Chirospecific Synthesis of Nitrogen and Side Chain Modified Analogues of (+)-Anatoxin

F. Javier Sardina, Michael H. Howard, Ari M. P. Koskinen, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received January 23, 1989

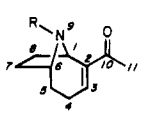
Improvements in the chirospecific synthesis of (+)-anatoxin from D-glutamic acid have resulted in a process that gives enantiomerically pure material in reproducible 25% overall yield. The major synthetic modifications have been in the decarbonylative iminium ion cyclization and in the introduction of the enone moiety. With multigram quantities of (+)-anatoxin thus available, a series of nitrogen and side chain modified analogues has been prepared. These analogues were chosen to provide probes for the agonist–receptor interaction model of acetylcholine. They include secondary, tertiary, and quaternary nitrogen derivatives and those in which the carbonyl function has been converted to secondary and tertiary alcohol and ester functions.

Introduction

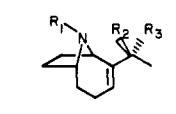
Some strains of the fresh-water blue-green alga *Anabaena flos-aquae* (Lyngb) de Breb produce a powerful toxin, (+)-anatoxin-a (anatoxin, 1) which exerts its action by depolarizing the postsynaptic acetylcholine receptors.[1] It is the most potent agonist known for the acetylcholine receptor. This potency and the conformational constraint of its 9-azabicyclo[4.2.1]nonane skeleton make anatoxin an ideal substrate for probing the geometrical requirement of the nicotinic acetylcholine receptor. Accordingly, anatoxin has been the object of active neurophysiological research.[2a,b]

The crystal structure and solution conformation of anatoxin, determined in our laboratories,[2k] are consistent with the proposed model[3] in which the receptor donates a hydrogen bond to the agonist and recognizes the plane defined by the hydrogen bond acceptor system (1, C3, C2, C10, O, s-cis conformation). A Coulombic interaction site (with the protonated N9 of 1) is positioned out of this plane at an optimal distance. In order to refine the agonist–receptor interaction model, synthetic anatoxin analogues are needed, modified on the two sites most likely to interact with the neuroreceptor. Despite all the attention focused on anatoxin, synthesis of only four anatoxin analogues has been reported,[4] three of them in racemic form. The pyridino analogue **2** was found to be equipotent with anatoxin in several receptor binding assays.[4a]

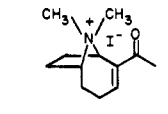
Since an almost infinite number of structural variations of these two sites of anatoxin are conceivable, we have limited our structure–activity investigation to compounds **3–14**. Analogues **3** and **4** will probe the effect of substitution at the Coulombic interaction site. Analogues **5–10** will reflect on the receptor's requirement of the hydrogen bond acceptor portion of the agonist. Compounds **11–14** represent constrained analogues of the syn and anti conformations of acetylcholine.[5] They were selected because the tropane analogues **15** and **16** have been shown to be nicotinic and muscarinic agonists.[5b]



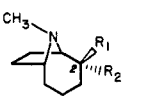
1 R = H
3 R = CH_3



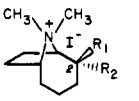
5 $R_1 = R_3 = H$; $R_2 = OH$
6 $R_1 = R_2 = H$; $R_3 = OH$
7 $R_1 = H$; $R_2 = CH_3$; $R_3 = OH$
8 $R_1 = CH_3$; $R_2 = OH$; $R_3 = H$
9 $R_1 = CH_3$; $R_2 = H$; $R_3 = OH$
10 $R_1 = R_2 = CH_3$; $R_3 = OH$



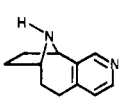
4



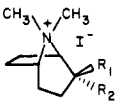
11 R_1 = OAc; R_2 = H
12 R_1 = H; R_2 = OAc



13 R_1 = OAc; R_2 = H
14 R_1 = H; R_2 = OAc



(±) **2**



15 R_1 = OAc; R_2 = H
16 R_1 = H; R_2 = OAc

The stringent stereochemical constraints imposed by the receptor site, illustrated by the fact that unnatural (−)-anatoxin is several orders of magnitude less active than its enantiomer,[2k] dictate the necessity of chirospecificity in the synthesis of analogues. Herein we report the chirospecific syntheses of anatoxin analogues **3–14** along with significant improvements on the synthesis of (+)-**1**, which we now routinely obtain in multigram quantities from D-glutamic acid in 25% overall yield and >99% ee.

Results and Discussion

Although anatoxin (1) has attracted much recent synthetic activity,[2c-q] the only total synthesis of (+)-**1** was reported from this laboratory.[2k,l] During the course of the present work we have considerably improved this synthesis both in regard to the overall yield and reproducibility as shown in Scheme I. Thus it became the basis for our analogue syntheses.

(1) (a) Carmichael, W. W.; Biggs, D. F.; Gorham, P. R. *Science* **1975**, *187*, 542. (b) Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Stavric, B. *Can. J. Chem.* **1977**, *55*, 1367. (c) Spivak, C. E.; Witkop, B.; Albuquerque, E. X. *Mol. Pharmacol.* **1980**, *18*, 384.

(2) Biology: (a) Aronstam, R. S.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4639. (b) Swanson, K. L.; Allen, C. N.; Aronstam, R. S.; Rapoport, H.; Albuquerque, E. X. *Mol. Pharmacol.* **1986**, *29*, 250. Synthesis: (c) Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 245. (d) Lindgren, B.; Stjernlof, P.; Trogen, L. *Acta Chem. Scand., Ser. B* **1987**, *41*, 180. (e) Shono, T.; Matsumura, Y.; Uchida, K.; Tagami, K. *Chem. Lett.* **1987**, 919. (f) Esch, P. M.; Hiemstra, H.; Klaver, W. J.; Speckamp. W. N. *Heterocycles* **1987**, *26*, 75. (g) Melching, K. H.; Hiemstra, H.; Klaver, W. J.; Speckamp. W. N. *Tetrahedron Lett.* **1986**, *27*, 4799. (h) Wiseman, J. R.; Lee, S. Y. *J. Org. Chem.* **1986**, *51*, 2485. (i) Tufariello, J. J.; Meckler, H.; Senaratne, K. P. A. *Tetrahedron* **1985**, *41*, 3447. (j) Danheiser, R. L.; Morin, J. M., Jr.; Salaski, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 8066. (k) Koskinen, A. M. P.; Rapoport, H. *J. Med. Chem.* **1985**, *28*, 1301. (l) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539. (m) Tufariello, J. J.; Meckler, H.; Sernaratne, K. P. A. *J. Am. Chem. Soc.* **1984**, *106*, 7979. (n) Petersen, J. S.; Toteberg-Kaulen, S.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 2948. (o) Campbell, H. F.; Edwards, O. E.; Elder, J. W.; Kolt, R. J. *Pol. J. Chem.* **1979**, *53*, 27. (p) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. (q) Campbell, H. F.; Edwards, O. E.; Kolt, R. *Can. J. Chem.* **1977**, *55*, 1372.

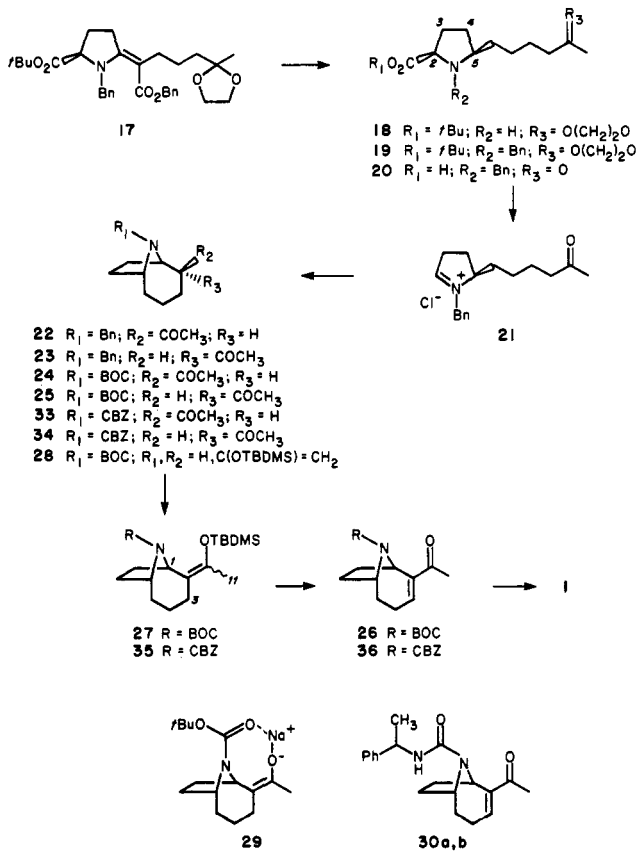
(3) Beers, W. H.; Reich, E. *Nature* **1970**, *228*, 917.

