× 3 × 3 min). Each coupling was carried out in duplicate to minimize error sequences. Each step of the coupling was thoroughly monitored by the semiquantitative ninhydrin method. Coupling of Boc-amino acid to the proline resin was monitored by the chloranil test.[24]

After each Boc-amino acid was incorporated, the resin was treated with 4 N HCl–dioxane (20 mL) for 30 min, filtered, and washed with dioxane (15 mL × 2 × 3 min) and $CH_2Cl_2$ (15 mL × 3 × 3 min). The deprotected resin was neutralized with 10% DIEA in $CH_2Cl_2$ (20 mL) by shaking for 10 min. The neutralized resin was washed with $CH_2Cl_2$ (15 mL × 3 × 3 min). The coupling, deprotection, and washings were repeated until the desired sequence was achieved.

**Preparation of Boc-Leu-Ala-Val-NHMe.** The tripeptide was assembled on resin **4a** (1 g, 0.54 mmol of NH/g) by the stepwise incorporation of the respective amino acid according to the general procedure of the solid-phase peptide synthesis. The peptide resin was suspended in TFE–$CH_2Cl_2$ (20% v/v, 100 mL) in an immersion-type photochemical reactor and was bubbled with dry $N_2$ for 1 h. The suspension was irradiated for 18 h at 350 nm. The crude peptide *N*-methylamide was obtained in 78% yield (103 mg) and purified by HPLC on a Bondapak C-18 column using chloroform–methanol (9:1): mp 188–190 °C; IR (KBr) 1650 (amide), 1710 (urethane) $cm^{-1}$; 270-MHz $^1H$ NMR ($CDCl_3$) $\delta$ 1.45 (s, 9 H, Boc), 0.95 (t, 6 H, $C_\delta H$, Leu), 1.37–1.42 (m, $C_\gamma H$ and $C_\beta H$, Leu), 1.25 (d, 3 H, $C_\beta H$, Ala), 2.2 (b, $C_\beta H$, Val), 2.8 (d, 3 H, $CH_3$, NHMe), 4.13 (b, 1 H, $C_\alpha H$, Ala), 4.3 (t, 1 H, $C_\alpha H$, Val), 4.4 (q, 1 H, $C_\alpha H$, Leu), 5.06 (d, 1 H, NH, Ala), 6.68 (br, 1 H, $NHCH_3$), 6.9 (d, 1 H, NH, Leu), 7.0 (d, 1 H, NH, Val). Anal. Calcd for $C_{20}H_{38}N_4O_5$: C, 57.95; H, 9.17; N, 13.52. Found: C, 57.50; H, 9.14; N, 13.97. Amino acid analysis: Leu, 1.09; Ala, 1.05; Val, 1.0.

**pGlu-His(Bzl)-Trp-Ser(Bzl)-Tyr(Bzl)-D-Trp-Leu-Arg-(Tos)-Pro-N($CH_3$)-Resin.** The nonapeptide was assembled on resin **4a** (2 g, 0.54 mmol of NH/g) according to the general protocol of the solid-phase synthesis. Symmetric anhydrides of each Boc-amino acid were prepared as described in the general procedure and incorporated stepwise. The elongation of the peptide chain was terminated with the incorporation of pGlu, and the peptide resin was thoroughly washed with $CH_2Cl_2$ (15 mL × 3 × 3 min) and MeOH (15 mL × 2 × 2 min).

**pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NHCH$_3$.** The nonapeptide resin (1.8 g) was suspended in a mixture of TFE–$CH_2Cl_2$ (20%, 200 mL) and placed in an immersion-type photochemical reactor. The suspension was degased with dry $N_2$ for 1 h and irradiated with a Philips HPK 125-W medium-pressure mercury lamp at 350 nm for 24 h as described previously.[15] The crude protected peptide *N*-methylamide was obtained in 66% yield. This was then treated with liquid HF (10 mL) for 30 min at 0 °C in the presence of anisole (1 mL). The excess HF was blown off through a NaOH solution with dry nitrogen. The residue was dried in vacuo over KOH, and the free peptide was treated with ether for the removal of anisole. The solvent was removed to obtain the ccrude deblocked nonapeptide *N*-methylamide and purified on a Sephadex LH-20 column in 56% yield. [$\alpha_D$] in 1% acetic acid, −58.6°. Amino acid analysis: Glu, 0.99; His, 1.0; Trp, 1.96; Ser, 0.99; Tyr, 1.01; Leu, 0.97; Arg, 0.98; Pro, 1.10.

**pGlu-His(Bzl)-Trp-Ser(Bzl)-Tyr(Bzl)-D-Trp-Leu-Arg-(Tos)-Pro-N($C_2H_5$)-Resin.** The peptide was assembled on resin **4b** (2 g, 0.54 mmol of NH/g) by using the symmetric anhydrides of the respective Boc-amino acids following the general protocol of the solid-phase peptide synthesis. After the incorporation of the pGlu residue, the peptide resin was thoroughly washed with $CH_2Cl_2$ (15 mL × 3 × 3 min) and MeOH (15 mL × 3 × 3 min).

**pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-NHC$_2$H$_5$.** The peptide resin (1.8 g) was suspended in a mixture of TFE–$CH_2Cl_2$ (20%, 200 mL) and irradiated as described previously. After photolysis the peptide *N*-ethylamide was obtained in 68% yield. The crude peptide was taken up in liquid HF (10 mL) and stirred in the presence of anisole (1 mL) for 30 min at 0 °C to remove the protecting groups. The excess HF was blown off, and the residue was taken up in water and extracted with ether. After lyophilization, the deprotected peptide *N*-ethylamide was obtained in 61% yield. The crude deprotected peptide was then purified on a Sephadex LH-20 column, resulting in 48% yield of the pure peptide. [$\alpha_D$] in 1% acetic acid, −56.9°. Amino acid analysis: Glu, 1.06; His, 0.96; Trp, 1.97; Ser, 0.99; Tyr, 1.03; Leu, 1.09; Arg, 0.99; Pro, 1.06.

**Acknowledgment.** A.A. thanks Dr. A. D. Damodaran and Dr. C. K. S. Pillai, Regional Research Laboratory, Trivandrum, for encouragement.

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# Chirospecific Syntheses of Nitrogen and Side-Chain Modified Anatoxin Analogues. Synthesis of (1*R*)-Anatoxinal and (1*R*)-Anatoxinic Acid Derivatives

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A straightforward and good yielding route to side-chain analogues of the potent neurotoxin and neurotransmitter (+)-anatoxin (**1**) has been developed. Peroxy acid oxidation of the (silyloxy)butadiene **43** derived from readily synthesized, optically pure (1*R*)-*t*-BOC-anatoxin (**42**) affords silyloxy ketone **44**. Fluorolysis of **44** followed by oxidative cleavage of the resultant $\alpha$-hydroxy ketone **45** gives a mixture of $\alpha,\beta$-unsaturated acid **46** and ester **41** in 57% combined yield. Other approaches to these compounds, based on literature precedent, failed. (1*R*)-*t*-BOC-anatoxinic acid (**46**) then serves as educt for the synthesis of a wide variety of anatoxin derivatives with modified side-chain functionality. These analogues, designed to serve as probes of the agonist binding site of the nicotinic acetylcholine receptor, include alcohol, aldehyde, amide, hydroxamate, and oxime ether functional groups.

Although the nicotinic acetylcholine receptor (nAChR) is the most well-characterized neurotransmitter receptor known,[1] there exists no high resolution X-ray crystal structure of this protein,[2] and the three-dimensional en-

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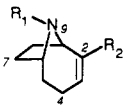
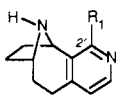
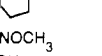
vironment of its agonist binding site is largely unknown. For a better understanding of the relationship between neurotransmitter structure and cholinergic response, the evaluation of low molecular weight agonist and antagonist molecules has been an invaluable tool.[3] The most active nicotinic agonists share two common features with acetylcholine: (1) a cationic center, often a quaternary ammonium group, and (2) a hydrogen-bond acceptor, a carbonyl group.[4] In addition to recognizing these two structural features, the nAChR also exhibits a high level of stereodiscrimination. A limitation to probing the binding site of the nAChR with small molecules has been the very small number of available optically active nicotinic agonists.[5] (+)-Anatoxin (1) is the most potent nicotinic agonist known,[6] and its unique homotropane ring system provides a chiral, semirigid frame for making structural modifications in order to correlate agonist structure with nicotinic activity.

Recently[7] we reported the chirospecific synthesis of 11 side-chain and *N*-methyl analogues of (+)-anatoxin (1) along with improvements in the synthesis of the parent compound. The side-chain analogues were of two types: (1) alcohols that were obtained from reduction of N-protected anatoxin and (2) acetoxy derivatives ("rigid acetylcholine analogues") obtained by Baeyer–Villiger oxidation of N-protected dihydroanatoxin.





**1** $R_1 = H, R_2 = COCH_3$
**2** $R_1 = H, R_2 = CHO$
**3** $R_1 = H, R_2 = CO_2H$
**4** $R_1 = H, R_2 = CO_2CH_3$
**5** $R_1 = CH_3, R_2 = CO_2CH_3$
**6** $R_1 = H, R_2 = CON(CH_3)_2$
**7** $R_1 = H, R_2 = CONHOCH_3$
**8** $R_1 = H, R_2 =$ 
**9** $R_1 = H, R_2 = CH{=}NOCH_3$
**10** $R_1 = H, R_2 = CH_2OH$
**11** $R_1 = H, R_2 = COCH_2OH$

(±) **12** $R_1 = CH_3$
(±) **13** $R_1 = H$

To delineate further the effect of the putative hydrogen-bond acceptor on the activation of the nAChR, we have modified the methyl ketone portion of anatoxin (1). The double-bond function has been left unchanged since it is known that dihydroanatoxin is ten times less potent than anatoxin (1).[8] From the myriad of possible side-chain analogues, we have chosen nine compounds (2, 4–11) that offer a wide variety of hydrogen-bonding capabilities. The inclusion of an *N*-methyl derivative (5) is intended to test the effect of further substitution at the proposed coulombic interaction site.

The rationale for choosing these particular compounds as targets is as follows. Aldehyde **2** amounts to replacement of the methyl group of anatoxin (**1**) by a hydrogen atom. Recent work[9] has shown that removal of the 2′-*C*-methyl group of pyridohomotropane (±)-**12** to give the unsubstituted pyridohomotropane (±)-**13** [analogous to going from anatoxin (**1**) to anatoxinal (**2**)] results in a substantial (up to $10^4$) increase in potency. The methoxy group of methyl anatoxinate (**4**) is the oxygen isostere of the methyl ketone in **1**. The ketone group of anatoxin (**1**) is believed to interact at the same receptor site as the acetylcholine ester carbonyl group.[5] While conversion of acetylcholine to the corresponding ketone (replacement of the ether oxygen of the ester group with a methylene group) does not result in increased nicotinic activity,[10] similar modification of another cholinergic agonist has a pronounced effect. Thus conversion of the ester group of arecoline methiodide (3-carbomethoxy-1-methyl-1,2,5,6-tetrahydropyridine methiodide), which shows modest nicotinic activity, to the corresponding methyl ketone, arecolone methiodide (3-acetyl-1-methyl-1,2,5,6-tetrahydropyridine methiodide), results in a 6.6-fold increase in potency.[11] The remaining analogues (**5**–**11**) possess different hydrogen-bond-accepting abilities and hydrophobicities.

We now report the chirospecific synthesis of these first-generation anatoxin analogues **2** and **4**–**11** via a general route that should provide access to almost any side-chain derivative. We also describe some unexpected chemistry encountered in our effort to prepare these compounds via two logical, but unsuccessful, alternative synthetic approaches.

## Synthesis of Anatoxinals and Anatoxinates

**Iminium Salt Cyclization of Aldehydes and Acetals.** All the target analogues can be divided into two subclasses: those derived from anatoxinal (**2**) and those derived from anatoxinic acid (**3**). Our strategy (Scheme I) involved preparing aldehydo acid **28** as a substrate for decarbonylation/iminium salt cyclization to give bicyclic aldehyde **31** in direct analogy to the known decarbonylation/iminium salt cyclization of the corresponding keto acid, which gives *N*-benzyldihydroanatoxin. The latter cyclization to give the 9-azabicyclo[4.2.1]nonane ring system is the high yielding key reaction in the synthesis of optically pure anatoxin (**1**).[7,8] Therefore we sought to extend the scope of this iminium salt cyclization to an additional substrate containing a nucleophilic $\alpha$-carbon such as in aldehydo acid **28**.

