the soft nucleophile CN^- afforded the 4-substituted adduct. The ambident nitronate anions do not form stable σ adducts with 1,2,4,6-tetraphenylpyridinium cation; interaction remained at the stage of π complex or CTC formation. The steric effect of the phenyl group is sufficient in the case of the nitronate anions to shift the equilibrium π to σ complex in favor of the former. Although we believe this to be a thermodynamic effect, it should be noted that the *kinetic* carbon basicities of nitronate ions appear to be very low;[18] cf. their low kinetic proton basicity in contrast to the nearly equal thermodynamic proton basicity of PhS^- and $Me_2CNO_2^-$.

Experimental Section

^1H NMR spectra were obtained on a Varian EM360L spectrometer and ^{13}C NMR spectra on a JEOL JNM FX-100 spectrometer; chemical shifts in ppm from tetramethylsilane are reported from spectra taken in Me_2SO-d_6. UV spectra were obtained on a Perkin-Elmer 330 spectrophotometer, and the ESR studies were carried out on a BRUKER ER 200D-SRC spectrometer.

The following compounds were prepared by the literature method quoted: 1,2,6-triphenylpyridinium perchlorate, mp 197–199 °C (lit.[19] mp 198–199 °C); 1,2,4-triphenylpyridinium tetrafluoroborate, mp 235 °C (lit.[20] mp 235 °C), 1,2,4,6-tetraphenylpyridinium tetrafluoroborate, mp 251–252 °C (lit.[21] mp 251 °C). The nucleophiles were either commercially available (NaCN) or prepared by standard methods: NaOMe from NaH and dry MeOH, all others by reacting the appropriate nitroalkane or thiophenol with 1 equiv of NaOMe in MeOH. Me_2SO was dried by distillation in vacuo from CaO.

General Procedure for the Reaction of the Pyridinium Cations with the Nucleophiles. In a typical experiment, 1 equiv of nucleophile was added to the pyridinium cation in Me_2SO-d_6 (0.30 M) for the ^1H NMR and ^{13}C NMR measurements. A lower concentration of the pyridinium salt (4.50×10^{-5} M) and a fivefold excess of nucleophile was used for the UV studies.

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Registry No. **2**·BF_4^-, 102107-74-4; **3** (R = OMe), 102107-80-2; **3** (R = CN), 102107-81-3; **3** (R = CMe_2NO_2), 102107-82-4; **3** (R = CH_2NO_2), 102107-83-5; **3** (R = c-$C_6H_{10}NO_2$), 102072-54-8; **3** (R = PhS), 102107-84-6; **4**·BF_4^-, 80576-32-5; **5** (R = OMe), 102107-75-5; **5** (R = CN), 102107-76-6; **5** (R = CMe_2NO_2), 102107-77-7; **5** (R = CH_2NO_2), 102107-78-8; **5** (R = c-$C_6H_{10}NO_2$), 102072-53-7; **5** (R = PhS), 102107-79-9; **7**·BF_4^-, 59834-94-5; **8**, 75102-76-0; **9** (Nu^- = $NO_2CMe_2^-$), 102107-86-8; **9** (Nu^- = $NO_2CH_2^-$), 102107-87-9; **9** (Nu^- = c-$C_6H_{10}NO_2^-$), 102107-88-0; 4-cyano-1,2,4,6-tetraphenyl-1,4-dihydropyridine, 102107-85-7.

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Synthesis of Anatoxin-*a*

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A short efficient synthesis of (±)-anatoxin-*a*, the alkaloidal toxin from *Anabaena flos-aquae*, is described. Bromination of 9-methyl-9-azabicyclo[3.3.1]nonan-1-ol (**3b**) provides the key intermediate 9-methyl-9-azabicyclo[4.2.1]nonan-2-one (**6**). Reaction of **6** with diethyl (1-cyanoethyl)phosphonate gives 2-(1-cyano-1-ethylidene)-9-methyl-9-azabicyclo[4.2.1]nonane (**8**). Oxygenation of **8**, followed by reduction and hydrolysis, gives *N*-methylanatoxin-*a* (**1b**) which has been earlier converted into anatoxin-*a*.