(4) (a) Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506. (b) Kanne, D. B.; Ashworth, D. J.; Cheng, M. T.; Mutter, L. C.; Abood, L. G. *J. Am. Chem. Soc.* **1986**, *108*, 7864. (c) Compound (+)-**3** is the precursor of (+)-**1** in Edwards' synthesis of (+)-anatoxin from cocaine;[2q] **3** has also been synthesized in racemic form.

(5) (a) Maelicke, A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 195. (b) Archer, S.; Lands, A. M.; Lewis, T. R. *J. Med. Pharm. Chem.* **1962**, *5*, 423.

0022-3263/89/1954-4654$01.50/0

Scheme I. Synthesis of (+)-Anatoxin



Modification[6] of the previous transfer hydrogenolysis of enantiomerically pure vinylogous carbamate 17[2k] afforded the desired cis-disubstituted pyrrolidine **18**, which was directly rebenzylated to give *N*-benzylpyrrolidine **19** in 83% yield from **17**. The decarbonylative cyclization of keto acid **20** to afford a mixture of bicyclo ketones **22** and **23**, is based on the known instability of tertiary amino acid chlorides toward decarbonylation,[7] and the electrophilic character of the resulting iminium ions (i.e., **21**).[8]

This decarbonylation/cyclization reaction, reported[2k] to proceed in 65% yield, was found to be fickle, prompting a search for a method of achieving the decarbonylation by a cleaner and milder process. Oxalyl chloride[7] appeared to be a suitable reagent since it readily converts acids to acid chlorides, produces only gaseous byproducts, and allows the use of nonpolar solvents, which should favor displacement of the equilibrium toward the cyclized products. Thus reaction of amino acid **20** with oxalyl chloride in a variety of nonpolar solvents gave the iminium salt **21** within 2 h at room temperature and then, after heating, a mixture of amino ketones **22** and **23**. 1,2-dichloroethane gave the best results for iminium salt formation while the addition of toluene improved the cyclization step. Under these conditions a 2/1 mixture of **22** and **23** was reproducibly obtained in 66–72% combined yield.

Some details of this reaction merit further comment. The reaction of **20** with oxalyl chloride provided the corresponding acid chloride (or mixed anhydride), which was stable below 0 °C since quenching with methanol/pyridine gave the expected methyl ester. However, this intermediate decomposed to the iminium salt **21** at room temperature, and trapping experiments with KCN gave the corresponding amino nitrile as a mixture of epimers at C2. Cyclization of **21** to give **22** and **23** was very slow at temperatures below 40 °C and was more conveniently carried out at 60 °C overnight. The presence of 5–6% of iminium ion **21** in the equilibrium mixture was demonstrated by ^{1}H NMR spectroscopy and confirmed by quenching with KCN/NH_4Cl to form the corresponding amino nitriles. Thus at equilibrium the ratio of cyclized products **22** and **23** to iminium ion **21** is 11/1.

Hydrogenolytic removal of the nitrogen protecting group and reprotection as the *tert*-butyl carbamate were best carried out under neutral conditions in one step and in a considerably improved yield by hydrogenolysis of a mixture of **22** and **23** in methanol in the presence of $(BOC)_2O$, affording **24** and **25** directly in 95% yield. The oxidation of the t-BOC-dihydroanatoxins (**24** and **25**) to t-BOC-anatoxin (**26**) has been previously carried out in 50% yield by $Pd(OAc)_2$ dehydrogenation of the TMS enol ether mixture obtained from **24** and **25** (KH, TMSCl).[2k] This conversion has two weaknesses: no regiochemical control has been affected in the formation of the TMS enol ether of ketones **24** and **25** (only the more substituted enol ether will be oxidized to t-BOC-anatoxin), and the oxidation step has been capricious. An alternative for this transformation was thus sought.

We first examined the regiochemistry of the enol ether formation. Treatment of a mixture of ketones **24** and **25** with KH at 40 °C for 3 h followed by quenching with excess TBDMSCl at 0 °C gave a mixture of thermodynamic (**27**, Z/E ratio 3.5/1 by NMR) and kinetic (**28**) silyl enol ethers in a 5/1 ratio. Since alcohols have been involved as the actual proton transfer agents in reactions of ketones with the insoluble, polymeric NaH,[9] trace amounts of methanol or benzyl alcohol were added to the reaction mixture of ketones **24** and **25** with NaH (THF, room temperature). Quenching this reaction with TBDMSCl after 9 h gave a >40:1 mixture of thermodynamic (Z/E ratio 35:1) and kinetic silyl enol ethers in 98% yield. The double bond geometry of (*Z*)-**27** was deduced from the observation of a NOE at H3 (δ 2.25 ppm) when the proton resonance for the enol ether methyl group (H11, δ 1.77 ppm) was irradiated. It should be pointed out that commercial NaH has not been previously used for the generation of ketone enolates at room temperature.[10] The very high stereoselectivity observed in this reaction can be rationalized by assuming the formation of chelate **29**. Complexation of the carbamate carbonyl with sodium cation might be more effective than with the larger, less polarizing potassium cation, thus explaining the diminished selectivity of the KH reaction.

Reaction of TBDMS enol ether **27** with PhSeCl followed by oxidation with mCPBA afforded t-BOC-anatoxin (**26**) in 84% yield. Cleavage of the t-BOC protecting group with TFA proceeded quantitatively. The optical integrity of the synthetic anatoxin (+)-**1** was examined through con-

(6) Trace amounts of sulfur containing compounds adversely affect the yield of the hydrogenolysis reaction.

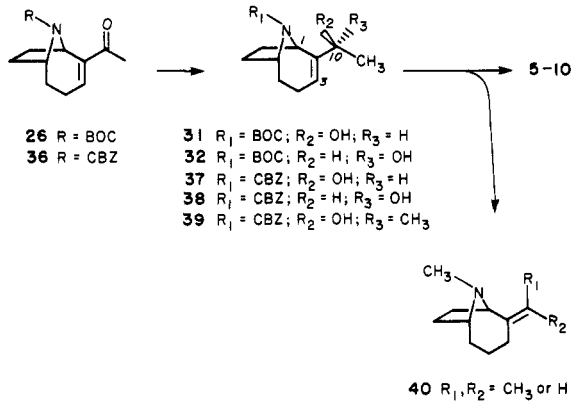
(7) (a) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. (b) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875.

(8) Rapoport, H. *Lectures in Heterocyclic Chemistry* **1978**, *4*, S-47.

(9) (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (b) t-BuOH has been used as a catalyst in NaH induced ketone enolate formation in refluxing xylene: Fried, J. H.; Nutile, A. N.; Arth, G. E. *J. Am. Chem. Soc.* **1960**, *82*, 5704. (c) Fried, J. H.; Arth, G. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1960**, *82*, 1684.

(10) We are currently exploring the generality of this reaction as a mild method for the generation of thermodynamic sodium enolates. A highly reactive, highly pyrophoric form of NaH, generated by hydrogenation of sodium/naphthalene, was observed to convert cyclohexanone to the enolate rapidly at room temperature; no details are given: Bank, S.; Lois, T. A. *J. Am. Chem. Soc.* **1968**, *90*, 4505.

Scheme II. Synthesis of Anatoxinols



version to the diastereomeric ureas **30a,b** by reaction with (*R*)- and (*S*)-α-methylbenzyl isocyanate. The enantiomeric purity of **1** was thus determined to be >99% ee (NMR doping analysis). A crystalline hydrogen fumarate of (+)-**1** was readily obtained from isopropyl alcohol.

With an efficient synthesis of anatoxin that can provide multigram quantities of (+)-**1** in hand we proceeded to synthesize the analogues **3–14**. *N*-Methylanatoxin (**3**) was synthesized through a formaldehyde–formic acid methylation[11] of anatoxin in 93% yield and was characterized as its amorphous hydrochloride hydrate. *N*-Methylanatoxin methiodide (**4**) was obtained in 80% yield by reaction of tertiary amine **3** with excess methyl iodide in acetone.

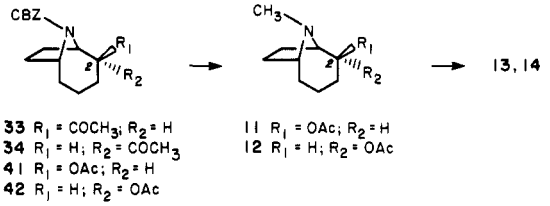
The syntheses of the anatoxinols **5–10**, Scheme II, proved to be far more challenging than anticipated. Direct reduction of anatoxin (**1**) using $NaBH_4$·$CeCl_3$[12] gave only complex mixtures; however, reduction of t-BOC-anatoxin (**26**) under the same conditions afforded a 41/59 mixture of the BOC-anatoxinols **31** and **32** in 97% yield. Use of $LiAlH_4$ or DIBAL gave approximately 5% of 1,4 reduction products **24** and **25**.

