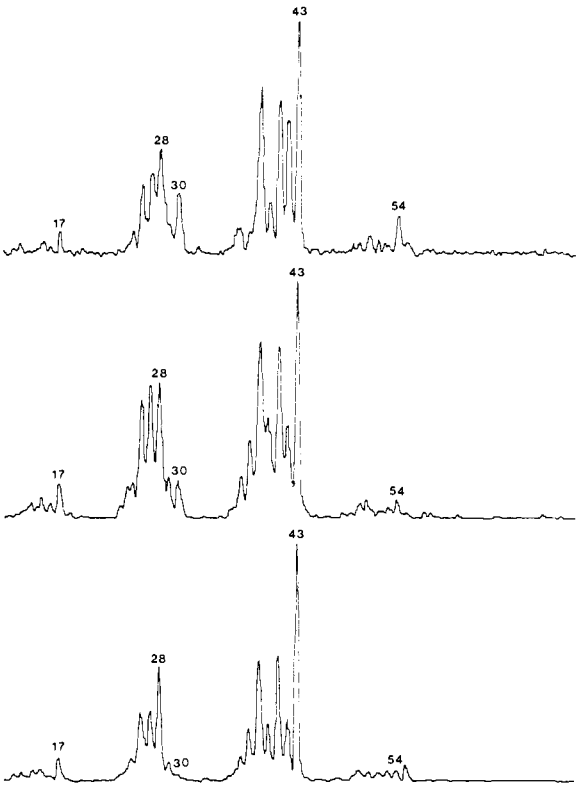


Figure 9. Hg/O_2 NR mass spectra of, top to bottom: (A) **7** and (B) **8**. (C) He/O_2 NR mass spectrum of **7**.

II). By analogy to the smaller distonic homologues $CH_2CH_2N^+H_3$ (**13**) and $\cdot CH_2CH_2CH_2N^+H_3$ (**18**), it is the distonic isomer **8**, not **7**, which should show this high tendency for CAD.[22] Thus the close similarity of the Hg/O_2 NR spectra of **7** and **8** indicates that the distonic isomer **8** is the dominant species resulting from the equilibrium **7** $\rightleftarrows$ **8**. The *m/z* 26–28 could arise (Scheme II) from the C_2H_4 neutral formed with **13** by CAD/Hg (see Figure 1B). Neutralization of **7** with sodium vapor does not appreciably increase the low relative proportion of neutralization vs. CAD.[12]

Lower Isomerization Barrier of Ionized Amines vs. Alcohols. The transition state for the more exothermic rearrangement of alcohol molecular ions must be much less favorable than that of amine molecular ions, with activation energy values of ~20 and <9 kcal mol^{-1} for $C_3H_7OH^+\cdot$ (**15**) and $C_3H_7NH_2^+\cdot$ (**17**), respectively. Recent ab initio calculations of Nishimoto et al.[5d,25] indicate that the transition states for these isomerizations are approached from the gauche conformations of **15** and **17**. The positive charge for both is distributed over the entire molecule, primarily on the hydrogen periphery, so that the migrating γ hydrogen has a net positive charge. However, the net charge on the heteroatom accepting the hydrogen is positive for the alcohol (**15**) and negative for the amine (**17**). The resulting coulombic repulsion for **15**, and attraction for **17**, should then lead to a much higher activation energy for **15** → **16** vs. **17** → **18**, as observed.[33]

Summary

The distonic oxonium and ammonium radical ions are more stable than their molecular ion isomers, as shown by the isomerization direction for **4** → **5**/**5′**, **17** → **18**, **21** → **22**, and **7** → **8**/**8′**. Although isomerization to form the oxonium ions is more exothermic (by 4–8 kcal mol^{-1}, Table I) than such formation of the ammonium ions, the latter isomerization (**17** vs. **15**, **21** vs. **19**, **7** vs. **4**) must have substantially lower activation energies than those producing the oxonium ions, consistent with previous conclusions[3d,e] that radical site reactions at nitrogen are favored over those at oxygen. Consistent with previous labeling evidence,[3a,f-h,7g] 1,5- are favored over 1,4-hydrogen rearrangements; 1,3- and 1,2-H rearrangements (e.g., Figure 8D) were not observed.

Acknowledgment. We are grateful to R. F. Porter, T. F. Moran, and L. Radom for helpful discussions and to the National Institutes of Health (Grant GM16609) and Army Research Office (Grant DAAG29-82-K-0179) for generous financial support.

Registry No. 4, 99033-61-1; **4-*d***, 99033-62-2; **5**, 99033-63-3; **7**, 70677-55-3; **7-*N*,*N*-d_2**, 99033-64-4; **7**-1,1-d_2, 99033-65-5; **8**, 20694-05-7; **9**, 99095-69-9; **10**, 60786-90-5; **12**, 65764-66-1; **13**, 20694-01-3; **15**, 34538-82-4; **16**, 90263-55-1; **17**, 70677-54-2; **18**, 20694-02-4; **19**, 99033-66-6; **20**, 99033-67-7; **21**, 99033-68-8; **21-d_2**, 99033-69-9; **22**, 20694-07-9; 1-propanol, 71-23-8; ethanol, 64-17-5; ethylene, 74-85-1; ethylamine, 75-04-7; propylamine, 107-10-8; isobutyl alcohol, 78-83-1; isobutylamine, 78-81-9; 1-butanol, 71-36-3; butylamine, 109-73-9.

(33) These authors[5d,25] actually reached the opposite conclusion from these data, explaining the large loss of H_2O from ionized propanol as due to the attraction between the positive net charge on oxygen and the negative net charge on the γ-carbon atom.

Efficient Total Synthesis of (±)-Anatoxin *a*

Rick L. Danheiser,*[1] John M. Morin, Jr., and Edward J. Salaski

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received June 14, 1985*

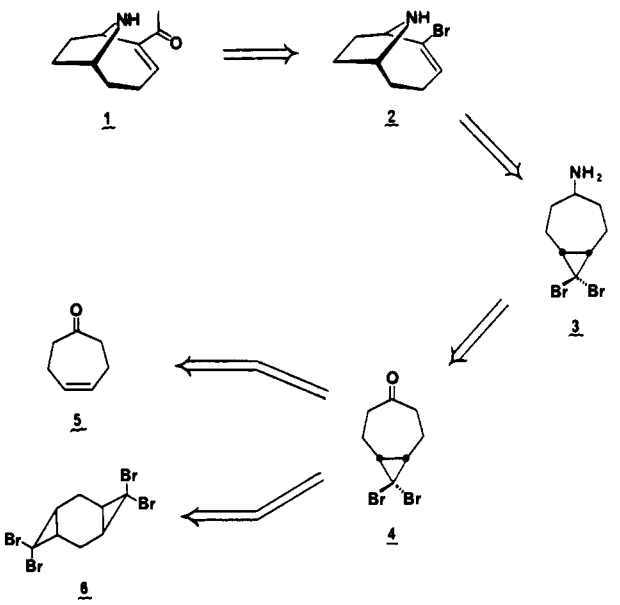
Abstract: A practical and efficient synthetic route to the neurotoxic alkaloid anatoxin *a* has been developed. In this new strategy, the bicyclooctanone **4** is prepared in one to two steps from either 4-cycloheptenone or the tricyclooctane 6 and is then converted to the aminobicyclooctane intermediate **3** by reductive amination. The pivotal step in the synthetic strategy involves the electrocyclic cleavage-transannular cyclization of the amine **3**, which generates the 9-azabicyclo[4.2.1]nonene ring system of the target alkaloid. Overall, the synthesis involves only seven steps (17% overall yield) beginning with 4-cycloheptenone, or alternatively, eight steps (8.3% overall yield) starting with the tetrabromotricyclooctane **6**.

Certain strains of the freshwater blue-green alga *Anabaena flos-aquae* produce a potent toxin which has been responsible for numerous incidents of livestock and waterfowl poisoning in the midwestern United States and Canada.[2] This substance, originally designated "*very fast death factor*" (VFDF), rapidly causes death in a variety of species via respiratory paralysis, with an intra-

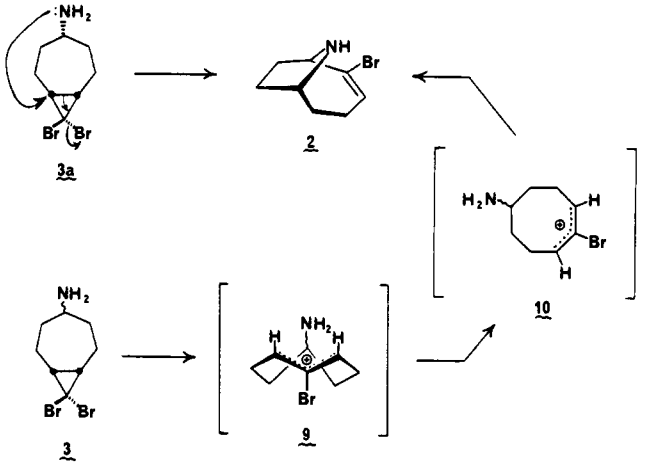
(1) Fellow of the Alfred P. Sloan Foundation, 1981–1985.