This synthetic route commenced with alkylation of thioamide **14**[12] with methyl 5-bromo-4-oxopentanoate (**15**)[13] followed by sulfur extrusion[14] to give vinylogous amide **16** in 70% yield. For the reduction and deoxygenation of **16** the vinylogous amide carbonyl group of **16** was thionated by treatment with Lawesson's reagent,[15] re-

(1) nAChR reviews: (a) Spivak, C., E.; Albuquerque, E. X. "Dynamic Properties of the Nicotinic Acetylcholine Receptor Ionic Channel Complex: Activation and Blockade" In *Progress in Cholinergic Biology: Model Cholinergic Synapses*; Hanin, I., Goldberg, A. M., Eds.; Raven Press: New York, 1982; p 323. (b) Changeux, J.-P.; Devillers-Thiery, A.; Chemouilli, P. *Science* **1984**, *225*, 1335. (c) Conti-Tronconi, B. M.; Raftery, M. A. *Ann. Rev. Biochem.* **1982**, *51*, 491. (d) Karlin, A.; Kao, P. N.; Dipaola, M. *Trends Pharmacol. Sci.* **1986**, *7*, 304.

(2) Stroud, R. M. "Topological Mapping and the Ionic Channel in an Acetylcholine Receptor" In *Proteins of Excitable Membranes*; Hille B., Fambrough, D. M., Eds.; Wiley: New York, 1987; pp 67–77.

(3) Witkop, B. *Heterocycles* **1982**, *17*, 431.

(4) Beers, W. H.; Reich, E. *Nature* **1970**, *288*, 917.

(5) For a discussion of the stereoselectivity of the nAChR, see: Witkop, B.; Brossi, A. "Natural Toxins and Drug Development" In *Natural Products and Drug Development*, Alfred Benzon Symposium 20; Krogsgaard-Larsen, P., Christensen, S. B., Kofod, H., Eds.; Munksgaard: Copenhagen, 1984; pp 283–298.

(6) (a) Swanson, K. L.; Allen, C. N.; Aronstam, R. S.; Rapoport, H.; Albuquerque, E. X. *Mol. Pharmacol.* **1986**, *29*, 250. (b) Koskinen, A. M. P.; Rapoport, H. *J. Med. Chem.* **1985**, *28*, 1301.

(7) Sardina, F. J.; Howard, M. H.; Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654.

(8) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539.

(9) Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506.

(10) Albert, A. *Selective Toxicity, The Physico-Chemical Basis of Therapy*, 5th ed.; Chapman and Hall: London, 1973; p 455.

(11) Albuquerque, E. X.; Spivak, C. E. "Natural Toxins and Their Analogues that Activate and Block the Ionic Channel of the Nicotinic Acetylcholine Receptor" In *Natural Products and Drug Development*, Alfred Benzon Symposium 20; Krogsgaard-Larsen, P., Christensen, S. B., Kofod, H., Eds.; Munksgaard: Copenhagen, 1984; pp 301–321.

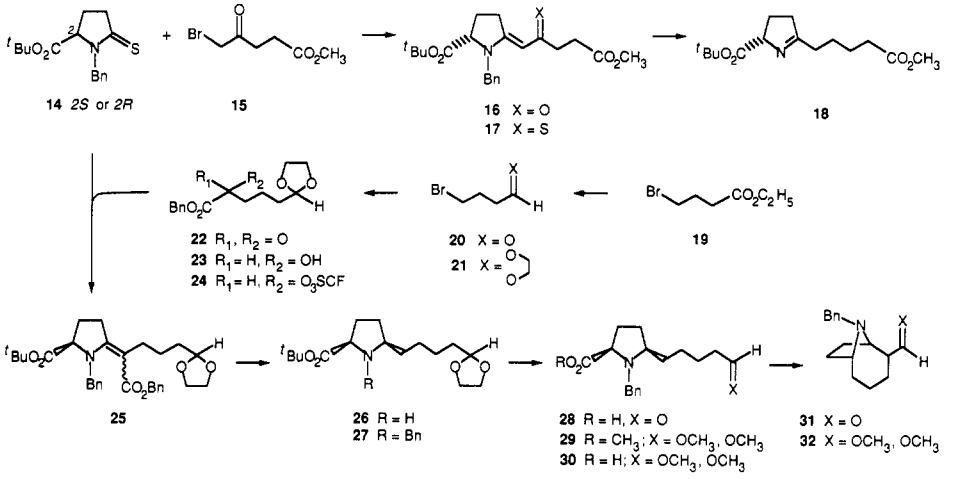
(12) For some initial studies, the thioamide having the 2*S* absolute stereochemistry, derived from L-glutamic acid, was used. Once experimental conditions were established, the same sequence was repeated using the (2*R*)-thioamide, derived from D-glutamic, to give the absolute stereochemistry corresponding to natural (+)-anatoxin.

(13) Rappe, C. *Arkiv. Kemi* **1959**, *14*, 467.

(14) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229.

(15) Scheibye, S.; Pederson, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

**Scheme I**



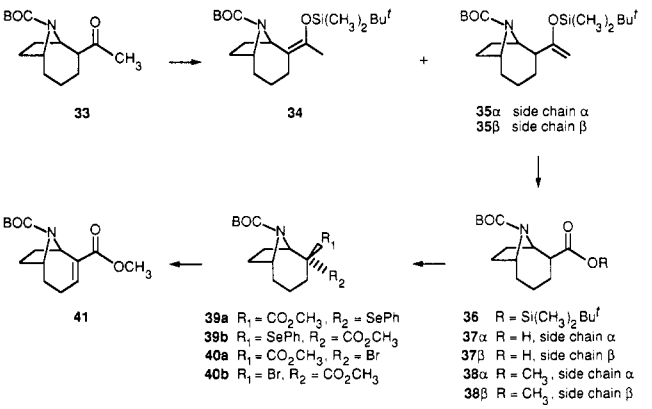

sulting in vinylogous thioamide **17** in 90% yield. Unfortunately, exhaustive examination of Raney nickel desulfurization of the vinylogous thioamide gave at best only 34% yield of imine **18**.

Discouraged by these low yields, we turned to a synthetic approach that followed more closely the well-established route to (+)-anatoxin (**1**).[6b,7,8] Thus we prepared α-hydroxy ester **23** in four steps[16] from ethyl 4-bromobutyrate (**19**) as shown in Scheme I. The hydroxy ester **23** was converted to triflate ester **24**, which was used to alkylate thioamide **14**. Sulfur extrusion was carried out under standard conditions to give vinylogous carbamate **25** in 64% yield as a 4/1 mixture of *E*/*Z* isomers, which we were unable to separate. Transfer hydrogenolysis of vinylogous carbamate **25** gave the crude secondary amine **26**, which was re-benzylated to give the desired cis 2,5-disubstituted pyrrolidine **27** in 64% yield for the two steps. Both the ketal and ester of **27** were hydrolyzed to give aldehydo acid **28** in 90% yield.

With the cyclization precursor in hand, we investigated methods to effect decarbonylation of the aldehydo amino acid and ring closure of the resulting iminium salt to give the desired bicyclic aldehyde **31**. Treatment of aldehydo acid **14** with $POCl_3$, the usual decarbonylation reagent, followed by methanolic HCl was ineffective for the desired cyclization, yielding only decomposition products. Also, oxalyl chloride as a reagent for decarbonylation[7,17] gave none of desired bicyclic aldehyde **31**.

Following this discovery that the aldehyde functionality of aldehydo acid **28** is incompatible with the conditions of iminium salt cyclization, other side-chain functionalities were considered that would provide the necessary nucleophilic carbon to effect ring closure. Since acetals and ketals are weak oxygen bases that have been used as sources of transient enol ethers for nucleophilic addition to various iminium salts,[18] we prepared the amino acid dimethyl acetal **30** by base hydrolysis of methyl ester **29**, itself prepared by treatment of aldehydo acid **28** with methanesulfonic acid in methanol and trimethyl orthoformate.

**Scheme II**




Decarbonylation of amino acid dimethyl acetal **30** under standard conditions ($POCl_3$, 100 °C, 10 min) followed by concentration in vacuo and treatment of the residue with anhydrous methanolic HCl (55 °C, 18 h) gave only a dark brown polymeric residue. The $^1H$ NMR spectrum of the crude product did not indicate the presence of the desired bicyclic acetal **32** or of the bicyclic aldehyde **31**. Again, as with the aldehyde **28**, use of oxalyl chloride as the decarbonylating reagent did not change the results.

These unexpected results indicate that the equilibrium between the iminium salt derived from decarbonylation of acetal **30** and the bicycle **32** lies heavily in favor of the uncyclized material, which then proceeds to decompose or polymerize. The inability of substrates **28** and **30** to undergo iminium salt cyclization, as well as the similar limitation reported[19] for bicyclization via a malonate, leads to the conclusion that iminium salt cyclizations[20] to give the 9-azabicyclo[4.2.1]nonane ring system are limited to substrates having ketone groups as the source of the α-nucleophilic carbon. This limitation led us to abandon attempts at preparing side-chain-shortened analogues of dihydroanatoxin by direct iminium salt cyclization and instead to focus on effecting the necessary transformations using the known bicycle *t*-BOC-dihydroanatoxin (**33**) as educt.

(16) (a) Preparation of ethyl 4-bromobutyrate (**19**): Lavety, J.; Proctor, G. R. *Organic Syntheses*, Collect. Vol. 5; Wiley: New York, 1973; p 545. (b) Conversion of **19** to bromo acetal **21**: Orsini, F.; Pelizzoni, F. *Gazz. Chim. Ital.* **1980**, *110*, 499.

(17) (a) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. (b) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875.

(18) (a) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2404. (b) Takano, S.; Ogawa, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 915. (c) Wenkert, E.; Chauney, B.; Dave, K. G.; Jeffcoat, A. R.; Schell, F. M.; Schenk, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 8427. (d) Wenkert, E.; Dave, K. G.; Stevens, R. V. *J. Am. Chem. Soc.* **1968**, *90*, 6177.

(19) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259.

(20) In a related reaction acyliminium ions have been alkylated intramolecularly with allyl- and propargylsilanes to give the 9-azabicyclo-[4.2.1]nonane ring system in racemic form by Esch, P. M.; Hiemstra, H.; Klaver, W. J.; Speckamp, W. N. *Heterocycles* **1987**, *26*, 75.

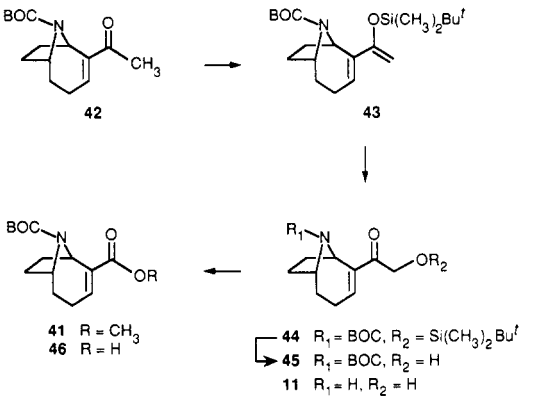
**Transformations of *t*-BOC-dihydroanatoxin (33).** Application of a classical ketone degradation method, the haloform reaction,[21] to ketone **33** (KOCl, MeOH/$H_2O$) resulted in multiple products with no single product predominating. Alternatively, ozonolysis of silyl enol ethers to give carboxylic acids[22] allows, in principle, the regiospecific cleavage of an unsymmetrical ketone. The *tert*-butyldimethylsilyl (TBDMS) enol ether **35** was prepared quantitatively by trapping the kinetically generated potassium enolate of ketone **33** with *tert*-butylchlorodimethylsilane (TBDMSCl). Neither the starting ketone **33** nor any of the thermodynamic enol ether **34** were detected in the $^1H$ NMR spectrum of the crude reaction mixture.[23]

Continuing as shown in Scheme II, cleavage of **35** with ozone gave silyl ester **36**, which was hydrolyzed to give *t*-BOC-dihydroanatoxinic acid (**37**) in 89% crude yield from ketone **33**. The diastereomeric dihydro acids **37**$\alpha$ and **37**$\beta$ were esterified to afford the separable dihydro methyl esters **38**$\alpha$ (mp 49–51 °C) and **38**$\beta$ (mp 46–47 °C); the isolated yield of analytically pure mixed dihydro ester **38** was 82% based on starting ketone **33**. The less-polar dihydro ester diastereomer (**38**$\alpha$) was assigned the $\alpha$-configuration on the basis of a resonance at $\delta$ 2.9–3.2 (m, 1 H) in its $^1H$ NMR spectrum, attributable to the H-2$\beta$ proton, that is shifted downfield by approximately 0.6 ppm (relative to the H-2$\alpha$ resonance in **38**$\beta$) due to its proximity to the bridgehead carbon–nitrogen bond.

