Enantioselective Conversion of Anthranilic Acid Derivatives to Chiral Cyclohexanes. Total Synthesis of (+)-Pumiliotoxin C

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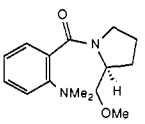
Abstract: Procedures are described for the enantioselective Birch reduction and reductive alkylation of anthranilic acid derivatives. Reduction of pyrrolobenzodiazepine-5,11-dione (**3a**) in NH_3–THF with potassium (4.4 equiv) and *t*-BuOH (2 equiv) followed by alkylation with methyl iodide at −78 °C gives α-alkylation products **6a** (54%) and **7a** (**6a**/**7a** = 85:15) via enolate **4**, along with γ-alkylated dihydrobenzene **8a** (15%). Stereoselectivity for alkylation of **4** improves with more sterically demanding alkyl halides; cf., **6a–6f**. On protonation with excess NH_4Cl at −78 °C, enolate **4** gives trans-fused β,γ-unsaturated amide **5** in 73% yield. The influence of reaction variables on product distribution is discussed in detail, and the application of the processes to conversions of pyrrolobenzodiazepine-5,11-diones **13a–c** into **14–18** is presented. Single-crystal X-ray structure determinations were carried out for **5** and **18** to establish the stereoselectivity of protonation at C(5a) and C(9). Birch reductions of **3a**, **13a**, and **13c** to the hexahydrobenzene oxidation state occur in excellent yield with 8 equiv of potassium and 5 equiv of *t*-BuOH to give **12**, **25**, and **26**, respectively; **13b** could not be converted to **27** in a synthetically useful yield because of a reluctance of the trisubstituted double bond in intermediate **16** to move into conjugation with the amide carbonyl group. Methods for removal of the chiral auxiliary are presented, and these give enantiomerically pure amino lactone derivatives **31–36**. Alternative methodology (Scheme V) provides 2-aminocyclohexane carboxylic acid derivatives, e.g., **39**. A total synthesis of (+)-pumiliotoxin C (**45**) based on the stereocontrolled Birch reduction of **13a** to give **14b** was developed. A key step in the synthesis of **45** is the amide carbonyl directed hydrogenation of the C(6)–C(7) double bond in **14b** exclusively from the β-face via presumed bidentate substrate coordination with a soluble iridium catalyst.

We have been interested in the development of enantioselective methods for the conversion of substituted benzoic acids into chiral cyclohexanes for use in organic synthesis.[1] The Birch reductions and reductive alkylations of *o*-anisic and *o*-toluic acid derivatives have figured prominently in this work. Anthranilic acids were expected to serve as precursors to several ring systems of potential utility in natural products synthesis. We especially desired conversions to perhydroindole, perhydroquinoline, and chiral aminocyclohexanes (Scheme I). By using oxidative deamination procedures, cyclohexanone-2-carboxylic acid derivatives also were anticipated. A projected total synthesis of the poison frog toxin pumiliotoxin C (**1**)[2] provided an early incentive to explore enantioselective reductions of 6-methylanthranilic acid. Other substitution patterns have been examined, and, in this paper, we report chemistry that provides access to enantiomerically pure aminocyclohexanes and related derivatives and a total synthesis of (+)-pumiliotoxin C.[3]

Results and Discussion

The Birch reduction of anthranilic acid does not seem to have been previously reported.[4] In the course of investigating the use of L-proline as a chiral auxiliary, we found the Birch reduction–alkylation of the *N*,*N*-dimethylanthranilic acid amide **2** to be



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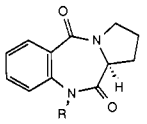
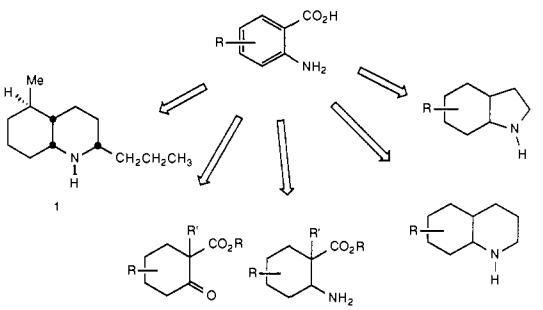


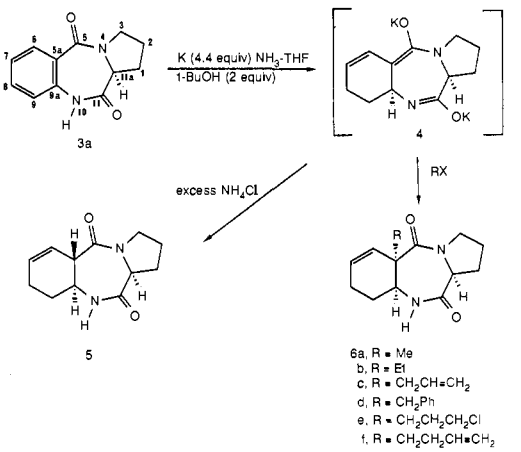
3a, R = H
b, R = Me

somewhat problematic.[5] Prior studies[3] with the L-proline derived substrate **3a** demonstrated the viability of Birch reductions of the diazepine dione ring system. We, therefore, focused attention on the development of chemistry of **3** and related substrates.

Scheme I



Scheme II



Preparation, Birch Reductions, and Reductive Alkylations of Pyrrolobenzodiazepine-5,11-diones. Excellent methods for the preparation of pyrrolobenzodiazepine-5,11-diones are available.[6]

(1) (a) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591. (b) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915. (c) Schultz, A. G.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. *Tetrahedron Lett.* **1985**, *26*, 4575. (d) McCloskey, P. J.; Schultz, A. G. *Heterocycles* **1987**, *25*, 437.

(2) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Eldefrawi, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharm.* **1982**, *22*, 565 and references cited therein.

(3) For a preliminary report of a portion of this work, see: Schultz, A. G.; McCloskey, P. J.; Sundararaman, P.; Springer, J. P. *Tetrahedron Lett.* **1985**, *26*, 1619.

(4) Kaiser, E. M. *Synthesis* **1972**, 91.

(5) Schultz, A. G.; Court, J. C.; Lavieri, F. P.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M., manuscript submitted for publication.

(6) (a) Carabateas, P. M.; Harris, L. S. *J. Med. Chem.* **1966**, *9*, 6. (b) Leimgruber, W.; Batcho, A. D.; Czajkowski, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 5641. (c) Kim, D. H. *J. Heterocycl. Chem.* **1975**, *12*, 1323.

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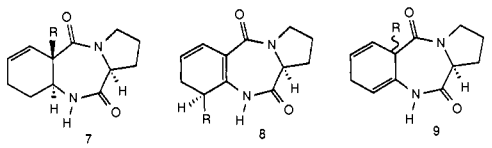
Isatoic anhydrides readily condense with L-proline (1 equiv) in refluxing pyridine with 1 equiv of pyridine hydrochloride. Crystalline products are obtained in good to excellent yields, and the method is applicable to the use of other amino acids.

Birch reduction of **3a** in NH_3–THF in the presence of *tert*-butyl alcohol required 4.4 equiv of potassium to maintain a blue coloration for more than 10 min (Scheme II). After having cooled the reaction mixture to −78 °C, pentadiene was added to consume excess metal. Methyl iodide (2–3 equiv) was added, and the mixture was stirred at −78 °C for 1.5 h. Ammonium chloride was added to the reaction mixture at −78 °C, after which ammonia was allowed to evaporate from the reaction flask. This procedure for quenching the reaction minimized *N*-alkylation of the secondary amide. Chromatographic separation of reaction components provided crystalline **6a** (54% isolated yield) and the diastereoisomer **7a** (**6a**/**7a** = 85:15), γ-alkylated dihydrobenzene **8a** (15%), but none of the corresponding α-alkylated **9a**.

Alkylation with ethyl iodide proceeded with higher diastereoselectivity to give **6b** (68%) and **7b** (**6b**/**7b** = 91:9); the minor diastereoisomer could not be detected when allyl bromide and benzyl bromide were used. Small amounts of the α-alkylated dihydrobenzenes **9b–d** along with γ-alkylated **8b–d** were detected



when alkyl halides more sterically demanding than methyl iodide were used. Attempts to optimize formation of **9a–d** by employing only 2.2 equiv of potassium resulted in recovery of significant amounts of starting material without a relative increase in the yield of α-alkylated dihydrobenzenes. The use of 2 equiv rather than 1 equiv of *tert*-butyl alcohol resulted in a favorable increase in yield of α-alkylated tetrahydrobenzenes with all alkyl halides examined except methyl iodide.

Reductive alkylation of **3a** with 1,3-dibromopropane provided the allyl derivative **6c** rather than the corresponding bromopropyl analogue. Remarkably, the yield for this process (88%) is higher than the yield obtained with allyl bromide (62%). The chloropropyl derivative **6e** was generated in ~50% yield by addition of lithium bromide to the Birch reduction mixture prior to alkylation with 1-bromo-3-chloropropane.