0002-7863/85/1507-8066$01.50/0

Scheme I



Scheme II



peritoneal LD_{90} of 0.25 mg/kg and an oral LD_{50} ranging from 1 to 10 mg/kg.[3] VFDF has been identified as a powerful depolarizing neuromuscular blocking agent possessing both muscarinic and nicotinic activity.[4] As one of the most potent agonists at the nicotinic acetylcholine receptor discovered to date, the compound has proved to be a valuable research tool in elucidating the mechanism of intramuscular neurotransmission.[5]

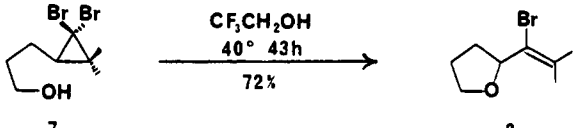
The structure of VFDF (subsequently renamed anatoxin *a*) was identified as 2-acetyl-9-azabicyclo[4.2.1]non-2-ene (**1**) in 1977 by Edwards, Gorham, and their co-workers at the Canadian National Research Council laboratories in Ottawa.[6] This assignment has been confirmed by an X-ray crystallographic study.[7] The chemical synthesis of anatoxin *a* has since been the subject of considerable attention, and partial[8] and total syntheses of both racemic[9] and homochiral[10] anatoxin have been reported.

In connection with our interest in the design of general methods for the synthesis of cyclooctanoid natural products,[11] we have undertaken the development of efficient synthetic routes to this structurally novel[12] and biologically significant alkaloid. The objectives of the current study were twofold: (1) to demonstrate the utility of our previously reported electrocyclic cyclopropane cleavage–cationic cyclization strategy[13] in the synthesis of cyclooctane derivatives and (2) to develop a practical synthetic route to anatoxin *a* capable of supporting the preparation of *multigram quantities* of the alkaloid, as well as certain derivatives with potential utility in the chemotherapy of nervous disorders.

Results and Discussion

Synthetic Strategy. Scheme I outlines the key features of our strategy for the total synthesis of anatoxin *a*. The pivotal step in this approach is the disrotatory electrocyclic cleavage–transannular cyclization of the bicyclic amine **3**. This process would be predicted to generate a vinyl bromide intermediate (**2**), which could then be transformed to the target alkaloid via the acylation of an organometallic derivative or by means of one of several transition-metal-mediated coupling procedures. Reductive amination of the bicyclooctanone **4** would provide access to **3**; the former intermediate would in turn be easily prepared by dibromocarbene addition to 4-cycloheptenone, or via an alternative route starting with 1,4-cyclohexadiene (vide infra). Thus, the proposed strategy could conceivably produce anatoxin *a in as few as four steps* beginning with the known compound 4-cycloheptenone.

In this strategy, the unusual azabicyclo[4.2.1]nonene ring system is generated via the thermal or Lewis acid-promoted electrocyclic cleavage-transannular cyclization of the dibromobicyclo[5.1.0]octane derivative **3**. The groundwork for this key reaction was laid in an earlier study, in which we demonstrated that a related electrocyclic opening–cationic cyclization process could serve as an efficient strategy for the synthesis of a variety of oxygen heterocycles.[13,14] The conversion of **7** to **8** is representative of the transformations achieved in this previous investigation.



On the basis of well-established stereoelectronic features of electrocyclic cyclopropane cleavage reactions,[15-19] two alternative

(2) Gorham, P. R.; McLachlan, J.; Manner, U. T.; Kim, W. K. *Verh.-Int. Ver. Theor. Angew. Limnol.* **1964**, *15*, 796. (b) Gorham, P. R. In "Algae and Man"; Jackson, D. F., Ed.; Plenum Press: New York, 1964; p 307. (c) Moore, R. E. *Bioscience* **1977**, *27*, 797. (d) Carmichael, W. W.; Gorham, P. R. In "Algae Biomass"; Shelef, G., Soeder, C. J., Eds.; Elsevier: Amsterdam, 1980; pp 437–448 and references cited therein.

(3) (a) Carmichael, W. W.; Biggs, D. F.; Gorham, P. R. *Science (Washington, D.C.)* **1975**, *187*, 542. (b) Carmichael, W. W.; Biggs, D. F. *Can. J. Zool.* **1978**, *56*, 510.

(4) Carmichael, W. W.; Biggs, D. F.; Peterson, M. A. *Toxicon* **1979**, *17*, 229.

(5) (a) Spivak, C. E.; Witkop, B.; Albuquerque, E. X. *Mol. Pharmacol.* **1980**, *18*, 384. (b) Aronstam, R. S.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4639. (c) Spivak, C. E.; Waters, J.; Witkop, B.; Albuquerque, E. X. *Mol. Pharmacol.* **1983**, *23*, 337.

(6) Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Stavric, B. *Can. J. Chem.* **1977**, *55*, 1367.

(7) Huber, C. S. *Acta Crystallogr., Sect. B: Struct. Sci.* **1972**, *B28*, 2577.

(8) Campbell, H. F.; Edwards, O. E.; Kolt, R. *Can. J. Chem.* **1977**, *55*, 1372.

(9) (a) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. (b) Campbell, H. F.; Edwards, O. E.; Elder, J. W.; Kolt, R. J. *Pol. J. Chem.* **1979**, *53*, 27. (c) Tufariello, J. J.; Meckler, H.; Senaratne, K. P. A. *J. Am. Chem. Soc.* **1984**, *106*, 7979.

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

(11) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

(12) Anatoxin *a* is the only naturally occurring 9-azabicyclo[4.2.1]nonane derivative identified to date. By contrast, the structures of numerous alkaloids incorporate the 8-azabicyclo[3.2.1]octane ring system.

(13) Danheiser, R. L.; Morin, J. M.; Yu, M.; Basak, A. *Tetrahedron Lett.* **1981**, *22*, 4205.

(14) The electrocyclic cleavage of cyclopropanes can also initiate cationic cyclizations, leading to the formation of *carbocyclic* systems: Danheiser, R. L.; Bronson, J. J.; Teng, C.-Y.; Ikemoto, N., manuscript in preparation.

(15) See: (a) Sorensen, T. S.; Rauk, A. In "Pericyclic Reactions"; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, pp 3–17. (b) Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980; pp 23–53 and references cited therein.

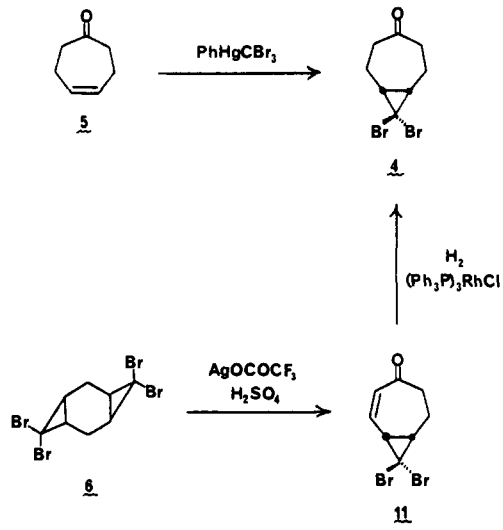
(16) (a) DePuy, C. H.; Schnack, L. G.; Hausser, J. W.; Wiedemann, W. *J. Am. Chem. Soc.* **1965**, *87*, 4006. (b) Cristol, S. J.; Sequeira, R. M.; DePuy, C. H. *Ibid.* **1965**, *87*, 4007. (c) DePuy, C. H.; Schnack, L. G.; Hausser, J. W. *Ibid.* **1966**, *88*, 3343.

plans were devised for the execution of the key step in our synthetic strategy. As outlined in Scheme II, one plan called for the direct conversion of **3a** to **2** via nucleophilic participation of a suitably oriented[20] amino group during the thermal electrocyclic opening of the cyclopropane ring. Alternatively, it was recognized that ring cleavage might proceed via the expulsion of the exo bromine atom to afford a *trans,trans*-cyclooctenyl cation **9**, which would not be amenable to cyclization. In this event, it was envisioned that suitable conditions could be contrived to encourage the isomerization of this intermediate to the corresponding *cis,cis*-allylic carbocation **10**. Inspection of molecular models indicated that the transannular closure of **10** to **2** would then be a facile process.

Synthesis of 8,8-Dibromobicyclo[5.1.0]octan-4-one. As outlined in Scheme I, our strategy for the total synthesis of anatoxin *a* called for the preparation of the key bicyclic amine **3** via reductive amination of *cis*-8,8-dibromobicyclo[5.1.0]octan-4-one (**4**). Two alternative routes were developed for the efficient synthesis of this key intermediate.

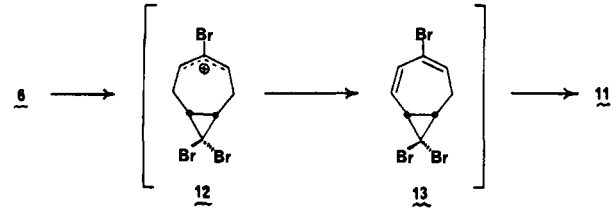
Our first approach simply involved the addition of dibromocarbene to the known compound 4-cycloheptenone (**5**).[21-26] The Seyferth reagent phenyl(tribromomethyl)mercury[28] proved uniquely effective in bringing about this transformation and furnished the bicyclic ketone **4** in 71% yield after chromatographic purification.

