25.8. MS (hr): 269.1622; calcd. for $C_{14}H_{23}NO_4$: 269.1627.

(5*R*)-1-methoxycarbonyl-5-(1-(5-oxohexyl))-*L*-proline methyl ester (4). Oxygen gas was bubbled into a well stirred mixture of $PdCl_2(MeCN)_2$ (19.2 mg, 0.074 mmol) and CuCl (221 mg, 2.23 mmol) in a mixture

of DMF and H_2O (7:1, 20 ml). The mixture was heated to 50 °C an stirred for 1h. Compound **3** (2.0 g, 7.43 mmol) dissolved in DMF-H_2O (7:1, 10 ml) was then added and the reaction mixture was stirred at 50 °C with oxygen bubbling for 72 h. The reaction mixture was poured into cold 10 % HCl (20 ml) and extracted with ether (3x20 ml). The combined organic phases were washed with $NaHCO_3$ (30 ml), dried, filtered and evaporated. Purification by column chromatography (petroleum ether:ethyl acetate, 2:3) gave 1.7 g (81 %) of **4** as a colorless oil: $[\alpha]_D^{25}$ -84.3 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (1H, dd, J= 12.5, 8.5 Hz) 3.94 (1H, m) 3.63 (6H, 4s, CO_2Me) 2.45 (2H, t, J= 7.4 Hz) 2.20 (1H, m) 2.10 (3H, 2s, $COCH_3$) 2.08-1.49 (6H, m) 1.25 (3H, m); ^{13}C NMR (two rotamers) δ 208.9, 208.7, 173.2, 173.1, 155.5, 154.9, 59.5, 59.4, 58.5, 57.8, 52.4, 52.2, 52.1, 43.4, 34.1, 33.3, 29.8, 28.7, 28.1, 27.5, 27.3, 25.9, 25.8, 23.6. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.78; H, 8.17; N, 4.97.

(5*R*)-2-Methoxy-1-methoxycarbonyl-5-(1-(5-oxohexyl))-pyrrolidine (5). Compound **4** (0.71 g, 2.5 mmol) was dissolved in methanol (3.5 ml). After cooling to 0 °C, a solution of KOH (0.83 g) in water (3.5 ml) was slowly added. The mixture was then stirred at ambient temperature for 5 hours. Partial evaporation followed by acidification with 3M HCl and extraction with CH_2Cl_2 (3x15 ml) gave the free acid in 99 % yield. The acid was then dissolved in methanol (25 ml) containing 0.1 equivalent of NaOMe in a water-cooled cell containing a Pt wire anode (1 mm diameter) and a Pt-foil cathode. 2.0 F/mol was passed through the solution at a constant current of 150 mA. Evaporation of the solvent followed by column chromatography (petroleum ether:ethyl acetate, 1:1) gave 0.67 g (87 %) of **5** as a mixture of C-2 diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (0.5H, s) 4.93 (0.5H, s) 3.85-3.60 (1H, m) 3.75-3.65 (3H, 4s, CO_2Me) 3.51-3.22 (3H, 4s, OMe) 2.43 (2H, t, J= 7.4 Hz) 2.10 (3H, s) 1.85 (4H, m) 1.57 (2H, t, J= 7.4 Hz) 1.35 (4H, m).

(1*R*)-2-Acetyl-9-methoxycarbonyl-9-azabicyclo-[4.2.1]nonane (6a and **6b)**. Methanol (70 ml) was saturated with HCl gas at -50 °C. The α-methoxy carbamate **5** (700 mg, 2.78 mmol) was dissolved in methanol (5 ml) and added slowly to the saturated methanol. The reaction mixture was kept at -45 °C for 5 hours and was then allowed to attain room temperature slowly. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x50 ml). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried, filtered, and evaporated. Purification by column chromatography (CH_2Cl_2:acetone, 91:9) gave 0.66 g (93 %) of **6a** and **6b** as a colorless oil. **6a**: $[\alpha]_D^{25}$ -76.2 (c 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (0.5H, m) 4.59 (0.5H, m) 4.36 (0.5H, t, J= 8.0

Hz) 4.24 (0.5H, t, J= 8.1 Hz) 3.70 (3H, 2s, CO_2Me) 3.16 (0.5H, m) 2.96 (0.5H, m) 2.16 (3H, 2s, COMe) 2.15-1.82 (3H, m) 1.79-1.48 (5H, m) 1.44-1.20 (2H, m); ^{13}C NMR (two rotamers): δ 209.6, 209.2, 154.6, 57.1, 56.6, 56.3, 55.0, 54.8, 54.6, 52.5, 52.3, 34.7, 33.8, 32.8, 31.9, 29.3, 29.2, 25.6, 25.0, 24.9, 24.6, 22.6, 22.6. MS (hr): 225.1361; calcd. for $C_{12}H_{19}NO_3$: 225.1365. **6b**: $[\alpha]_D^{25}$ -13.7 (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 4.65, 4.55 (1H, 2d, 2:3, J= 9.2 Hz) 4.40, 4.29 (1H, 2d, 3:2, J= 5.8 Hz) 3.66, 3.58 (3H, 2s, CO_2Me) 2.30, 2.19 (3H, 2s, COMe) 2.05 (1H, m) 2.50-1.40 (10H, m); ^{13}C NMR (two rotamers): δ 209.5, 209.4, 208.7, 154.9, 154.2, 60.7, 60.6, 56.6, 56.4, 56.1, 56.0, 52.4, 51.9, 34.9, 33.9, 33.8, 33.0, 27.9, 27.7, 27.6, 27.1, 26.3,21.6. MS (hr): 225.1367; calcd. for $C_{12}H_{19}NO_3$: 225.1365.