We do not understand the reasons for the shift of reaction composition to favor formation of tetrahydro products when 1,3-dibromopropane is used as the alkylation reagent. At this time, we suggest that alkyl halides may be involved in electron-transfer processes occurring between **3a** and species resulting from partial reduction of **3a**.[7]

Reductive alkylation of **6a** with homoallylic halides is inefficient, presumably because of the basicity of the intermediate enolate **4** and the relative acidity of the allylic hydrogen atom in the alkylation reagent. Alkylation with 4-bromo-1-butene gave **6f** in ~25% yield along with **10** (up to 58%), the product of γ-protonation of enolate **4**. Attempting to reduce the basicity of the enolate by the use of lithium in the Birch reduction step resulted in the formation of gummy, insoluble aggregates. Addition of cosolvents such as tetramethylenediamine (TMEDA) did not appreciably solubilize the aggregates, and, in general, these and other reaction modifications did not provide an increase in the yield of **6f**.

Because of the strongly basic reaction conditions used in the reductive alkylation process, we were concerned about the possibility of racemization at C(11a) in **3a**. A chiral NMR shift reagent study with **6a** was performed, and data collected were compared to those obtained from racemic **6a** (prepared from *dl*-proline). At maximum resolution, the angular methyl group resonance for racemic **6a** was separated into two equivalent singlets

(7) Sargent, G. D.; Lux, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 7160 and references cited therein.

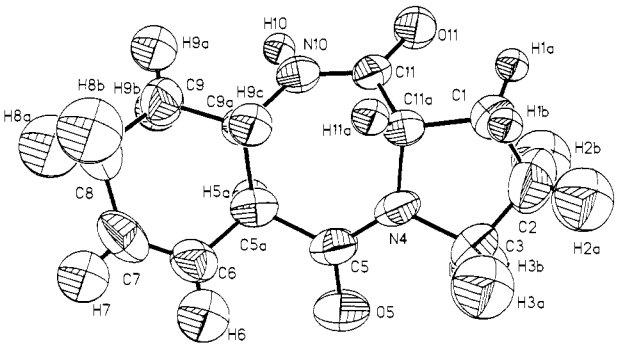
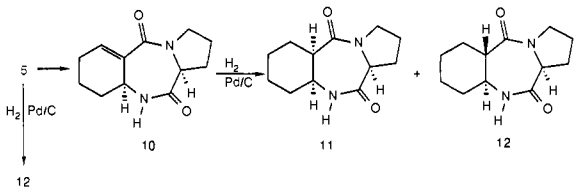


Figure 1. Molecular structure of **5**.

while **6a** prepared from L-proline gave only one singlet.

The enolate **4** generated by Birch reduction of **3a** undergoes protonation with excess NH_4Cl at −78 °C to give **5** in 73% isolated yield; diene **8** also is obtained (R = H, 15–20%). We had tentatively assigned[3] configuration of the β,γ-unsaturated amide as that corresponding to the cis fused series **6a–f**. Configurational assignments were based on X-ray crystallographic studies with **6a**[3] and ^1H NMR spectral comparisons of the β,γ-unsaturated amide and **6b–f** with **6a**. Additional experimentation with ring-substituted derivatives of **3a** (vide infra) gave reason to doubt the tentative configurational assignment for the β,γ-unsaturated amide, and we, therefore, performed an X-ray structure determination. The molecular structure for this substance **5** is shown in Figure 1.

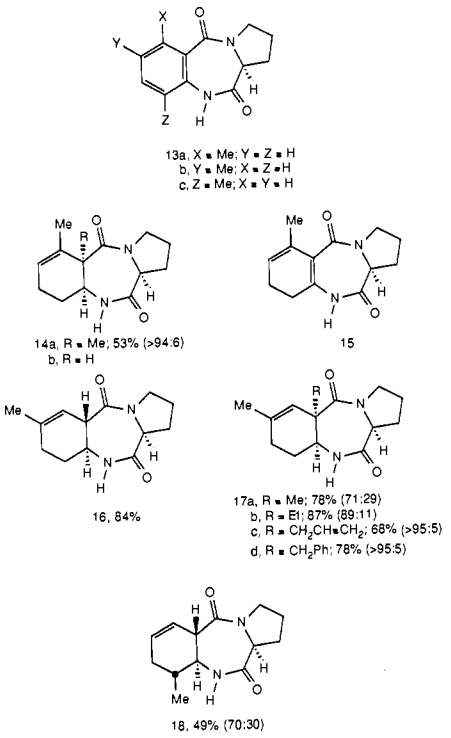
The β,γ-unsaturated amide **5** was completely isomerized to the α,β-isomer **10** on treatment with potassium carbonate in methanol. Hydrogenation of **10** occurred nonstereoselectively and gave hexahydrobenzene derivatives **11** and **12**. On the other hand, hydrogenation of **5** proceeded without double bond migration during reduction to give **12** in approximately quantitative yield.



The propensity for overreduction of **3a** to the tetrahydro oxidation state, relative to the behavior of **2**[5] and the anisic acid derivatives,[1] seems to be directly related to the presence of the NH group in **3a**. Birch reduction–methylation of the *N*-methyl derivative **3b** gave a complex reaction mixture, but the major product was that corresponding to **9** (NH = NMe). It is possible that this conversion can be developed into a synthetically useful process; however, the complete stereocontrol at C(9a) and the high degree of stereoselectivity at C(5a) afforded by reduction of **3a** to the tetrahydro oxidation state inspired a more detailed examination of reactions of secondary amides of type **3a**.

The 6-methyl, 7-methyl, and 9-methylpyrrolobenzodiazepine-5,11-diones **13a–c** were prepared from the corresponding isatoic anhydride and L-proline. Birch reduction–methylation of **13a** occurred with stereoselectivity (>94:6) significantly higher than that for **3a** (85:15) to give **14a** in 53% isolated yield. In contrast to **4**, the enolate generated from **13a** provided mainly the cis-fused β,γ-unsaturated amide **14b** on protonation with NH_4Cl; dihydrobenzene **15** also is obtained in yields of up to 30%. Protonation at C(5a) is dependent on the precise method of addition of NH_4Cl with stereoselectivities ranging from 5:1 to 10:1 in favor of the **14b** diastereoisomer. Stereochemical configuration of **14b** was unambiguously demonstrated by conversion to (+)-pumiliotoxin C (vide infra).

The stereoselectivity of alkylation of the enolate obtained from the 7-methyl derivative **13b** is somewhat less than that of **4**, but yields for isolation of tetrahydro products are significantly higher (see formulas). Of particular importance is the efficiency (up to 84% isolated yield) and variable stereoselectivity for formation



of the β,γ-unsaturated amide **16**. Only **16** is obtained when NH_4Cl (2 equiv) is slowly added to the enolate mixture, but stereoselectivity decreases to 2.5:1, favoring **16** over the C(5a) diastereoisomer, when a vast excess of NH_4Cl is added quickly.

Finally, **13c** gave **18** on Birch reduction–protonation (49% isolated yield), but the stereoselectivity is only 70:30 (favoring **18**); configuration of **18** was determined by X-ray crystallographic studies (Figure 2). The combined stereoselectivity for protonations at C(9) and C(9a) is excellent (vide infra), but yields for reductive alkylation of **13c** are inferior to those obtained with **3a**, **13a**, and **13b**.

Mechanism and Stereocontrol of the Birch Reduction and Reductive Alkylation of Pyrrolobenzodiazepine-5,11-diones. Birch reductions of **3** and **13** using 4 equiv of potassium and 2 equiv of *tert*-butyl alcohol are obviously complicated processes. While we haven't any spectroscopic evidence for intermediates, we can use the substantial body of facts accumulated for dissolving metal reductions[8] to propose a sequence of events proceeding from starting material to enolate dianion **4**, the putative intermediate undergoing reaction with alkyl halides and protonation with NH_4Cl (Scheme III).

Transfer of one electron to **3a** or **13** would generate radical anion **19**, which need not consume an equivalent of the added proton donor (*tert*-butyl alcohol) because of the presence of the NH group in **19**. The stereoselectivity of proton transfer to C(8) has not been addressed in this study, but we presume that this step occurs without stereocontrol to give radical anion **20**. Transfer of a second electron would generate dianion **21**, which apparently undergoes a highly stereoselective protonation by *t*-BuOH to give anion **22**. Alternatively, **22** might be formed from **20** by a reversal of the electron-transfer–protonation steps, thus avoiding the intermediacy of dianion **21**.[8c] In any event, protonation of **20** or **21** (X = Y = H; Z = Me) to give **22** and methylation of **20** or **21** (X = Y = Z = H) to give **8** both occur at C(9) exclusively from the β-face.

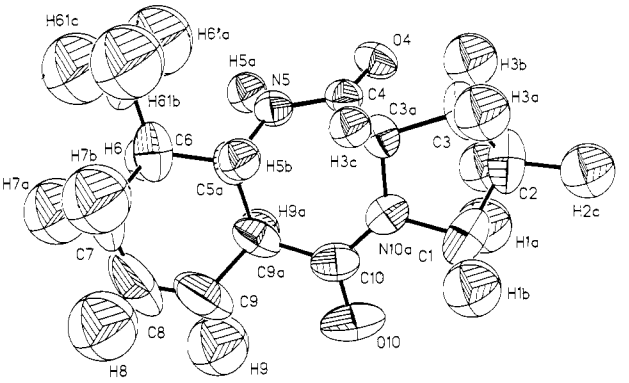
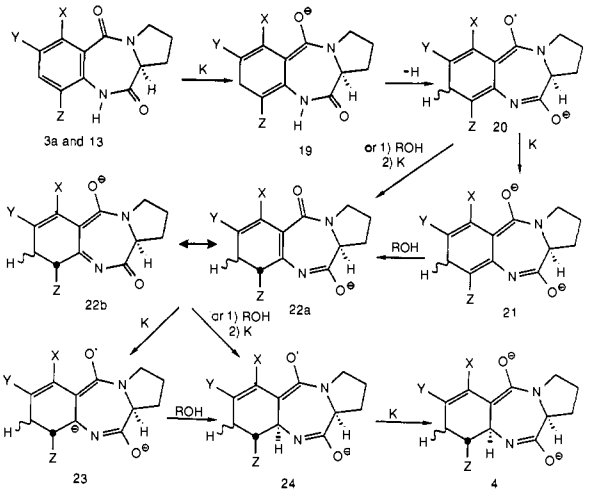


Figure 2. Molecular structure of **18**.