Clean t-BOC cleavage could not be achieved since the allylic amine–allylic alcohol moiety present in **31** and **32** was too unstable under the acidic conditions needed. The inability to use t-BOC as a protecting group forced alternative protection with the CBZ group because it can be cleaved under a variety of neutral and alkaline conditions.[13] A mixture of *N*-benzyldihydroanatoxins (**22** and **23**) was submitted to the usual hydrogenolysis conditions, and the crude product from this reaction was treated with an excess of CBZ-Cl at pH 9 to give a mixture of the desired CBZ-dihydroanatoxins (**33** and **34**) in 92% combined yield.

The stereochemistry at C2 in **33** and **34** is assigned on the basis of the chemical shift of H2 in both compounds. In the less polar epimer **34**, H2 appeared as a ddd at 2.93 and 3.17 ppm, due to the existence of two rotamers. In the more polar epimer **33**, H2 appeared at higher field (<2.50 ppm). The large downfield shift experienced by H2 in **34** was attributed to the deshielding effect of the C1–N bond; this effect should be present only when the C1–N and C2–H2 bonds are syn (2*R* configuration).

Formation of the TBDMS enol ether **35** and selenation–oxidation of **35** to give CBZ-anatoxin (**36**) proceeded in the same way as with the t-BOC analogue. The overall yield for this transformation was 81%. Sodium borohydride reduction of enone **36** in the presence of Ce(III)[12] provided a 45/55 mixture of the CBZ-anatoxinols **37** and **38** in 99% combined yield. The stereochemical assignment at the carbinol center was established by 2D NOE experiments.[14] In both alcohols **37** and **38** the side chain is locked in one conformation due to a strong intramolecular hydrogen bond between the allylic alcohol and the carbamate carbonyl (OH stretch 3380 cm^{-1} for **37**, 3400 cm^{-1} for **38**). This plus the observation of an NOE between H3 (δ 5.6 and 5.7 ppm)–CH_3 (H11, δ 1.17 and 1.28 ppm) and H1 (δ 4.44 and 4.53 ppm)–H10 (δ 4.18 and 4.21) for the more polar epimer and between H3 (δ 5.53 and 5.6 ppm)–H10 (δ 4.14 and 4.22 ppm) and H1 (δ 4.58 ppm)–CH_3 (H11, δ 1.15 and 1.21 ppm) for the less polar epimer established the 10*S* configuration for **37** (more polar epimer) and 10*R* for **38** (less polar epimer).

Scheme III



Hydrogenolysis of **37** or **38** failed to give the desired anatoxinols **5** and **6**; double-bond reduction was a serious competing process. Nucleophilic conditions to achieve this deprotection were then tried.[15] *n*-Butyllithium (at −78 °C or 0 °C) did cleave the carbamate group but also led to double-bond isomerization. Since this side reaction was undoubtedly due to the strong basicity of *n*-butyllithium, we turned to the less basic 2-lithiofuran.[15b] Reaction of the CBZ-anatoxinols (**37** and **38**) with 2-lithiofuran at 0 °C cleanly cleaved the benzyl carbamate and afforded the anatoxinols (**5** and **6**) in 93% and 100% crude yields, respectively. Anatoxinol **5** was converted to its crystalline hydrogen fumarate while anatoxinol **6** afforded an amorphous hydrogen fumarate hydrate. The tertiary anatoxinol **7** was obtained by treatment of CBZ-anatoxin (**36**) with CH_3Li to give tertiary alcohol **39** in 79% yield (91% yield based on consumed **36**), and treatment of **39** with 2-lithiofuran cleaved the benzyl carbamate and gave the desired tertiary anatoxinol **7** in quantitative yield.

The syntheses of the *N*-methylanatoxinols **8**, **9**, and **10** were achieved by hydride reduction of the carbamate protecting group of **37**, **38**, and **39**. When $LiAlH_4$ was used in refluxing THF, the desired products **8**, **9**, and **10** were contaminated with up to 20% of a byproduct with the general structure **40**. Since this side reaction was most probably caused by the combination of the high nucleophilicity and strong Lewis acid character of $LiAlH_4$, we sought a hydride reagent with diminished Lewis acid character. Thus with sodium bis(2-methoxyethoxy)aluminum hydride, the desired *N*-methylanatoxinols **8**, **9**, and **10** were obtained free of byproduct **40** in 90% yield.

Baeyer–Villiger oxidation[16] of **33** afforded the acetate **41** in 82% yield. Deprotection and N-methylation were carried out essentially in one operation in quantitative yield by hydrogenolysis of **41** in methanol/acetic acid for 1 h; then excess aqueous formaldehyde was added, and the hydrogenation was continued for 16 h. The crude (2*S*)-*N*-methyl acetate **11** was pure by NMR and TLC analyses

(11) Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829 and references therein.
(12) (a) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (b) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (c) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(13) Greene, T. W. *Protecting Groups in Organic Synthesis*; Wiley: New York, 1981; pp 239–241.
(14) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon: Oxford, 1987; pp 239–244.
(15) (a) Scilly, N. F. *Synthesis* **1973**, 160. (b) Michael, U.; Hornfeldt, A.-B. *Tetrahedron Lett.* **1970**, 5219.
(16) Emmons, W. D.; Lucas, G. B. *J. Am. Chem. Soc.* **1955**, *77*, 2287.

and was crystallized as its hydrogen fumarate. Treatment of crude **11** with excess CH_3I in acetone gave the methiodide **13** in 70% yield. In a parallel fashion Baeyer–Villiger oxidation of **34** gave **42** in 95% yield. No cross-contamination was observed on the ^1H NMR spectra of crude **41** and **42**, thus demonstrating that the Baeyer–Villiger reactions had proceeded completely stereospecifically. Hydrogenolysis/N-methylation of **42** gave a quantitative yield of **12** which upon treatment with CH_3I gave **14** in 75% yield (Scheme III).

Summary

The chirospecific synthesis of (+)-anatoxin (>99% ee) has been considerably improved to where it proceeds from D-glumatic acid in 25% overall yield. Efficient and convenient synthetic entries to a number of nitrogen and side chain modified anatoxin analogues have been developed. The neuropharmacological activities of these analogues are currently being evaluated, and the detailed results will be published elsewhere.

Experimental Section

General Methods. Reactions were run under a dry nitrogen atmosphere except when noted otherwise. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone; CH_2Cl_2, 1,2-dichloroethane (1,2-DCE), toluene, and CH_3CN were distilled from CaH_2; CH_3OH was distilled from $Mg(OCH_3)_2$. Benzyl bromide and oxalyl chloride were distilled prior to use. Melting points (Büchi apparatus, open capillary) are uncorrected. NMR spectra were recorded in $CDCl_3$ or D_2O; chemical shifts are reported in parts per million (δ) downfield from Me_4Si (^1H, $CDCl_3$), sodium 3-(trimethylsilyl)-1-propanesulfonate (^1H, D_2O). All evaporations were done in vacuo using a rotary evaporator.

(2*R*)-*cis*-5-[4-(2-Methyl-1,3-dioxolan-2-yl)butyl]proline *tert*-Butyl Ester (18). Ammonium formate (21.9 g, 336 mmol) and 10% Pd/C (6.3 g) were added (in that order) to a degassed (Ar) solution of **17** (18.0 g, 34 mmol)[2k] in methanol (700 mL). The mixture was immersed in a bath at 95–100 °C and vigorously stirred for 25 min, then it was allowed to cool under a stream of Ar and filtered. The precipitate was washed with CH_2Cl_2 (100 mL) and CH_3OH (100 mL), and from the combined filtrate and washings was isolated, as described,[2k] crude **18** (10.2 g, 97% yield), which was directly used in the next step.

(2*R*)-*cis*-1-Benzyl-5-[4-(2-methyl-1,3-dioxolan-2-yl)butyl]proline *tert*-butyl ester (19) was prepared as described.[2k] Purification of the resulting pale yellow oil by flash chromatography[17] (SiO_2, 1/5, EtOAc/hexanes) gave pure **17** (11.2 g, 83% yield for the two steps).

(2*R*)-*cis*-1-Benzyl-5-(5-oxohexyl)proline (20) was prepared as reported.[2k]

(1*R*)-2-Acetyl-9-benzyl-9-azabicyclo[4.2.1]nonane (22 and 23). A solution of keto acid **20** (6.52 g, 21 mmol) in 1,2-DCE (100 mL) was added to a cold (−10 °C) solution of oxalyl chloride (3.68 g, 2.53 mL, 29 mmol) in 1,2-DCE (200 mL) at a rate of 1.4 mL/min. After the addition was completed, the yellow solution was stirred for 3 h (−10 °C to −5 °C), toluene (400 mL) was added, and the solution was immersed in a preheated bath (60 °C) and stirred overnight in an Ar atmosphere. The mixture was allowed to cool and then washed with saturated $NaHCO_3$, and the aqueous washings were extracted with 3 × 50 mL of CH_2Cl_2. The combined organic phase was washed with brine, dried, filtered, and evaporated to give a brown oil. Purification by column chromatography (SiO_2, 1/4, EtOAc/hexanes) gave a 2/1 mixture of **22** and **23** (3.66 g, 66% yield) as a clear oil.