(1*R*)-2-((Z)-1-(Dimethyl-tert-butylsiloxy)ethylidene)-9-methoxycarbonyl-9-azabicyclo-[4.2.1]nonane (7). Prepared from a mixture of **6a** and **6b** according to Rapoport et al.[3] Yield 97 %. ^1H NMR (300 MHz, $CDCl_3$): δ 5.02, 4.94 (1H, 2d, 2:3, J= 8.5 Hz) 4.43, 4.32 (1H, 2d, 3:2, J= 7.4 Hz) 3.67 (3H, 2s, CO_2Me) 2.38-2.10 (2H, m) 2.10-1.25 (8H, m) 1.82 (3H, 2s) 0.95 (9H, s) 0.20 (6H, 2s).

(1*R*)-2-Acetyl-9-methoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (8). Prepared from **7** according to Rapoport et al.[3] Yield 85 %. $[\alpha]_D^{25}$ -40.9 (c 1.0, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (1H, t, J= 5.7 Hz) 5.21 (1H, d, J= 8.9 Hz) 4.47 (0.5H, m) 4.36 (0.5H, m) 3.63 (3H, 2s, CO_2Me) 2.55-1.95 (5H, m) 2.28 (3H, s) 1.85-1.60 (3H, m); ^{13}C NMR δ 197.9, 142.6, 141.6, 55.9, 53.3, 52.3, 31.8, 30.8, 28.6, 24.2. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.46; H, 7.74; N, 6.24.

(1*R*)-2-Acetyl-9-azabicyclo[4.2.1]-2-nonene (1). Compound **8** (135 mg, 0,61 mmol) was dissolved in CH_2Cl_2 (343 µl) and Me_3SiI (104 µl) was added and the solution was stirred for 2.5 hours at 50 °C . After quenching with methanol and sodium methoxide, aqueous work-up gave the free amine. Yield 93 %. $[\alpha]_D^{25}$ +39.8 (c 0,676, abs. EtOH) [lit.[3] $[\alpha]_D^{24}$ +43.2 (c 0.676, abs. EtOH), lit.[4] $[\alpha]_D^{20}$ +37.0 (c 1.0 methanol)]; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (1H, m) 4.68 (1H, d, J= 8.7 Hz) 3.38-3.77 (1H, m) 2.55-2.39 (2H, m) 2.29 (3H, s) 2.27-1.50 (7H, m); ^{13}C NMR δ 198.6, 152.3, 143.2, 57.8, 54.2, 33.5, 32.9, 30.3, 25.5, 25.0.

(1*R*)-2-Acetyl-9-t-butyloxycarbonyl-9-azabicyclo[4.2.1]nonane (9). A solution of (+)-anatoxin-a (60 mg, 0.364 mmol) and di-*tert*-butyl dicarbonate (109 mg, 0.502 mmol) in MeOH (4 ml) was stirred for 30h. Et_2O (15 ml) was added and the solution was washed with 0.2 M aq. H_3PO_4 (5 ml) and $NaHCO_3$ (5 ml).

The aqueous phases were extracted with Et_2O (3x10 ml) and the organic phase was dried, filtered, and evaporated. Purification by column chromatography (ethyl acetate:hexane, 3:7) gave 69.5 mg (72%) of **9**. $[\alpha]_D^{25}$ -46.8 (c 0.839, CH_2Cl_2) [lit.[3] $[\alpha]_D^{24}$ -47.2 (c 0.839, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (1H, t, J= 5.9 Hz) 5.18-5.10 (1H, m) 4.50-4.25 (1H, m) 2.50-2.05 (5H, m) 2.29 (3H, s) 1.70-1.50 (3H, m) 1.58, 1.38 (9H, 2s).

Mosher amide 10. To a solution of freshly prepared (+)-**1** (63 mg, 0.823 mmol) in THF containing a few drops of triethylamine was added (-)-MTPA chloride (130 mg, 0.517 mmol) and CH_2Cl_2 (2 ml) and a catalytic amount of DMPA. The solution was stirred for 16 hours at ambient temperature. CH_2Cl_2 was added and the solution was washed with a saturated aqueous solution of $NaHCO_3$. After drying ($MgSO_4$) and evaporation, the crude product was purified by column chromatography (ethyl acetate:hexane, 1:2). Yield: 75 mg (24 %). ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.32 (8H, m), 6.82 (1H, t, J=5.5 Hz), 5.03-4.93 (1H, m), 4.88-4.81 (1H, m), 3.65-3.42 (1H, m), 2.32, 2.24 (3H, 2s), 2.61-1.18 (8H, m). ^{13}C NMR δ 197.1, 163.3, 145.6, 141.9, 129.4, 129.3, 128.3, 128.2, 126.9, 126.7, 55.9, 55.8, 55.3, 54.9, 31.8, 30.7, 25.8, 25.6, 25.5, 24.6. ^{19}F NMR δ 8.07 (s). $[\alpha]_D^{25}$ -123.3 (c 1.0, MeOH).

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NOTES AND REFERENCES

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