Anatoxin-*a* (**1**) is a powerful alkaloidal toxin isolated from the filamentous freshwater cyanophyte *Anabaena flos-aquae*.[1a] This toxin, also designated as "very fast death factor", VFDF,[1b] is responsible for the death of livestock, waterfowl, and other wildlife following ingestion of toxic blooms of the alga in freshwater lakes of midwestern United States and Canada.[1c] The structure and the absolute configuration of (+)-anatoxin-*a* has been established as (1*R*,6*R*)-2-acetyl-9-azabicyclo[4.2.1]non-2-ene by X-ray crystallography in 1972[2a] and was in full agreement with the spectroscopic studies obtained by Edwards and his co-workers.[1a] The stereospecific synthesis of (+)-anatoxin-*a* from (2*R*,3*S*)-cocaine by Campbell, Edwards, and Kolt in 1976 further confirmed the absolute configuration of this toxin.[2b]

Pharmacological studies have shown (+)-anatoxin-*a* (**1**) to be a powerful nicotinic agonist with a long duration of action.[3] Since (+)-anatoxin-*a* is a naturally occurring alkaloid that has the 9-azabicyclo[4.2.1]nonane ring system, its unusual bicyclic ring structure has stimulated the interest of many synthetic organic chemists. Syntheses of (+)-anatoxin-*a* have been reported by Campbell, Edwards, Elder, and Kolt in 1979[4] and Rapoport and Bates in 1979.[5]

Recently, Tufariello, Meckler, and Senaratne have reported a nitrone based entry to the reacemic natural

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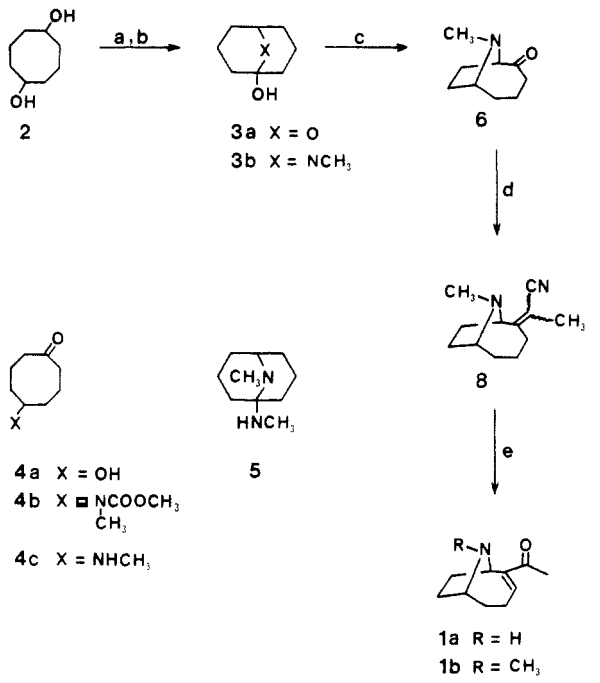
Scheme I[a]



[a] (a) 1.0 equiv of CrO_3, H_2SO_4, acetone; (b) 40% aqueous CH_3NH_2, TsOH, 100 °C, 2 days; (c) pyr·HBr·Br_2, AcOH, 115 °C 15 h; (d) $NaNH_2$, $(EtO)_2P(O)CH(CH_3)CN$ (7), THF, 20 °C, 14 h; (e) LDA; O_2; Na_2SO_3; NaOH.

product.[6a] The stereospecific synthesis of both (+)- and (−)-anatoxin-*a* from D- or L-glutamic acid has been achieved by Rapoport, Peterson, and Fels in 1984.[6b]

In this paper we report a short and efficient synthesis of anatoxin-*a* (1) (Scheme I). A key feature of this synthesis is the development of a new method for construction of the 9-azabicyclo[4.2.1]nonane ring system by reorganization of 9-methyl-9-azabicyclo[3.3.1]nonan-1-ol (**3b**), an easily accessible compound.[7] Chromic acid oxidation of *cis*-1,5-cyclooctanediol[8] provides hemiketal **3a**, which shows no evidence in its infrared spectrum for any of the keto form **4a**.