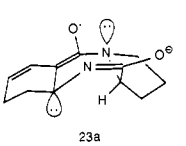
Scheme III



The formation of **22** sets the stage for further reduction by the third equivalent of potassium to give **23**. The potential for generation of the highly conjugated π-electron system in **22** provides the key to understanding why pyrrolobenzodiazepine-5,11-diones containing the secondary amide group tend to "overreduce" while the *N*-methyl derivative **3b** (and **2**)[5] are relatively resistant toward reduction past the dihydrobenzene oxidation state.

Radical dianion **23** undergoes protonation at C(9a) by the second equivalent of *t*-BuOH with complete stereoselectivity from the α-face to give radical anion **24**. Once again, we cannot distinguish between the conversion **22** → **23** → **24** and the alternative protonation of **22** followed by electron transfer to give **24**. Electron transfer from the fourth equivalent of potassium gives **4**.

Protonation of **23** at C(9a) probably occurs by kinetic control,[9a] perpendicular to the plane of the allylic carbanion system. If negative charge is localized at C(9a), then this carbon atom will be pyramidal, and protonation should occur with retention of configuration. In what appears to be the most stable configuration for **23**, perspective drawing **23a** shows that good orbital overlap is present, and electrostatic destabilization[9c] is minimized when the carbanion is in the α-orientation.[10]



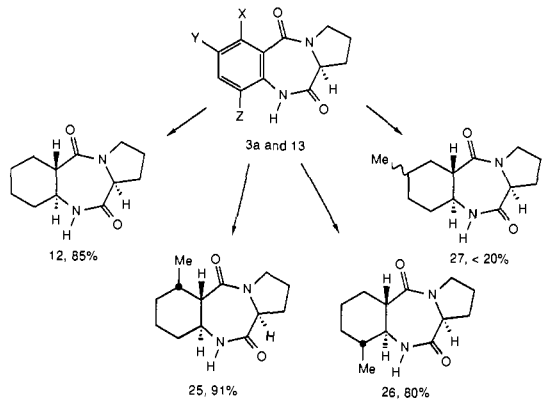
23a

(8) (*a*) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; Chapter 3. (b) Hook, J. M.; Mander, L. N. *Natl. Prod. Rep.* **1986**, *3*, 35. (c) Alternative routes for reductive alkylation of unsaturated hydrocarbons in liquid ammonia have recently been described: Müllen, K.; Huber, W.; Veumann, G.; Schnieders, C.; Unterberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 801.

(9) (a) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263. (b) Ghatak, U. R.; Chatterjee, N. R.; Banerjee, A. K.; Chakravarty, J.; Moore, R. E. *J. Org. Chem.* **1969**, *34*, 3739.

(10) Molecular mechanics minimization of **4** using Still's MacroModel molecular modeling program (version 1.1) revealed that 4 is ~2.6 kcal/mol more stable than the C(9a) diastereoisomer of **4**.

Scheme IV



The next question to be considered is the stereoselectivity of alkylation and protonation of enolate dianion **4** at C(5a). While we recognize that enolates exist as aggregates of dimers, tetramers, and even hexamers in the solid state,[11] the involvement of aggregates in the solution phase alkylation and protonation of enolates encountered in this study is at present unknown. For purposes of this discussion, we will assume that monomeric enolates are the species that undergo alkylation and protonation at C(5a).[12]

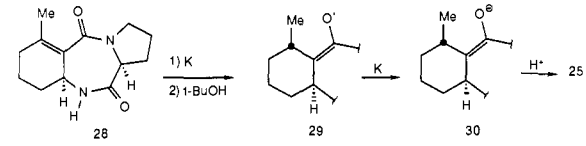
Alkylation of **4** occurs predominately from the α-face of the enolate with methyl iodide; stereoselectivity tends to improve in reductive alkylations of **3a** and **13a–c** with more sterically hindered alkyl halides. We view the ionized secondary amide bridge of **4** as a large structural unit because it ought to be solvated with ammonia (vide infra). Thus, steric approach control is sufficient to explain the preference for alkylation from the less-hindered α-face of the enolate.

Protonation of **4** at C(5a) is thought to occur by thermodynamic control when the enolate is quenched by slow addition of NH_4Cl. This procedure gave the more stable trans-fused β,γ-unsaturated amide **16** from Birch reduction of **13b** and predominately the more stable cis-fused **14b** from **13a**.[13] Rapid quenching of **4** (X = Z = H; Y = Me) with an excess of NH_4Cl resulted in increased amounts of the corresponding C(5a) diastereoisomer. Only the trans-fused isomer **5** could be detected in Birch reductions of **3**; slow addition of NH_4Cl in the enolate quenching step resulted in formation of substantial α,β-unsaturated amide **10**.

A consideration of mechanisms for protonation of enolate **4** is complicated by the potential for solvation of the enolate with ammonia. A recent X-ray characterization of a dimeric *N,N*-dimethylpropionamide lithium enolate–secondary amine complex has revealed hydrogen bonding between the hydrogen atom of the secondary amine and the pyramidalized amide enolate nitrogen atom.[14a] The arrangement of atoms in the complex is in agreement with experimental and theoretical studies that suggest enamines are kinetically protonated on the nitrogen atom.[14b,c] Furthermore, it is known that in the presence of proton-donating additives, proton transfer to an enolate on quenching with D_2O proceeds intramolecularly to some extent since only partial deuterium incorporation in the product is observed.[15,16] Thus, diastereoisomer ratios obtained from protonation of enolate **4** by rapid addition of excess NH_4Cl may reflect substantial intramolecular proton delivery. Stereoselectivities are at present difficult to predict (rationalize) under these conditions. Mechanistic arguments based on equilibrium control are amenable to molecular modeling of the relative stability of potential products; consequently, the stereoselectivity of Birch reductions of analogues of **3** and **13** under equilibrium control ought to be predictable.

Birch Reductions to the Hexahydrobenzene Oxidation State. In Birch reductions of **3** and **13**, traces of products containing saturated benzene rings were isolated from chromatographic separation of crude reaction mixtures. We have found that these hexahydrobenzenes can be obtained in excellent yields by the use of 8 equiv of potassium and 5 equiv of *t*-BuOH (Scheme IV). Thus, **3a** is converted to **12** in 85% isolated yield. This material was spectroscopically identical with that obtained from **5** by hydrogenation and clearly different from the C(5a) diastereoisomer **11** obtained from hydrogenation of **10**.

Pyrrolobenzodiazepine-5,11-dione **13a** provided **25** in 91% yield. Here, stereoselectivity follows from the suggestion that **14b** is produced during Birch reduction of **13a** with a large excess of *t*-BuOH. Base-induced isomerization of **14b** to the conjugated ene amide **28**, followed by electron transfer and protonation at



C(6) from the β-face of the radical anion would give **29**, in which steric interactions between the C(6) methyl substituent and the oxygen atom at C(5) are minimized. Electron transfer would give enolate **30**, and protonation with NH_4Cl under conditions of equilibrium control gives the trans-fused hexahydrobenzene derivative **25**. In contrast to **14b**, the trans ring fusion in **25** is the more stable because in **25** the C(6) methyl substituent is in a pseudoaxial orientation, away from the oxygen atom at C(5).

As expected **13c** gave **26** (80%), but **13b** could not be converted to **27** in a synthetically useful yield. With **13b**, the major reaction product was always the tetrahydro derivative **16**. An aversion toward further reduction is explained by a reluctance of the trisubstituted double bond in **16** to move into conjugation with the amide carbonyl group. This characteristic of Birch reductions of **13b** is what contributes to the excellent yields of tetrahydro products obtainable from **13b** and why the previously discussed equilibration at C(5a) proceeds without isomerization of the C(6)–C(7) double bond.

Removal of the Chiral Auxiliary. Several methods have been developed for removal of the proline unit from products of Birch reduction and reductive alkylation. The most straightforward consists of treatment with 50% aqueous sulfuric acid at 100 °C. Under these reaction conditions, the olefinic carboxylic acids liberated from **6a**, **6b**, and **6d** undergo protiolactonization to give the amino lactones **31a–c** in good to excellent yields. With the allyl derivative **6c** protiolactonization occurs at the side chain resulting in formation of a diastereoisomeric mixture of spirolactones **32**. The sulfuric acid method also was used for removal of the chiral auxiliary from the 7-methyl derivatives **17b** and **17d** to give amino lactones **33a,b**; however, the yield for conversion of the C(5a) hydro derivative **5** to **34** by the harsh sulfuric acid reaction conditions was poor and difficult to reproduce. By using an alternative hydrolysis procedure, **16** was converted to the

(11) (a) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. (b) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. (c) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764. (d) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462.