Although the cycloheptenone approach provided convenient access to the desired bicyclooctanone in a single step, we ultimately turned to an alternative route for the prearation of large quantities of this key intermediate. This second route utilized the tetrabromotricyclooctane **6** as starting material and was based on the earlier observation by Birch and co-workers[29] that electrocyclic cleavage of **6** could be restricted to one of the two cyclopropane rings, thereby generating a bicyclo[5.1.0]octane derivative. A conceptually appealing feature of this new strategy was that it



would consequently employ the disrotatory electrocyclic cyclopropane cleavage process twice in the course of the synthesis to assemble the eight-membered carbocyclic framework of the target alkaloid.

The starting material for the tetrabromotricyclooctane route was the known tetrabromide **6**,[30] which we found could be conveniently prepared in 100–120-g batches by using the phase-transfer dibromocyclopropanation procedure of Makosza and Fedorynski.[31] Controlled electrocyclic opening of one cyclopropane ring in **6** was then achieved by stirring a suspension of the tetrabromide and silver trifluoroacetate in a two-phase mixture of concentrated sulfuric acid and methylene chloride. The bicyclooctenone **11** was obtained as colorless crystals in 29–35% yield by employing this procedure. This remarkable transfor-



mation appears to proceed via the initial electrocyclic cleavage of one cyclopropane ring to generate an allylic carbocation **12**, which then suffers loss of a proton to afford the intermediate diene **13**. Hydrolysis of **13** next produces the α,β-unsaturated ketone **11**, in which the electron-withdrawing capacity of the enone moiety serves to deactivate the remaining cyclopropane ring toward a second electrocyclic cleavage reaction.

Our plan for the synthesis of the target bicyclooctanone **4** now required the selective reduction of the carbon–carbon double bond in **11**, a step complicated by the propensity of the dibromocyclopropane ring to suffer hydrogenolysis upon attempted catalytic hydrogenation with conventional procedures.[29] Fortunately, we found that the desired selective reduction could be smoothly accomplished in 99% yield by *homogeneous* catalytic hydrogenation of **11** over Wilkinson's catalyst[32] in benzene at 25 °C for 6 h.

Preparation of the Key Aminobicyclooctane Intermediate. The reductive amination[33] of the bicyclooctanone **4** proceeded in high yield when a 2-propanol solution of the ketone was treated with 3 equiv of sodium cyanoborohydride and 10 equiv of ammonium acetate in the presence of 3-Å molecular sieves at room tem-

(17) (a) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395. (b) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim, 1970; pp 46–48.

(18) (a) Schleyer, P. v. R.; Van Dine, G. W.; Schöllkopf, U.; Paust, J. *J. Am. Chem. Soc.* **1966**, *88*, 2868. (b) Schleyer, P. v. R.; Sliwinski, W. F.; Van Dine, G. W.; Schöllkopf, U.; Paust, J.; Fellenberger, K. *Ibid.* **1972**, *94*, 125. (c) Sliwinski, W. F.; Su, T. M.; Schleyer, P. v. R. *Ibid.* **1972**, *94*, 133 and references cited therein.

(19) Dihalobicyclo[5.1.0]octane derivatives have been found to rearrange to afford either *cis*- or *trans*-cyclooctenes, depending on the conditions employed to effect the electrocyclic opening. For examples, see: (a) Baird, M. S.; Lindsay, D. G.; Reese, C. B. *J. Chem. Soc. C* **1969**, 1173. (b) Whitham, G. H.; Wright, M. *Ibid.* **1971**, 883. (c) Reese, C. B.; Shaw, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2422. (d) Baird, M. S. *J. Chem. Soc., Chem. Commun.* **1974**, 196. (e) Loozen, H. J. J.; Robben, W. M. M.; Richter, T. L.; Buck, H. M. *J. Org. Chem.* **1976**, *41*, 384. (f) Loozen, H. J. J.; de Haan, J. W.; Buck, H. M. *Ibid.* **1977**, *42*, 418 and references cited therein.

(20) This process would presumably require nucleophilic attack on the same face of the cyclopropane ring as the departing bromine atom; see: Fleming, I.; Thomas, E. J. *Tetrahedron* **1972**, *28*, 4989.

(21) The synthesis of 4-cycloheptenone was first reported by Bahurel and co-workers: Bahurel, Y.; Collonges, F.; Menet, A.; Pautet, F.; Poncet, A.; Descotes, G. *Bull. Soc. Chim. Fr.* **1971**, 2203.

(22) Wilson and Wiesler have recently reported the synthesis of **5** by using a more efficient version of the Bahurel route: Wilson, S. R.; Wiesler, D. P. *Synth. Commun.* **1980**, *10*, 339.

(23) For the preparation of **5** via the degradation of 4-cycloheptenecarboxylic acid,[24,25] see: Glazer, E. S.; Knorr, R.; Ganter, C.; Roberts, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 6026. Cope, A. C.; Park, C. H.; Scheiner, P. *Ibid.* **1962**, *84*, 4862.

(24) Stork, G.; Landesman, H. K. *J. Am. Chem. Soc.* **1956**, *78*, 5129.

(25) We have found that the oxidative decarboxylation of 4-cycloheptenecarboxylic acid to **5** can be accomplished most efficiently (see Experimental Section) by using the method of Trost and Tamaru: Trost, B. M.; Tamaru, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3101.

(26) As an alternative route, we have also prepared the enone **5** from readily available 2-carbomethoxycyclohept-4-en-1-one[27] via decarbomethoxylation using lithium iodide (see Experimental Section). For a review on decarbomethoxylation, see: McMurry, J. E. *Org. React.* **1976**, *24*, 187.

(27) This compound has been prepared via the reaction of (*Z*)-1,4-dichloro-2-butene with the dianion derivative of methyl acetoacetate: Borch, R. F.; Ho, B. C. *J. Org. Chem.* **1977**, *42*, 1225. Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1977**, *55*, 996.

(28) Seyferth, D. *Acc. Chem. Res.* **1972**, *5*, 65.

(29) Birch, A. J.; Iskander, G. M.; Magboul, B. I.; Stansfield, F. *J. Chem. Soc C* **1967**, 358.

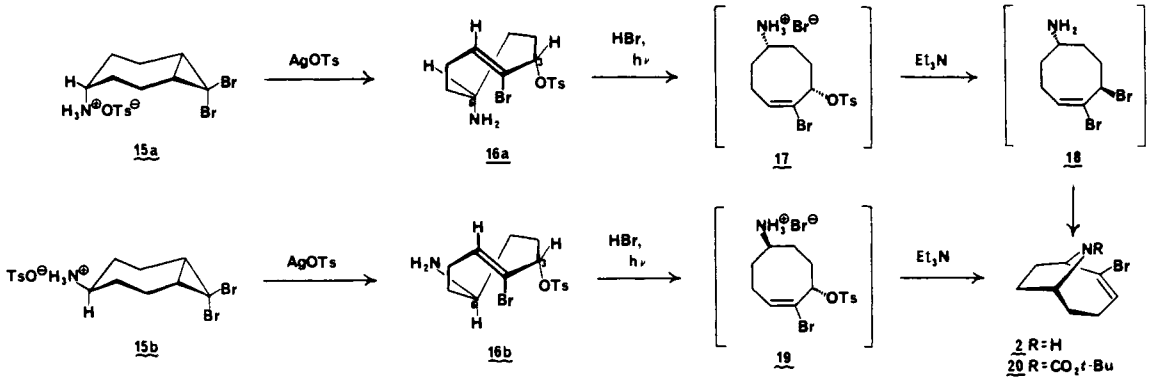
(30) Hofmann, K.; Orochena, S. F.; Sax, S. M.; Jeffrey, G. A. *J. Am. Chem. Soc.* **1959**, *81*, 992. Winstein, S.; Sonnenberg, J. *Ibid.* **1961**, *83*, 3235. Banwell, M. G.; Halton, B. *Aust. J. Chem.* **1979**, *32*, 849.

(31) Makosza, M.; Fedorynski, M. *Pol. J. Chem.* **1976**, *50*, 2223.

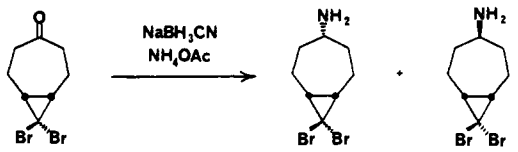
(32) Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *J. Chem. Soc., Chem. Commun.* **1965**, 131.

(33) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

Scheme III

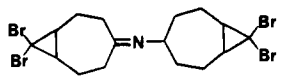


perature for 72 h. Under these conditions, the desired aminobicyclooctane was produced in 94% yield as a 71:29 mixture of endo (**3a**) and exo (**3b**) isomers.[34] Both amines were expected



to function as viable intermediates for the synthesis of anatoxin, and consequently no effort was made to optimize conditions for the selective formation of one or the other stereoisomer.[35]

Conducting the reductive amination in the absence of molecular sieves resulted in a significantly lower yield (ca. 50%) of the desired amines. Interestingly, the use of *unactivated* powdered 3-Å sieves also proved crucial to the success of this operation. The dimeric imine **14** was formed as a significant byproduct when sieves which had been activated at 100 °C/0.1 mmHg were employed for the reaction. We were also surprised to find that the dimethyl ketal



derivative of **4** was the principal product obtained when the reductive amination step was carried out in methanol, the most commonly employed solvent for these reactions.[33] However, the formation of ketal byproducts could be completely suppressed simply by conducting the reductive amination reaction in 2-propanol.

