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TOTAL SYNTHESIS OF (±)-ANATOXIN-a VIA N-ACYLIMINIUM INTERMEDIATES

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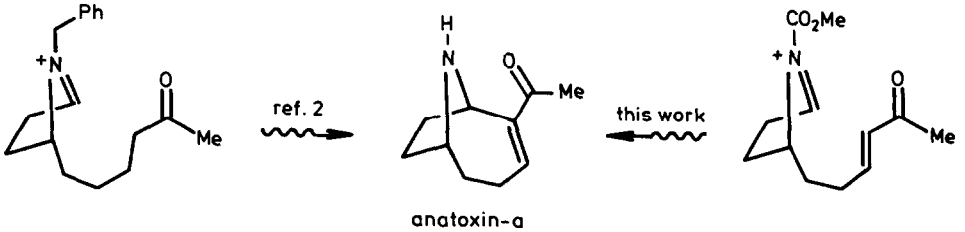
Abstract: (±)-Anatoxin-a has been synthesized in 8 steps, starting from succinimide, 4-bromo-1--butene and dimethyl (2-oxopropyl)phosphonate, by employing as the key step an intramolecular reaction of an N-acyliminium precursor with an α,β-unsaturated ketone moiety, induced by saturated HCl in MeOH at -50°C.

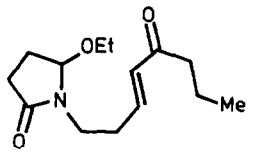
Anatoxin-a (1) is a potent neurotoxin, produced by certain strains of the fresh water blue green alga Anabaena flos-aquae[1]. Both its unique structure (the only natural product identified to date with the 9-azabicyclo[4.2.1]nonane skeleton), and its significant biological properties (powerful nicotinic acetylcholine receptor agonist[2]) have aroused the interest of synthetic chemists. This has resulted in a number of successful syntheses of the alkaloid (1), both as racemate[3] and as pure enantiomer[2,4]. In this letter we wish to report yet another synthesis of racemic anatoxin-a, which, however, stands out, because it numbers only 8 steps from commercially available and inexpensive starting materials. In addition, our synthesis features a novel reaction mode of N-acyliminium ions, in which the α-carbon of an α,β-unsaturated ketone formally reacts as the nucleophilic centre.

Our approach bears resemblance to Rapoport's synthesis[2,5], in which the key step is the Mannich type cyclization of iminium ion 2. In connection with our work on N-acyliminium chemistry, we reasoned that a successful conversion of 3 to 1 could mean a major improvement compared to Rapoport's route for two reasons. Firstly, use of a carbomethoxy group on nitrogen would enhance the electrophilicity of the iminium ion[6] and reduce the number of protection-deprotection steps of nitrogen[2]. Secondly, use of an α,β-unsaturated ketone as a nucleophile



2 anatoxin-a (1) 3

would lead in a more direct way to the desired unsaturated bicyclic system. The latter objective was based on a recent finding, during our studies toward the synthesis of elaeokanine-B[7a], that dissolution of enone 4 in methanol, saturated with HCl, gives rise to quantitative formation of chloride 5[7b]. On dehydrochlorination of 5 using 1,5-diazabicyclo[4.3.0]-5-nonene (DBN) in refluxing toluene the desired enone 6 was obtained[7].



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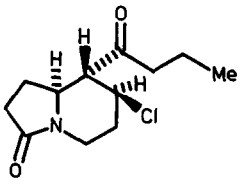

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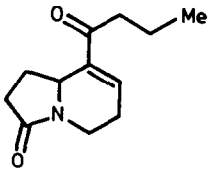

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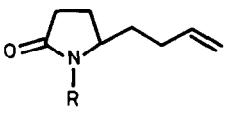
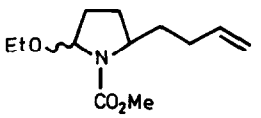
Our synthesis of anatoxin-a began with the conversion of succinimide into butenylpyrrolidone 7 in a one-pot reaction. Succinimide was first transformed into a Mg-salt (MeMgCl, THF) and then treated with 2 eq of the Grignard reagent, derived from 4-bromo-1-butene (THF, 18 h, 20°C)[8]. To the resultant mixture was added 1 eq of $NaBH_3CN$ and some Methyl Orange indicator (1M in water) followed by 6 N HCl, until the colour changed to red[9]. Usual work-up provided 7[10] in 53% yield based on succinimide (27% based on 4-bromo-1-butene).



7 R = H
8 R = CO_2Me



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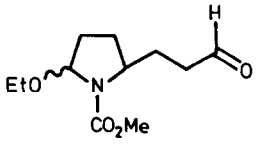
Reaction of the lithium salt of 7 (LDA, THF, -78°C) with methyl cyanoformate[12] (THF, -78°C → 20°C) afforded carbamate 8[10] in 69% yield. Reduction[13] of 8 ($NaBH_4$, little H_2SO_4, EtOH, -20°C), followed by in situ ethanolysis[13] (EtOH, excess H_2SO_4, -20°C → 20°C) gave ethoxycarbamate 9[10] in 77% yield, which was >95% a single stereoisomer according to ^{13}C NMR spectrometry. With the precursor for an N-acyliminium intermediate in place, the side chain was next elaborated. Ozonolysis of 9 (CH_2Cl_2, -78°C) followed by reduction with dimethyl sulfide (48 h, 20°C) furnished aldehyde 10[10] in 75% yield. This aldehyde was converted into enone 11[10] through reaction with dimethyl (2-oxopropyl)phosphonate under the Masamune-Roush conditions[14] (iPr_2NEt, LiCl, MeCN, 20°C) in 83% yield, thus completing the synthesis of the precursor for the key cyclization step.