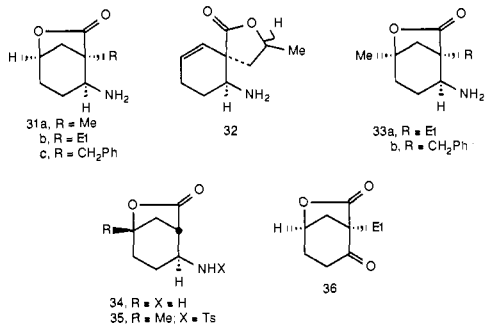
(12) In the case of hydrazone alkylations, for which X-ray structural data demonstrate aggregation in the solid state, stereoselectivities are said to be a result of steric and stereoelectronic factors rather than aggregation effects: Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078.

(13) Rankings of stabilities of diastereoisomers followed from an examination of Dreiding stereomodels, and relative energies were determined by use of the MacroModel program.[10] Stabilization of cis-fused **14b** relative to the trans-fused isomer by ~1.6 kcal/mol is the result of unfavorable eclipsing interactions between the C(6) methyl substituent and the carbonyl group at C(5) in the trans-fused isomer.

(14) (a) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (b) Müller, K.; Brown, L. D. *Helv. Chim. Acta* **1978**, *61*, 1407. (c) Müller, K. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1.

(15) (a) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318. (c) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M. *J. Org. Chem.* **1972**, *37*, 451. (d) Schultz, A. G.; Berger, M. H. *J. Org. Chem.* **1976**, *41*, 585. (e) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (f) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507. (g) Strazewski, P.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 1041.

(16) For a theoretical study of proton transfer to lithium enolate complexes, see: McKee, M. L. *J. Am. Chem. Soc.* **1987**, *109*, 559.



N-tosyl derivative **35** in reasonable overall yield (see Experimental Section).

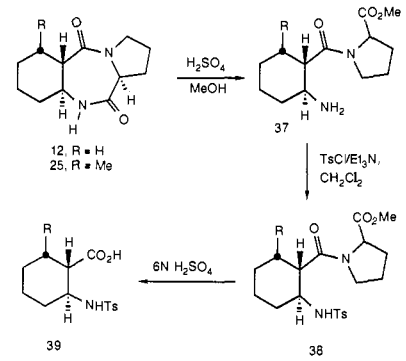
Lactonization is desirable for purposes of separation of the substrate from the chiral auxiliary.[17] Pure amino lactones are obtained after partitioning reaction components between chloroform and aqueous sodium carbonate solution. Amino lactones are somewhat unstable in neutral solvents and storage in the liquid state because of the potential for oligomerization via lactone ring aminolysis. The amino group of these substances is protonated in acid media, and, in this form, amino lactones are able to withstand the high reaction temperatures (100 °C) required for hydrolysis of the amide bonds in **6**, etc.

Oxidative deamination procedures allow a connection to be made between substrates of type **31** and products obtained from reductive alkylation of *o*-anisic acid derivatives.[1] The connection was demonstrated with **31b** by sequential treatment with 4-formyl-1-methylpyridinium benzene sulfonate and 1,4-diazabicyclo[4.3.0]non-5-ene (DBN);[18] the resulting keto lactone **36** was obtained in 82% isolated yield. The absolute configuration at C(2) in **36** is the same as that reported for Birch reduction–alkylation of the L-prolinol derived amide of *o*-anisic acid[1c] and opposite that obtained via the benzoxazepinone route.[1a]

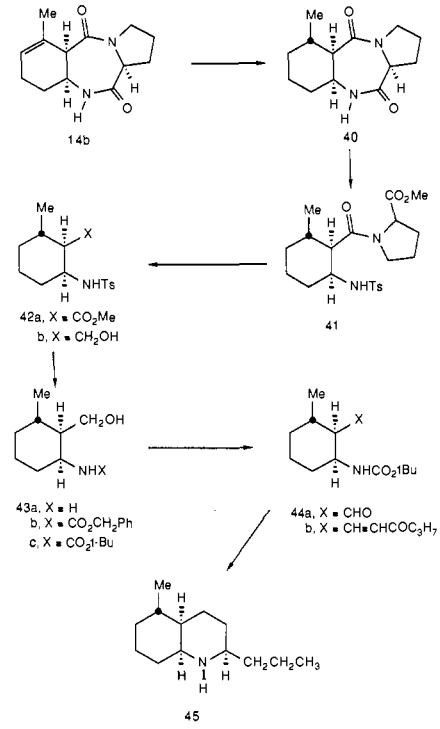
A special procedure for removal of the chiral auxiliary from hexahydrobenzene derivatives was required and is demonstrated here for **12** and **25** (Scheme V). Conversion to methyl esters **37a** and **37b**, followed by treatment with tosyl chloride–triethylamine gave **38a** and **38b**. Amide hydrolysis with 6 N H_2SO_4 gave tosylamide carboxylic acids **39a** and **39b** in 74 and 68% overall yields.

Total Synthesis of (+)-Pumiliotoxin C. The Dendrobatidae family of poison frogs native to South and Central America produce a wide variety of alkaloids.[19] The dendrobatid alkaloids have been grouped into six major classes, from which the pumiliotoxin C class is distinguished by a decahydroquinoline ring system. Several imaginative syntheses of pumiliotoxin C (**1**) have been recorded,[20,21] but none of these have employed an aromatic ring in a stereocontrolled synthesis of the trisubstituted cyclohexane ring present in **1**. Diels–Alder cycloadditions, a 2-methylcyclohexanone annelation, and a novel utilization of a chiral piperidine have characterized previous synthetic routes to **1**. Our completely

Scheme V



Scheme VI



enantioselective synthesis of (+)-pumiliotoxin C (**45**) features the previously discussed preparation of cis-fused tetrahydrobenzene **14b** from the pyrrolobenzodiazepine-5,11-dione **13a** (Scheme VI).

To realize a properly controlled synthesis of **45** from **14b**, we required a stereoselective reduction of the C(6)–C(7) double bond exclusively from the β-face. Hydrogenation of **14b** under heterogeneous conditions with 5% palladium on carbon gave an unfavorable 1:9 ratio of the desired **40** and its C(6) diastereoisomer (not shown). Molecular models of **14b**[13] show that the tertiary amide carbonyl group very effectively shields the β-face of the C(6)–C(7) double bond.

The proximity of the carbonyl group was used to advantage via coordination with a soluble iridium catalyst. As presented in an earlier report,[22] **14b** was hydrogenated with the homogeneous catalyst/solvent system $[Ir(cod)py(PCy_3)]PF_6/CH_2Cl_2$[23] to give **40** in quantitative yield with better than 99:1 diastereoselectivity[24] (Scheme VI). This highly stereoselective process for olefin hydrogenation is applicable to a wide range of substrates[22,25] and

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(18) (a) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446. (b) Steinberg, G. M.; Poziomek, E. J.; Hackley, B. E., Jr. *J. Org. Chem.* **1961**, *26*, 368.

(19) (a) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Meyers, C. W. *Toxicon* **1978**, *16*, 163. (b) Daly, J. W. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: Wien, 1982; Vol. 41, p 205. (c) Myers, C. W.; Daly, J. W.; Martinez, V. *American Museum Novitates*; 1984; no. *2783*, p 1.

(20) (a) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. (b) Oppolzer, W.; Frosti, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 590. (c) Hattori, K.; Matsumura, Y.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 7368. (d) Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441. (e) Abe, K.; Tsugoshi, T.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 335. (f) Bonin, M.; Royer, J.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1986**, *27*, 1569.

(21) For a review of syntheses of pumiliotoxin C prior to 1982, see: Witkop, B.; Gossinger, E. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, p 190.

(22) Schultz, A. G.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5905.

(23) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.

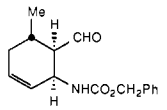
(24) Professor H. W. Thompson was one of the first investigators to report the control of stereochemistry in olefin hydrogenations by catalyst coordination to a neighboring functional group: Thompson, H. W. *J. Org. Chem.* **1971**, *36*, 2577 and references cited therein. For a more recent report and further examples of hydrogenations using the iridium catalyst, see: Thompson, H. W.; Wong, J. K. *J. Org. Chem.* **1985**, *50*, 4270.

(25) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

has proven to be an especially useful complement to the enantioselective Birch reduction–alkylation.[26]

Removal of the chiral auxiliary from **40** required acid-catalyzed methanolysis of the secondary amide followed by protection of the resulting primary amine as the tosylamide to give **41** without observable epimerization at C(5a). However, hydrolysis of the remaining amide bond in refluxing 6 N H_2SO_4 resulted in some epimerization, and, for this reason, the crude reaction product was treated with diazomethane; separation of reaction components by flash chromatography on silica gel gave the desired methyl ester **42a** (68% yield) and the C(5a) diastereoisomer (~8%).

Amino alcohol **43a** was obtained by lithium aluminum hydride reduction of **42a** to give **42b**, followed by reductive cleavage of the tosylamide with sodium in ammonia. At this stage, we were able to compare the relative configuration of **43a** with that of an intermediate **46** in the Overman synthesis of racemic pumiliotoxin C.[20a] This was accomplished by treatment of **43a** with benzyl chloroformate to give **43b** and conversion of **46** to racemic **43b** by reduction to the alcohol, olefin hydrogenation, and rederivatization with benzyl chloroformate.