Electrocyclic Cleavage–Transannular Cyclization Step. The development of an efficient three-step synthesis of the aminobicyclooctane **3** from **6** set the stage for the investigation of the pivotal step in our synthetic plan: the conversion of the key intermediate **3** to the azabicyclononene **2** via our electrocyclic cleavage–transannular cyclization strategy. Unfortunately, the direct rearrangement of either **3a** or **3b** to **2** via the thermally induced electrocyclic opening of the cyclopropane ring proved unsuccessful under a variety of conditions. No reaction occurred upon heating a toluene solution of these amines at 160 °C for 24 h, indicating that nucleophilic participation by the amino group apparently cannot operate in this system to facilitate the electrocyclic cleavage of the cyclopropane ring. Although at higher temperatures (e.g., 225 °C for 1.5 h) the formation of trace amounts (ca. 1%) of the desired azabicyclononene **2** could be detected by NMR, the principal result of reaction under these conditions was the production of uncharacterizable polymers. Despite extensive efforts, we were similarly unable to achieve the direct conversion of **3** to **2** by employing silver(I) salts to initiate the electrocyclic cleavage process.

In most of the latter experiments, *trans*-cyclooctene derivatives were isolated as the principal rearrangement products. This observation suggested that it was the exo bromine atom which was functioning as the departing group in the electrocyclic opening of the cyclopropane ring, and that furthermore, the *trans*-cyclooctenyl intermediates thus generated were not subject to isomerization under our reaction conditions. Although this observation implied that the *direct* conversion of **3** to **2** was not likely to prove feasible, it also suggested that the desired transformation might be realized by employing a simple *two-step* modification of our original strategy. Thus, by choosing an appropriate silver salt (AgX) to initiate the electrocyclic cleavage, a *trans*-cyclooctene could conceivably be generated, bearing a potential leaving group X at the allylic position (C-3) of the new eight-membered ring. Photoisomerization of the cyclooctene double bond would then produce an intermediate in which transannular displacement of X by the C-6 amino group could proceed as a facile process.

Using this modified strategy, the desired rearrangement of **3** to **2** was efficiently accomplished in two synthetic operations (Scheme III). Silver tosylate proved to be the reagent of choice for initiating the electrocyclic ring opening, and best results were obtained by employing the ammonium salts **15a** and **15b** in place of the corresponding free amines.[36] Thus, heating a solution of the isomeric tosylate salts (generated in situ from **3a** and **3b**) with 10 equiv of silver tosylate in acetonitrile at 80 °C for 36–48 h produced the diastereomeric (*Z*)-cyclooctenes **16a** and **16b** in 60% combined yield. Photoisomerization and transannular cyclization were then accomplished in a single operation by employing the following protocol. The hydrobromide salts derived from **16a** and **16b** were first irradiated in a mixture of benzene and acetonitrile[37,38] for 10–15 min at 25 °C with a 450-W medium-pressure Hanovia lamp. Triethylamine (1.0 equiv) was next added, and the resulting solution was heated at 70 °C for 12–18 h. Aqueous workup then provided the desired azabicyclononene **2** as a brown oil, which was converted without further purification to its *tert*-butyl carbamate derivative by treatment with 1.0 equiv of di-*tert*-butyl dicarbonate in methylene chloride at room temperature

(34) Chromatographic separation provided crystalline samples of each amine for characterization purposes; the configuration of the amino substituent in these diastereomers was then easily established by high-resolution ^{1}H NMR spectroscopic analysis. For the application of similar arguments to the assignment of configuration of bicyclo[5.1.0]octanol derivatives, see: (a) Cope, A. C.; Moon, S.; Park, C. H. *J. Am. Chem. Soc.* **1962**, *84*, 4843. (b) Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B. *J. Org. Chem.* **1982**, *47*, 3960.

(35) For accounts of studies on the stereochemical course of the reduction of cycloalkanone imine and oxime derivatives, see: (a) Wrobel, J. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 3447. (b) Sternbach, D. D.; Jamison, W. C. L. *Ibid.* **1981**, *22*, 3331. (c) Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412 and references cited therein.

(36) Reaction of the free aminobicyclooctanes **3a** and **3b** with AgOTs led to the precipitation of an insoluble brown silver complex of the amines.

(37) In this reaction, benzene serves as a photosensitizer,[38] and acetonitrile is employed to achieve a homogeneous solution of the amine salts.

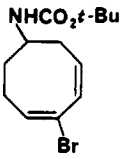
(38) For a discussion of the cis–trans isomerization of cyclooctene, see: Inoue, Y.; Takamuku, S.; Sakurai, H. *J. Phys. Chem.* **1977**, *81*, 7 and references cited therein.

for 16–24 h. The vinyl bromide **20**[39] was produced in 60% overall yield (starting with a mixture of **16a** and **16b**) by employing this procedure.

The significant stereochemical details of these electrocyclic cleavage and transannular cyclization reactions were elucidated through separate experiments carried out on the pure aminobicyclooctane diastereomers **3a** and **3b**. As outlined in Scheme III, treatment of the endo amine derivative **15a** with silver tosylate produced only the cis amino tosylate **16a**, whereas rearrangement of the diastereomeric amine salt **15b** resulted in the exclusive formation of the isomer **16b** in which the C-6 amino and C-3 tosyloxy groups are disposed trans about the cyclooctene ring.[40] Note that the structures of these (*Z*)-cyclooctene rearrangement products incorporate *three* chiral moieties: two chiral carbon atoms (C-3 and C-6), and the chiral plane defined by the C_1–C_2 double bond.[41,42]

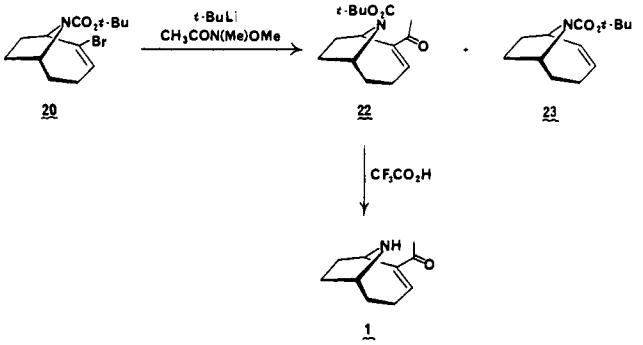
Inspection of molecular models suggested that the next step in the sequence—transannular cyclization to generate the azabicyclononene system—would only be feasible for the (*E*)-cyclooctenylamine that would be obtained from the photoisomerization of **16b**. The diastereomeric amine derived from **16a** does not appear to possess a conformation permitting the syn- or antiperiplanar arrangement of the nucleophilic nitrogen atom and C–OTs bond required for intramolecular S_N2 or S_N2' displacement. These predictions were confirmed experimentally. Thus, irradiation of the hydrobromide salt derived from **16a** furnished the (*E*)-cyclooctene **17**, which could be isolated as the corresponding free amine after treatment with aqueous sodium hydroxide. By contrast, neutralization of the (*E*)-cyclooctene **19** derived from the isomerization of **16b** led not to the corresponding free amine but instead gave the desired azabicyclononene **2** directly. The transannular cyclization of the diastereomer **17** was eventually accomplished simply by heating this intermediate in the presence of triethylamine. Nucleophilic displacement of tosylate by bromide ion inverts the configuration at C-3, thus generating a cyclooctenyl bromide **18** in which transannular cyclization can take place as a stereoelectronically feasible process.

In preparative runs, the electrocyclic cleavage–transannular cyclization sequence was easily carried out on a multigram scale. A mixture of the diastereomeric amines **3a** and **3b** was employed in the electrocyclic cleavage step, and the resulting mixture of (*Z*)-cyclooctenes was converted to the azabicyclononene **2** without prior separation or purification. The rearrangement of **15a** and **15b** proceeded most efficiently when excess silver tosylate was employed to maximize the rate of the electrocyclic cleavage reaction.[43] The excess silver salts were routinely recovered in 94% yield by employing the simple procedure detailed in the Experimental Section. The only significant byproduct (3% yield) produced in the electrocyclic cleavage–transannular cyclization sequence was the cyclooctadiene **21** resulting from the base-promoted elimination of tosylate from the (*E*)-cyclooctene **17** (or the corresponding free amine).