The epimeric mixture of methyl *t*-BOC-dihydroanatoxinate (**38**) was treated with LDA at −78 °C and quenched with benzeneselenenyl bromide to give a diastereomeric mixture of selenides **39**$\alpha$ and **39**$\beta$ along with 10% of recovered ester **38**. This incomplete conversion of the dihydro esters to the selenides **39** was troublesome as both sets of diastereomers had identical chromatographic mobility, thus precluding the removal of unreacted starting material. The individual diastereomers **38**$\alpha$ and **38**$\beta$ also gave identical amounts of unreacted starting material. Therefore, the crude, mixed selenides were oxidized (MCPBA) and elimination took place smoothly to give the desired $\alpha,\beta$-unsaturated ester **41** in 74% yield; at this stage the 10% of starting ester **38** could be easily separated. Unfortunately, the selenylation of dihydro ester **38** was capricious, often leaving substantial amounts of unselenenylated material and resulting in difficult purifications. Variation of the reaction conditions (temperature, base, selenenylating reagent, HMPA as cosolvent) did not overcome the inconsistency of the reaction.

As an alternative to the selenenylation/selenoxide elimination method, we also examined dehydrohalogenation to introduce the desired double bond. Bromination of the epimeric dihydro esters **38** (NBS, AIBN) gave the diastereomeric bromo esters **40a** and **40b**[24] in 78% yield. Base-induced dehydrohalogenation of the bromo esters **40** was extremely sluggish, with prolonged reaction times leading to substantial decomposition and low yields.

**Scheme III**




Parallel to these experiments, improvements in the synthesis of (+)-anatoxin were being made.[7] Key among these improvements was the conversion of *t*-BOC-dihydroanatoxin (**33**) to *t*-BOC-anatoxin (**42**) via selenenylation/oxidation of the regiochemically pure TBDMS enol ether **34**, which proceeds in 84% overall yield. Given the difficulty of introducing the necessary unsaturation into dihydro ester **38**, this highly effective introduction of the double bond in the parent series enabled us to change our sequence and reverse the order of events. Instead of effecting the one-carbon degradation of ketone **33** to ester **38** first and then introducing the endo double bond, we could now start with the double bond in place and then effect the synthetically simpler step of side-chain degradation.

Thus, starting with the optically pure $\alpha,\beta$-unsaturated ketone (1*R*)-*t*-BOC-anatoxin (**42**, available from D-glutamic acid in 25% overall yield[7]), we prepared 2-(silyloxy)butadiene **43** by generating the potassium enolate of **42** under conditions of kinetic control followed by quenching with TBDMSCl as depicted in Scheme III. Oxidation of diene **43** with MCPBA[25] gave silyloxy ketone **44**, which was desilylated with HF in acetonitrile[26] to give (1*R*)-*t*-BOC-$\alpha$-hydroxyanatoxin (**45**) cleanly and in very good yield. The $\alpha$-ketol **45** could be cleaved to the carboxylic acid **46** with lead tetraacetate in benzene, but better results were obtained by treating $\alpha$-hydroxy ketone **45** with sodium periodate in $H_2O$/MeOH resulting in (1*R*)-*t*-BOC-anatoxinic acid (**46**, mp 158–159 °C), in 60% crude yield based on *t*-BOC-anatoxin (**42**). An additional 10% of the ester methyl (1*R*)-*t*-BOC-anatoxinate (**41**) was obtained from chromatography of the neutral extract of the crude reaction mixture. The total yield of purified product (ester **41** and acid **46**) for the four-step degradation process starting with *t*-BOC-anatoxin (**42**) was 57%. The sequence is operationally simple, amenable to scale-up (multigram quantities of key intermediate acid **46** can be readily prepared), and involves no intermediate chromatographic purifications, the best results being obtained when the intermediates are used without purification.

With a reliable route to optically pure *t*-BOC-anatoxinic acid (**46**) now in hand, the preparation of side-chain analogues was fairly straightforward. The *N*-methyl derivative **5** was prepared from the corresponding *t*-BOC-protected analogue by treatment of **41** with formic acid to cleave the

(21) Taschner, M. J.; Shahripour, A. *J. Am. Chem. Soc.* **1985**, *107*, 5570.

(22) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.

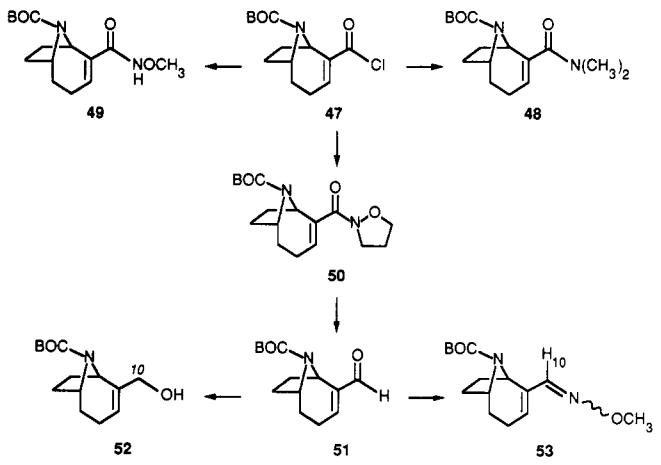
(23) A strong cation dependency was noted in these reactions. The lithium enolate of **33** (derived by inverse addition of **33** to a THF solution of LDA at −78 °C) gave less than 15% of the desired enol ether **35** on quenching with TBMSCl, with the remainder of the product being recovered as unsilylated ketone **33**. Addition of HMPA (23% v/v) to the −78 °C enolate solution before quenching did not improve the conversion to enol ether.

(24) Bromo ester **40** was isolated as a mixture of diastereomers (relative stereochemistry at C-2 uncertain). Less-polar diastereomer: TLC (EtOAc/hexanes, 1/4) $R_f$ 0.52; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.25–1.80 (m, 4 H), 1.42 (s, 9 H), 1.90–2.35 (m, 4 H), 2.40–2.70 (m, 2 H), 3.82 (s, 3 H), 4.20–4.50 (m, 1 H), 4.95–5.05 (m, 1 H). More-Polar diastereomer: TLC (EtOAc/hexanes, 1/4) $R_f$ 0.34; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.2–2.45 (m, 10 H), 1.51 (br s, 9 H), 3.81 (s, 3 H), 4.32–4.58 (m, 1 H), 4.95–5.22 (m, 1 H).

(25) (a) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599. (b) Brook, A. G.; MacRae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19.

(26) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

**Scheme IV**




nitrogen protecting group followed by addition of formaldehyde[27] to afford an 84% yield of the *N*-methyl tertiary amine **5**.

The amide and hydroxamate side chains were introduced by conventional coupling to the acid chloride **47** (Scheme IV). Addition of aqueous dimethylamine to **47** gave *N,N*-dimethylamide **48** (mp 94–95 °C, 88% yield), and the hydroxamate **49** was obtained in 62% isolated yield. Isoxazolidide **50**, a key intermediate for target analogues **2** and **8–11**, was formed in 76% yield from **47** and isoxazolidine.[28a]

Reduction of isoxazolidide **50** with $LiAlH_4$[28b] gave a 93% yield of (1*R*)-*t*-BOC-anatoxinal (**51**, mp 64–66 °C) along with 7% of the overreduction product alcohol **52**. Purified aldehyde **51** was deprotected with trifluoroacetic acid (TFA) in $CH_2Cl_2$ to give (1*R*)-anatoxinal (**2**) cleanly in 97% yield. This aldehyde analogue of anatoxin is rather unstable and is best handled as its TFA salt after *t*-BOC cleavage.

*t*-BOC-anatoxinal (**51**) reacts cleanly with methoxyamine to give oxime ether **53** in 94% yield as a 6/1 mixture of *E/Z* isomers. The less-polar (TLC) oxime ether was the major isomer under these conditions and was assigned the *E* configuration because of the downfield chemical shift of H-10 ($\delta$ 7.57, s, 1 H) in the $^1H$ NMR spectrum. This is due to the proximity of the electronegative oxygen atom, which deshields the adjacent proton (H-10).[29] The oxime ether proton (H-10) of the more-polar (TLC), minor product had a more upfield chemical shift ($\delta$ 6.82, s, 1 H) leading to assignment of the *Z* configuration to that isomer. The crude mixture of *E/Z* isomers of *t*-BOC oxime ether **53** when treated with TFA in $CH_2Cl_2$ gave (1*R*)-anatoxinal *O*-methyloxime (**9**) as a single isomer in 91% yield. The chemical shift of H-10 for this product was $\delta$ 7.56 (s, 1 H), indicating that it was of the same configuration (*E*) as the major (less-polar) isomer of the starting material **53**. Assignment of the oxime ether configuration by NOE difference spectroscopy of **9** was not conclusive.

Preparation of allylic alcohol **52** by $LiAlH_4$ reduction of $\alpha,\beta$-unsaturated ester **41** was unsuccessful and gave several side products, some apparently derived from 1,4-attack by the reagent. However, reduction of *t*-BOC-anatoxinal (**51**) with $NaBH_4$ in the presence of stoichiometric $CeCl_3$[30] gave an 86% yield of the allylic alcohol **52** as a clear oil. The remaining *t*-BOC-protected analogues were deprotected smoothly in anhydrous TFA/$CH_2Cl_2$ in excellent yields. All of the resulting amine free bases (**4–11**) were then converted to crystalline hydrogen fumarate salts, thus completing this set of functional group analogues of anatoxin (**1**).

## Summary

Crystalline salts of nine new analogues (**2**, **4–11**) of the powerful nicotinic agonist (+)-anatoxin (**1**) have been prepared in optically pure form by ketone degradation of (1*R*)-*t*-BOC-anatoxin (**42**) followed by side-chain elaboration. This process, in combination with our improvements in the synthesis of enone **42** (described elsewhere[7]), provides an efficient method for preparing a wide variety of side-chain-modified analogues. Biological evaluation of the target analogues will be reported in detail elsewhere.

The scope of the chirospecific iminium salt cyclization to give the 9-azabicyclo[4.2.1]nonane ring system was also examined with a view to obtaining the bicyclic aldehyde **31** or acetal **32** directly. Our lack of success in this regard, along with the already demonstrated inability of the corresponding malonate to undergo similar cyclization[19] after decarbonylation, indicates that, because of equilibrium and/or product stability, the reaction is thus far restricted to substrates having a ketone as the source of the $\alpha$-nucleophilic carbon.

## Experimental Section

**General Methods.** General experimental details have been described recently.[7] Reaction temperatures refer to bath temperatures unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) on E. Merck 60F-254 precoated aluminum-backed TLC sheets. Organic layers from aqueous extractions were dried over anhydrous $Na_2SO_4$ and concentrated with a Berkeley rotary evaporator using water aspirator vacuum. Low pressure chromatography (LPC) was carried out by applying air pressure to columns packed with EM Reagents silica gel 60 (0.040–0.063-mm particle size, 230–400 mesh). Column chromatography was carried out on EM Science kieselgel 60 (0.063–0.200 mm, 70–230 mesh). $^1H$ chemical shifts are reported in ppm downfield from internal $(CH_3)_4Si$ (TMS) in $CDCl_3$ or sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) in $D_2O$ or $CD_3OD$ and coupling constants are reported in hertz. $^{13}C$ chemical shifts are reported in ppm relative to TMS (0 ppm), DSS (0 ppm), DMSO-$d_6$ (39.0 ppm), $CD_3OD$ (49.0 ppm), dioxane (66.5 ppm), or $CDCl_3$ (77.0 ppm) as noted. In cases where DEPT experiments were carried out during $^{13}C$ NMR experiments, the carbon multiplicities are listed as (0) quaternary, (1) methine, (2) methylene, (3) methyl.

**9-(*tert*-Butoxycarbonyl)-2-[1-[(*tert*-butyldimethylsilyl)oxy]ethenyl]-9-azabicyclo[4.2.1]nonane (35$\alpha$ and 35$\beta$).** A solution of (±)-BOC-dihydroanatoxin[31,32] (**33**, $\beta$-epimer, 932 mg, 3.49 mmol) in THF (9 mL) was added at 0.27 mL/min to a −78 °C 1.0 M solution of KHMDS[33] in THF (10.5 mL, 10.5 mmol). The mixture was stirred at −78 °C for 45 min; then a solution of

(27) Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829 and references cited therein.

(28) (a) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972. (b) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

(29) McCarty, G. In *The Chemistry of the Carbon Nitrogen Double Bond*; Patai, S., Ed.; Wiley: New York, 1970; pp 386–387.

(30) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(31) Anticipating the need for large quantities of *t*-BOC-dihydroanatoxin (**33**) we worked with the more readily accessible racemic form of **33** while developing the synthetic routes. Thus we were able, in less than 2 weeks, to prepare 10-mmol quantities of (±)-*N*-benzyldihydroanatoxin in six steps (28% yield) via regiospecific dialkylation of acetone dimethylhydrazone followed by copper(II) oxidative hydrazone cleavage, reductive N-benzylation, and finally intramolecular Mannich cyclization.[32] Deprotection/reprotection as described[7] then gave (±)-*t*-BOC-dihydroanatoxin ((±)-**33**) in excellent yield.