(1*R*)-2-Acetyl-9-(*tert*-butoxycarbonyl)-9-azabicyclo[4.2.1]nonane (24 and 25). Di-*tert*-butyl dicarbonate (7.76 g, 35.5 mmol) was added to a solution of **22** and **23** (3.66 g, 14.2 mmol) in CH_3OH (140 mL) followed by 10% Pd/C (0.73 g), and the resulting suspension was hydrogenated at 50 psig for 2 h. The catalyst was filtered off and thoroughly washed with CH_3OH, and the combined filtrates were evaporated. The residue was diluted with Et_2O, washed with saturated $NaHCO_3$ and brine, dried, and evaporated, leaving a pale oil that was column chromatographed (SiO_2, 1/4, EtOAc/hexanes) to give a mixture of **24** and **25** (3.64 g, 95% yield).

(1*R*,2*R*)- and (1*R*,2*S*)-9-(*tert*-Butoxycarbonyl)-2-((*Z*)-1-(dimethyl-*tert*-butylsiloxy)ethylidene)-9-azabicyclo[4.2.1]nonane (27). A suspension of NaH (856 mg, 37% oil dispersion, 13.2 mmol) was washed with THF (2 × 4 mL), and the washed NaH powder was suspended in THF (10 mL). A solution of ketones **24** and **25** (1.17 g, 4.4 mmol) in THF (5 mL, plus 2 × 2-mL rinses) containing a trace of CH_3OH (20 μL) was added. The resulting suspension was stirred for 7 h and then cooled to −15 °C, and a centrifuged solution of TBDMSCl (1.99 g, 13.19 mmol) and Et_3N (0.5 mL) in THF (4 mL) was added. The resulting solution was stirred at room temperature overnight, poured into 1 M KH_2PO_4, and extracted with 3 × 100 mL of CH_2Cl_2. The combined organic phase was dried, filtered, and evaporated. Purification of the residue by column chromatography (SiO_2, 1/9, EtOAc/hexanes) gave pure **27** as a clear viscous oil (1.64 g, 98% yield): ^1H NMR ($CDCl_3$) (two rotamers) δ 0.04, 0.09, 0.10, and 0.13 (s, 6 H, Me_2Si), 0.89 and 0.90 (s, 9 H, t-BuSi), 1.2–2.1 (m, 9 H), 1.38 and 1.42 (s, 9 H, t-BuO), 1.77 (s, 3 H, CH_3-11), 2.25 (dd, J = 14.7, 7.0 Hz, 1 H, H-3), 4.20 and 4.31 (m, 1 H, H-6), 4.82 and 4.87 (d, J = 8.4 Hz, 1 H, H-1). Anal. Calcd for $C_{21}H_{39}NO_3Si$: C, 66.1; H, 10.3; N, 3.7. Found: C, 66.2; H, 10.3; N, 3.7.

The double-bond geometry of (*Z*)-**27** was deduced from the presence of an NOE at H3 (δ 2.25) when the proton resonance for the enol ether CH_3 (H11, δ 1.77) was irradiated.

(1*R*)-2-Acetyl-9-(*tert*-butoxycarbonyl)-9-azabicyclo[4.2.1]-2-nonene (26). A solution of PhSeCl (945 mg, 4.94 mmol) in THF (7 mL) was slowly added to a cold (−78 °C) solution of silyl enol ether **27** (1.63 g, 4.3 mmol) in THF (20 mL). The resulting solution was stirred at −78 °C for 2 h and then warmed to 0 °C, and mCPBA (2.18 g, 10.74 mmol) was added in portions over 5 min. The resulting solution was stirred at 0 °C for 30 min, poured onto 10% Na_2CO_3 (15 mL), and extracted with 3 × 50 mL of CH_2Cl_2. The organic phase was dried, filtered, and evaporated. Purification of the residue by column chromatography (SiO_2, 2/3, EtOAc/hexanes) gave pure **26** (959 mg, 84% yield).

Anatoxin (1) was prepared as reported.[2k,l] A solution of **1** (crude from the deprotection reaction) in i-PrOH (1-2 mL per 100 mg of **1**) was added to a hot solution of fumaric acid (100 mol %) in i-PrOH (1–2 mL). The resulting solution was allowed to cool to room temperature and then was stored in the freezer. The crystalline **1** hydrogen fumarate (70–80% yield) was filtered, washed with ether, and dried under high vacuum at room temperature: mp 126–127 °C; ^1H NMR (D_2O) δ 1.7–2.5 (m, 6 H), 2.37 (s, 3 H, CH_3-11), 2.63 (m, 2 H), 4.31 (m, 1 H, H-6), 5.05 (d, J = 9.3 Hz, 1 H, H-1), 6.68 (s, 2 H, vinylic), 7.49 (dd, J = 8.4, 3.9 Hz, 1 H, H-3). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.8; N, 5.0. Found: C, 59.6; H, 7.1; N, 4.8.

9-[((*R*)-α-Methylbenzyl)carbamoyl]anatoxin (30a). (*R*)-α-Methylbenzyl isocyanate (21 mg, 0.145 mmol) was added to a cold (0 °C) solution of **1** (12 mg, 0.073 mmol) in THF (1 mL) and stirred at room temperature for 16 h. Volatiles were removed under high vacuum to give crude **30a** (22 mg, 97% yield), which was directly used for optical purity studies: ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 7.0 Hz, 3 H), 1.4–2.5 (m, 8 H), 2.23 (s, 3 H), 4.65 (m, 1 H), 4.79 (m, 1 H), 5.00 (d, J = 9.7 Hz, 1 H), 5.48 (m, 1 H), 6.91 (m, 1 H), 7.1–7.4 (m, 5 H).

9-[((*S*)-α-Methylbenzyl)carbamoyl]anatoxin (30b) was prepared as above: ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 7.0 Hz, 3 H), 1.3–2.6 (m, 8 H), 2.36 (s, 3 H), 4.62 (m, 1 H), 4.84 (m, 1 H), 4.96 (d, J = 9.6 Hz, 1 H), 5.67 (br d, J = 7.1 Hz, 1 H), 6.99 (m, 1 H), 7.1–7.4 (m, 5 H).

***N*-Methylanatoxin (3).** Formaldehyde (68 mg, 37% in H_2O, 0.87 mmol) was added to a cold (0 °C) solution of crude **1** (111 mg, 0.67 mmol) in HCO_2H (95%, 1 mL). The resulting solution was stirred at 0 °C for 20 min and then at 95 °C for 2 h. It was then allowed to cool to room temperature, poured into 10 mL of saturated $NaHCO_3$, adjusted to pH 9 with 2 M NaOH, and extracted with 3 × 10 mL of $CHCl_3$. The organic extracts were dried, filtered, and concentrated to give **3** as a light brown oil (111 mg, 93% yield, pure by NMR): ^1H NMR ($CDCl_3$) δ 1.2–2.5 (m, 8 H), 2.29 (s, 3 H, CH_3-11), 2.31 (s, 3 H, N-CH_3), 3.42 (m, 1 H, H-6), 4.45 (br d, J = 9.0 Hz, 1 H, H-1), 6.94 (m, 1 H, H-3). Due to the

(17) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

inherent instability of **3** the hydrochloride of **3** was prepared immediately following distillation (Kugelrohr, bp 130 °C, 0.1 mmHg) of the free base (excess HCl/CH_3OH). Excess acid was removed under high vacuum, leaving the hydrochloride monohydrate of **3**: ^1H NMR (D_2O) δ 1.8–2.7 (m, 8 H), 2.37 and 2.39 (s, 3 H, CH_3-11), 2.69 and 2.88 (s, 3 H, N-CH_3), 4.11 (br s, 1 H, H-6), 5.00 (m, 1 H, H-1), 7.51 and 7.62 (d, J = 8.8 Hz, 1 H, H-3). Anal. Calcd for $C_{11}H_{18}NOCl\cdot H_2O$: C, 56.5; H, 8.6; N, 6.0. Found: C, 56.9; H, 8.6; N, 5.9.

***N*-Methylanatoxin Methiodide (4).** Excess CH_3I was added to crude **3** (49 mg, 0.27 mmol) in deoxygenated acetone (1 mL). The resulting solution was stirred overnight. Then ether (5 mL) was added, and the solid was collected by filtration and dried under high vacuum to give pure **4** (70 mg, 80% yield): mp 186–187 °C dec; ^1H NMR (D_2O) δ 1.87 (m, 1 H), 2.24 (m, 3 H), 2.39 (s, 3 H, CH_3-11), 2.63 (m, 2 H), 2.76 (m, 2 H), 2.98 (s, 3 H, N-CH_3), 3.22 (s, 3 H, N-CH_3), 4.08 (br s, 1 H, H-6), 4.94 (dq, J = 9.5, 1.5 Hz, 1 H, H-1), 7.62 (ddd, J = 9.1, 3.2, 1.4 Hz, 1 H, H-3). Anal. Calcd for $C_{12}H_{20}INO$: C, 44.9; H, 6.3; N, 4.4. Found: C, 44.7; H, 6.1; N, 4.2.