21

Conversion of the Vinyl Bromide 20 to Anatoxin *a*. The last step in our plan for the total synthesis of anatoxin *a* called for the acylation of an organometallic derivative of the vinyl bromide **20**. After considerable experimentation, we found that this transformation could be efficiently accomplished by the reaction of *N*-methoxy-*N*-methylacetamide with the organolithium compound obtained by halogen–metal exchange of **20** with *tert*-butyllithium. The utility of *N*-methoxy-*N*-methylamides as acylating agents for the synthesis of ketones from organometallic compounds has previously been demonstrated by Nahm and Weinreb,[44] and we found this method to be uniquely effective in bringing about the desired transformation of **20** to **22**.[45] Thus, exposure of the vinyl bromide **20** to 2.2 equiv of *tert*-butyllithium in THF at −78 °C for 15 min generated the expected lithium derivative, which was treated with 1.2 equiv of *N*-methoxy-*N*-methylacetamide[46] at −78 °C for 30 min and then at 25 °C for 15 min. In this



20 **22** **23**

1

manner, the *t*-BOC derivative of anatoxin *a* (**22**)[39] was obtained in 73% yield following purification by preparative radial thin-layer chromatography. The only significant byproduct produced under these conditions was the olefin **23** (10% yield), which most likely results from the protonation of the vinyllithium intermediate by either *tert*-butyl bromide or the amide acylating agent.

Exposure of the *tert*-butyl carbamate derivative **22** to a solution of trifluoroacetic acid in methylene chloride at 0 °C for 5 min smoothly produced (±)-anatoxin *a*, which for characterization purposes was converted to its hydrochloride salt (98% yield from **22**) by treatment with anhydrous HCl. This material exhibited spectral characteristics fully consistent with those previously reported for natural[6] and synthetic[10] anatoxin *a* hydrochloride.

Conclusion

In summary, we have developed a new strategy for the total synthesis of (±)-anatoxin *a* which involves only seven steps (17.0% overall yield) beginning with 4-cycloheptenone or, alternatively, eight steps (8.3% overall yield) starting with the tetrabromotricyclooctane **6**. Every step leading to the *t*-BOC derivative of

(39) The ^1H and ^{13}C NMR spectra of **20** (and **22**) indicate that these carbamate derivatives exist as mixtures of conformational isomers at 25 °C (see Experimental Section). Similar restricted rotation in the *t*-BOC derivatives of anatoxin and dihydroanatoxin has been noted by Rapoport and co-workers.[10]

(40) The stereochemical outcome of these reactions can be rationalized on the basis of either of two alternative mechanisms. Thus, the observed course of these electrocyclic rearrangements would be predicted on stereoelectronic grounds if the reactions were stereospecific processes in which nucleophilic attack was concerted with the electrocyclic opening of the cyclopropane ring. However, our results are also consistent with a mechanism involving the *stereoselective* capture of tosylate by an intermediate *trans,trans*-cyclooctenyl cation **9**; approach of tosylate would only be possible from the sterically accessible "outside" face of this carbocation.

(41) For discussions of the chiral integrity of *trans*-cyclooctene, see: Cope, A. C.; Ganellin, C. R.; Johnson, H. W.; Van Auken, T. V.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1963**, *85*, 3276. Cope, A. C.; Pawson, B. A. *Ibid.* **1965**, *87*, 3649.

(42) The stereochemistry of the double bond in the cyclooctenes **16–19** was determined by using ^1H and ^{13}C NMR spectroscopy as previously described by Reese and Shaw[19c] and by Loozen and co-workers.[19f] Thus, in the *cis*-cyclooctene derivatives, the C-3 allylic carbon resonates at higher field and the C-3 methine proton appears at lower field relative to the corresponding *trans*-cyclooctene isomers.

(43) The rate of related electrocyclic cleavage reactions has been found to be proportional to $[Ag^+]^2$: see ref 19c and: Bach, R. D.; Willis, C. L. *J. Am. Chem. Soc.* **1975**, *97*, 3844.

(44) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(45) No acylation occurred upon attempted acetylation of **20** employing a variety of other coupling procedures: (a) Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. *J. Am. Chem. Soc.* **1974**, *96*, 3654. (b) Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777. (c) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181. (d) Jabri, N.; Alexakis, A.; Normant, J. F. *Ibid.* **1983**, *24*, 5081.

(46) Chervin, I. I.; Nasibov, Sh. S.; Rudchenko, V. F.; Shtamburg, V. G.; Kostyanovskii, R. G. *Bull. Acad. Sci. USSR* **1981**, *30*, 389. Oster, T. A.; Harris, T. M. *Tetrahedron Lett.* **1983**, *24*, 1851.

anatoxin has been carried out on at least a gram scale, and our route thus constitutes the most practical and efficient synthesis of this important neurotoxic alkaloid reported to date.

Experimental Section

Instrumentation. Infrared spectra were obtained by using Perkin-Elmer 283B and 1320 grating spectrophotometers. ^{1}H NMR spectra were measured with Perkin-Elmer R-24B (60 MHz) and Bruker WM-250 (250 MHz) and WM-270 (270 MHz) spectrometers. ^{13}C NMR spectra were determined on a Bruker WM-270 (67.9 MHz) spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. UV spectra were measured on a Varian Cary Model 118 UV-vis spectrophotometer. Low-resolution mass spectra (MS) were determined on Varian MAT 44 or Finnegan MAT 8200 instruments; high-resolution mass spectra (HRMS) were measured with a Dupont CEC-110B or Finnegan MAT 8200 spectrometer. Elemental analyses were performed by Guelph Chemical Laboratories, Ltd., Guelph, Ontario, and by the Robertson Laboratory, Inc., of Florham Park, NJ. Melting points and boiling points are uncorrected.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Bromoform was distilled under vacuum before use. Acetonitrile, hexamethylphosphoramide, 2,6-lutidine, tri-*n*-butylamine, triethylamine, diisopropylamine, methyl disulfide, and methylene chloride were distilled from calcium hydride. Trifluoroacetic acid was distilled from phosphorus pentoxide. Benzene, diethyl ether, and tetrahydrofuran were distilled from sodium benzophenone dianion. Sodium iodide was dried at 100 °C (0.1 mmHg) for 15 h before use. *tert*-Butyllithium was titrated by the method of Watson and Eastham.[47]

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated by using a Buchi rotary evaporator at 15–20 mmHg. Column chromatography was performed by using Baker or E. Merck silica gel 60 (230–400 mesh). Ether and hexane were distilled prior to use as eluants. Radial preparative thin-layer chromatography was carried out by using a Harrison Research, Inc., Chromatotron on plates coated with E. Merck PF-254 silica gel 60 ($CaSO_4 \cdot {}^1/_2H_2O$ binder).

4-Cycloheptenone (5). Preparation from 2-Carbomethoxycyclohept-4-en-1-one. A solution of 2-carbomethoxycyclohept-4-en-1-one[27] (1.97 g, 11.71 mmol) and lithium iodide trihydrate (3.49 g, 18.57 mmol) in 30 mL of 2,6-lutidine was heated at 140 °C for 10 h. The reaction mixture was allowed to cool to 25 °C, poured into ether, and extracted with six 25-mL portions of 10% aqueous H_2SO_4. The combined aqueous layers were back-extracted with 100 mL of ether, and the combined organic phases were then washed with 10 mL of H_2O, 25 mL of saturated $NaHCO_3$ solution, and 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.26 g of a brown oil. Kugelrohr distillation (oven temp 100 °C, 35 mmHg) gave 0.87 g (67%) of **5** as a yellow oil: 2,4-DNP mp 139–141 °C [lit.[21] mp 141 °C]; IR (film) 3020, 2940, 2900, 2845, 1695, 1655, 1435, 1345, 1315, 1200, 1165, 1135, 1085, 1065, 1020, 920, 860, 750, 690, and 635 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.75–5.95 (m, 2 H) and 2.20–2.80 (m, 8 H).

1-(Methylthio)cyclohept-4-enecarboxylic Acid. A solution of lithium diisopropylamide was prepared by the dropwise addition of *n*-butyllithium solution (2.39 M in hexane, 53.7 mL, 128.4 mmol) to a solution of diisopropylamine (13.5 g, 132.7 mmol) in 250 mL of THF at 0 °C. To the resulting cold solution was added 4-cycloheptenecarboxylic acid[24] (6.00 g, 42.8 mmol, in five portions over 15 min) and then 50 mL of HMPT. The yellow reaction mixture was stirred at 0 °C for 7 h and then treated dropwise over 5 min with methyl disulfide (8.06 g, 85.6 mmol). After 2 h, the cold reaction mixture was diluted with 50 mL of H_2O. THF was removed by rotary evaporation at reduced pressure, and the residue was diluted with 100 mL of ether and extracted with five 50-mL portions of saturated $NaHCO_3$ solution. The combined aqueous extracts were acidified to pH 1 with cold concentrated aqueous H_2SO_4 and then extracted with five 125-mL portions of ether. The combined organic phases were washed with two 100-mL portions of H_2O, 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 6.93 g of the desired acid as a yellow solid used in the next step without purification. Recrystallization from petroleum ether furnished a pure sample of 1-(methylthio)cyclohept-4-enecarboxylic acid as colorless prisms: mp 99.5–102 °C; IR (CH_2Cl_2) 3350–2300, 3010, 2920, 2840, 1685, 1535, 1430, 1285, 1250, 1220, 1185, 1150, 1135, 1070, 1040, 1015, 955, 940, 860, and 830 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 11.65 (s, 1 H), 5.65 (m, 2 H), 2.1 (s, 3 H), and 1.5–2.6 (m, 8 H); HRMS, *m/e* calcd for $C_9H_{14}O_2S$ (M^+) 186.0715, found 186.0709.