(32) Petersen, J. S.; Töteberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948.

(33) We prepared KHMDS in THF following the "excess substrate" procedure of Brown: Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913. We have since found that commercial (Callery Chemical Co.) supplies of KHMDS in toluene are of acceptable quality.

TBDMSCl (788 mg, 5.22 mmol) in THF (8 mL) was added at 0.84 mL/min. The mixture was stirred at −78 °C for 10 min more, the cooling bath was removed, and when the mixture had reached approximately 0 °C it was diluted with hexanes (20 mL) and washed with 0.01 M phosphate buffer (pH 7, 2 × 35 mL). The separate aqueous layers were back-extracted with hexanes (2 × 30 mL) and the combined organic phase was dried, filtered, and concentrated to afford enol ether **35β** (1.54 g, crude) as a single regio- and stereoisomer: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.58; IR (film) 2960, 2930, 2850, 1700, 1660, 1640, 1410, 1260, 1230, 1110, 1020, 840 $cm^{-1}$; $^1H$ NMR (two rotamers, 4/1) δ 0.15, 0.17 (s, 6 H), 0.92, 0.93 (s, 9 H), 1.12–2.32 (m, 11 H), 1.42, 1.46 (s, 9 H), 4.01 (s, 1 H), 4.04 (s, 1 H), 4.29–4.46 (m, 2 H).

In the same manner as described above, (±)-BOC-dihydroanatoxin (**33**, α-epimer, 1.15 g, 4.30 mmol) was regio- and stereospecifically converted to TBDMS enol ether **35α** (1.91 g, crude). A 216-mg portion of the crude residue was purified by LPC (EtOAc/hexanes, 1/19) to give 171 mg (92% yield) of analytically pure product **35α**: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.58; $^1H$ NMR (two rotamers, 2/1) δ 0.16, 0.19 (s, 6 H, $Me_2Si$), 0.94 (s, 9 H, *t*-BuSi), 1.24–1.56 (m, 6 H), 1.46, 1.48 (s, 9 H, *t*-BuO), 1.63–1.86 (m, 2 H), 2.03–2.31 (m, 2 H), 2.51–2.62, 2.68–2.77 (m, 1 H, H-2), 4.04 (s, 1 H, H-11), 4.08 (s, 1 H, H-11), 4.17, 4.28 (br t, 1 H, $J$ = 7.5, H-1), 4.35–4.48 (m, 1 H, H-6); $^{13}C$ NMR ($CDCl_3$) (two rotamers) δ −5.07, −4.89, 18.11, 23.01, 23.99, 24.09, 25.74 (3 C), 27.20, 28.56, 28.66 (3 C), 32.55, 32.91, 34.12, 34.94, 46.89, 48.07, 54.16, 54.65, 58.26, 58.55, 78.85, 89.12, 89.50, 153.56, 160.81. Anal. Calcd for $C_{21}H_{39}NO_3Si$: C, 66.1; H, 10.3; N, 3.7. Found: C, 66.5; H, 10.2, N, 3.7.

**9-(*tert*-Butoxycarbonyl)-2-carboxy-9-azabicyclo[4.2.1]nonane (37α and 37β).** The crude TBDMS enol ether **35β** (1.54 g, 3.49 mmol) was dissolved in $CH_2Cl_2$ (6 mL) and chilled to −78 °C and methanol (12 mL) was added, and the solution was treated with ozone until a light-blue color persisted. The solution was then purged first with oxygen and then with nitrogen and finally methyl sulfide (1.33 mL, 17.4 mmol) was added to the −78 °C solution. After being warmed to room temperature, the solution was concentrated to an oily residue (1.54 g, crude) having spectroscopic and chromatographic properties consistent with *tert*-butyldimethylsilyl ester **36**: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.56; $^1H$ NMR δ 0.27, 0.30 (s, 6 H, $Me_2S$), 0.92, 0.94 (s, 9 H, *t*-BuSi), 1.33–2.43 (m, 11 H), 1.43, 1.51 (s, 9 H, *t*-BuO), 4.14–4.24, 4.29–4.43 (m, 1 H, H-6), 4.49–4.56, 4.67–4.74 (m, 1 H, H-1).

The crude silyl ester **36** was dissolved in THF (10 mL) and $H_2O$ (10 mL), and lithium hydroxide monohydrate (292 mg, 6.97 mmol) was added. The solution was stirred at room temperature for 30 min and then diluted with 1 M $K_2CO_3$ (20 mL) and extracted with $Et_2O$ (25 mL). The organic layer was dried, filtered, and concentrated to afford 74 mg (8%) of recovered ketone **33**.

The aqueous layer from above was acidified with dilute $H_3PO_4$ to pH 3.5 and extracted with $CHCl_3$ (3 × 25 mL). The combined organic phase was dried, filtered, and concentrated to give a white solid (840 mg, 89% crude based on **33**). Recrystallization of a portion of the crude product from toluene gave white crystals of the carboxylic acid **37β**: mp 196–197 °C; TLC ($MeOH/CHCl_3$, 1/9) $R_f$ 0.43; IR (KBr pellet) 3360–2600 (br), 2960, 1710, 1690, 1420, 1270, 1250, 960 $cm^{-1}$; $^1H$ NMR δ 1.20–1.98 (m, 7 H), 1.51 (s, 9 H, *t*-BuO), 2.03–2.22 (m, 2 H), 2.31–2.51 (m, 1 H), 2.64–2.74 (m, 1 H, H-2), 4.32–4.47 (m, 2 H, H-1 and H-6), carboxylic acid proton not located; $^{13}C$ NMR ($CDCl_3$) δ 20.41, 25.73, 25.98, 26.51 and 26.81 (rotamers, 3 C total), 32.00, 33.78, 51.41, 55.52, 56.41, 79.32, 153.11, 175.83. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.4; H, 8.6; N, 5.2. Found: C, 62.4; H, 8.7; N, 5.2.

In the same manner as described above, the crude α-TBDMS enol ether **35α** (1.7 g, 4.30 mmol) was treated with excess ozone and the resulting silyl ester was hydrolyzed to give α-carboxylic acid **37α** (1.23 g, crude) as a foamy white solid: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.48; $^1H$ NMR (two rotamers, 1/1) δ 1.18–1.94 (m, 7 H), 1.47, 1.49 (s, 9 H, *t*-BuO), 1.85–2.32 (m, 3 H), 2.90–3.06, 3.10–3.25 (m, 1 H, H-2), 4.20, 4.31 (dist. t, 1 H, $J$ = 7.2, H-1), 4.47–4.58, 4.58–4.68 (m, 1 H, H-6), carboxylic acid proton not located.

**9-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]nonane (38α and 38β).** A suspension of crude (±)-BOC-dihydroanatoxinic acid (**37β**, 817 mg, 3.49 mmol) in $Et_2O$ (25 mL) was chilled to 0 °C and treated with a 0.33 M solution of diazomethane (21 mL, 6.98 mmol) in $Et_2O$. The mixture was allowed to warm to room temperature as it was stirred for 1.5 h. After chilling to 0 °C, a few drops of acetic acid were added until the yellow color disappeared, then solution was then treated with solid $NaHCO_3$ until saturated and then saturated aqueous $NaHCO_3$ (25 mL) was added. The mixture was shaken and the layers were separated, the aqueous layer was extracted with $CHCl_3$ (2 × 25 mL), and the combined organic phase was washed with brine (60 mL), dried, filtered, and concentrated to a clear oil (901 mg crude). The crude residue was purified by LPC (EtOAc/hexanes, 3/17) to give pure methyl (±)-BOC-dihydroanatoxinate (**38β**) (814 mg, 82% isolated yield based on ketone **33**) as a white solid: mp 46–47 °C; TLC (EtOAc/hexanes, 1/3) $R_f$ 0.36; IR (KBr pellet) 2960, 2880, 1740, 1685, 1415 $cm^{-1}$; $^1H$ NMR (two rotamers, 2.5/1) δ 1.20–2.15 (m, 10 H), 1.41, 1.44 (s, 9 H, *t*-BuO), 2.25–2.55 (m, 1 H, H-2), 3.70, 3.72 (s, 3 H, $OCH_3$), 4.17–4.25, 4.33–4.43 (m, 1 H, H-6), 4.55, 4.69 (br d, 1 H, $J$ = 9.2, H-1); $^{13}C$ NMR ($CDCl_3$) (two rotamers, 2.5/1) major rotamer δ 21.84 (2), 26.39 (2), 26.86 (2), 28.27 (3), ($CH_3$)$_3$CO), 32.66 (2), 35.43 (2), 51.58 ($CH_3O$), 53.17 (1), 56.18 (1), 56.71 (1), 79.48 (($CH_3$)$_3$*C*O), 153.32 (NC(O)O), 174.63 (*C*C(O)O); minor rotamer δ 21.69 (2), 26.67 (2), 26.86 (2), 28.43 (($CH_3$)$_3$CO), 33.54 (2), 33.98 (2), 51.58 ($CH_3O$), 51.88 (1), 56.18 (1), 57.06 (1), 78.90 (($CH_3$)$_3$*C*O), 153.32 (NC(O)O), 174.63 (*C*C(O)O). Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.6; H, 8.9; N, 4.9. Found: C, 63.5; H, 9.0; N, 5.1.

In the same manner as described above crude (±)-BOC-dihydroanatoxinic acid (**37α**) (1.23 g, 4.3 mmol) gave pure methyl (±)-BOC-dihydroanatoxinate (**38α**) (985 mg, 81% based on ketone **33**) as a white solid: mp 49–51 °C; TLC (EtOAc/hexanes, 1/3) $R_f$ 0.43; $^1H$ NMR (two rotamers, 1/1) δ 1.16–2.25 (m, 10 H), 1.46, 1.48 (s, 9 H, *t*-BuO), 2.92–3.01, 3.07–3.17 (m, 1 H, H-2), 3.66, 3.68 (s, 3 H, $OCH_3$), 4.19, 4.31 (br t, 1 H, H-1), 4.44–4.54, 4.56–4.64 (m, 1 H, H-6); $^{13}C$ NMR ($CDCl_3$) (two rotamers, 1/1) δ 22.52 (2), 22.68 (2), 25.21 (2), 25.77 (2), 26.00 (2), 26.23 (2), 28.48 (($CH_3$)$_3$CO), 31.59 (2), 32.58 (2), 33.99 (2), 34.78 (2), 46.56 (1), 47.63 (1), 51.47, 51.58 ($CH_3O$), 54.60 (1), 54.81 (1), 57.24 (1), 79.11, 79.24 (($CH_3$)*C*O), 153.45 (NC(O)O), 174.21, 174.32 (*C*C(O)O).

**9-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]non-2-ene (41).** A 1.6 M solution of *n*-butyllithium (1.25 mL, 2.0 mmol) in hexanes was added to a 0 °C solution of diisopropylamine (0.31 mL, 2.2 mmol) in THF (5.2 mL), and the resulting solution was stirred for 20 min at 0 °C and then chilled further to −78 °C. A solution of methyl (±)-BOC-dihydroanatoxinate (**38α/38β**) (473 mg, 1.67 mmol) in THF (3 mL) was added at 0.19 mL/min. The mixture was stirred at −78 °C for 20 min after the addition was complete and then a mixture of benzeneselenenyl bromide[34] (473 mg, 2.0 mmol) and diphenyl diselenide (78 mg, 0.25 mmol) in THF (2 mL) was added at 2.3 mL/min. The yellow mixture was stirred at −78 °C for 20 min and the cold reaction mixture was poured into 1 M $KH_2PO_4$ (25 mL) and extracted with 50% hexanes/$Et_2O$ (2 × 25 mL). The combined organic phase was washed with $H_2O$, saturated aqueous $NaHCO_3$, and brine (25 mL each), and the separate aqueous washes were back-extracted with 50% hexanes/$Et_2O$ (25 mL). The total, combined organic phase was dried, filtered and concentrated to an orange-yellow oil (840 mg, crude), which was purified by LPC (EtOAc/hexanes, 3/17) to give 625 mg (85%) of the diastereomeric selenides **39a** and **39b** as thick yellow oils. Each diastereomer of the selenide was contaminated with approximately (as judged by $^1H$ NMR spectroscopy) 10% of the corresponding diastereomer of the dihydro ester starting material. No attempt was made to assign the relative stereochemistry at C-2 of the selenide diastereomers.

Less-polar selenide diastereomer **39**: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.41; $^1H$ NMR δ 1.17–2.29 (m, 9 H), 1.38 (s, 9 H, *t*-BuO), 2.33–2.50 (m, 1 H), 3.37–3.61 (s, 3 H, $OCH_3$), 4.16–4.53 (m, 1 H, H-6), 5.02 (dd, 1 H, $J$ = 2.4, 8.9, H-1), 7.22–7.42 (m, 3 H, Ar), 7.56 (br d, 2 H, $J$ = 6.8, Ar).