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Manipulation of the benzyloxycarbonyl derivative **43b** proved troublesome, so that **43a** was converted to the *tert*-butyloxycarbonyl derivative **43c** in preparation for conversion to (+)-pumiliotoxin C. Swern oxidation[27] proceeded smoothly to give crystalline aldehyde **44a** in 88% yield. With **44a** in hand, we used Overman's procedure for condensation of **44a** with dimethyl-2-oxopentylphosphonate to give **44b** (90%) and conversion of **44b** to **45** by (1) hydrogenation, (2) cleavage of the *tert*-butyloxycarbonyl group and cyclization of the resulting saturated amino ketone to the imine, and (3) hydrogenation of the imine. The hydrochloride of **45** was crystallized from 2-propanol and exhibited the same rotation and melting point range as described in the literature.[28]

Experimental Section

Preparation of Isatoic Anhydrides. General Procedure. Isatoic anhydrides were obtained by a modification of a literature procedure.[29] Phosgene in toluene (20% w/w) was added over 30 min to a solution of the anthranilic acid (2.1 g, 13.9 mmol) in 3 mL of aqueous sodium hydroxide (1.2 g, 30 mmol) cooled to 0 °C. After the addition was complete, the mixture was stirred an additional 1 h at 0 °C and then was allowed to warm to room temperature. The product was collected by filtration, washed with water (2 × 10 mL) and ether (2 × 10 mL), and dried overnight under vacuum. The crystalline product was weighed to provide a yield of material suitable for use in the next experimental step. Analytical samples were prepared by recrystallization from ethanol.

5-Methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione. Quantitative yield of colorless crystals: mp 216–217 °C; IR (KBr) 5.63, 5.87 (broad), 6.32, 7.32 μm; ^{1}H NMR δ 2.75 (s, 3 H), 6.96 (d, 1 H, J = 8 Hz), 7.12 (d, 1 H, J = 8 Hz), 7.36 (t, 1 H, J = 7 Hz), 9.32 (br s, 1 H); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100), 160 (31). Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98. Found: C, 60.96; H, 3.85.

6-Methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione. Quantitative yield of colorless crystals: mp 244–246 °C; IR (KBr) 5.64, 5.74, 6.62, 7.45 μm; ^{1}H NMR δ 2.30 (s, 3 H), 6.94 (d, 1 H, J = 10 Hz), 7.28 (m, 1 H), 7.52 (d, 1 H, J = 8 Hz), 7.93 (br s, 1 H); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100), 160 (36). Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98. Found: C, 60.84; H, 4.04.

8-Methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione. Quantitative yield of colorless crystals: mp 274–276 °C (dec); IR (KBr) 3.10, 5.70 (br), 5.90 (br), 6.25, 9.90 μm; ^{1}H NMR δ 2.40 (s, 3 H), 7.14 (t, 1 H, J = 7.6 Hz), 7.50 (d, 1 H, J = 7.2 Hz), 7.93 (d, 1 H, J = 7.4 Hz); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100), 160 (33). Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98. Found: C, 60.88; H, 4.03.

Preparation of Pyrrolobenzodiazepine-5,11-diones. General Procedure. A mixture of the isatoic anhydride (10 g, 56.5 mmol), pyridine hydrochloride (6.53 g, 56.5 mmol), and L-proline (7.15 g, 62.2 mmol) was refluxed in pyridine for 6 h.[6c] Pyridine was removed under reduced pressure, and the remaining semisolid was partitioned between water and chloroform. The organic layer was washed with 1 N HCl (2 × 15 mL) and brine and dried over anhydrous magnesium sulfate. Concentration and trituration of the solid product with ethyl acetate gave colorless crystals of analytical purity.

(11a*S*)-6-Methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione (13a). 9.49 g, 73%: mp 207–208 °C; IR (KBr) 3.09, 6.20, 6.35, 7.28 μm; ^{1}H NMR δ 2.20 (m, 3 H), 2.54 (s, 3 H), 2.70 (m, 1 H), 3.54 (m, 1 H), 3.88 (m, 1 H), 4.06 (d, 1 H, J = 7 Hz), 5.78 (d, 1 H, J = 8 Hz), 6.08 (d, 1 H, J = 8 Hz), 7.30 (t, 1 H, J = 7 Hz), 7.66 (br s, 1 H); $[\alpha]^{22}_D$ +437° (c 0.49, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.85; H, 6.15.

(11a*S*)-7-Methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione (13b). 11.8 g, 91%: mp 248.5–249.5 °C; IR (KBr) 3.11, 6.00, 6.25 μm; ^{1}H NMR δ 2.00 (m, 3 H), 2.36 (s, 3 H), 2.72 (m, 1 H), 3.60 (m, 1 H), 3.80 (m, 1 H), 4.06 (d, 1 H, J = 6 Hz), 6.86 (d, 1 H, J = 9 Hz), 7.30 (d, 1 H), 7.76 (br s, 1 H), 7.80 (br s, 1 H); $[\alpha]^{23}_D$ +402° (c 1.00, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity), M + 1 (100). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.88; H, 6.23.

(11a*S*)-9-Methyl-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione (13c). 9.88 g, 76%: mp 160–161 °C; ^{1}H NMR δ 2.00 (m, 3 H), 2.32 (s, 3 H), 2.70 (m, 1 H), 3.58 (m, 1 H), 3.84, (m, 1 H), 4.06 (d, 1 H, J = 7 Hz), 7.18 (t, 1 H, J = 8 Hz), 7.36 (d, 1 H, J = 8 Hz), 7.58 (br s, 1 H), 8.82 (d, 1 H, J = 8 Hz); $[\alpha]^{23}_D$ +396° (c 2.48, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13. Found: C, 67.74; H, 6.14.

Birch Reduction and Reductive Alkylation of Pyrrolobenzodiazepine-5,11-diones. To a mixture of **3a**[6] or **13** (2.3 mmol) in dry THF (3 mL) and *tert*-butyl alcohol (0.42 mL, 4.6 mmol) was added ~60 mL of ammonia (distilled from sodium). Potassium (0.394 g, 10.1 mmol) was added at −33 °C, and the resulting blue solution was stirred at −78 °C for 45 min. The blue coloration was dissipated with pentadiene (several drops), the alkylation agent was added via syringe (3–5 equiv), and the mixture was stirred for 1.5 h at −78 °C. Solid NH_4Cl was added, and the ammonia was allowed to evaporate. The resulting residue was partitioned between $CHCl_3$ and water. The organic layer was washed with 10% sodium thiosulfate solution (5 mL), dried over $MgSO_4$, concentrated, and purified as described.

Protonation of the enolate under "kinetic conditions" was accomplished with a large excess of solid ammonium chloride that was added *rapidly* at −78 °C to give a colorless mixture. Evaporation of the ammonia and standard workup gave **5**, **16**, and **18**. **10** as well as diastereomerically pure **16** were obtained under "equilibrating conditions" when only several equiv of solid ammonium chloride were added to the Birch reduction mixture. Reductive alkylation and protonation of **13a** needed only 1 equiv of *tert*-butyl alcohol for the best yields of **14a** and **14b**. Hexahydrobenzenes **12** and **25** were obtained by addition of 5 equiv of *tert*-butyl alcohol (**26** required 6 equiv), followed by addition of ~8 equiv of potassium; under these conditions, the blue coloration persisted for ~20 min.

(5a*R*,9a*S*,11a*S*)-5a-Methyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6a). Reductive alkylation of **3a** with methyl iodide and product separation by flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1, R_f .25) gave essentially pure **6a** as a colorless solid (286 mg, 54%). Recrystallization from ethyl acetate gave colorless crystals: mp 245.5–247 °C; IR (KBr) 3.12, 3.43, 6.05, 6.25, 7.24 μm; ^{1}H NMR δ 1.38 (s, 3 H), 1.82 (m, 3 H), 2.04 (m, 3 H), 2.60 (m, 1 H), 3.47 (m, 1 H), 3.66 (m, 1 H), 4.03 (br s, 1 H), 4.63 (m, 1 H, J = 7.6, 4.5 Hz), 5.64 (br d, 1 H), 5.68 (br s, 1 H), 6.17 (br d, 1 H, J = 10 Hz); $[\alpha]^{25}_D$ +44.4° (c 0.27, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{17}N_2O_2$: C, 66.93; H, 7.35. Found: C, 66.74; H, 7.48.

An earlier fraction contained a mixture of **6a** and **7a** (~1:4) from which ^{1}H NMR signals for **7a** compared favorably to those of the minor diastereoisomer corresponding to **17a** (isolated from reductive methylation of **13b**). Diagnostic resonances in the ^{1}H NMR used to determine the diastereomeric ratio as well as to characterize the minor diastereomer were the C(5a) angular methyl at 1.24 ppm (s, 3 H), and the C(11a) methine proton at 4.50 (t, 1 H, J = 8 Hz).

(26) Reference 1d describes the utilization of carboxamide group-directed hydrogenations of enol ethers in total syntheses of nitramine alkaloids.
(27) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(28) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204.
(29) Hardtmann, G. E.; Koletar, G.; Pfister, O. R. *J. Heterocycl. Chem.* **1975**, *12*, 565.