4-Cycloheptenone (5). Preparation from 1-(Methylthio)cyclohept-4-enecarboxylic Acid. A mixture of 1-(methylthio)cyclohept-4-enecarboxylic acid (6.93 g, 37.2 mmol) and $NaHCO_3$ (15.60 g, 186.0 mmol) in 100 mL of methanol was stirred at 25 °C for 30 min and then cooled to 0 °C. *N*-Chlorosuccinimide (9.94 g, 74.4 mmol) was added in five portions over 30 min, and the resulting suspension was stirred at 0 °C for 6 h. Saturated Na_2SO_3 solution (50 mL) and solid Na_2SO_3 (5.0 g) were then added, and the resulting mixture was stirred at 0 °C for 30 min and then poured into 150 mL of cold 10% aqueous HCl and 200 mL of ether and stirred further at 0 °C for 2 h and at 25 °C for 10 h. The aqueous phase was then separated, saturated with NaCl, and extracted with five 100-mL portions of ether. The combined organic layers were washed with three 100-mL portions of 15% aqueous NaOH solution, 100 mL of H_2O, and 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. Column chromatography on silica gel (elution with ether–pentane) provided 3.10 g (67% overall from 4-cycloheptenecarboxylic acid) of **5** as a yellow oil.

***cis*-8,8-Dibromobicyclo[5.1.0]octan-4-one (4). Preparation from 5.** A solution of 4-cycloheptenone (**5**) (1.30 g, 11.81 mmol) and phenyl(tribromomethyl)mercury[28] (15.20 g, 28.71 mmol) in 150 mL of benzene was heated at reflux for 25 h, cooled to room temperature, and then filtered with the aid of 200 mL of benzene. Concentration of the filtrate furnished 9.03 g of a light-brown solid. Column chromatography on silica gel (elution with ethyl acetate–hexane) gave 2.38 g (71%) of **4** as a tan solid: mp 98–102 °C; 2,4-DNP mp 203–204 °C; IR (film) 2975, 2905, 2870, 1680, 1450, 1390, 1370, 1325, 1310, 1240, 1215, 1180, 1140, 1115, 1095, 1040, 1025, 1010, 940, 890, 855, 795, 760, 750, 710, and 655 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.29–2.65 (m, 6 H), 1.89–2.01 (m, 2 H), and 1.41–1.56 (m, 2 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 210.2 (s), 42.4 (t), 36.0 (s), 32.7 (d), and 22.1 (t); HRMS, *m/e* calcd for $C_8H_{10}O^{81}Br_2$ (M^+) 283.9057, found 283.9059. Anal. Calcd for $C_8H_{10}OBr_2$: C, 34.08; H, 3.57. Found: C, 34.08; H, 3.71.

A sample of 8,8-dibromo-3,3,5,5-tetradeuteriobicyclo[5.1.0]octan-4-one was prepared by treatment of **4** with Na_2CO_3 in D_2O–THF: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.34 (dd, J = 6.3, 15.1 Hz, 2 H), 1.95 (m, 2 H), and 1.46 (dd, J = 7.8, 15.1 Hz, 2 H).

(1α,3β,5β,7α)-4,4,8,8-Tetrabromotricyclo[5.1.0.0^{3,5}]octane (6). A 5-L, three-necked, round-bottomed flask was equipped with a thermometer, mechanical stirrer, and a condenser fitted with a nitrogen inlet adapter. The flask was charged with 1,4-cyclohexadiene (25.0 g, 312 mmol), bromoform (788.5 g, 3120 mmol), tri-*n*-butylamine (5.0 mL), 500 mL of dichloromethane, and 1500 mL of 50% aqueous NaOH solution. The resulting brown mixture was heated at 45 °C for 24 h, allowed to cool to room temperature, and then poured into 1 L of ice–water. Chloroform (1 L) was added, and the resulting two-phase mixture was warmed on a steam bath until the chloroform began to reflux and then immediately filtered through Celite. The aqueous phase of the filtrate was separated and set aside, while the filtered solid was washed with three 1-L portions of hot chloroform. Each of the resulting chloroform filtrates was reheated and used to extract the aqueous phase of the initial filtrate; the organic phases were then combined and concentrated to ca. 2 L. The resulting yellow solution was washed with 500 mL of saturated NaCl solution and concentrated. Trituration of the oily brown solid residue with two 200-mL portions of pentane furnished 135.8 g of a brown solid, which was recrystallized from dichloromethane to yield 101.4 g (77%) of 6 as tan crystals: mp 207–209 °C [lit.[30] mp 205–206 and 205–207 °C]; IR (Nujol) 1340, 1295, 1235, 1180, 985, and 920 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.09–2.13 (m, 4 H) and 1.73–1.77 (m, 4 H).

(±)-*cis*-8,8-Dibromobicyclo[5.1.0]oct-2-en-4-one (11). A 1-L, three-necked, round-bottomed flask was equipped with a thermometer, mechanical stirrer, and a condenser fitted with an argon inlet adapter. The flask was charged with finely ground tetrabromide **6** (45.0 g, 104.9 mmol), 100 mL of dichloromethane, and 250 mL of concentrated sulfuric acid. Silver trifluoroacetate (100.0 g, 440.5 mmol) was then added, and the reaction mixture was warmed to 40 °C. After 6 h, the mixture was allowed to cool to room temperature, stirred at that temperature for 20 h, and then poured into a mixture of 1 L of cold saturated NaCl solution and 1 L of dichloromethane. The resulting two-phase mixture was filtered through Celite with the aid of four 200-mL portions of hot dichloromethane, and the aqueous phase of the filtrate was separated and then extracted with eight 500-mL portions of dichloromethane. The combined organic layers were divided into two portions of equal volume, and each was washed with 500 mL of H_2O and 500 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a total of 26.3 g of an oily black solid. Column chromatography on silica gel (elution with ethyl acetate–hexane) provided 8.6 g (29%) of **11** as white crystals: mp 75.5–76.5 °C [lit.[29] mp 75–76 °C]; 2,4-DNP (orange needles) mp 174–175 °C [lit.[29] mp 168–170 °C]; spectral data for **11**

(47) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

were consistent with that previously reported:[29] IR (film) 3035, 2935, 2895, 2870, 1659, 1444, 1383, 1323, 1242, 1224, 1160, 1072, 1045, 1001, 939, 887, 838, 799, 675, and 546 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.36 (dd, J = 3.2, 11.6 Hz, 1 H), 6.00 (dd, J = 1.2, 11.6 Hz, 1 H), 2.63–2.81 (m, 2 H), 2.15–2.50 (m, 3 H), and 1.71–1.88 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 202.5, 137.3, 133.8, 41.0, 35.8, 34.5, 32.8, and 23.0.

***cis*-8,8-Dibromobicyclo[5.1.0]octan-4-one (4).** A 500-mL, three-necked, round-bottomed flask was equipped with a gas dispersion tube, an argon inlet adapter, and a glass stopper. The flask was charged with the enone **11** (11.636 g, 41.56 mmol), tris(triphenylphosphine)rhodium(I) chloride (1.164 g, 1.26 mmol), and 200 mL of benzene, and the resulting solution was stirred at room temperature for 6 h while hydrogen was bubbled in via the gas dispersion tube. The reaction mixture was then concentrated, and the residual dark-red solid was triturated with five 300-mL portions of hot petroleum ether which were then filtered and combined. Concentration afforded 11.926 g of a yellow-orange solid which as triturated with five 300-mL portions of hot petroleum ether, decolorized and dried over a mixture of charcoal and $MgSO_4$, filtered, and concentrated on a steam bath to yield (in three crops) 11.682 g (99%) of **4** as colorless prisms, mp 103–105 °C.

***cis-endo*- and *-exo*-4-Amino-8,8-dibromobicyclo[5.1.0]octane (3a and 3b).** A 250-mL, one-necked, round-bottomed flask equipped with an argon inlet tube was charged with the ketone **4** (4.00 g, 14.19 mmol), sodium cyanoborohydride (0.888 g, 14.13 mmol), ammonium acetate (10.90 g, 141.4 mmol), powdered 3-Å molecular sieves (4.00 g), and 80 mL of 2-propanol. The resulting suspension was stirred at room temperature for 72 h and then filtered with the aid of 500 mL of methanol. The filtrate was concentrated to afford a viscous yellow oil to which was added 250 mL of dichloromethane and 100 mL of 15% aqueous NaOH solution. The aqueous phase of the resulting mixture was separated and extracted with two 250-mL portions of dichloromethane, and the combined organic phases were washed with 100 mL of H_2O and 100 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 4.58 g of a yellow oil. Column chromatography on silica gel (elution with methanol–methylene chloride) provided a yellow solid which was triturated with ether to yield 3.77 g (94%) of a mixture of **3a** and **3b** as a white solid, used in the next step without further separation.