More-polar selenide diastereomer **39**: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.35; $^1H$ NMR δ 1.21–2.51 (m, 10 H), 1.50–1.55 (s, 9 H, *t*-BuO), 3.56, 3.64 (s, 3 H, $OCH_3$), 4.27–4.44, 4.46–4.62 (m, 1 H, H-6), 4.81–4.96, 4.98–5.11 (m, 1 H, H-1), 7.2–7.45 (m, 3 H, Ar), 7.50–7.62 (m, 2 H, Ar).

(34) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

The purified mixture of selenides **39ab** (625 mg, contaminated with approximately 10 mol % of unreacted starting material **39α** and **39β**) was dissolved in $CH_2Cl_2$ (25 mL) and chilled to 0 °C. A solution of 85% MCPBA (679 mg, 3.34 mmol) in $CH_2Cl_2$ (10 mL) was added incrimentally over 15 min, and the mixture was stirred at 0 °C for 45 min and room temperature for 30 min and then chilled to 0 °C. After filtration, the filtrate was extracted with saturated aqueous $NaHCO_3$ (2 × 20 mL), $H_2O$ (20 mL), and brine (20 mL), the separate aqueous layers were back-extracted with $CH_2Cl_2$ (15 mL), and the combined organic phase was dried, filtered, and concentrated to a dark yellow oil (496 mg, crude). Purification by LPC (EtOAc/hexanes, 3/17) gave recovered starting material **38** (45 mg, 9.5%) followed by methyl (±)-BOC-anatoxinate (**41**) (350 mg, 74%) as a clear oil: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.31; IR (film) 2980, 1695, 1405, 1235 $cm^{-1}$; $^1H$ NMR (two rotamers, 2/1) δ 1.40, 1.45 (s, 9 H, *t*-BuO), 1.54–1.86 (m, 3 H, H-5α, H-7α, H-8α), 2.01–2.50 (m, 5 H, H-4α,β, H-5β, H-7β, H-8β), 3.74 (s, 3 H, $OCH_3$), 4.23–4.34, 4.36–4.47 (m, 1 H, H-6), 5.04 (br d, 0.67 H, *J* = 8.8, H-1), 5.16 (br d, 0.33 H, *J* = 7.6, H-1), 6.98 (t, 1 H, *J* = 6.0, H-3); $^{13}C$ NMR ($CDCl_3$) (two rotamers, 2/1) major rotamer δ 23.88 (2), 28.37 ($(CH_3)_3CO$), 28.64 (2), 30.31 (2), 31.61 (2), 51.76 ($CH_3O$), 54.58 (1), 55.65 (1), 79.32 ($(CH_3)_3CO$), 140.60 (0, C-2), 141.73 (1, C-3), 153.19 (NC(O)O), 167.16 (C(O)O); minor rotamer δ 23.88 (2), 28.51 ($(CH_3)_3CO$), 29.81 (2), 30.93 (2), 32.64 (2), 51.76 ($CH_3O$), 54.96 (1), 55.32 (1), 79.23 ($(CH_3)_3CO$), 138 (0, C-2), 141.30 (1, C-3), 153.19 (NC(O)O), 167.16 (C(O)O). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0. Found: C; 64.0; H, 8.3; N, 5.0.

**(1*R*)-9-(*tert*-Butoxycarbonyl)-2-[1-(*tert*-butyldimethylsiloxy)ethenyl]-9-azabicyclo[4.2.1]non-2-ene (43).** A solution of (1*R*)-BOC-anatoxin (**42**)[7] (2.52 g, 9.50 mmol) in THF (25 mL) was added at 1.0 mL/min to a −78 °C, 0.5 M solution of KHMDS in toluene[33] (26.6 mL, 13.30 mmol). After being stirred at −78 °C for 60 min, the orange enolate solution was quenched with a centrifuged solution of TBMSCl (2.00 g, 13.30 mmol) and triethylamine (0.66 mL, 4.75 mmol) in THF (4 mL) added over 2 min. Stirring at −78 °C was continued for 45 min, the bath was removed, and the reaction mixture was allowed to come to room temperature. Hexanes (50 mL) were added and the reaction mixture was washed with 0.5 M phosphate buffer (pH 7, 100 mL). The aqueous layer was extracted with hexanes (25 mL) and then $CH_2Cl_2$ (3 × 30 mL), and the combined organic phase was washed with brine (100 mL), dried, filtered, and concentrated to afford the desired (silyloxy)butadiene **43** (3.74 g, crude) as a yellow oil that was pure by $^1H$ NMR spectroscopy and TLC analysis.

An analytical sample of **43** was obtained as a clear oil in 86% yield by column chromatography (EtOAc/hexanes, 1/9) of a portion of the crude product: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.63; $[\alpha]^{22}_D$ +29.0° (*c* 1.75, MeOH); IR (neat) 690, 1630, 1590, 1110, 1015 $cm^{-1}$; $^1H$ NMR δ 0.16, 0.17 (s, 6 H, $SiMe_2$), 0.95, 0.96 (s, 9 H, *t*-BuSi), 1.10–2.35 (m, 8 H), 1.42, 1.45 (s, 9 H, *t*-BuO), 4.21–4.33, 4.34–4.45 (m, 1 H, H-6), 4.26, 4.30 (s, 1 H, H-11), 4.48, 4.54 (s, 1 H, H-11), 4.71–4.80, 4.85–4.95 (m, 1 H, H-1) 6.17 (dd, 1 H, *J* = 6.1, 10.5, H-3); $^{13}C$ NMR ($CDCl_3$) (two rotamers, 2/1) major rotamer δ −4.87 (3), 18.04 (0), 23.24 (2), 25.65 (3), 28.23 (3), 29.58 (2), 31.67 (2), 32.00 (2), 54.83 (1), 55.94 (1), 78.78 (0), 90.81 (2), 126.68 (1), 143.37 (0), 153.15 (0), 155.56 (0); minor rotamer δ −4.69 (3), 18.04 (0), 22.94 (2), 25.65 (3), 28.32 (3), 30.74 (2), 30.81 (2), 33.60 (2), 54.71 (1), 56.34 (2), 78.55 (0), 91.65 (2), 126.13 (1), 141.80 (0), 154.82 (0), 154.99 (0). Anal. Calcd for $C_{21}H_{37}NO_3Si$: C, 66.4; H, 9.8; N, 3.7. Found: C, 66.1; H, 10.0; N, 3.9.

Although the crude product can be purified as described above, best overall yields are obtained by taking the slightly impure crude **43** directly on to the next step.

**(1*R*)-9-(*tert*-Butoxycarbonyl)-2-[2-(*tert*-butyldimethylsiloxy)acetyl]-9-azabicyclo[4.2.1]non-2-ene (44).** A solution of the crude (silyloxy)butadiene **43** (3.74 g, 9.50 mmol) in hexanes (19 mL) was added to a −10 °C suspension of 85% MCPBA (2.51 g, 12.35 mmol) in hexanes (136 mL), and the flask was then removed from the cooling bath and stirred at room temperature for 30 min. The mixture was chilled to 0 °C and filtered, and the filtrate was washed with 10% $Na_2CO_3$ (3 × 30 mL). The combined aqueous layers were extracted with $CH_2Cl_2$ (2 × 40 mL) and the combined organic phase was dried, filtered, and concentrated to give crude silyloxy ketone **44** as a yellow oil (3.80 g, crude). An analytical sample of silyloxy ketone **44** was obtained as a clear oil in 53% yield by column chromatography (EtOAc/hexanes, 1/1) of a portion of the crude product: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.41; $[\alpha]^{22}_D$ −9.5° (*c* 1.9, absolute MeOH); IR (neat) 2920, 1680, 1390, 1240, 1165, 1105, 820 $cm^{-1}$; $^1H$ NMR δ 0.10 (s, 6 H, $SiMe_2$), 0.92 (s, 9 H, *t*-BuSi), 1.38, 1.44 (s, 9 H, *t*-BuO), 1.57–1.76 (m, 3 H), 1.99–2.52 (m, 5 H), 4.22–4.35, 4.35–4.47 (m, 1 H, H-6), 4.49, 4.56, 4.59, 4.66 (s, 2 H, H-11), 5.07 (d, 1 H, *J* = 8.8, H-1), 6.80 (t, 1 H, *J* = 5.8, H-3); $^{13}C$ NMR ($CDCl_3$) δ −5.44 (2 C), 18.28, 24.11, 25.69 (3 C), 28.28 (3 C), 28.58, 30.45, 31.54, 53.61, 55.27, 66.15, 79.20, 140.87, 147.25, 152.90, 196.69. Anal. Calcd for $C_{21}H_{37}NO_4Si$: C, 63.8; H, 9.4; N, 3.5. Found: C, 63.5; H, 9.5; N, 3.6.

Although the siloxy ketone **44** can be purified as described above, best overall yields are obtained by taking the slightly impure crude product directly on to the next step.

**(1*R*)-9-(*tert*-Butoxycarbonyl)-2-(2-hydroxyacetyl)-9-azabicyclo[4.2.1]non-2-ene (45).** Crude silyloxy ketone **44** (3.80 g, 9.50 mmol) was dissolved in a mixture of acetonitrile (19 mL) and aqueous 49% HF (1 mL) and stirred at room temperature for 20 min. The reaction mixture was diluted with $CHCl_3$ (100 mL) and washed with brine (75 mL), saturated aqueous $NaHCO_3$ (90 mL), and brine (75 mL) again. The separate aqueous layers were back-extracted with $CHCl_3$ (2 × 25 mL) and the combined organic phase was dried, filtered, and concentrated to give hydroxy ketone **45** (2.67 g, crude) as a thick yellow oil.

An analytical sample was obtained as a clear oil in 80% yield by column chromatography (2/3, EtOAc/hexanes + 0.2% $Et_3N$) of a portion of the crude product to give pure α-hydroxy ketone **45**: TLC (EtOAc/hexanes, 1/1) $R_f$ 0.32; $[\alpha]^{19}_D$ −21.3° (*c* 3.3, absolute MeOH); IR (neat) 3460, 2960, 2920, 1670, 1400 $cm^{-1}$; $^1H$ NMR δ 1.36, 1.44 (s, 9 H, *t*-BuO), 1.60–1.77 (m, 3 H), 2.00–2.54 (m, 5 H), 3.39–3.51 (s, 1 H, OH), 4.29–4.65 (m, 3 H, H-6, H-11), 5.10–5.21 (m, 1 H, H-1), 6.75–6.82 (m, 1 H, H-3); $^{13}C$ NMR ($CDCl_3$) (two rotamers, 2/1) δ 24.14, 24.26, 24.28, 28.37, 29.53, 29.84, 30.57, 31.42, 31.86, 53.04, 53.77, 55.32, 55.68, 63.84, 64.02, 79.36, 79.50, 141.86, 142.59, 147.13, 152.86, 197.47. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0. Found: C, 63.7; H, 8.1; N, 4.9.

Although the crude α-hydroxy ketone **45** can be purified as described above, best overall yields are obtained by taking the slightly impure crude product on to the next step.

**(1*R*)-9-(*tert*-Butoxycarbonyl)-2-carboxy-9-azabicyclo[4.2.1]non-2-ene (46).** Sodium periodate (10.16 g, 47.5 mmol) in $H_2O$ (75 mL) was added to a solution of the crude α-hydroxy ketone **45** (2.67 g, 9.50 mmol) in MeOH (75 mL). After being stirred for 1 h at room temperature, the reaction mixture was concentrated by rotary evaporation to remove most of the methanol. After the mixture was adjusted to pH 9 by adding solid $K_2CO_3$ and stirring, it was filtered and the filtrate was extracted with $Et_2O$ (3 × 30 mL). The combined ether extract was dried, filtered, and concentrated to afford the neutral fraction (900 mg, crude). Purification of the neutral fraction by LPC (15–35% EtOAc/hexanes gradient) to give pure methyl (1*R*)-BOC-anatoxinate (**41**, 251 mg, 9.4% yield based on enone **42**) as a clear oil: $[\alpha]^{20}_D$ −2.1° (*c* 2.0, absolute MeOH).