(9*R*,11a*S*)-9-Methyl-1,2,3,8,10,11,11a-heptahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8a). The reaction that produced **6a** also gave **8a** from the flash chromatography (79 mg, 15%, R_f 0.43). Recrystallization from ethyl acetate gave colorless crystals: mp 216–218 °C; ^{1}H NMR δ 1.08 (d, 3 H, J = 7 Hz), 1.90–2.36 (m, 4 H), 2.44–2.78 (m, 3 H), 3.52 (m, 1 H), 3.68 (m, 1 H), 4.16 (br d, 1 H), 5.66 (br t, 1 H), 6.54 (dd, 1 H, J = 9, 3 Hz), 7.50 (br s, 1 H); $[\alpha]^{23}_D$ +348° (c 0.41, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.23; H, 6.94. Found: C, 67.26; H, 6.93.

(5a*R*,9a*S*,11a*S*)-5a-Ethyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6b). Reductive alkylation of **3a** with ethyl iodide and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (388 mg, 68%). Recrystallization from ethyl acetate gave colorless crystals: mp 220.5–221.5 °C; IR (KBr) 3.10, 3.38, 5.93, 6.23, 7.10 μm; ^{1}H NMR δ 0.91 (t, 3 H, J = 8 Hz), 1.53 (m, 1 H), 1.64–2.10 (m, 8 H), 2.59 (m, 1 H), 3.60 (m, 1 H), 3.67 (m, 1 H), 4.23 (br s, 1 H), 4.64 (dd, 1 H, J = 8, 5 Hz), 5.88 (m, 2 H), 6.10 (br d, 1 H, J = 11 Hz), $[\alpha]^{26}_D$ +48.8° (c 0.76, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12. Found: C, 67.58; H, 8.03.

(5a*R*,9a*S*,11a*S*)-5a-Allyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6c). Reductive alkylation of **3a** with 1,3-dibromopropane and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (526 mg, 88%). Recrystallization from ethyl acetate gave colorless crystals: mp 176–177 °C; IR (KBr) 3.11, 3.38, 5.95, 6.22 μm; ^{1}H NMR δ 1.70–2.34 (m, 8 H), 2.60 (m, 1 H), 2.84 (dd, 1 H, J = 14, 6 Hz), 3.56 (m, 1 H), 3.64 (m, 1 H), 4.28 (br s, 1 H), 4.62 (dd, 1 H, J = 8, 4 Hz), 5.12 (m, 1 H), 5.20 (s, 1 H), 5.75 (m, 2 H), 5.94 (br s, 1 H), 6.15 (m, 1 H); $[\alpha]^{23}_D$ +103° (c 0.64, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74. Found: C, 68.98; H, 7.74.

This same material was obtained in 62% yield by reductive alkylation of **3a** with allyl bromide.

(5a*R*,9a*S*,11a*S*)-5a-Benzyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6d). Reductive alkylation of **3a** with benzyl bromide and flash chromatography on silica gel (EtOAc–hexane, 4:1) gave a colorless solid (485 mg, 68%). Recrystallization from ethyl acetate–hexane (4:1) gave colorless crystals: mp 170–171 °C; IR (KBr) 3.11, 3.24, 3.43, 5.98, 6.15, 7.10 μm; ^{1}H NMR 1.40–2.44 (m, 8 H), 2.71 (d, 1 H, J = 15 Hz), 3.55 (m, 3 H, 3.43 overlapping doublet, 1 H, J = 15 Hz), 4.25 (m, 1 H), 5.63 (br s, 1 H), 5.82 (m, 1 H), 6.33 (br d, J = 10 Hz), 7.20 (m, 2 H), 7.28 (m, 3 H); $[\alpha]^{23}_D$ +61.3° (c 1.94, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14. Found: C, 73.68; H, 7.05.

(5a*R*,9a*S*,11a*S*)-5a-(3-Chloropropyl)-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6e). Reductive alkylation of **3a** with 1-bromo-3-chloropropane and chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (300 mg, 44%) which slowly decomposed at room temperature: ^{1}H NMR δ 1.66–2.30 (m, 11 H), 2.64 (m, 1 H), 3.38–3.66 (m, 2 H, 3.72 overlapping hept, 1 H), 4.22 (br s, 1 H), 4.68 (dd, 1 H, J = 8, 5 Hz), 5.72–5.88 (m, 2 H), 6.16 (br d, 1 H, J = 11 Hz); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100), 261 (43).

(5a*R*,9a*S*,11a*S*)-5a-(3-Butenyl)-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (6f). Reductive alkylation of **3a** with 4-bromo-1-butene and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (158 mg, 25%): ^{1}H NMR δ 1.50–2.30 (m, 10 H), 2.60 (m, 1 H), 3.56 (m, 1 H), 3.68 (m, 1 H), 4.28 (br s, 1 H), 4.66 (dd, 1 H, J = 8, 5 Hz), 4.88 (d, 1 H, J = 10 Hz, 5.06 overlapping doublet, 1 H, J = 16 Hz), 5.64–5.96 (m, 3 H), 6.10 (br d, 1 H, J = 10 Hz); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100).

(5a*S*,9a*R*,11a*S*)-1,2,3,5a,8,9,9a,10,11,11a-Decahydro-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepine-5,11-dione (5). Birch reduction of **3a** and enolate quenching under "kinetic conditions" followed by flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (369 mg, 73%, R_f .20). Recrystallization from ethyl acetate gave colorless crystals: mp 185–186 °C; IR (KBr) 3.10, 3.40, 5.92, 6.22, 6.94 μm; ^{1}H NMR δ 1.55–2.16 (m, 5 H), 2.27 (m, 2 H), 2.61 (m, 1 H), 3.06 (m, 1 H), 3.65 (t, 3 H, J = 7 Hz), 3.86 (m, 1 H), 4.67 (t, 1 H, J = 8 Hz), 5.78 (m, 1 H), 6.12 (d, 1 H, J = 10 Hz), 6.37 (br s, 1 H); $[\alpha]^{22}_D$ +51.2° (c 1.16, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32. Found: C, 65.39; H, 7.35.

(11a*S*)-1,2,3,8,10,11,11a-Heptahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (8, R = H). Obtained from Birch reduction of **3a** (125 mg, 25%, R_f 0.30). Recrystallization from ethyl acetate–hexane (9:1) gave colorless needles: mp 181–183 °C; IR (KBr) 3.08, 5.96, 6.25, 7.04 μm; ^{1}H NMR δ 1.76–2.14 (m, 4 H), 2.20–2.50 (m, 4 H), 2.70 (m, 1 H), 4.56 (m, 1 H), 4.63 (m, 1 H), 4.12 (dd, 1 H, J = 11, 3 Hz), 5.98 (m, 1 H), 6.67 (d, 1 H, J = 10 Hz), 8.20 (br s, 1 H); $[\alpha]^{27}_D$ +766° (c 1.28, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.05; H, 6.46. Found: C, 66.16; H, 6.40.

(9a*S*,11a*S*)-1,2,3,7,8,9,9a,10,11,11a-Decahydro-5*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-dione (10). Birch reduction of **3a** and enolate quenching under "equilibrating conditions" with NH_4Cl followed by chromatography on silica gel (EtOAc–MeOH, 19:1) gave a colorless solid (405 mg, 80%). Recrystallization from ethyl acetate-hexane (4:1) gave colorless cubes: mp 95–96 °C; IR (KBr) 3.80, 3.41, 5.99, 6.14, 6.28 μm; ^{1}H NMR δ 1.20–2.40 (m, 9 H), 2.60 (m, 1 H), 3.66 (m, 2 H), 4.42 (br s, 1 H), 4.61 (dd, 1 H, J = 8, 4 Hz), 6.00 (br s, 1 H), 7.24 (br s, 1 H); $[\alpha]^{23}_D$ −60.6° (c 1.04, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32. Found: C, 65.39; H, 7.31.

10 also was prepared by isomerization of **5** in potassium carbonate–methanol solution (>90%).

(5a*S*,9a*S*,11a*S*)-5a,6-Dimethyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (14a). Reductive alkylation of **13a** with methyl iodide and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (284 mg, 53%). Recrystallization from ethyl acetate gave colorless crystals: mp 168–169 °C; IR (film) 3.37, 5.98, 6.18, 7.19 μm; ^{1}H NMR δ 1.51 (s, 3 H), 1.76–1.86 (m, 6 H), 2.00–2.24 (m, 4 H), 2.42–2.61 (m, 1 H), 3.48–3.80 (m, 2 H), 3.88 (t, 1 H, J = 6 Hz), 4.54 (t, 1 H, J = 7.6 Hz), 5.40 (br s, 1 H), 5.96 (br d, 1 H); $[\alpha]^{28}_D$ −45.6° (c 1.54, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.68; H, 8.11. Found: C, 67.41; H, 8.13.

(5a*R*,9a*S*,11a*S*)-6-Methyl-1,2,3,5a,8,9,9a,10,11,11a-decahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione (14b). Birch reduction of **13a** and flash chromatography on silica gel (EtOAc–$CHCl_3$, 9:1) gave ~300 mg of a colorless solid as an inseparable mixture of **14a** and the C(5a) epimer (~5:1). The yield of **14a** based on ^{1}H NMR integration of this mixture was 49%: IR (KBr) 3.12, 3.42, 6.13 (br), 7.04 μm; ^{1}H NMR (major diastereoisomer) δ 1.50–2.32 (m, 7 H), 1.76 (overlapping br singlet, 3 H), 2.78 (m, 1 H), 3.38–3.80 (m, 4 H), 4.58 (br d, 1 H), 5.52 (br s, 1 H), 5.67 (br s, 1 H); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$ (mixture of diastereomers): C, 66.65; H, 7.74. Found: C, 66.57; H, 7.66.