Further careful column chromatography on silica gel (elution with methanol–methylene chloride) furnished pure samples of **3a** and **3b**. Endo isomer **3a**: mp 239–242 °C dec; hydrochloride mp 252–254 °C dec; IR (film) 3360, 3280, 2990, 2910, 2850, 1600, 1460, 1440, 1355, 1255, 1225, 1190, 1115, 1080, 1055, 995, 925, 845, 805, 770, 745, 715, and 640 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.37–3.41 (m, 1 H), 1.90–1.96 (m, 2 H), 1.53–1.77 (m, 8 H), and 1.18 (br s, 2 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 47.9 (d), 40.2 (s), 34.5 (d), 34.4 (t), and 21.3 (t); HRMS, m/e calcd for $C_8H_{13}{}^{79}Br^{81}BrN$ (M^+) 282.9394, found 282.9378. Anal. Calcd for $C_8H_{13}Br_2N{\cdot}HCl$: C, 30.08; H, 4.42; N, 4.38. Found: C, 30.00; H, 4.53; N, 4.26. Exo isomer **3b**: mp 127–134 °C dec; hydrochloride mp 261–262 °C dec; IR (film) 3330, 3260, 2910, 2850, 1585, 1455, 1370, 1355, 1225, 1180, 1120, 1080, 1045, 1005, 935, 900, 875, 795, and 740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.69 (apparent tt, J = 3.4, 10.6 Hz, 1 H), 2.13–2.23 (m, 2 H), 1.84–1.93 (m, 2 H), 1.66–1.79 (m, 2 H), 1.45 (s, 2 H), and 1.19–1.38 (m, 4 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 55.6 (d), 38.9 (s), 37.2 (t), 33.4 (d), and 24.3 (t); HRMS, m/e calcd for $C_8H_{13}{}^{79}Br^{81}BrN$ (M^+) 282.9394, found 282.9370. Anal. Calcd for $C_8H_{13}Br_2N{\cdot}HCl$: C, 30.08; H, 4.42; N, 4.38. Found: C, 30.05; H, 4.41; N, 4.27.

***(S*)*-(*Z*)-(6*R**)- and -(6*S**)-Amino-2-bromo-(3*S**)-(*p*-toluenesulfonyloxy)cyclooctene (16a and 16b).** A 200-mL, one-necked, Kjeldahl flask equipped with an argon inlet adapter was charged with the epimeric amines **3a** and **3b** (2.110 g, 7.46 mmol), *p*-toluenesulfonic acid monohydrate (1.844 g, 9.69 mmol), and 60 mL of benzene, and the resulting solution was stirred at room temperature for 10 min. Benzene and water were then removed by azeotropic distillation by using a rotary evaporator, and the residual solid was suspended in another 60-mL portion of benzene. The resulting mixture was again concentrated by rotary evaporation, and the solid residue was dried further at 0.1 mmHg for 20 min. The amine salt was next suspended in 60 mL of acetonitrile, silver *p*-toluenesulfonate (20.807 g, 74.56 mmol) was added, and the Kjeldahl flask was wrapped with aluminum foil and then equipped with a Claisen adapter fitted with a cold-finger condenser and an argon inlet stopcock. The reaction mixture was stirred at 80 °C for 45 h, allowed to cool to room temperature, diluted with 50 mL of benzene, and then washed with 100 mL of 20% aqueous NH_4OH solution, 100 mL of H_2O, and 75 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 1.766 g of a mixture of **16a** and **16b** as a viscous yellow oil, used in the next step without further purification.

Pure samples of the cis and trans amino tosylates were obtained via an alternative route.[48] For the trans amino tosylate **16b**: hydrobromide mp 132–134 °C dec; IR (film) 3365, 3297, 3030, 2935, 2875, 1688, 1631, 1600, 1498, 1448, 1403, 1364, 1308, 1293, 1202, 1189, 1178, 1128, 1096, 1019, 959, 909, 856, 815, 757, 707, 691, and 620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 6.15 (dd, J = 4.3, 11.7 Hz, 1 H), 4.91 (dd, J = 5.5, 10.4 Hz, 1 H), 2.87–3.14 (m, 1 H), 2.76 (br s, 2 H), 2.63–2.76 (m, 1 H), 2.44 (s, 3 H), 1.99–2.37 (m, 3 H), 1.65–1.85 (m, 2 H), 1.51–1.59 (m, 1 H), and 1.25–1.43 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 144.9 (s), 133.5 (s), 131.9 (d), 129.6 (d), 128.0 (d), 127.6 (s), 83.0 (d), 51.8 (d), 44.8 (t), 38.1 (t), 36.4 (t), 30.6 (t), and 21.6 (q); UV max (hydrobromide, MeOH) 224 nm (ϵ 11 100).

For the cis amino tosylate **16a**: hydrobromide mp 123–125 °C dec; IR (film) 3383, 3322, 3065, 3035, 2928, 2870, 2842, 1721, 1633, 1598, 1549, 1495, 1438, 1401, 1365, 1307, 1291, 1263, 1210, 1189, 1175, 1153, 1131, 1128, 1096, 1072, 1039, 1018, 992, 978, 952, 853, 825, 793, 735, 705, 692, 670, and 649 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 5.99 (dd, J = 3.4, 12.0 Hz, 1 H), 4.94 (dd, J = 4.0, 11.1 Hz, 1 H), 3.20–3.26 (m, 1 H), 2.66 (apparent dq, J = 4.3, 12.0 Hz, 1 H), 2.44 (s, 3 H), 2.20–2.37 (m, 2 H), 1.87–2.07 (m, 3 H), 1.69–1.83 (m, 1 H), 1.37 (br s, 2 H), and 1.18–1.29 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 144.8 (s), 133.4 (s), 132.6 (d), 129.6 (d), 127.9 (d), 126.8 (s), 83.1 (d), 48.4 (d), 43.7 (t), 35.2 (t), 33.0 (t), 29.3 (t), and 21.6 (q); UV max (hydrobromide, MeOH) 226 nm (ϵ 12 400).

Recovery of Silver(I) Oxide. The ammonium hydroxide and water extracts from the preceding reaction were combined, and the suspended silver bromide was allowed to precipitate and then was separated by decantation. The resulting solid was washed with two 25-mL portions of H_2O, and the combined aqueous phases were concentrated to afford a gray-white solid, which was dissolved in 75 mL of H_2O and 75 mL of 15% aqueous NaOH solution and then stored at room temperature in the dark for 1 week. The brown–black solid which formed was separated by centrifugation, and this material was further purified by washing with five 100-mL portions of H_2O and three 100-mL portions of ether (each was was separated by centrifugation). The resulting black powder was dried at ca. 0.1 mmHg (25 °C) to provide 7.281 g (84% recovery of total silver; 94% yield based on excess silver used) of silver(I) oxide, suitable for conversion to AgOTs without further purification.

(±)-2-Bromo-9-(*tert*-butoxycarbonyl)-9-azabicyclo[4.2.1]non-2-ene (20). A 500-mL, four-necked, photochemical reaction vessel was equipped with a rubber septum, argon outlet adapter, a sparger tube for the introduction of argon, and a double-walled, water-jacketed quartz immersion well containing a Vycor filter and a 450-W medium-pressure Hanovia mercury lamp. The reaction vessel was charged with the unpurified cyclooctenes **16a** and **16b** (1.766 g) prepared in the preceding reaction and 350 mL of benzene, and anhydrous HBr was bubbled through the solution via a Teflon tube for 5 min. Excess HBr was then flushed from the resulting solution of amine hydrobromide salts by bubbling argon through the reaction mixture for 15 min. Acetonitrile (175 mL) was next added, and the resulting solution was degassed by vigorous argon bubbling for 15 min. The rate of bubbling was then reduced, and the solution was irradiated for 12–14 min. The reaction mixture was transferred to a 1-L, one-necked flask, concentrated to a volume of ca. 20 mL, transferred to a 100-mL, one-necked, pear-shaped flask with the aid of CH_2Cl_2, and concentrated to a volume of ca. 5 mL. The flask was fitted with an argon inlet adapter, triethylamine (0.477 g, 4.72 mmol) and 10 mL of acetonitrile were added, and the resulting mixture was heated with stirring at 70 °C. After 18 h, the reaction mixture was allowed to cool to room temperature, diluted with 75 mL of benzene, washed with 75 mL of 15% aqueous NaOH solution, dried over Na_2SO_4, filtered, and concentrated. The resulting viscous brown oil was dissolved in 10 mL of dichloromethane and transferred to a 100-mL, one-necked, pear-shaped flask equipped with a 10-mL addition funnel fitted with an argon inlet adapter. A solution of di-*tert*-butyl dicarbonate (1.031 g, 4.72 mmol) in 5 mL of dichloromethane was then added dropwise over 5 min, and the resulting mixture was stirred at room temperature for 22 h and then concentrated to afford 1.463 g of a viscous brown oil. Preparative radial thin-layer chromatography on a 2-mm silica gel plate (elution with ether-hexane) gave 0.677 g (32% overall from **3a,b**) of **20** as a pale-yellow oil and 0.045 g (3%) of **21** as a colorless oil. Azabicyclononene **20**: IR (film) 2975, 2940, 2895, 1691, 1638, 1391, 1359, 1309, 1242, 1169, 1108, 1070, 1011, 995, 968, 939, 910, 898, 862, 830, 813, 770, 702, and 665 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.00 (t, J = 6.0 Hz, 1 H), 4.75 and 4.61 (conformational isomers, m, 1 H),

(48) This route involved electrocyclic rearrangement of the separate *tert*-butyl carbamate derivatives of **3a** and **3b**, followed by the cleavage of the *t*-BOC group using trifluoroacetic acid. See: Morin, J. M. Ph.D. Dissertation, Massachusetts Institute of Technology, Cambridge, 1982.