Reaction of hemiketal **3a** with aqueous methylamine gives amino alcohol **3b** along with diamine **5**.[7b] These transformations evidently involve reversible oxidation–reductions by transannular hydride shifts. Diamine **5** is converted to **3b** by gentle acid hydrolysis.

The bicyclic amino ketone **6** was initially prepared from **3b** in a two-step sequence. Reaction of bicyclic amino alcohol **3b** with methyl chloroformate gave the monocyclic ketocarbamate **4b**, 58% yield. Bromination of **4b** with pyridinium bromide perbromide, followed by hydrolysis of the carbamate, gave the amino ketone **6**.[9,10] Later it was found that bromination of **3b** gave the [4.2.1] amino ketone **6** directly, presumably through bromination and cyclization of 5-(methylamino)cyclooctanone (**4c**).

The method of Watt and Wroble for bishomologation of ketones into α,β-unsaturated ketones[11] was used for the conversion of amino ketone **6** into *N*-methylanatoxin-*a* (**1b**). Reaction of **6** with diethyl (cyanoethyl)phosphonate (**7**)[12] provided a mixture of the *Z* and *E* isomers of **8** in 64% yield. Deprotonation of **8** with lithium diisopropylamide afforded the delocalized anion which was trapped with oxygen at the α-position. The hydroperoxide was reduced with aqueous sodium sulfite, and hydrolysis of the cyanohydrin produced *N*-methylanatoxin-*a* (**1b**). The infrared and proton NMR spectra of our synthetic *N*-methylanatoxin-*a* (**1b**) agree with the spectra reported by Campbell.[4b] Since *N*-methylanatoxin-*a* (**1b**) has been converted into anatoxin-*a* (**1a**) by demethylation with diethyl azodicarboxylate,[4a] this completes a total synthesis of racemic anatoxin-*a* (**1a**).

In conclusion, we have developed a new four-step synthesis of anatoxin-*a* (**1a**) starting from the amino alcohol **3b**. The success of this method and the overall good yields suggest the general utility of this process for the synthesis of analogues for pharmacological study.

Experimental Section

General Methods. NMR spectra were recorded in $CDCl_3$ of 360 MHz. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (^1H) or relative to $CDCl_3$ at 77.0 ppm (^{13}C).

9-Methyl-9-azabicyclo[3.3.1]nonan-1-ol (3b). A solution of 12.0 g (0.084 mol) of 9-oxabicyclo[3.3.1]nonan-1-ol (**3a**) and 1.0 g of *p*-toluenesulfonic acid in 100 mL of 40% aqueous methylamine was heated at 100 °C for 2 days. The solution was extracted with diethyl ether (3 × 50 mL) and the ether solution was washed with saturated sodium chloride solution and dried over magnesium sulfate. Evaporation of the solvent gave a mixture of products **3b** and **5**. Crystallization from ethyl acetate gave 8.8 g (67%) of amino alcohol **3b**, mp 92–93 °C. The residues from the mother liquors containing mainly diamine **5** were dissolved in 10% sulfuric acid. After 12 h the solution was neutralized with 10% sodium hydroxide and extracted with ether. The ether extracts were dried over magnesium sulfate and evaporated. The residue was crystallized from ethyl acetate to give an additional 2.0 g of amino alcohol **3b**, total yield 82%: IR ($CHCl_3$) λ_{max} 3560, 3240, 1140, 1100, 1005, 890 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (1 H, s), 3.14 (1 H, br), 2.47 (3 H, s), 2.30–1.23 (12 H); MS, *m/e* 155.