The aqueous phase from the extraction above was chilled in an ice water bath and acidified with concentrated $H_3PO_4$ to pH 3.5. This solution was extracted with $CHCl_3$ (4 × 40 mL) and the combined organic phase was dried, filtered, and concentrated to give crude acid **46** as a foamy white solid (1.68 g, crude). Column chromatography (EtOAc/hexanes, 1/1) gave pure BOC-anatoxinic acid (**46**) (1.22 g, 48% yield based on enone **42**) as a white solid. The total yield of products **46** and **41** was 57% over four steps. An analytical sample of BOC-anatoxinic acid (**46**) was prepared by recrystallization from toluene/hexanes: mp 158–159 °C; TLC (MeOH/$CHCl_3$, 10/90) $R_f$ 0.41; $[\alpha]^{20}_D$ −6.8° (*c*, 1.0, absolute MeOH); IR (KBr) 3400–2500, 2960, 1715, 1670, 1410 $cm^{-1}$; $^1H$ NMR δ 1.41, 1.45 (s, 9 H, *t*-BuO), 1.56–1.88 (m, 3 H), 1.92–2.53 (m, 5 H), 4.25–4.37, 4.37–4.54 (m, 1 H, H-6), 5.06 (d, 1 H, *J* = 7.5, H-1), 7.04, 7.12 (t, 1 H, *J* = 5.8, H-3), carboxylic acid proton not located; $^{13}C$ NMR ($CDCl_3$) (two rotamers, 2/1) major rotamer δ 24.08 (2), 28.38 (3), 28.66 (2), 30.32 (2), 31.53 (2), 54.33 (1), 55.64 (1), 79.71 (0), 140.11 (1), 144.19 (1), 153.34 (0), 171.80 (0); minor rotamer δ 23.87 (2), 28.52 (3), 29.64 (2), 30.89 (2), 32.21 (2), 55.07 (1), 55.41 (1), 79.89 (0), 138.95 (0), 142.85 (1), 153.56 (0), 171.08 (0). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.9; H, 7.9; N, 5.2. Found: C, 62.6; H, 7.9; N, 5.2.

**General Procedure for the Preparation of (1*R*)-9-(*tert*-Butoxycarbonyl)-2-(chlorocarbonyl)-9-azabicyclo[4.2.1]-non-2-ene (47).** Oxalyl chloride (250 mol %) was added over 2 min to a 0.15 M solution of (1*R*)-BOC-anatoxinic acid (**46**, 100 mol %) in benzene containing *N*,*N*-dimethylformamide (DMF, three drops). Gas evolution commenced almost immediately and the mixture was stirred at room temperature for 1 h and then concentrated to dryness on a rotary evaporator to give the crude acid chloride **47** as an oil: TLC (MeOH/$CHCl_3$, 10/90) $R_f$ 0.73; IR (neat) 2960, 1740, 1685, 1390 $cm^{-1}$; $^1H$ NMR $\delta$ 1.30–2.70 (m, 8 H), 1.42, 1.44 (s, 9 H, *t*-BuO), 4.3–4.5 (m, 1 H, H-6), 4.95–5.20 (m, 1 H, H-1), 7.41 (t, 1 H, $J$ = 5.4, H-3); $^{13}C$ NMR ($CDCl_3$) $\delta$ 24.43 (2, 2 C), 28.20 (3, 3 C, $(CH_3)_3CO$), 29.30 (2), 31.09 (2), 54.56 (1), 55.79 (1), 79.94 ($(CH_3)_3CO$), 126.2 (1, C-3), 145.70 (0, C-2), 152.19 and 152.74 (NC(O)O), 167.41 (C(O)Cl).

**(1*R*)-*t*-BOC-anatoxinic Acid *N*,*N*-Dimethylamide (48).** (1*R*)-BOC-anatoxinic acid (**46**) (181 mg, 0.68 mmol) was converted to acid chloride **47** as described above. Aqueous 25% dimethylamine (2 mL) was added to a 0 °C solution of the crude acid chloride **47** in THF (5 mL). After being allowed to come to room temperature, the reaction mixture was diluted with EtOAc (25 mL) and washed with 1 M $KH_2PO_4$ (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic phase was dried, filtered, and concentrated to a light yellow oil that solidified under high vacuum and was recrystallized from hexanes to give the amide **48** as light yellow crystals (131 mg), mp 94–95 °C. The mother liquor from the recrystallization was concentrated and purified by column chromatography (EtOAc/hexanes, 1/1) to provide additional pure product **48** (45 mg, total yield: 88%): TLC (MeOH/$CHCl_3$, 10/90) $R_f$ 0.67; $[\alpha]^{20}_D$ +68.9° (*c*, 1.8, absolute MeOH); IR (film) 3500, 2980, 2920, 1690, 1620 $cm^{-1}$; $^1H$ NMR $\delta$ 1.43, 1.46 (s, 9 H, *t*-BuO), 1.60–1.82 (m, 2 H), 1.95–2.60 (m, 6 H), 2.90–3.20 (s, 6 H, $N(CH_3)_2$), 4.25–4.35, 4.38–4.50 (m, 1 H, H-6), 4.57 (d, 1 H, $J$ = 8.3, H-1), 5.69, 5.80 (t, 1 H, $J$ = 5.8, H-3); $^{13}C$ NMR ($CDCl_3$) (two rotamers, 5/4) major rotamer $\delta$ 23.54 (2), 28.47 (3), 29.47 (2), 31.34 (2), 32.53 (2), 34.79 (3), 39.32 (3), 55.47 (1), 57.23 (1), 79.40 (0), 131.06 (1), 143.64 (0), 152.84 (0), 172.01 (0); minor rotomer $\delta$ 23.52 (2), 28.51 (3), 29.47 (2), 31.41 (2), 32.42 (2), 34.79 (3), 39.32 (3), 55.71 (1), 57.23 (1), 79.18 (0), 128.91 (1), 144.28 (0), 153.31 (0), 172.01 (0). Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.3; H, 8.9; N, 9.5. Found: C, 64.8; H, 8.6; N, 9.4.

**(1*R*)-9-(*tert*-Butoxycarbonyl)-2-[(methoxyamino)-carbonyl]-9-azabicyclo[4.2.1]non-2-ene (49).** A solution of methoxyamine in DMF was prepared by dissolving methoxyamine hydrochloride (197 mg, 2.36 mmol, 300 mol %) in DMF (2.5 mL) (gentle heating was necessary). The solution was cooled back to room temperature, and 4-methylmorpholine (260 $\mu$L, 2.36 mmol, 300 mol %) was added. A white precipitate rapidly formed, the mixture was stirred for 30 min and the solid was allowed to settle. A 1.5-mL aliquot (approximately 150 mol % of methoxyamine) of the clear solution was added dropwise over 1 min to a −10 °C solution of acid chloride **47** (prepared from 210 mg, 0.79 mmol, of (1*R*)-BOC-anatoxinic acid (**46**) as described above) in THF (8 mL). After being allowed to come to room temperature, the reaction was diluted with $CH_2Cl_2$ (40 mL) and washed with 1 M $KH_2PO_4$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL). The separate aqueous layers were extracted with $CH_2Cl_2$ (2 × 10 mL) and the combined organic phase was washed with brine (45 mL), dried, filtered, and concentrated to give crude hydroxamate **49** as a yellow oil. The crude residue was purified by column chromatography (EtOAc/hexanes, 1/1) to give pure (1*R*)-*N*-BOC-anatoxinic acid *N*-methoxyamide (**49**, 145 mg, 62%) as a clear oil: TLC (MeOH/$CHCl_3$, 1/9) $R_f$ 0.61; $[\alpha]^{19}_D$ +12.5° (*c* 1.3, MeOH); IR (film) 3500, 3240, 1670, 1420, 1170, 1120 $cm^{-1}$; $^1H$ NMR $\delta$ 1.46 (s, 9 H, *t*-BuO), 1.53–2.23 (m, 6 H), 2.30–2.50 (m, 3 H), 3.81 (s, 3 H, $OCH_3$), 4.31–4.39 (m, 1 H, H-6), 4.54 (d, 1 H, $J$ = 9.5, H-1), 6.58–6.67 (m, 1 H, H-3); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.19, 28.13, 28.43, 29.73, 30.90, 54.38, 56.96, 63.60, 80.14, 137.67, 144.35, 153.79, 167.48. Anal. Calcd for $C_{15}H_{24}N_2O_4$: C, 60.8; H, 8.2; N, 9.4. Found: C, 60.6; H, 8.3; N, 9.0.

**(1*R*)-BOC-anatoxinic Acid Isoxazolidide (50).** A solution of isoxazolidine in DMF was prepared by dissolving isoxazolidine hydrochloride (392 mg, 3.78 mmol) in DMF (2 mL) wth gentle heating. After being cooled to room temperature, 4-methylmorpholine (416 $\mu$L, 3.78 mmol) was added to the clear solution, and the mixture was stirred at room temperature for 30 min and then the solid was allowed to settle.

(1*R*)-*t*-BOC-anatoxinic acid (**46**) (502 mg, 1.89 mmol) was converted to acid chloride **47** according to the general procedure described above, and the clear DMF solution of isoxazolidine was added over 3 min to a −10 °C solution of acid chloride **47** in THF (20 mL). The reaction mixture was allowed to come to room temperature and was diluted with EtOAc (30 mL) and washed with 1.5 M $KH_2PO_4$ (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The separate aqueous layers were back-extracted with EtOAc (2 × 20 mL) and the combined organic phase was dried, filtered, and concentrated to afford crude isoxazolidide **50**, which was purified by column chromatography (EtOAc/hexanes, 1/1) to give pure (1*R*)-*N*-BOC-anatoxinic acid isoxazolidide (**50**, 463 mg, 76% isolated yield) as a clear oil: TLC (MeOH/$CHCl_3$, 10/90) $R_f$ 0.57; $[\alpha]^{22}_D$ +48.6° (*c* 1.8, MeOH); IR (neat) 3580 (w), 3520, (w), 1670, 1400, 1170, 1110 $cm^{-1}$; $^1H$ NMR $\delta$ 1.20–2.50 (m, 10 H), 1.41, 1.44 (s, 9 H, *t*-BuO), 3.45–4.10 (m, 4 H), 4.26–4.36, 4.38–4.49 (m, 1 H, H-6), 4.75 (d, 1 H, $J$ = 8.4, H-1), 6.27 (dd, 0.4 H, $J$ = 5.1, 6.4, H-3), 6.40 (t, 0.6 H, $J$ = 5.9, H-3); $^{13}C$ NMR ($CDCl_3$, TMS = 0 ppm) (two rotamers, 2/1) major rotamer $\delta$ 23.77 (2), 27.56 (2), 28.19 (2), 28.29 (3, 3 C), 29.78 (2), 32.32 (2), 44.31 (2, $NCH_2$), 56.15 (1), 56.25 (1), 68.94 (2, $OCH_2$), 79.39 (0), 136.7 (1, C-3), 145.66 (0, C-2), 152.94 (0), 171.98 (0, C-10); minor rotamer $\delta$ 23.77 (2), 27.56 (2), 28.50 (3, 3 C), 28.93 (2), 31.18 (2), 31.39 (2), 45.99 (2), 55.86 (1), 56.49 (1), 68.77 (2), 79.14 (0), 135.81 (1), 144.84 (0), 153.21 (0), 172.28 (0). Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.3; H, 8.1; N, 8.7. Found: C, 63.1; H, 8.1; N, 8.7.

**(1*R*)-9-(*tert*-Butoxycarbonyl)-2-formyl-9-azabicyclo-[4.2.1]non-2-ene (51).** Lithium aluminum hydride (68.5 mg, 1.81 mmol) was added portionwise over 2 min to a −10 °C solution of isoxazolidide **50** (582 mg, 1.81 mmol) in THF (24 mL). After 15 min a solution of $KHSO_4$ (393 mg, 2.89 mmol) in $H_2O$ (2 mL) was added to the cold reaction mixture (*CAUTION: VIGOROUS GAS EVOLUTION*). The cooling bath was removed, the reaction mixture was allowed to come to room temperature, $H_2O$ (20 mL) and EtOAc (15 mL) were added, and the mixture was filtered through a plug of glass wool. The insoluble material was stirred with EtOAc (3 × 5 mL) and filtered, and the combined filtrates were shaken. The aqueous layer was extracted with EtOAc (2 × 20 mL) and the combined organic phase was washed with brine (50 mL), dried, filtered, and concentrated to afford crude aldehyde **51**, which was purified by column chromatography (EtOAc/hexanes, 1/4) to give pure (1*R*)-*N*-*t*-BOC-anatoxinal (**51**) (375 mg, 79%, mp 64–66 °C) along with a 1/1 mixture of aldehyde **51** and allylic alcohol **52** in a later fraction (65 mg, 14%; combined 93% yield). (1*R*)-*N*-*t*-BOC-anatoxinal (**51**): TLC (EtOAc/hexanes, 1/1) $R_f$ 0.44; $[\alpha]^{22}_D$ −41.4° (*c* 1.9, MeOH); IR (film) 2980, 2720, 1680, 1400, 1175 $cm^{-1}$; $^1H$ NMR $\delta$ 1.38, 1.44 (s, 9 H, *t*-BuO), 1.55–1.78 (m, 3 H), 2.01–2.37 (m, 3 H), 2.50–2.63 (m, 2 H), 4.27–4.39, 4.42–4.53 (m, 1 H, H-6), 5.06, 5.12 (d, 1 H, $J$ = 8, H-1), 6.66 (t, 1 H, $J$ = 5.4, H-3), 9.35 (s, 1 H, H-10); $^{13}C$ NMR ($CDCl_3$) (two rotamers, 5/1) major rotamer $\delta$ 24.80 (2), 28.36 (3), 27.83 (2), 29.69 (2), 31.21 (2), 51.21 (1), 55.32 (1), 79.40 (0), 150.75 (0), 152.88 (0), 153.38 (1), 192.13 (1); minor rotamer $\delta$ 24.65 (2), 28.28 (3), 29.01 (2), 30.51 (2), 31.65 (2), 52.03 (1), 55.04 (1), 79.40 (0), 150.75 (0), 152.4 (1), 152.88 (0), 192.46 (1). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 66.9; H, 8.2; N, 5.6.