(1*R*,10*S*)- and (1*R*,10*R*)-9-(*tert*-Butoxycarbonyl)-2-(1-hydroxyethyl)-9-azabicyclo[4.2.1]-2-nonene (31 and 32). Sodium borohydride (15 mg, 0.40 mmol) was added to BOC-anatoxin (**26**, 100 mg, 0.37 mmol) and $CeCl_3\cdot 4.73H_2O$ (125 mg, 0.4 mmol) in CH_3OH (5 mL). The resulting mixture was stirred at room temperature for 20 min, diluted with 0.5 M phosphate pH 7 buffer (5 mL), and extracted with 3 × 20 mL of CH_2Cl_2. The organic extracts were dried, filtered, and evaporated to a clear oil. Purification by flash chromatography (1/4, EtOAc/hexanes) gave pure **31** (less polar) (40 mg, 40%) and **32** (more polar) (57 mg, 57%) as white crystalline solids.

31: mp 80–80.5 °C; $[\alpha]^{22}_D$ +142.3° (*c* 0.69, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.19 (d, J = 6.5 Hz, 3 H, CH_3-11), 1.44 (s, 9 H, t-Bu), 1.6 (m, 1 H), 1.6–1.9 (m, 3 H), 2.05–2.5 (m, 4 H), 4.17 (q, J = 6.5 Hz, 1 H, H-10), 4.32 (ddd, J = 8.0, 3.2, 3.2 Hz, 1 H, H-6), 4.48 (ddd, J = 9.6, 1.6, 1.6 Hz, 1 H, H-1), 5.0 (br s, 1 H, OH), 5.57 (m, 1 H, H-3). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.4; H, 9.4; N, 5.2. Found: C, 67.2; H, 9.5; N, 5.2.

32: mp 98.5–99 °C; $[\alpha]^{22}_D$ +116.0° (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 6.5 Hz, 3 H, CH_3-11), 1.44 (s, 9 H, t-Bu), 1.5–2.5 (m, 9 H), 4.20 (dq, J = 6.5, 2.2 Hz, 1 H, H-10), 4.40 (m, 2 H, H-1 and H-6), 5.65 (m, 1 H, H-3). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.4; H, 9.4; N, 5.2. Found: C, 67.3; H, 9.5; N, 5.2.

The stereochemistry at C10 was established by 2D NOE experiments[14] as 10*S* for **31** and 10*R* for **32**.

(1*R*,2*S*)- and (1*R*,2*R*)-2-Acetyl-9-(benzyloxycarbonyl)-9-azabicyclo[4.2.1]nonane (33 and 34). To a solution of **22** and **23** (840 mg, 3.27 mmol) in CH_3OH (30 mL) was added 10% Pd/C (170 mg) and concentrated HCl (0.5 mL). The resulting suspension was hydrogenated at 50 psig for 15 h, and then the catalyst was filtered off and washed with 3 × 5 mL of CH_3OH. The combined filtrate and washings were adjusted to pH 9 by addition of 2 M NaOH, calcined K_2CO_3 (1.66 g, 12.0 mmol) and CBZ-Cl (1.67 g, 1.40 mL, 9.81 mmol) were added, and the resulting suspension was stirred at room temperature for 1 h, diluted with H_2O (50 mL), and extracted with 3 × 100 mL of CH_2Cl_2. The organic extracts were dried, filtered, and evaporated, followed by treatment under high vacuum (0.01 mmHg, 45 °C). The resulting clear brown oil was purified by flash chromatography (SiO_2, 1/4, EtOAc/hexanes) to give pure **33** (more polar, 728 mg, 74%) and **34** (less polar, 182 mg, 18%) as clear viscous oils.

33: $[\alpha]^{22}_D$ −11.5° (*c* 1.05, CH_3OH); ^1H NMR ($CDCl_3$, two rotamers) δ 1.4–2.5 (m, 10 H), 1.96 and 2.30 (s, 3 H, CH_3-11), 4.39 (m, 1 H), 4.57 and 4.67 (d, J = 9.2 Hz, 1 H), 4.86 and 5.14 (d, J = 12.0 Hz) and 5.11 (s) (2 H, benzylic), 7.25–7.35 (m, 5 H). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7; N, 4.6. Found: C, 71.8; H, 7.7; N, 4.6.

34: $[\alpha]^{22}_D$ −75.6° (*c* 0.86, CH_3OH); ^1H NMR ($CDCl_3$) (two rotamers) δ 1.2–2.4 (m, 10 H), 2.10 and 2.18 (s, 3 H, CH_3-11), 2.93 and 3.17 (ddd, J = 8.5, 4.2, 4.2 Hz, 1 H, H-2), 4.35 (m, 1 H, H-1), 4.67 (m, 1 H, H-6), 5.15 (m, 2 H, benzylic), 7.25–7.45 (br s, 5 H). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7; N, 4.6. Found: C, 71.6; H, 7.7; N, 4.6.

(1*R*)-9-(Benzyloxycarbonyl)-2-((*Z*)-1-((dimethyl-*tert*-butylsilyl)oxy)ethylidene)-9-azabicyclo[4.2.1]nonane (35) was prepared from **33** and **34** (767 mg, 2.55 mmol) in the same way as was **27**. Purification by column chromatography (SiO_2, 1/13, EtOAc/hexanes) gave **35** (1.01 g, 95% yield) as a clear oil: $[\alpha]^{22}_D$ −44.4° (*c* 0.88, CH_3OH); ^1H NMR ($CDCl_3$) δ 0.10–0.20 (m, 6 H, Me_2Si), 0.90–0.95 (m, 9 H, t-BuSi), 1.2–2.4 (m, 10 H), 1.80 and 1.82 (s, 3 H, CH_3-11), 4.46 (m, 1 H, H-6), 5.03 (m, 1 H, H-1), 5.11 (m, 2 H, benzylic), 7.25–7.35 (m, 5 H). Anal. Calcd for $C_{24}H_{37}NO_3Si$: C, 69.3; H, 9.0; N, 3.4. Found: C, 69.2; H, 8.7; N, 3.3.

(1*R*)-2-Acetyl-9-(benzyloxycarbonyl)-9-azabicyclo-[4.2.1]-2-nonene (36) was prepared from **35** (1.01 g, 2.43 mmol) in the same way as was **26**. Purification by column chromatography (3/7, EtOAc/hexanes) gave **36** (618 mg, 85% yield) as a clear oil: $[\alpha]^{22}_D$ −37.5° (C 1.12, CH_3OH); ^1H NMR ($CDCl_3$) (two rotamers) δ 1.6–1.8 (m, 3 H), 2.0–2.5 (m, 5 H), 2.17 and 2.30 (s, 3 H, CH_3-11), 4.51 (m, 1 H, H-6), 5.02 and 5.15 (d, J = 12.6 Hz) and 5.11 (s) (2 H, benzylic), 5.28 (d, J = 8.7 Hz, 1 H, H-1), 6.79 (t, J = 5.7 Hz, 1 H, H-3), 7.2–7.5 (m, 5 H). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.1; N, 4.7. Found: C, 72.1; H, 7.0; N, 4.7.

(1*R*,10*S*)- and (1*R*,10*R*)-9-(benzyloxycarbonyl)-2-(1-hydroxyethyl)-9-azabicyclo[4.2.1]-2-nonene (37 and 38) were prepared from **36** (719 mg, 2.41 mmol) in the same way as were **31** and **32**. Purification by flash chromatography (SiO_2, 1/4, EtOAc/hexanes) gave pure **37** (more polar, 305 mg, 42% yield) as a clear oil and **38** (less polar, 415 mg, 57% yield) as a clear oil which crystallized on standing.

37: $[\alpha]^{22}_D$ +52.5° (*c* 1.34, CH_3OH); ^1H NMR ($CDCl_3$) (two rotamers) δ 1.17 and 1.28 (d, J = 6.3 Hz, 3 H, CH_3-11), 1.5–2.5 (m, 10 H), 4.18 and 4.21 (q, J = 6.3 Hz, 1 H, H-10), 4.44 and 4.53 (m, 2 H, H-1 and H-6), 5.12 (s) and 5.08 and 5.18 (d, J = 12.4 Hz, 2 H, benzylic), 5.60 and 5.70 (m, 1 H, H-3), 7.35 (br s, 5 H). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7; N, 4.6. Found: C, 71.9; H, 7.9; N, 4.6.

38: mp 79.5–80 °C; $[\alpha]^{22}_D$ +61.7° (*c* 1.75, CH_3OH); ^1H NMR ($CDCl_3$, two rotamers) δ 1.15 and 1.21 (d, J = 6.5 Hz, 3 H, CH_3-11), 1.55 (m, 1 H), 1.65–2.00 (m, 4 H), 2.05–2.50 (m, 5 H), 4.14 and 4.22 (q, J = 6.4 Hz, 1 H, H-10), 4.45 and 4.55 (ddd, J = 8.0, 3.1, 3.1 Hz, 1 H, H-6), 4.58 (br d, J = 11.8 Hz, 1 H, H-1), 4.68 (d, J = 2.7 Hz, 1 H, OH), 5.09 (d, J = 12.4 Hz, 1 H, benzylic), 5.18 (d, J = 12.4 Hz, 1 H, benzylic), 5.53 and 5.60 (br d, J = 8.0 Hz, 1 H, H-3), 7.35 (m, 5 H). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.7; N, 4.6. Found: C, 71.8; H, 7.8; N, 4.6.