9-Methyl-9-azabicyclo[4.2.1]nonan-2-one (6). A solution of 1-hydroxy-9-methyl-9-azabicyclo[3.3.1]nonane (**3b**) (2 g, 12.88 mmol) in 80 mL of glacial acetic acid was heated for 3 h at 80–90 °C. Pyridinium bromide perbromide (4.12 g, 12.88 mmol) was added and the solution was heated for 4 h at 85–90 °C. The red solution turned to clear or slightly yellow. The mixture was heated under reflux for 15 h and then cooled and diluted with 50 mL of water. The acidic solution was basified with potassium carbonate and extracted with dichloromethane (3 × 50 mL). The dichloromethane solution was washed with saturated sodium chloride solution (20 mL), dried, and evaporated to give the crude product. Column chromatography (hexane/acetone, 1:1) gave **6** as a light yellow oil: 1.1 g, 7.19 mmol, 55.8% yield: TLC (hexane/acetone, 1/1) R_f 0.44; ^1H NMR δ 3.49 (2 H, m), 2.79 (1 H, m), 2.52 (3 H, s), 2.34–2.52 (2 H, m), 1.98–2.23 (2 H, m), 1.82–1.92 (1 H, m), 1.57–1.81 (4 H, m); ^{13}C NMR δ 217.05, 74.72, 65.44, 42.35, 41.17, 34.44, 29.44, 26.64, 19.56. IR: 2929.0, 2883.2, 2803.6, 1700.9 cm^{-1}; MS, *m/e* 153, 125, 96, 82, 55, 42.

Reaction with camphorsulfonic acid-d_{10} gave white crystals, mp 234–235 °C dec.

Anal. Calcd for $C_{19}H_{31}NO_5S$: C, 59.20; H, 8.11; N, 3.63; S, 8.32. Found: C, 59.45; H, 8.05; N, 3.63; S, 8.65.

2-(1-Cyano-1-ethylidene)-9-methyl-9-azabicyclo[4.2.1]nonane (8). A solution of diethyl (1-cyanoethyl)phosphonate[12] (2.62 g, 13.7 mmol) in 15 mL of tetrahydrofuran was added dropwise

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with stirring under nitrogen to a suspension of sodium amide (0.54 g, 13.7 mmol) in 70 mL of tetrahydrofuran. The yellow mixture was stirred for 4 h. A solution of ketone **6** (0.5 g, 3.3 mmol) in 5 mL of tetrahydrofuran was added dropwise to the yellow reaction mixture, which was then stirred under nitrogen for 14 h. The reaction mixture was heated under reflux for an additional 2 h to obtain a clear light brown solution. It was then cooled and evaporated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with dichloromethane (2 × 25 mL). The combined organic phases were extracted with 5% hydrochloric acid (2 × 10 mL). The aqueous phase was then basified with potassium carbonate and extracted with dichloromethane (2 × 20 mL). The combined organic phases were washed with saturated sodium chloride solution, dried, filtered, and evaporated to give 0.4 g (64%) of a 3:2 mixture of the isomers of **8**. The ^{1}H NMR spectrum of the mixture showed peaks at δ 3.87, 2.88, 2.42 (s), and 1.84 (d) in addition to the peaks listed below for the major isomer. The ratio of isomers was determined by integration of the spectrum. The isomers were separated by column chromatography on silica gel (hexane/acetone, 1:1): TLC (hexane/acetone, 1:1) R_f 0.41 (major), 0.37 (minor); ^{1}H NMR (major isomer) δ 4.28 (1 H, d), 3.3 (1 H, m), 2.43 (3 H, s), 2.03–2.6 (4 H, m), 1.85 (3 H, d), 1.4–1.8 (6 H, m); ^{13}C NMR δ 165.64, 119.77, 101.21, 69.52, 65.09, 40.94, 34.27, 32.13, 30.19, 27.38, 21.99, 16.30. IR: 2927.8, 2878.6, 2804.4 2206.4, 1616 cm^{-1}; MS, *m/e* 190, 175, 147, 134, 119, 108, 96, 91, 82, 55, 42.

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.81; H, 9.55; N, 14.67.

Camphorsulfonate-*d* salt: mp 219–220 °C.

Anal. Calcd for $C_{22}H_{34}N_2O_4S$: C, 62.53; H, 8.11; N, 6.63. S, 7.59. Found: C, 62.54; H, 7.99; N, 6.67; S, 7.66.