**(1*R*)-*t*-BOC-anatoxinal *O*-Methyloxime (53).** A solution of methoxyamine in THF was prepared by dissolving methoxyamine hydrochloride (193 mg, 2.32 mmol) in THF (4 mL) and $H_2O$ (0.1 mL) by gentle heating. After the solution cooled to room temperature, anhydrous $K_2CO_3$ (960 mg) was added and the mixture was stirred for 30 min and then filtered through a millipore filter into a mixture of aldehyde **52** (194 mg, 0.77 mmol) and 3-Å molecular sieves (194 mg, 100 wt %) in $CH_2Cl_2$ (10 mL). Pyridinium *p*-toluenesulfonate (19 mg, 0.08 mmol) was added and the mixture was stirred for 1 h at room temperature, then diluted with $CH_2Cl_2$ (20 mL), decanted from the sieves, and washed with 1 M $KH_2PO_4$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL). The separate aqueous layers were extracted with $CH_2Cl_2$ (2 × 10 mL) and the combined organic phase was washed with brine (30 mL), dried, filtered, and concentrated to afford oxime ether **53** (202 mg, 94%) as a 6/1 mixture of *E*/*Z* isomers whose geometry was inferred from the $^1H$ NMR spectrum. The product obtained

in this manner is of sufficient quality to be taken on directly to *t*-BOC cleavage.

An analytical sample was obtained in low yield by column chromatography (EtOAc/hexanes, 1/4) of the crude product to afford both isomers of (1*R*)-*N*-BOC-anatoxinal *O*-methyloxime (**53**). More-polar (*Z*) diastereomer **53**: TLC (EtOAc/hexane, 1/3) $R_f$ 0.31; $^1$H NMR (two rotamers, 2/1) δ 1.10–2.40 (m, 8 H), 1.43, 1.46 (s, 9 H, *t*-BuO), 3.85, 3.87 (s, 3 H, $OCH_3$), 4.23–4.34, 4.36–4.44 (m, 1 H, H-6), 4.95, 5.18 (d, 1 H, $J$ = 7.5, H-1), 6.15, 6.26 (t, 1 H, $J$ = 6, H-3), 6.82 (s, 1 H, H-10). Less-polar (*E*) diastereomer **53**: TLC (EtOAc/hexanes, 1/3) $R_f$ 0.57; $[\alpha]^{21}_D$ – 53.8° (*c* 2.4, MeOH); IR (neat) 3470, 2960, 2930, 1775, 1390, 1165, 1050 cm$^{-1}$; $^1$H NMR δ 1.42, 1.46 (s, 9 H, *t*-BuO) 1.53–1.84 (m, 3 H), 2.02–2.42 (m, 5 H), 3.86 (s, 3 H, $OCH_3$), 4.26–4.36, 4.38–4.48 (m, 1 H, H-6), 5.10 (d, 0.67 H, $J$ = 9.0, H-1), 5.18 (d, 0.33 H, $J$ = 7.3, H-1), 5.82 (t, 1 H, $J$ = 6.0, H-3), 7.57 (s, 1 H, H-10); $^{13}$C NMR ($CDCl_3$) (two rotamers, 2/1) major rotamer δ 24.24 (2), 28.45 (2), 28.69 (3, 3 C), 30.87 (2), 31.29 (2), 54.52 (1), 55.52 (1), 61.66 (3), 79.17 (0), 136.79 (1), 143.18 (0), 150.56 (1), 153.35 (0); minor rotamer δ 24.09 (2), 28.53 (2), 28.69 (3, 3 C), 30.35 (2), 30.63 (2), 54.86 (1), 55.52 (1), 61.66 (3), 79.17 (0), 136.79 (1), 143.18 (0), 150.56 (1), 153.35 (0). Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.3; H, 8.6; N, 10.0. Found: C, 63.9; H, 8.6; N, 9.7.

**(1*R*)-9-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-9-azabicyclo[4.2.1]non-2-ene (52).** Solid $CeCl_3$·4.5$H_2O$ (211 mg, 0.64 mmol) and sodium borohydride (26 mg, 0.70 mmol) were added (in that order and in rapid succession[35]) to a stirring solution of aldehyde **51** (160 mg, 0.64 mmol) in MeOH (5 mL). Gas evolution was noted immediately and TLC of the mixture after 15 min showed the reaction to be complete. The mixture was poured into brine (15 mL) and extracted with $CH_2Cl_2$ (4 × 10 mL). The combined organic phase was dried, filtered, and concentrated to afford the crude product, which was purified by column chromatography (EtOAc/hexanes, 1/1) to give pure allylic alcohol **52** (138 mg, 86%) as a clear oil: TLC (EtOAc hexanes, 1/1) $R_f$ 0.41; $[\alpha]^{21}_D$ +40.8° (*c* 2.3, MeOH); IR (neat) 3410, 1670 cm$^{-1}$; $^1$H NMR δ 1.45, 1.46 (s, 9 H, *t*-BuO), 1.51–1.93 (m, 5 H), 2.06–2.43 (m, 3 H), 3.45–3.50 (s, 1 H, OH), 3.88 (d, 1 H, $J$ = 10, H-10a), 4.10 (d, 1 H, $J$ = 10, H-10b), 4.25–4.52 (m, 1 H, H-6), 4.37 (d, 1 H, $J$ = 10, H-1), 5.67 (d, 1 H, $J$ = 10, H-3); $^{13}$C NMR ($CDCl_3$) (two rotamers, 4/1) major rotamer δ 22.80 (2), 28.37 (3, 3 C), 28.61 (2), 30.58 (2), 30.79 (2), 55.27 (1), 57.03 (1), 67.15 (2), 79.82 (0), 127.44 (1), 149.93 (0), 153.72 (0); minor rotamer δ 23.06 (2), 28.37 (3, 3 C), 27.90 (2), 30.46 (2), 31.90 (2), 55.79 (1), 55.92 (1), 67.08 (2), 79.33 (0), 125.09 (1), 147.98 (0), 152.69 (0). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.4; H, 9.1; N, 5.5. Found: C, 66.1; H, 9.0; N, 5.5.

**(1*R*)-2-Formyl-9-azabicyclo[4.2.1]non-2-ene (2).** The *t*-BOC-protected aldehyde **51** (193 mg, 0.77 mmol) was dissolved in $CH_2Cl_2$ (21 mL) and treated with TFA (2.07 mL, 26.9 mmol). After being stirred for 1 h at room temperature, the reaction mixture was concentrated and the crude TFA salt was suspended in brine (5 mL) and 1 M $K_2CO_3$ was added until pH 10. The resulting solution was extracted with 3/1 $CHCl_3$/*i*-PrOH (3 × 10 mL). The combined organic phase was dried, filtered, and concentrated to give (1*R*)-anatoxinal (**2**, 112 mg, 97%) as a bright yellow foamy solid: TLC (MeOH/$CHCl_3$, 10/90) $R_f$ 0.06; $^{13}$C NMR ($CDCl_3$, TMS = 0 ppm) δ 25.78, 29.06, 33.15, 33.25, 52.57, 57.53, 153.05, 154.60, 193.37.

A portion of the crude aldehyde **2** (81 mg, 0.54 mmol) was treated with fumaric acid according to the general procedure below to give a hygroscopic solid, mp 139–141 °C. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 58.0; H, 7.1; N, 5.2. Found: C, 58.1; H, 7.2; N, 5.1.

**General Procedure for Trifluoroacetic Acid Cleavage of N-*t*-BOC-Protected Analogues and Conversion to Hydrogen Fumarate Salts.** The N-*tert*-butoxycarbonyl-protected analogues **41**, **45**, **48**, **49**, **50**, **52**, and **53** were deprotected by adding trifluoroacetic acid (TFA, 3500 mol %) to a room temperature solution of the N-*t*-BOC-protected substrate in $CH_2Cl_2$ (0.03–0.07 M in substrate). When the substrate was judged (TLC analysis) to be completely consumed (usually 1–10 h), the solvent and excess TFA were evaporated and the crude TFA salt of the deprotected amine was dissolved in brine (5–10 mL), adjusted with $K_2CO_3$ to pH 10 (unless otherwise noted), and then extracted with $CHCl_3$/*i*-PrOH (3/1). Drying and concentrating the organic layers gave the amine, which was then converted to a salt with fumaric acid (100 mol %, unless otherwise noted) and crystallized from *i*-PrOH/$Et_2O$ as described for (+)-anatoxin.[7]

The hydrogen fumarate of (1*R*)-2-(methoxycarbonyl)-9-azabicyclo[4.2.1]non-2-ene (**4**) was prepared from **41**: 197 mg, 67% yield; mp 189–190 °C; TLC (MeOH/$CHCl_3$, 1/4) $R_f$ 0.08; $[\alpha]^{22}_D$ + 48.5 (*c* 1.5, MeOH); $^1$H NMR ($CD_3OD$ = 4.78 ppm) δ 1.69–1.97 (m, 4 H), 2.02–2.15 (m, 1 H), 2.17–2.53 (m, 3 H), 3.09–3.14 (m, 1 H, H-6), 3.76 (s, 3 H, $OCH_3$), 4.05–4.13 (m, 1 H, H-1), 6.65 (s, 2 H, HC=CH), 7.15–7.21 (m, 1 H, H-3); $^{13}$C NMR ($CD_3OD$ = 49.0 ppm) δ 24.24, 27.89, 28.82, 31.61, 52.99, 55.86, 60.20, 135.89, 147.96, 167.27, 171.94. Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.4; N, 4.7. Found: C, 56.5; H, 6.5; N, 4.6.

**(1*R*)-2-(Methoxycarbonyl)-9-methyl-9-azabicyclo[4.2.1]non-2-ene (5).** Methyl (1*R*)-*N*-*t*-BOC-anatoxinate (**41**, 144 mg, 0.51 mmol) was dissolved in formic acid (2 mL) and stirred at room temperature for 2 h. The reaction mixture was chilled to 0 °C, aqueous 37% formaldehyde (W/W, 77 μL, 1.02 mmol) was added, and the mixture was stirred for 1 h at 0 °C then heated to 95 °C. After another 2 h the reaction mixture was cooled to room temperature, the excess formic acid was evaporated, and the residue was suspended in brine (5 mL) and 1 M $K_2CO_3$ was added to pH 10. The resulting solution was extracted with $CHCl_3$/*i*-PrOH (3/1, 3 × 10 mL) and the combined organic phase was dried, filtered, and concentrated to afford methyl *N*-methylanatoxinate (**5**) (84 mg, 84%) as a brown oil: $^1$H NMR δ 1.61–1.82 (m, 4 H), 1.85–2.02 (m, 2 H), 2.08–2.26 (m, 2 H), 2.36 (s, 3 H, $NCH_3$), 3.41–3.50 (m, 1 H, H-6), 3.72 (s, 3 H, $OCH_3$), 4.34 (d, 1 H, $J$ = 8.9, H-1), 7.09 (t, 1 H, $J$ = 5.9, H-3).

The hydrogen fumarate of **5** was prepared as described above: mp 127–128 °C; $^1$H NMR ($D_2O$) (two epimers at N-9, 3/1) δ 1.76–1.88 (m, 2 H), 1.93–2.19 (m, 3 H), 2.29–2.64 (m, 4 H), 2.60, 2.73 (s, 3 H, $NCH_3$), 3.60 (s, 3 H, $OCH_3$), 3.91–4.00 (m, 1 H, H-6), 4.58 (d, 1 H, $J$ = 8.4, H-1), 6.51 (s, 2 H, HC=CH), 7.26 (dd, 0.75 H, $J$ = 3.7, 8.4, H-3), 7.34–7.39 (m, 0.25 H, H-3); $^{13}$C NMR ($D_2O$, dioxane = 66.5 ppm) (two epimers at N-9, 3/1) major epimer δ 22.14 (2), 24.83 (2), 28.41 (2), 42.11 ($NCH_3$), 52.68 ($OCH_3$), 64.18 (1), 69.28 (1), 133.21 (0, C-2), 134.48 (1, 2C, C=C), 149.03 (1, C-3), 167.49 (C(O)$OCH_3$), 171.30 (2 C, C(O)OH); minor epimer (partial) δ 21.30 (2), 22.50 (2), 26.14 (2), 29.12 (2), 64.72 (1), 150.34 (0). Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.9; H, 6.8; N, 4.5. Found: C, 57.6; H, 6.9; N, 4.7.