(1*R*)-9-(Benzyloxycarbonyl)-2-(1-hydroxy-1-methylethyl)-9-azabicyclo[4.2.1]-2-nonene (39). Methyllithium (0.44 mL, 1.5 M in ether, 0.67 mmol) was added to a cold (−78 °C) solution of **36** (153 mg, 0.51 mmol) in THF (5 mL), stirred at −78 °C for 12 min, and then quenched with 20 mL of 1 M KH_2PO_4. The resulting suspension, after warming to room temperature, was extracted with 3 × 20 mL of CH_2Cl_2. The organic extracts were dried, filtered, and evaporated. Purification by flash chromatography (SiO_2, 3/7, EtOAc/hexanes) gave pure **39** (128 mg, 79% yield, 91% based on consumed **36**) as a clear oil and recovered **36** (20 mg). **39**: $[\alpha]^{22}_D$ +61.3° (*c* 1.19, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.24 (s, 3 H, CH_3-11), 1.36 (s, 3 H, CH_3-12), 1.5–2.5 (m, 8 H), 4.43 (m, 1 H, H-6), 4.79 (ddd, J = 9.8, 1.9, 1.8 Hz, 1 H, H-1), 5.09 (d, J = 12.5 Hz, 1 H, benzylic), 5.14 (d, J = 12.5 Hz, 1 H, benzylic), 5.65 (m, 1 H, H-3), 7.33 (br s, 5 H). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.3; H, 8.0; N, 4.4. Found: C, 72.5; H, 8.1; N, 4.2.

(1*R*,10*S*)-2-(1-Hydroxyethyl)-9-azabicyclo[4.2.1]-2-nonene (5). *n*-Butyllithium (13.4 mL, 1.65 M solution in hexanes, 22.1 mmol) was added to a cold (−10 °C) solution of furan (distilled from sodium under N_2, 1.67 g, 1.79 mL, 24.6 mmol) in ether (20 mL). The resulting solution was refluxed for 2.5 h, the resulting yellow suspension was cooled to −15 °C, and then a solution of **37** (296 mg, 0.98 mmol) in ether (5 mL plus of 2 × 2-mL rinses) was added. The resulting suspension was stirred overnight, allowing the temperature to rise to 20 °C, after which it was quenched with 25 mL of 1 M H_3PO_4. The layers were separated, and the organic layer was extracted with 3 × 25 mL of 1 M H_3PO_4. The combined aqueous layer was washed with ether, adjusted to pH 11 with 40% KOH, and extracted with 3 × 100 mL of $CHCl_3$. Drying, filtering, and evaporating left **5** (146 mg, 93%) as an orange oil (pure by NMR): ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 6.4 Hz, 3 H, CH_3-11), 1.7–2.3 (m, 8 H), 3.65 (m, 1 H, H-6), 3.70 (d, J = 9.1 Hz, 1 H, H-1), 4.09 (q, J = 6.4 Hz, 1 H, H-10), 5.53 (dd, J = 7.9,

3.2 Hz, 1 H, H-3). **5** hydrogen fumarate: mp 148–150 °C; ^{1}H NMR (D_2O) δ 1.26 (d, J = 6.6 Hz, 3 H, CH_3-11), 1.83 (m, 2 H), 2.12 (m, 3 H), 2.35 (m, 1 H), 2.46 (m, 2 H), 4.28 (m, 1 H, H-6), 4.29 (d, J = 9.0 Hz, 1 H, H-1), 4.32 (q, J = 6.5 Hz, 1 H, H-10), 6.00 (dd, J = 5.7, 1.0 Hz, 1 H, H-3), 6.67 (s, 2 H, vinylic). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.3; H, 7.5; N, 4.9. Found: C, 59.2; H, 7.5; N, 4.9.

(1*R*,10*R*)-2-(1-Hydroxyethyl)-9-azabicyclo[4.2.1]-2-nonene (6) was prepared from **38** (405 mg, 1.35 mmol) in the same way as was **5**. Crude **6** was obtained in a quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.4 Hz, 3 H, CH_3-11), 1.56 (m, 2 H), 1.69 (m, 2 H), 1.90 (m, 1 H), 2.05 (m, 3 H), 3.72 (m, 1 H, H-6), 3.93 (d, J = 9.0 Hz, 1 H, H-1), 4.12 (q, J = 6.4 Hz, 1 H, H-10), 5.50 (dd, J = 7.9, 3.0 Hz, 1 H, H-3). By adding 100 mol % of fumaric acid to base **6** in i-PrOH the hydrogen fumarate was obtained: ^{1}H NMR (D_2O) δ 1.23 (d, J = 6.5 Hz, 3 H, CH_3-11), 1.83 (m, 2 H), 2.05 (m, 2 H), 2.11 (m, 1 H), 2.43 (m, 3 H), 4.29 (m, 3 H, H-1, H-6, and H-10), 6.00 (dd, J = 6.1, 1.0 Hz, 1 H, H-3), 6.67 (s, 2 H, vinylic). Anal. Calcd for $C_{14}H_{21}NO_5 \cdot {}^1/_4H_2O$: C, 58.4; H, 7.5; N, 4.9. Found: C, 58.6; H, 7.5; N, 4.9.

(1*R*)-2-(1-Hydroxy-1-methylethyl)-9-azabicyclo[4.2.1]-2-nonene (7) was prepared from **39** (128 mg, 0.41 mmol) in the same way as was **5**. Crude **7** was obtained in quantitative yield: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3 H, CH_3-11), 1.28 (s, 3 H, CH_3-12), 1.8–2.4 (m, 8 H), 3.69 (m, 1 H, H-6), 4.07 (d, J = 9.1 Hz, 1 H, H-1), 5.63 (ddd, J = 8.0, 3.6, 1.6 Hz, 1 H, H-3). The hydrogen fumarate was obtained as described above: mp 183–184 °C (i-PrOH/Et_2O); ^{1}H NMR (D_2O) δ 1.33 (s, 3 H, CH_3-11), 1.35 (s, 3 H, CH_3-12), 1.82 (m, 2 H), 2.16 (m, 3 H), 2.24 (m, 3 H), 4.27 (m, 1 H, H-6), 4.46 (d, J = 9.7 Hz, 1 H, H-1), 6.09 (d, J = 8.6 Hz, 1 H, H-3), 6.67 (s, 2 H, vinylic). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.8; H, 7.9; N, 4.8.

(1*R*,10*S*)-2-(1-Hydroxyethyl)-9-methyl-9-azabicyclo-[4.2.1]-2-nonene (8). Sodium bis(2-methoxyethoxy)aluminum hydride (1.07 mL, 3.4 M in toluene, 3.65 mmol) was added to a cold (0 °C) solution of **37** (109 mg, 0.37 mmol) in THF (5 mL). The resulting solution was refluxed for 2 h and then cooled to 0 °C. EtOAc (1 mL) was added followed by 10% Na_2CO_3 (0.2 mL), $CHCl_3$ (10 mL), KH_2PO_4 (0.3 g), and anhydrous Na_2SO_4 (0.3 g). The resulting suspension was stirred at room temperature for 1 h and then filtered. The precipitate was washed thoroughly with $CHCl_3$, the combined, clear filtrate and washings were evaporated, and the residue was taken up in 10 mL of ether and extracted with 3 × 10 mL of 2% HCl. The aqueous extracts were washed with ether, adjusted to pH 11 with 10% NaOH, and extracted with 3 × 15 mL of $CHCl_3$. The organic extracts were dried, filtered and evaporated to give **8** (pure by NMR, 59 mg, 90% yield) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.5 Hz, 3 H, CH_3-11), 1.15–1.30 (m, 1 H), 1.45–1.95 (m, 4 H), 2.0–2.6 (m, 4 H), 2.33 (s, 3 H, N-CH_3), 3.40 (m, 1 H, H-6), 3.54 (br d, J = 9.0 Hz, 1 H, H-1), 4.14 (q, J = 6.5 Hz, 1 H, H-9), 5.64 (m, 1 H, H-3). The fumarate was prepared as described above: mp 191–192 °C; ^{1}H NMR (D_2O) (two epimers at N-9) δ 1.24 and 1.26 (d, J = 6.4 Hz, 3 H, CH_3-11), 1.87 (m, 2 H), 2.16 (m, 2 H), 2.32 (m, 1 H), 2.48 (m, 2 H), 2.63 (m, 1 H), 2.80 and 2.88 (s, 3 H, N-CH_3), 4.06 and 4.20 (m, 2 H, H-1 and H-6), 4.31 (q, J = 6.4 Hz, 1 H, H-10), 6.05 and 6.15 (m, 1 H, H-3), 6.51 (s, 1 H, vinylic). Anal. Calcd for $C_{26}H_{42}N_2O_6$: C, 65.2; H, 8.9; N, 5.8. Found: C, 65.1; H, 8.8; N, 5.9.