4.32 and 4.18 (conf. isomers, m, 1 H), 1.86–2.30 (m, 6 H), 1.54–1.80 (m, 2 H), and 1.45 and 1.44 (conf. isomers, s, 9 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 153.4, 130.4, and 130.3 (conf. isomers), 127.5 and 126.3 (conf. isomers), 79.8 and 79.6 (conf. isomers), 64.6 and 64.4 (conf. isomers), 54.4 and 54.0 (conf. isomers), 34.9, 32.7, 31.0, 30.5, 29.4, 28.4, 24.4, and 24.0. Anal. Calcd for $C_{13}H_{20}BrNO_2$: C, 51.67; H, 6.67; N, 4.63; Br, 26.44. Found: C, 51.73; H, 6.82; N, 4.52; Br, 26.56. Cyclooctadiene **21**: IR (film) 3455, 3342, 2979, 2932, 2872, 2868, 1700, 1497, 1456, 1392, 1364, 1353, 1327, 1243, 1170, 1163, 1093, 1046, 1028, 1000, 988, 915, 865, 828, 815, 770, 735, 668, and 648 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.03–6.16 (m, 2 H), 5.66–5.77 (m, 1 H), 4.42–4.50 (br m, 1 H), 3.63–3.71 (br m, 1 H), 2.35–2.44 (m, 2 H), 2.01–2.24 (m, 2 H), 1.67–1.88 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 155.2 and 154.9 (conf. isomers), 132.8, 130.9, 129.8, 118.2, 79.3, 48.3, 33.9, 33.5, 31.8, 29.6, 28.4, 22.6, and 22.4; HRMS, *m/e* calcd for $C_9H_{12}{}^{81}BrNO_2$ ($M^+ - C_4H_8$) 247.0031, found 247.0055.

(±)-2-Acetyl-9-(*tert*-butoxycarbonyl)-9-azabicyclo[4.2.1]non-2-ene (22). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with 4.14 mL of a 1.76 M solution of *tert*-butyllithium in pentane (7.29 mmol) and 10 mL of THF and then cooled below −75 °C with a dry ice–acetone bath. A cold (−78 °C) solution of the vinyl bromide **20** (1.001 g, 3.31 mmol) in 13 mL of THF was then transferred via cannula over 2 min into the *tert*-butyllithium solution, and the resulting yellow solution was stirred at −78 °C for 15 min. A cold (−78 °C) solution of *N*-methoxy-*N*-methylacetamide (0.410 g, 3.97 mmol) in 7 mL of THF was prepared in a 25-mL, two-necked, pear-shaped flask and transferred via cannula over 30 s to the cold vinyllithium solution prepared above. After 30 min, the reaction mixture was allowed to warm to room temperature and then was poured into 30 mL of 20% aqueous NH_4Cl solution buffered to pH 8 with NH_4OH. The resulting mixture was extracted with two 30-mL portions of ether, and the combined organic phases were washed with 50 mL of H_2O and 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.865 g of a pale-yellow oil. Preparative radial thin-layer chromatography on a 2-mm silica gel plate (elution with ethyl acetate–hexane) furnished 0.640 g (73%) of **22** as a pale-yellow oil and 0.075 g (10%) of **23** as a colorless oil. Enone **22**: IR (film) 3018, 2990, 2945, 2903, 2895, 2875, 1693, 1670, 1636, 1480, 1457, 1412, 1409, 1401, 1395, 1369, 1341, 1311, 1288, 1260, 1235, 1178, 1111, 1060, 1020, 994, 961, 933, 867, 842, 838, 775, 735, 699, and 668 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.83 (apparent t, J = 5.7 Hz, 1 H), 5.12–5.20 (m, 1 H), 4.28–4.43 (m, 1 H), 2.39–2.49 (m, 2 H), 2.30 (s, 3 H), 2.04–2.20 (m, 3 H), 1.60–1.77 (m, 3 H), 1.38 and 1.45 (conf. isomers, s, 9 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 197.7, 153.1, 150.3 and 148.3 (conf. isomers), 142.1 and 141.3 (conf. isomers), 79.3, 55.6, and 55.2 (conf. isomers), 54.1 and 53.0 (conf. isomers), 32.5, 31.4, 30.8, 30.3, 30.0, 28.7, 28.4, 25.6, 25.3, and 24.1; UV max (absolute EtOH) 228 nm (ϵ 10 200); MS, *m/e* 265 (M^+). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.81; H, 8.69; N, 5.24. Olefin **23**: IR (film) 3350, 2975, 2930, 1594, 1478, 1454, 1410, 1390, 1363, 1357, 1332, 1308, 1247, 1172, 1105, 1008, 931, 897, 878, 865, 832, 813, 768, 723, and 666 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82–5.91 (m, 1 H), 5.59–5.68 (m, 1 H), 4.54–4.59 and 4.41–4.46 (conf. isomers, m, 1 H), 4.34–4.41 and 4.23–4.28 (conf. isomers, m, 1 H), 1.96–2.23 (m, 5 H), 1.58–1.71 (m, 3 H), and 1.45 and 1.46 (conf. isomers, s, 9 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 153.4, 134.7, and 134.3 (conf. isomers), 129.1 and 128.8 (conf. isomers), 78.8, 56.0, and 55.8 (conf. isomers), 54.8, 33.2, 32.0, 31.4, 30.7, 29.9, 29.6, 29.0, 28.5, and 23.5; MS, *m/e* 223 (M^+); HRMS, *m/e* calcd for $C_{13}H_{21}NO_2$ (M^+) 223.1573, found 223.1573.

(±)-2-Acetyl-9-azabicyclo[4.2.1]non-2-ene Hydrochloride (1·HCl). A 25-mL, two-necked, pear-shaped flask equipped with an argon inlet adapter and rubber septum was charged with the carbamate **22** (0.119 g, 0.45 mmol) and 3 mL of dichloromethane. The reaction mixture was cooled to 0 °C, and 1.0 mL of trifluoroacetic acid was added rapidly by syringe. After 5 min, the solution was diluted with 20 mL of chloroform and washed with 20 mL of cold (−15 °C) 15% aqueous NaOH solution. The aqueous phase was separated and extracted with 10 mL of chloroform, and the combined organic layers were dried over Na_2SO_4 and then filtered. HCl gas was bubbled through the filtrate for 10 s, and the resulting solution was concentrated to afford a yellow oil. Further drying at 25 °C (0.1 mmHg) for 14 h and at 60 °C (0.1 mmHg) for 0.5 h gave 0.089 g (98%) of anatoxin *a* hydrochloride (**1**·HCl) as a pale-yellow glass: IR (film) 3400, 2930, 2760, 2700, 2567, 2472, 2400, 2260, 2075, 1666, 1640, 1587, 1470, 1429, 1403, 1360, 1320, 1297, 1270, 1227, 1160, 1118, 1099, 1072, 1042, 1018, 1000, 986, 963, 911, 851, 821, 754, and 664 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.90 (br s, 1 H), 9.22 (br s, 1 H), 7.18 (dd, J = 3.7, 7.6 Hz, 1 H), 5.24 (apparent d, J = 8.4 Hz, 1 H), 2.32–2.73 (m, 5 H), 2.37 (s, 3 H), and 1.83–2.00 (m, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 196.6 (s), 146.2 (d), 143.5 (s), 58.4 (d), 52.0 (d), 30.2 (t), 27.6 (t), 27.5 (t), 25.4 (q), and 23.6 (t); UV max (absolute EtOH) 226 nm (ϵ 10 500).

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Registry No. (±)-**1**, 85514-42-7; (±)-**1**·HCl, 70470-07-4; **3a**, 98875-52-6; **3a**·HCl, 98973-83-2; **3b**, 98973-82-1; **3b**·HCl, 99031-62-6; **4**, 98875-50-4; **5**, 19686-79-4; (±)-**5**(CO_2Me derivative), 61259-92-5; 6, 50843-61-3; (±)-**11**, 98875-51-5; **15a**, 98973-86-5; **15b**, 99031-64-8; (±)-**16a**, 98875-53-7; (±)-**16a**·HBr, 98973-85-4; (±)-**16b**, 98973-84-3; (±)-**16b**·HBr, 99031-63-7; (±)-**20**, 98875-54-8; (±)-**21**, 98875-55-9; (±)-**22**, 92998-50-0; Ag_2O, 20667-12-3; $H_3CCON(OCH_3)CH_3$, 78191-00-1; 1-(methylthio)cyclohept-4-enecarboxylic acid, 98875-49-1; 4-cycloheptenecarboxylic acid, 1614-73-9; 1,4-cyclohexadiene, 628-41-1.