The hydrogen fumarate of (1*R*)-2-[(dimethylamino)-carbonyl]-9-azabicyclo[4.2.1]non-2-ene (**6**) was prepared from **48** as described above: 52% yield; mp 110 °C (broad range); TLC (MeOH/$CHCl_3$, 1/9) $R_f$ 0.13 (**6** TFA salt); $^1$H NMR ($D_2O$, DSS) δ 1.85–2.05 (m, 2 H), 2.10–2.35 (m, 3 H), 2.43–2.70 (m, 3 H), 2.96 (s, 3 H, $NCH_3$), 3.10 (s, 3 H, $NCH_3$), 4.33 (br s, 1 H, H-6), 4.40 (d, 1 H, $J$ = 8.8, H-1), 6.33–6.41 (m, 1 H, H-3), 6.68 (s, 2 H, HC=CH); $^{13}$C NMR ($D_2O$, DSS) δ 25.29, 28.99, 30.01, 33.37, 37.90, 42.26, 59.59, 62.19, 137.43 (2 C), 142.03, 174.7 (2 C), 175.7. Anal. Calcd for $C_{15}H_{22}N_2O_5$: C, 58.2; H, 6.8; N, 9.1. Found: C, 57.9; H, 7.2; N, 8.9.

The hydrogen fumarate of (1*R*)-2-[(methoxyamino)-carbonyl]-9-azabicyclo[4.2.1]non-2-ene (**7**) was prepared from **49** as described, adjusting the pH to 9.2 before extraction: 73% yield; $^1$H NMR ($D_2O$) δ 1.64–1.83 (m, 2 H), 1.90–2.13 (m, 3 H), 2.26–2.48 (m, 3 H), 3.55 (s, 3 H, $OCH_3$), 4.09–4.18 (m, 1 H, H-6), 4.48 (d, 1 H, $J$ = 9.3, H-1), 6.47 (s, 2 H, HC=CH), 6.53–6.61 (m, 1 H, H-3); $^{13}$C NMR ($D_2O$, dioxane = 66.5 ppm) δ 22.68 (2), 26.40 (2), 27.08 (2), 30.30 (2), 55.07 (1), 59.34 (1), 63.96 (3, $CH_3O$), 134.75 (1, C-3), 134.87 (0), 142.31 (1, 2 C), 167.28 (0), 167.30 (0), 171.79 (0). Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.8; H, 6.5; N, 9.0. Found: C, 54.0; H, 6.5; N, 9.0.

The hydrogen fumarate of (1*R*)-anatoxinic acid isoxazolidide (**8**) was prepared from **50**: 77% yield; mp 149–150 °C; $^1$H NMR ($D_2O$) δ 1.64–1.83 (m, 2 H), 1.87–2.54 (m, 7 H) overlaps 2.22 (t, 2 H, $J$ = 7.1, 7.2, $NCH_2CH_2$), 3.56–3.74 (m, 2 H), 3.95 (t, 2 H, $J$ = 6.7, 6.8, $OCH_2CH_2$), 4.11–4.18 (m, 1 H, H-6), 4.37 (d, 1 H, $J$ = 9.7, H-1), 6.40–6.65 (m, 1 H, H-3) overlaps 6.50 (s, 2 H, HC=

(35) Allowing the aldehyde **51** to stir in methanol in the presence of the cerium reagent for as little 15 min results in substantial (10–15%) formation of the corresponding dimethyl acetal. The facile acetalization of aldehydes with lanthanides has been reported: Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.

CH); $^{13}C$ NMR ($D_2O$, dioxane = 66.5 MHz) δ 22.67 (2), 26.51 (2), 26.90 (2), 27.13 (2), 30.35 (2), 47.46 (2, $NCH_2$), 56.23 (1), 59.48 (1), 70.01 (2, $OCH_2$), 134.72 (0, C-2), 143.21 (1, 3 C, C-3 and C=C), 166.22 (C(O)N), 171.43 (C(O)O). Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.6; H, 6.6; N, 8.2.

The hydrogen fumarate of (1*R*)-anatoxinal *O*-methyloxime (**9**) was prepared from crude **53**: 72% yield; mp 197-199 °C; $^1H$ NMR ($D_2O$/DMSO-$d_6$, 2.49 ppm) δ 1.65-1.79 (m, 2 H), 1.84-2.13 (m, 3 H), 2.22-2.47 (m, 3 H), 3.72 (s, 3 H, $OCH_3$), 4.08-4.15 (m, 1 H, H-6), 4.75 (d, 1 H, *J* = 9.2, H-1), 6.24 (dd, 1 H, *J* = 4.0, 8.1, H-3), 6.46 (s, 2 H, HC=CH), 7.64 (s, 1 H, H-10); $^{13}C$ NMR ($D_2O$/DMSO-$d_6$ = 39.50 ppm) δ 24.32, 27.73, 28.70, 31.01, 53.97, 60.04, 62.92, 136.32, 137.12, 144.03, 152.27, 171.15. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.7; H, 6.8; N, 9.4. Found: C, 56.7; H, 6.9; N, 9.2.

The hydrogen fumarate of (1*R*)-2-(Hydroxymethyl)-9-azabicyclo[4.2.1]non-2-ene (**10**) was prepared from **52**: mp 139-141 °C; $^1H$ NMR ($D_2O$) δ 1.63-1.70 (m, 2 H), 1.86-2.07 (m, 4 H), 2.10-2.33 (m, 4 H), 3.85 (s, 2 H, H-10a,b), 4.03 (d, 1 H, *J* = 9.2, H-6), 4.07-4.13 (m, 1 H, H-1), 5.82 (dd, 1 H, *J* = 1.8, 8.4, H-3), 6.55 (s, 2 H, HC=CH); $^{13}C$ NMR ($D_2O$, dioxane = 66.5 ppm) δ 21.91 (2), 26.31 (2), 27.89 (2), 30.30 (2), 56.91 (1), 59.33 (1), 65.82 (2, C-10), 131.62 (1, C-3), 134.43 (1, 2C, C=C), 140.58 (0, C-2), 170.45 (2 C, fumarate $CO_2$). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 58.0; H, 7.1; N, 5.2. Found: C, 58.1; H, 7.2; N, 5.1.

The hydrogen fumarate of (1*R*)-2-(Hydroxyacetyl)-9-azabicyclo[4.2.1]non-2-ene (**11**) was prepared from hydroxy ketone **45**: 58% yield; mp 193-195 °C; $^1H$ NMR ($D_2O$) δ 1.58-2.10 (m, 5 H), 2.21-2.32 (m, 1 H), 2.37-2.57 (m, 2 H), 4.07-4.15 (m, 1 H, H-6), 4.50 (s, 2 H, H-10a,b), 4.85 (d, 1 H, *J* = 9.3, H-1), 6.52 (s, 2 H, HC=CH), 7.11 (d, 1 H, *J* = 8.5, H-3); $^{13}C$ NMR ($D_2O$, dioxane = 66.5 ppm) δ 23.23 (2), 26.56 (2), 27.05 (2), 29.58 (2), 52.76 (1), 59.13 (1), 63.51 (2), 134.54 (1, 2 C), 139.76 (0, C-2), 149.18 (1, C-3), 170.76 ($CO_2$). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.4; N, 4.7. Found: C, 57.0; H, 6.6; N, 5.2.

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**Registry No.** **2**, 125736-21-2; **4**·fumarate, 125736-23-4; **5**, 125736-24-5; **5**·fumarate, 125826-61-1; **6**·fumarate, 125736-26-7; **7**·fumarate, 125736-28-9; **8**·fumarate, 125736-30-3; **9**·fumarate, 125736-32-5; **10**·fumarate, 125736-34-7; **11**·fumarate, 125736-36-9; (*S*)-**14**, 90741-31-4; **15**, 53856-93-2; (*R*)-**16**, 125736-40-5; (*S*)-**16**, 125736-39-2; **17**, 125736-41-6; **18**, 125736-42-7; **23**, 125736-43-8; **24**, 125736-44-9; (*E*)-**25**, 125736-45-0; (*Z*)-**25**, 125762-84-7; **26**, 125736-46-1; **27**, 125736-47-2; **28**, 125736-48-3; **29**, 125736-49-4; **30**, 125736-50-7; **33** (α epimer), 112020-12-9; **33** (β epimer), 112020-13-0; **35**α, 125736-01-8; **35**β, 125736-00-7; **36**, 125736-02-9; **37**α, 125736-05-2; **37**α (α-TBDMS ester), 125736-04-1; **37**β, 125736-03-0; **38**α, 125736-07-4; **38**β, 125736-06-3; **39a**, 125736-08-5; **39b**, 125736-09-6; **40a**, 125736-37-0; **40b**, 125736-38-1; (±)-**41**, 125736-10-9; **41**, 125826-58-6; **42**, 90741-53-0; **43**, 125736-11-0; **44**, 125736-12-1; **45**, 125736-13-2; **46**, 125736-14-3; **47**, 125736-15-4; **48**, 125736-16-5; **49**, 125736-17-6; **50**, 125736-18-7; **51**, 125826-59-7; **52**, 125736-20-1; (*E*)-**53**, 125736-19-8; (*Z*)-**53**, 125826-60-0.

**Supplementary Material Available:** Analytical data for compounds **15**, **18**, **23-30** and full experimental procedures and analytical data for compounds **16** and **17** (4 pages). Ordering information is given on any current masthead page.

# Functionalization of 2-Methyl- and 2,7-Dimethyl-1,8-naphthyridine[1a]

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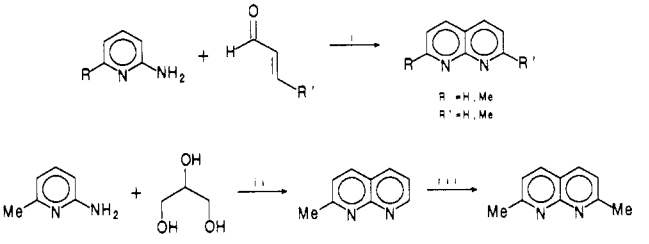
A new synthesis of 2,7-dimethyl-1,8-naphthyridine (dmnap) from 2-methyl-1,8-naphthyridine (mnap) upon treatment with 3 equiv of methyllithium is described. Oxidation of dmnap with 8 equiv of *N*-chlorosuccinimide gave (98%) 2,7-bis(trichloromethyl)-1,8-naphthyridine (**2**), while oxidation with 4 equiv gave (97%) 2,7-bis(dichloromethyl)-1,8-naphthyridine (**1**). Hydrolysis of **2** with phosphoric acid followed by esterification gave the corresponding diester **3** in 80% overall yield. Reduction of **3** with $NaBH(OMe)_3$ afforded (55%) diol **4**. Similar functionalization of mnap afforded 2-(trichloromethyl)-1,8-naphthyridine (**6**) in 85-94% yield along with 6-chloro-2-(trichloromethyl)-1,8-naphthyridine (**7**). Methanolysis of **6** gave (78%) 2-(methoxycarbonyl)-1,8-naphthyridine (**8**), which upon reduction with $NaBH(OMe)_3$ afforded (59%) the alcohol **9**. Treatment of **6** with KOH caused a displacement of the trichloromethyl moiety, generating 1,8-naphthyridin-2-one (**10**) as the sole product. Similarly, **2** gave 7-(trichloromethyl)-1,8-naphthyridin-2-one (**11**) under mild conditions or 7-(ethoxycarbonyl)-1,8-naphthyridin-2-one (**12**) when refluxed.

In 1967, Paudler and Kress first reported a feasible one-step synthesis of 2,7-dimethyl-1,8-naphthyridine [dmnap(s)],[2] 2-methyl-1,8-naphthyridine [mnap(s)],[2] and 1,8-naphthyridine [nap(s)][2,3] from commercially available starting materials. Since then, a plethora of novel inorganic complexes have been reported (Figure 1) using these potentially bidentate ligands, ranging from dodecahedral transition-metal complexes, to dinuclear complexes containing bridging naps, to 12-coordinate icosahedral lanthanide complexes. Despite this profusion of complexes, very few derivatives of 1,8-naphthyridine have been pre-

**Scheme I.**[a]



[a] (i) $H_2SO_4$, [O]; (ii) $H_2SO_4$, $H_3BO_3$, $Fe(SO_4)$, sodium *m*-nitrobenzenesulfonate; (iii) 3 equiv of MeLi, then $KMnO_4$, $Me_2CO$.

(1) (a) Chemistry of Heterocyclic Compounds. Part 143. (b) Based in part on the Ph.D. Dissertation, Louisiana State University, 1982. (c) Undergraduate researcher.

(2) Paudler, W. W.; Kress, T. J. *J. Org. Chem.* **1967**, *32*, 832.

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