(5a*S*,9a*R*,11a*S*)-7-Methyl-1,2,3,5a,8,9,9a,10,11,11a-decahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (16). Birch reduction of **13b** and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (454 mg, 84%). Recrystallization from ethyl acetate gave colorless needles: mp 193–195 °C; IR (KBr) 3.13, 5.94, 6.15, 7.10 μm; ^{1}H NMR δ 1.54–2.30 (m, 7 H, 1.73 overlapping br singlet, 3 H), 2.60 (m, 1 H), 3.02 (br d, 1 H), 3.65 (t, 2 H, J = 6.7 Hz), 3.81 (m, 1 H), 4.54 (t, 1 H, J = 8 Hz), 5.82 (br s, 2 H); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.65; H, 7.74. Found: C, 66.50; H, 7.67.

(5a*R*,9a*S*,11a*S*)-5a,7-Dimethyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (17a). Reductive alkylation of **13b** with methyl iodide and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a 2.4:1 mixture of diastereomers. Recrystallization from ethyl acetate gave **17a** as colorless crystals: mp 172–173 °C; R_f 0.31; IR (film) 3.36, 5.96, 6.20, 7.10 μm; ^{1}H NMR δ 1.39 (s, 3 H), 1.70 (s, 1 H), 1.80–2.18 (m, 7 H), 2.65 (m, 1 H), 3.40–3.80 (m, 2 H), 4.00 (br d, 1 H, J = 4 Hz), 4.68 (dd, 1 H, J = 8, 6 Hz), 5.78 (br s, 1 H), 5.92 (br s, 1 H); $[\alpha]^{24}_D$ +57.7° (c 5.65, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100). Concentration of the mother liquor and recrystallization from ethyl acetate gave the minor diastereomer as colorless crystals: mp 200 °C dec; R_f 0.36; IR (film); ^{1}H NMR δ 1.21 (s, 3 H), 1.70 (s, 3 H), 1.72–2.20 (m, 7 H), 2.42–2.62 (m, 1 H), 3.48–3.82 (m, 2 H), 3.96–4.10 (m, 1 H), 4.50 (t, 1 H, J = 8 Hz), 5.66–5.80 (br s, 1 H), 5.96 (br s, 1 H); $[\alpha]^{27}_D$ −49.5° (c 4.44, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (100).

(5a*R*,9a*S*,11a*S*)-5a-Ethyl-7-methyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (17b). Reductive alkylation of **13b** with ethyl iodide and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave an 8:1 mixture of diastereomers as a colorless solid (494 mg, 87%). Recrystallization from ethyl acetate gave **17b** as colorless crystals: mp 168–169 °C; IR (film) 3.37, 5.96, 6.20, 7.14 μm; ^{1}H NMR δ 0.94 (t, 3 H, J = 7.6 Hz), 1.69 (s, 3 H), 1.82–2.06 (m, 9 H), 2.54–2.74 (m, 1 H), 3.48–3.80 (m, 2 H), 4.22 (br s, 1 H), 4.68 (dd, 1 H, J = 8, 6 Hz), 5.70 (br s, 1 H), 5.86 (s, 1 H), 6.16 (br d, 1 H); $[\alpha]^{25}_D$ +66.5° (c 10.6, $CHCl_3$); chemical ionization mass spectrum m/z (rel intensity) M + 1 (100).

(5a*R*,9a*S*,11a*S*)-5a-Allyl-7-methyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (17c). Reductive alkylation of **13b** with allyl bromide and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a collorless solid (403 mg, 68%). Recrystallization from ethyl acetate gave colorless crystals: mp 151–152 °C; IR (film) 3.40, 5.96, 6.20, 7.10 μm; ^1H NMR δ 1.58 (s, 3 H), 1.75–2.17 (m, 8 H), 2.52–2.70 (m, 1 H), 2.74–2.88 (m, 1 H), 3.40–3.78 (m, 2 H), 4.20 (d, 1 H, *J* = 2.7 Hz), 4.60 (dd, 1 H, *J* = 8, 6 Hz), 5.09 (d, 1 H, *J* = 5 Hz), 5.14 (s, 1 H), 5.62–5.82 (m, 2 H), 5.84 (s, 1 H); $[\alpha]^{27}_D$ +75.4° (*c* 1.11, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100), 303 (27), 315 (9). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08. Found: C, 70.03; H, 8.12.

(5a*R*,9a*S*,11a*S*)-5a-Benzyl-7-methyl-1,2,3,8,9,9a,10,11,11a-nonahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (17d). Reductive alkylation of **13b** with benzyl bromide and flash chromatography on silica gel (EtOAc–$CHCl_3$, 4:1) gave a colorless solid (546 mg, 78%). Recrystallization from ethyl acetate gave colorless crystals: mp 205–206 °C; IR (film) 3.30, 5.93, 6.20, 7.10 μm; ^1H NMR δ 1.24–2.10 (m, 9 H), 2.24–2.44 (m, 2 H), 2.62 (d, 1 H, *J* = 14 Hz), 3.28–3.64 (m, 3 H, overlapping doublet, 1 H, *J* = 14 Hz), 4.21 (br s, 1 H), 5.62 (br s, 1 H), 6.08 (s, 1 H), 7.15 (m, 3 H), 7.30 (m, 2 H); $[\alpha]^{27}_D$ +49.7° (*c* 1.77, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46. Found: C, 74.05; H, 7.42.

(5a*S*,9*R*,9a*R*,11a*S*)-9-Methyl-1,2,3,5a,8,9,9a,10,11,11a-decahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (18). Birch reduction of **13c** and flash chromatography on silica gel (EtOAc–$CHCl_3$, 9:1) gave a colorless solid (264 mg, 49%). Recrystallization from ethyl acetate–hexanes (9:1) gave colorless crystals: mp 176–177 °C; IR (KBr) 3.12, 5.95, 6.22 μm; ^1H NMR δ 1.10 (d, 3 H, *J* = 6 Hz), 1.68–2.01 (m, 4 H, 2.06 overlapping sextet, 1 H), 2.32 (m, 1 H), 3.00 (m, 1 H), 3.10 (br d, 1 H), 3.54 (dd, 1 H, *J* = 12, 8 Hz, 3.64, overlapping triplet, 2 H, *J* = 7 Hz), 4.56 (t, 1 H, *J* = 7.6 Hz), 5.66 (m, 1 H), 5.98 (br d, 1 H), 6.08 (d, 1 H, *J* = 10 Hz); $[\alpha]^{21}_D$ +26.1° (*c* 1.20, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.68; H, 7.74. Found: C, 66.69; H, 7.84.

(5a*S*,9a*S*,11a*S*)-Perhydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (12). Birch reduction of **3a** with ~8 equiv of potassium and flash chromatography on silica gel (EtOAc–MeOH, 9:1) gave a colorless solid (434 mg, 85%). Recrystallization from ethyl acetate gave colorless crystals: mp 225–226 °C; IR (KBr) 3.11, 3.42, 5.96, 6.30 μm; ^1H NMR δ 1.29 (br m, 4 H), 1.62–2.08 (m, 6 H), 2.18 (br t, 1 H), 2.34–2.68 (m, 2 H), 3.56 (m, 3 H), 4.56 (t, 1 H, *J* = 7 Hz), 6.36 (br s, 1 H); $[\alpha]^{20}_D$ +54.5° (*c* 0.61, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.85; H, 8.15. Found: C, 64.74; H, 8.14.

12 also was prepared in approximately quantitative yield by hydrogenation of **5** in methanol with 5% Pd/C. Hydrogenation of **10** under these same conditions provided an inseparable mixture of **11** and **12** (~40:60) as judged by ^1H NMR analysis. No further reaction characterization was attempted.

(5a*S*,6*S*,9a*S*,11a*S*)-6-Methylperhydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (25). Birch reduction of **13a** with ~8 equiv of potassium gave a crude reaction product that was obtained in an essentially pure state (490 mg, 91%). An analytical sample was prepared by recrystallization from ethyl acetate to give colorless crystals: mp 253 °C; IR (KBr) 3.12, 5.95, 6.34 μm; ^1H NMR δ 0.92 (d, 3 H, *J* = 7 Hz), 1.20 (m, 1 H), 1.50–2.16 (m, 8 H), 2.32 (dd, 1 H, *J* = 12, 4 Hz), 2.60 (m, 1 H), 2.82 (m, 1 H), 4.28–4.94 (m, 3 H), 4.56 (t, 1 H, *J* = 7 Hz), 5.48 (br s, 1 H); $[\alpha]^{25}_D$ +80.4° (*c* 0.98, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.04; H, 8.52. Found: C, 66.20; H, 8.67.