2-Acetyl-9-methyl-9-azabicyclo[4.2.1]non-2-ene (1b) (*N*-Methylanatoxin-*a*). *n*-Butyllithium in hexane (1 mL of 1.5 M solution, 1.57 mmol) was added dropwise to a solution of diisopropylamine (0.15 g, 1.5 mmol) in 10 mL of tetrahydrofuran. The solution was stirred under nitrogen for 2 h at 0 °C. Compound **8** (0.21 g, 1.1 mmol) in 40% hexamethylphosphoric amide and tetrahydrofuran was added to the lithium diisopropylamide solution at −78 °C. Oxygen gas was bubbled into the solution for 40 min. The reaction was stirred for 0.5 h before it was quenched with 8 mL of 1 M sodium sulfite. The mixture was stirred for an additional 1 h at 25 °C. The reaction mixture was diluted with 20 mL of 20% dichloromethane and ether and then washed with 40 mL of 1 M NaOH. The organic phase was washed with saturated sodium chloride solution (20 mL), dried, filtered, and evaporated to give the crude product.

The crude product was added to a solution containing excess *d*-10-camphorsulfonic acid-d_{10} in isopropyl alcohol. The solution was stirred briefly and evaporated to give the camphorsulfonate salt. Flash column chromatography (methanol/acetone/hexane/diethylamine, 4:4:1:0.1) allowed purification of the camphorsulfonate salt. The pure dried salt was then converted to the free base, *N*-methylanatoxin-*a*.

An aqueous solution of the salt was basified with potassium carbonate and extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution, dried and evaporated to give 0.084 g (42.7%) of pure *N*-methylanatoxin-*a*.

N-Methylanatoxin-*a* camphorsulfonate salt: TLC (methanol/acetone/hexane, 4:5:1), R_f 0.11; ^{1}H NMR (*N*-methylanatoxin-*a*) δ 6.91 (1 H, dd), 4.43 (1 H, d), 3.38 (1 H, m), 2.25 (3 H, s), 2.28 (3 H, s), 1.85–2.5 (5 H, m), 1.32–1.7 (3 H, m); ^{13}C NMR δ 198.98, 148.77, 142.75, 63.11, 58.63, 36.70, 31.38, 28.38, 25.87, 25.44, 24.83; IR 2929.1, 2880.4, 1659.6, 1630.9 cm^{-1}; MS, *m/e* 179, 164, 150, 136, 122, 108, 96, 82, 57, 43.

Registry No. (±)-**1a**, 85514-42-7; (±)-**1b**, 70470-06-3; (±)-**1b**·camphorsulfonic acid-d_{10}, 100514-09-8; **3a**, 37996-41-1; **3b**, 56258-84-5; **4b**, 100514-10-1; **5**, 63989-32-2; (±)-**6**, 70423-78-8; (±)-(*Z*)-**8**, 100514-06-5; (±)-(*E*)-**8**, 100514-07-6; (±)-(*E*)-**8**·camphorsulfonic acid-d_{10}, 100514-08-7; (±)-(*Z*)-**8**·camphorsulfonic acid-d_{10}, 100514-11-2; diethyl (1-cyanoethyl)phosphonate, 29668-61-9.

A Highly Convergent Total Synthesis of (+)-Compactin

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An intramolecular Diels–Alder approach to the construction of (+)-compactin is described. Alkylation of the lithium enolate of (acetylmethylene)triphenylphosphorane with the tosylate of allenic alcohol **15** affords phosphorane **16**, which condenses with aldehyde **6** (prepared from tri-*O*-acetyl-D-glucal) to afford enone **3**. Intramolecular Diels–Alder reaction, reduction with lithium tri-*sec*-butylborohydride, and acylation with (*S*)-(+)-2-methylbutyric anhydride yields a chromatographically separable mixture of diastereomers; conversion to compactin was accomplished by acid hydrolysis followed by oxidation.

The isolation of compactin (also known as ML-236 B) in 1976[1,2] and the demonstration that this material is a potent inhibitor of sterol biosynthesis, both in vitro and in vivo,[3,4] have led to extensive investigations of approaches to the total synthesis of **1** and related compounds.[5] In addition, considerable attention has been focused on defining the structural features of compactin necessary for potent activity as an inhibitor of HMG-CoA reductase (the enzyme which mediates the rate-limiting step in sterol biosynthesis) and also upon clarifying the mechanism of inhibition.[6,7] We record herein our studies on the con-

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