(1*R*,10*R*)-2-(1-Hydroxyethyl)-9-methyl-9-azabicyclo-[4.2.1]-2-nonene (9) was prepared from **38** (141 mg, 0.468 mmol) in the same way as was **8**. Crude **9** (pure by NMR) was obtained in 90% yield: ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.5 Hz, 3 H, CH_3-11), 1.2–1.4 (m, 2 H), 1.55–1.90 (m, 3 H), 1.95–2.45 (m, 3 H), 2.32 (s, 3 H, N-CH_3), 3.35 (m, 2 H, H-6 and OH), 3.61 (d, J = 9.0 Hz, 1 H, H-1), 4.12 (q, J = 6.5 Hz, 1 H, H-10), 5.56 (m, 1 H, H-3). The fumarate was prepared as described above: mp 130–131 °C (i-PrOH/Et_2O); ^{1}H NMR (D_2O) (two epimers at N-9) δ 1.21 (d, J = 6.5 Hz, 3 H, CH_3-11), 1.9–2.8 (m, 8 H), 2.79 and 2.87 (s, 3 H, N-CH_3), 4.07 (m, 2 H, H-1 and H-6), 4.29 (q, J = 6.5 Hz, 1 H, H-10), 6.02 (m, 1 H, H-3), 6.67 (s, 2 H, vinylic). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.7; N, 8.0; N, 4.6.

(1*R*)-2-(1-Hydroxy-1-methylethyl)-9-methyl-9-azabicyclo[4.2.1]-2-nonene (10) was prepared from **39** (151 mg, 0.479 mmol) in the same way as was **8**. Crude **10** (pure by NMR) was obtained in 90% yield as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3 H, CH_3-11), 1.29 (s, 3 H, CH_3-12), 1.2–2.4 (m, 8 H), 2.28 (s, 3 H, N-CH_3), 3.32 (m, 1 H, H-6), 3.73 (d, J = 9.0 Hz, 1 H, H-1), 5.72 (m, 1 H, H-3). The hydrogen fumarate melted at 128–130 °C (i-PrOH/Et_2O): ^{1}H NMR (D_2O) (two epimers at N-9) δ 1.31 and 1.32 (s, 3 H, CH_3-11), 1.34 and 1.35 (s, 3 H, CH_3-12), 1.86 (m, 2 H), 2.17 (m, 2 H), 2.38 (m, 1 H), 2.43 (m, 2 H), 2.69 (m, 1 H), 2.79 and 2.87 (s, 3 H, N-CH_3), 4.06 (m, 1 H, H-6), 4.27 and 4.45 (d, J = 9.0 Hz, 1 H, H-1), 6.12 and 6.20 (m, 1 H, H-3), 6.68 (s, 2 H, vinylic). Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.7; H, 8.1; N, 4.5. Found: C, 61.4; H, 8.0; N, 4.4.

(1*R*,2*S*)-2-Acetoxy-9-(benzyloxycarbonyl)-9-azabicyclo-[4.2.1]nonane (41). Trifluoroacetic anhydride (375 mg, 1.78 mmol) was added to a cold (0 °C) suspension of H_2O_2 (51 mg, 70% solution in H_2O, 1.19 mmol) in CH_2Cl_2 (1 mL). The resulting solution was stirred for 5 min at 0 °C, and then Na_2HPO_4 (253 mg, 1.78 mmol) was added followed by a solution of **33** (179 mg, 0.595 mmol) in CH_2Cl_2 (1 mL plus 2 × 1-mL rinses). The resulting suspension was stirred at room temperature overnight, poured into 10 mL of saturated $NaHCO_3$, and extracted with 3 × 10 mL of CH_2Cl_2. The organic extracts were dried, filtered, and evaporated, and the residue was column chromatographed (SiO_2, 1/5, EtOAc/hexanes) to give pure **41** (179 mg, 95% yield) as a clear oil: $[\alpha]^{22}_D$ −70.8° (*c* 0.90, CH_3OH); ^{1}H NMR ($CDCl_3$) (two rotamers) δ 1.4–2.3 (m, 10 H), 1.67 and 2.05 (s, 3 H, CH_3CO), 4.51 (m, 2 H, H-1 and H-6), 4.71 (m, 1 H, H-2), 5.13 (m, 2 H, benzylic), 7.35 (m, 5 H). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3; N, 4.4. Found: C, 67.9; H, 7.2; N, 4.4.

(1*R*,2*R*)-2-Acetoxy-9-(benzyloxycarbonyl)-9-azabicyclo-[4.2.1]nonane (42) was prepared from **34** (242 mg, 0.803 mmol) in the same way as was **41**. Purification by column chromatography (SiO_2, 1/5, EtOAc/hexanes) gave pure **42** (208 mg, 82% yield) as a clear oil: $[\alpha]^{22}_D$ −50.8° (*c* 0.48, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.25–2.4 (m, 10 H), 2.04 (s, 3 H, CH_3CO), 4.40 (m, 2 H, H-1 and H-6), 5.10 (m, 1 H, H-2), 5.17 (m, 2 H, benzylic), 7.35 (m, 5 H). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3; N, 4.4. Found: C, 68.3; H, 7.2; N, 4.3.

(1*R*,2*S*)-2-Acetoxy-9-methyl-9-azabicyclo[4.2.1]nonane (11). To a solution of **41** (244 mg, 0.77 mmol) in CH_3OH (10 mL) and glacial acetic acid (0.3 mL) was added 10% Pd/C (48 mg). The resulting suspension was hydrogenated at 50 psig for 1 h, H_2CO (0.5 mL, 37% in H_2O) was added, and the hydrogenation was continued overnight. The catalyst was filtered off and washed thoroughly with CH_3OH, and the combined filtrate and washings were evaporated. The residue was taken up in 10 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$, and the organic phase was dried, filtered, and concentrated to give crude **11** (pure by NMR, 151 mg, 100% yield): ^{1}H NMR ($CDCl_3$) δ 1.2–2.4 (m, 10 H), 2.04 (s, 3 H, CH_3CO), 2.41 (s, 3 H, N-CH_3), 3.22 (m, 2 H, H-1 and H-6), 4.68 (br t, J = 6.5 Hz, 1 H, H-2). The hydrogen fumarate melted at 132.5–133 °C (i-PrOH/Et_2O): ^{1}H NMR (D_2O) δ 1.69 (m, 1 H), 1.79 (m, 5 H), 2.00 (m, 2 H), 2.12 (s, 3 H, CH_3CO), 2.20 (m, 1 H), 2.52 (m, 2 H), 2.90 (s, 3 H, N-CH_3), 3.93 (br d, J = 8.4 Hz, 1 H, H-1), 4.00 (br s, 1 H, H-6), 5.02 (br t, J = 6.0 Hz, 1 H, H-2), 6.66 (s, 2 H, vinylic). Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.5; H, 7.4; N, 4.5. Found: C, 57.4; H, 7.4; N, 4.4.

(1*R*,2*R*)-2-Acetoxy-9-methyl-9-azabicyclo[4.2.1]nonane (12) was prepared from **42** (136 mg, 0.452 mmol) in the same way as was **11**. Crude **12** (pure by NMR) was obtained in 99% yield as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.3–1.65 (m, 5 H), 1.8–1.95 (m, 4 H), 2.03 (s, 3 H, CH_3CO), 2.32 (m, 1 H), 2.44 (s, 3 H, N-CH_3), 3.24 (m, 1 H, H-1), 3.32 (q, J = 5.4 Hz, 1 H, H-6), 4.97 (m, 1 H, H-2). The hydrogen fumarate melted at 133.5–134.5 °C: ^{1}H NMR (D_2O) δ 1.55–2.10 (m, 6 H), 2.10 (s, 3 H, CH_3CO), 2.25 (m, 1 H), 2.42 (m, 1 H), 2.57 (m, 1 H), 2.92 (s, 3 H, N-CH_3), 4.02 (m, 2 H, H-1 and H-6), 5.15 (q, J = 5.8 Hz, 1 H, H-2), 6.68 (s, 2 H, vinylic). Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.5; H, 7.4; N, 4.5. Found: C, 57.5; H, 7.4; N, 4.4.

(1*R*,2*S*)-2-Acetoxy-9-methyl-9-azabicyclo[4.2.1]nonane methiodide (13) was prepared in the same way as was **4**. Pure **13** (70% yield) was isolated by filtration: mp 258–259 °C; ^{1}H NMR (D_2O) δ 1.7–1.9 (m, 4 H), 2.09 (m, 1 H), 2.12 (s, 3 H, CH_3CO), 2.19 (m, 2 H), 2.49 (m, 2 H), 2.65 (m, 1 H), 3.18 (s, 3 H, N-CH_3), 3.45 (s, 3 H, N-CH_3), 3.99 (m, 1 H, H-6), 4.02 (br d, J = 10.0 Hz, 1 H, H-1), 5.15 (m, 1 H, H-2). Anal. Calcd for $C_{12}H_{22}INO_2$: C, 42.5; H, 6.5; N, 4.1. Found: C, 42.5; H, 6.5; N, 4.1.