A solution of HCl in MeOH, saturated at -50°C, was added to ethoxycarbamate 11 at -50°C. The resultant solution was stirred for 18 h, while the temperature was allowed to slowly rise to



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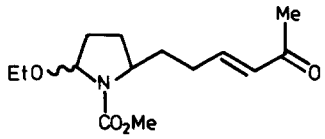

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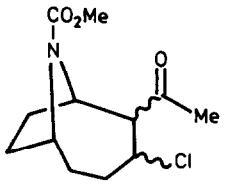
20°C. The reaction mixture was then poured out into saturated aqueous sodium bicarbonate and worked up as usual (including flash chromatography), to furnish an unseparable mixture of stereoisomeric chlorides 12[15] and enone 13, in yields of 47% and 11%, respectively, according to ^{1}H NMR spectroscopy. This mixture was refluxed in toluene in the presence of DBN to give pure enone 13[10] in 60% yield. The mechanism of the ring closure reaction was not investigated, but we suppose that 14 serves as an intermediate, since in 14 the α-carbon of the original α,β-unsaturated ketone is now strongly nucleophilic. Chloride 14 could arise via conjugate HCl addition followed by methyl enol ether formation.



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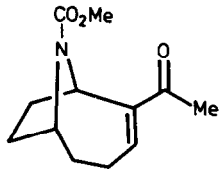

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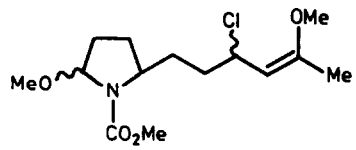

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Our synthesis of (±)-anatoxin-a (1) was completed through deprotection of nitrogen, by using in situ generated Me_3SiI (Me_3SiCl, NaI) in refluxing acetonitrile[16]. This last step (55% yield) provided 1 as a colourless oil, which showed a ^{1}H NMR spectrum, fully identical with literature data[4b]. Thus, we have synthesized racemic anatoxin-a in 8 steps from readily available starting materials. The overall yield (3-4% from succinimide) leaves something to be desired, but most steps are unoptimized. Results of optimization studies, which are currently in progress will be detailed in a full paper.

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10) This compound was purified by using flash chromatography[11] and then showed spectra (IR, ^{1}H NMR, ^{13}C NMR) in accord with its structure, and satisfactory high resolution mass spectral data[17].

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12) The corresponding chloroformate gave predominant O-acylation. For a related finding see: L.N. Mander, S.P. Sethi, Tetrahedron Lett., 24, 5425 (1983).

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15) Exact mass: calcd for $C_{12}H_{18}NO_3Cl$ 259.0970; found 259.0965.

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17) Some selected data are:

7: IR($CHCl_3$): 3210 (NH), 1685 cm^{-1} (C=O); ^{1}H NMR (100 MHz, $CDCl_3$): δ 7.32 (br s, NH), 5.60-6.08 (m, CH=CH_2), 4.84-5.24 (m, CH=CH_2), 3.68 (m, NCH), 1.40-2.54 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 178.4 (s), 137.3 (d), 115.0 (t), 54.0 (d), 35.7 (t), 30.1 (t), 29.9 (t), 27.0 (t).

8: IR($CHCl_3$): 1780 and 1720 (C=O), 1638 cm^{-1} (C=C); ^{1}H NMR (100 MHz, $CDCl_3$): δ 5.64-6.06 (m, CH=CH_2), 4.94-5.24 (m, CH=CH_2), 4.24 (m, NCH), 3.89 (s, CH_3), 1.46-2.74 (m, 8H).

9: IR($CHCl_3$): 1685 (C=O), 1638 cm^{-1} (C=C); ^{1}H NMR (100 MHz, $CDCl_3$): δ 5.66-6.10 (m, CH=CH_2), 5.34 (m, CHOEt), 4.88-5.20 (m, CH=CH_2), 3.75 (s, CO_2CH_3), 3.38-4.05 (m, NCH + OCH_2CH_3), 1.03-2.28 (m, 8H), 1.19 (t, J=7 Hz, OCH_2CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 156.0 (br s), 138.0 (d), 114.1 (t), 87.9 (br d), 62.4 (br t), 57.6 (br d), 51.9 (q), 35.1 (br t), 31.9 (br t), 29.8 (t), 28.7 (br t), 14.9 (q); some signals are broad due to hindered rotation.

11: IR($CHCl_3$): 1687 and 1670 (C=O), 1622 cm^{-1} (C=C); ^{1}H NMR (100 MHz, $CDCl_3$): δ 6.85 (dt, J=16, 6Hz, CH=CHCO), 6.14 (dt, J=16, 2Hz, CH=CHCO), 5.36 (m, CHOEt), 3.40-4.06 (m, NCH + OCH_2CH_3), 3.75 (s, CO_2CH_3), 2.26 (s, $COCH_3$), 1.38-2.44 (m, H), 1.18 (t, J=7Hz, OCH_2CH_3): ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.2 (s), 155.8 (br s), 147.5 (d), 131.1 (d), 87.9 (br d), 62.4 (br t), 57.4 (br d), 52.1 (q), 33.9 (br t), 31.8 (br t), 28.8 (br t), 28.3 (t), 26.5 (q), 14.9 (q).

13: IR($CHCl_3$): 1685 (C=O), 1630 cm^{-1} (C=C); ^{1}H NMR (100 MHz, $CDCl_3$): δ 6.85 (br t), J=5.5 Hz, C=CH), 5.24 (br d, J=6 Hz, NCH), 4.46 (m, NCH), 3.69 and 3.64 (br s, OCH_3), 2.31 (s, $COCH_3$), 1.35-2.63 (m, 8H). Exact mass calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1208.

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