(1*R*,2*R*)-2-Acetoxy-9-methyl-9-azabicyclo[4.2.1]nonane methiodide (14) was prepared in the same way as was 4. Pure 14 was isolated by filtration (75% yield): mp 215–217 °C; ^{1}H NMR (D_2O) δ 1.74 (m, 1 H), 1.88 (m, 1 H), 1.9–2.2 (m, 5 H), 2.09 (s, 3 H, CH_3CO), 2.39 (m, 1 H), 2.48 (m, 1 H), 2.60 (m, 1 H), 3.20 (s, 3 H, N-CH_3), 3.28 (s, 3 H, N-CH_3), 3.97 (br s, 1 H, H-6), 4.02 (br s, 1 H, H-1), 5.34 (m, 1 H, H-2). Anal. Calcd for $C_{12}H_{22}INO_2$: C, 42.5; H, 6.5; N, 4.1. Found: C, 42.2; H, 6.5; N, 4.0.

Acknowledgment. Marshall L. Morningstar, President's Undergraduate Fellow, provided significant assistance in the preparation of intermediates. F.J.S. thanks the Spanish Ministry of Education and Science and the Fulbright Commission for a fellowship. This research was supported in part by the NIH, Grant NS 25296.

Supplementary Material Available: IR spectral data for compounds **27**, **31–39**, **41**, and **42** and ^{13}C NMR spectral data for **1**, **3–14**, **27**, **33–39**, **41**, and **42** (4 pages). Ordering information is given on any current masthead page.

Formation of Cyclopentenethiones via Cyclization of β-Thioallyl Cations

Norihiro Tokitoh,[1a] Nami Choi,[1a] Midori Goto,[1b] and Wataru Ando*,[1a]

Department of Chemistry, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305, Japan, and National Chemical Laboratory for Industry, 1-1 Higashi, Tsukuba, Ibaraki 305, Japan

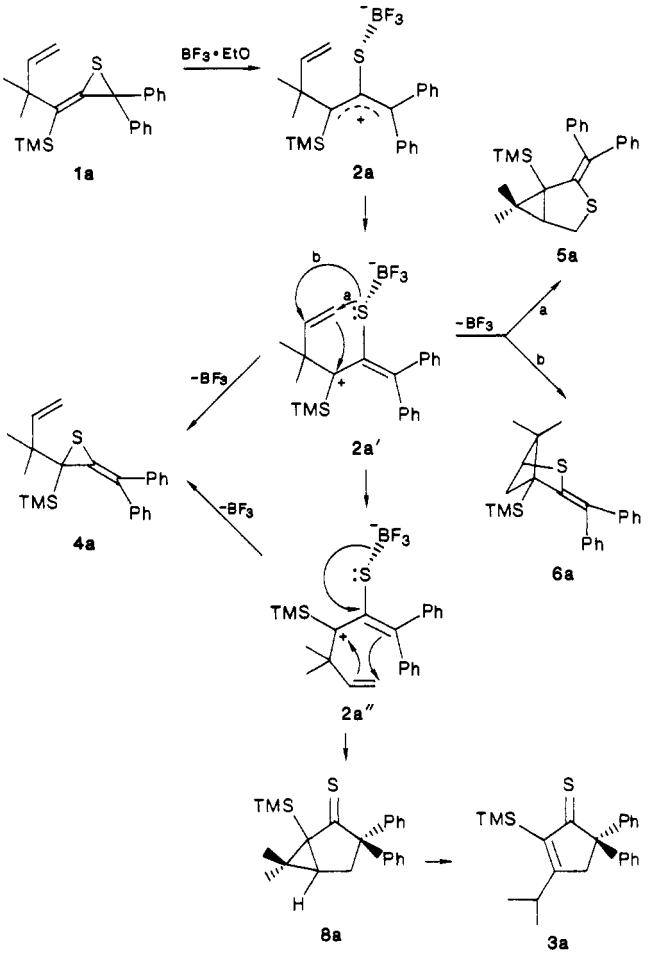
Received March 3, 1989

Reaction of 2,2-diaryl-3-[2′,2′-dimethyl-1′-(trimethylsilyl)-3′-butenylidene]thiiranes **1a** and **1b** with BF_3·Et_2O resulted in facile formation of stable cyclopentenethiones **3a** and **3b**, by a new type of cyclization via the initially generated thioallyl cations. The mechanism of this Lewis acid promoted isomerization of allene episulfides **1a** and **1b** is rationalized by taking into account the conformation of the thioallyl cation and the effect of the aromatic substituents. The structure of **3a**, a novel example of a crystalline aliphatic conjugated thione, has been determined by X-ray crystallographic analysis.

In contrast to the wide chemistry associated with oxyallyl ions and their versatile utility in organic synthesis,[2] the nature of sulfur-analogous reactive species, i.e., thioallyl intermediates, has not been fully investigated and its potential synthetic utility is undeveloped.[3]

We have recently described the thermal isomerization reactions of several types of substituted allene episulfides,[4] the substituent effects of which reveal the intrinsic nature of the thioallyl intermediate. The direct observation of the thioallyl cation from protonation of tetramethylallene episulfide with fluorosulfuric acid by low-temperature NMR spectroscopy and its interesting acid-promoted dimerization reactions have been reported.[5] In the case of sterically hindered aryl-substituted allene episulfides, an acid-catalyzed cyclization of the thioallyl intermediate onto the aromatic ring gave benzothiophene or indenethiol derivatives.[4b] However, no definite examples of inter- or intramolecular trapping reactions of the thioallyl cation

Scheme I[a]



[a] TMS = Me_3Si.

(1) (a) University of Tsukuba. (b) National Chemical Laboratory for Industry.

(2) (a) Zimmerman, H. E.; Dopp, D.; Huyffer, P. S. *J. Am. Chem. Soc.* **1966**, *88*, 5352. (b) Zimmerman, H. E.; Crumrine, D. S. *Ibid.* **1968**, *90*, 5612. (c) Hoffmann, R. *Ibid.* **1968**, *90*, 1475. (d) Camp, R. L.; Greene, F. D. *Ibid.* **1968**, *90*, 7349. (e) Turro, N. J.; Edelson, S. S.; Williams, J. R.; Darling, T. R.; Hammond, W. B. *Ibid.* **1969**, *91*, 2283. (f) Schaafsma, S. E.; Steinberg, H.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1170. (g) Grimaldi, J.; Bertrand, M. *Tetrahedron Lett.* **1969**, 3269. (h) Havel, J. J. *J. Am. Chem. Soc.* **1974**, *96*, 530. (i) Grimaldi, J.; Malacria, M.; Bertrand, M. *Tetrahedron Lett.* **1974**, 275. (j) Chan, T. H.; Li, M. P.; Mychajlowskij, W.; Harrp, D. N. *Ibid.* **1974**, 3511. (k) Grimaldi, J.; Malacria, M.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1975**, 1725. (l) Bertrand, M.; Dulcere, J. P.; Gil, G.; Grimaldi, J.; Sylvestre-Panthet, P. *Tetrahedron Lett.* **1976**, 1507, 3305. (m) Chan, T. H.; Ong, B. S. *J. Org. Chem.* **1978**, *43*, 2994. (n) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61 and references cited therein. (o) Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269 and references cited therein. (p) Osamura, Y.; Borden, W. T.; Morokuma, K. *J. Am. Chem. Soc.* **1984**, *106*, 5112.

(3) (a) Block, E.; Penn, R. E.; Ennis, M. D.; Owens, T. A.; Yu, S.-L. *J. Am. Chem. Soc.* **1978**, *100*, 7436. (b) Longejan, E.; Buys, Th. S. V.; Steinberg, H.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas.* **1978**, *97*, 214. (c) Saalfrank, R. W.; Winfreid, P.; Schierling, P.; Schuler, H.; Wilhelm, E. *Chem. Ber.* **1982**, *115*, 57. (d) Furuhata, T.; Ando, W. *Tetrahedron Lett.* **1986**, *27*, 4035.

(4) (a) Furuhata, T.; Ando, W. *Tetrahedron* **1986**, *42*, 5301. (b) Ando, W.; Itami, A.; Furuhata, T.; Tokitoh, N. *Tetrahedron Lett.* **1987**, *28*, 1787. (c) Tokitoh, N.; Choi, N.; Ando, W. *Chem. Lett.* **1987**, 2177.

(5) Ando, W.; Hanyu, Y.; Furuhata, T.; Takata, T. *J. Am. Chem. Soc.* **1983**, *105*, 6151.

0022-3263/89/1954-4660$01.50/0