(5a*S*,9*R*,9a*S*,11a*S*)-9-Methylperhydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (26). Birch reduction of **13c** with ~8 equiv of potassium and flash chromatography on silica gel (EtOAc–MeOH, 9:1) gave a colorless solid (440 mg, 86%). Recrystallization from ethyl acetate gave colorless crystals: mp 199–200 °C; IR (film) 3.33, 3.40, 5.95, 6.24, 7.04 μm; ^1H NMR δ 1.08 (d, 3 H, *J* = 6 Hz), 1.12–1.58 (m, 4 H), 1.62–2.10 (m, 5 H), 2.14–2.34 (m, 1 H), 2.36–2.70 (m, 2 H), 3.08–3.30 (m, 1 H), 3.40–3.72 (m, 2 H), 4.58 (t, 1 H, *J* = 7 Hz), 6.66 (br d, 1 H); $[\alpha]^{25}_D$ +30.5° (*c* 6.70, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100).

General Procedure for Preparation of Amino Lactones. A mixture of **6** or **17** (1 mmol) in 2 mL of water–sulfuric acid (1:1, v/v) was heated to 100 °C for 6–12 h. The reaction mixture was cooled, diluted with water (1 mL), and made basic with solid sodium bicarbonate. Extraction with chloroform (3 × 10 mL), followed by drying over anhydrous magnesium sulfate, and concentration provided the essentially pure amino lactones; further purification by distillation in a Kugelrohr apparatus gave the analytical samples.

(1*R*,4*R*,5*S*)-4-Methyl-5-amino-2-oxabicyclo[3.2.1]octan-3-one (31a). Obtained 96 mg (62%) of a colorless oil: bp ~80–84 °C (0.5 mmHg); IR (film) 2.96, 3.40, 5.65, 9.25 μm; ^1H NMR δ 1.27 (s, 3 H), 1.27–1.68 (m, 2 H, 1.41, overlapping br singlet, 2 H), 1.72 (d, 1 H, *J* = 12 Hz), 2.10 (m, 2 H), 2.36 (m, 1 H), 2.71 (m, 1 H), 4.72 (t, 1 H, *J* = 6 Hz); $[\alpha]^{25}_D$ +19.7° (*c* 1.52, MeOH); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44. Found: C, 61.73; H, 8.56.

(1*R*,4*R*,5*S*)-4-Ethyl-5-amino-2-oxabicyclo[3.2.1]octan-3-one (31b). Obtained 138 mg (82%) of a colorless oil: bp ~80–82 °C (0.5 mmHg); IR (film) 2.94, 3.36, 5.68, 8.70 μm; ^1H NMR δ 0.91 (t, 3 H, *J* = 7 Hz), 1.20–1.42 (m, 2 H, 1.39, overlapping singlet, 2 H), 1.44–1.82 (m, 3 H), 1.96–2.16 (m, 2 H), 2.30 (m, 1 H), 2.84 (dd, 1 H, *J* = 12, 6 Hz), 4.71 (t, 1 H, *J* = 6 Hz); $[\alpha]^{24}_D$ +7.6° (*c* 2.4, MeOH); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93. Found: C, 63.79; H, 8.98.

(1*R*,4*R*,5*S*)-4-Benzyl-5-amino-2-oxabicyclo[3.2.1]octan-3-one (31c). Obtained 189 mg (82%) of a colorless oil: bp ~110 °C (0.5 mmHg); IR (film) 2.95, 3.36, 5.68, 6.87 μm; ^1H NMR δ 1.27–1.66 (m, 5 H), 1.96–2.28 (m, 3 H), 2.81 (t, 1 H, *J* = 6 Hz, 2.91 overlapping doublet, 1 H, *J* = 18 Hz), 3.25 (d, 1 H, *J* = 18 Hz), 4.64 (dd, 1 H, *J* = 7, 4 Hz), 7.26 (m, 5 H); $[\alpha]^{27}_D$ −16.4° (*c* 1.44, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.79; H, 7.51.

2-Oxo-4(*R*,*S*)-methyltetrahydrofuran-3(*R*)-spiro-2′-[(1*S*)-aminocyclohex-3′-ene] (32). Obtained as a 4:1 mixture of diastereomers (148 mg, 82%). The mixture was treated with acetic anhydride–pyridine to give a mixture of diastereoisomeric acetamides, and fractional crystallization from ethanol gave the acetamide derivative of the major diastereomer as colorless crystals: mp 140–141 °C; IR (KBr) 3.20, 3.42, 5.70, 6.05, 6.33 μm; ^1H NMR δ 1.39 (d, 3 H, *J* = 6 Hz), 1.70 (m, 1 H), 1.80–2.44 (m, 5 H), 2.00 (s, 3 H), 4.14 (m, 1 H), 4.50–4.79 (m, 1 H), 5.61, (br d, 1 H), 5.92 (br s, 1 H), 5.96 (m, 1 H); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.56; H, 7.67. Found: C, 64.59; H, 7.68.

(1*R*,4*R*,5*S*)-1-Methyl-4-ethyl-5-amino-2-oxabicyclo[3.2.1]octan-3-one (33a). Obtained 139 mg (76%) of a colorless oil: bp ~59 °C (0.5 mmHg); IR (film) 3.37, 5.75, 6.22; ^1H NMR δ 0.84 (t, 3 H, *J* = 7.5 Hz), 1.15–2.09 (m, 9 H), 1.28 (br s, 2 H), 1.40 (s, 3 H), 2.20–2.83 (dd, 1 H, *J* = 11.7, 6 Hz); $[\alpha]^{25}_D$ −12.7° (*c* 9.74, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35. Found: C, 65.46; H, 9.26.

(1*R*,4*R*,5*S*)-1-Methyl-4-benzyl-5-amino-2-oxabicyclo[3.2.1]octan-3-one (33b). Obtained 117 mg (60%) of a colorless oil: bp 80 °C (0.5 mmHg); solidifies on standing; mp 175–176 °C; IR (film) 3.40, 5.70, 6.25, 6.68, 6.86 μm; ^1H NMR δ 1.36 (s, 3 H), 1.18–1.64 (m, 5 H), 1.78–2.16 (m, 3 H), 2.75 (q, 1 H), 2.92 (d, 1 H, *J* = 14 Hz), 3.16 (d, 1 H, *J* = 14 Hz), 7.16–7.36 (m, 5 H); $[\alpha]^{27}_D$ +49.7° (*c* 1.77, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.50; H, 7.79.

(1*R*,4*S*,5*S*)-1-Methyl-5-(*N*-tosylamino)-2-oxabicyclo[3.2.1]octan-3-one (35). Treatment of the corresponding sulfonamide methyl ester (prepared as described for **38** in 55% yield) with 6 N sulfuric acid for 12 h at 100 °C followed by the usual workup gave the amino lactone **35**, along with minor amounts of the corresponding carboxylic acid which could be removed by washing with saturated sodium bicarbonate solution. Purification by flash chromatography on silica gel (EtOAc–CH_2Cl_2, 20:1) gave **35** (241 mg, 78%) as a colorless solid. Recrystallization from ethyl acetate–hexanes (9:1) gave colorless crystals: mp 130–131 °C; IR (film) 3.07, 5.68, 8.66 μm; ^1H NMR δ 1.38 (s, 3 H), 1.50–2.00 (m, 5 H), 2.10 (d, 1 H, *J* = 13 Hz), 2.41 (s, 3 H), 2.84 (br t, 1 H), 3.54 (br q, 1 H), 5.95 (br s, 1 H), 7.36 (d, 2 H, *J* = 8 Hz), 7.99 (d, 2 H, *J* = 8 Hz); $[\alpha]^{24}_D$ +17.0° (*c* 2.06, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{15}H_{18}NO_4S$: C, 58.42; H, 5.88. Found: C, 58.27; H, 6.13.

(1*R*,4*R*)-4-Ethyl-2-oxabicyclo[3.2.1]octan-3,5-dione (36). Following the procedure described by Rappoport and Buckley,[18a] a solution of the amino lactone **31a** (136 mg, 0.81 mmol) in 5.2 mL of dry CH_2Cl_2 and 2.3 mL of dry DMF was prepared, and to this was added 4-formyl-1-methylpyridinium benzenesulfonate (272 mg, 0.97 mmol). Monitoring the reaction by TLC showed that **31b** was consumed in 15 min. 1,5-Diazabicyclo[4.3.0]non-5-ene (301 mg, 2.43 mmol) was added, and the resulting solution was stirred for 10 min and quenched with 8 mL of cold, saturated oxalic acid solution. The mixture was extracted with ether (3 × 10 mL), and the combined ether extracts were washed with brine. After drying over anhydrous $MgSO_4$, the solvent was evaporated to give essentially pure **36**. An analytical sample was prepared by recrystallization from ether: colorless needles, mp 54–55 °C; IR (KBr) 3.38, 5.69, 5.88 μm; ^1H NMR δ 0.92 (t, 3 H, *J* = 7 Hz), 1.70–2.16 (m, 4 H), 2.48

(m, 1 H), 2.54–2.80 (m, 3 H), 5.00 (m, 1 H); chemical ionization mass spectrum, *m/z* (rel intensity) 169 (M + 1, 100), 124 (73). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.28; H, 6.97.

(1*S*,2*S*)-2-(*N*-Tosylamino)-1-[((2*S*)-2-carbomethoxypyrrolidinyl)-carbonyl]cyclohexane (38a). A solution of **12** (222 mg, 1 mmol) in dry methanol (5 mL) and sulfuric acid (~2 equiv) was refluxed for 18 h. The reaction mixture was cooled, and the volume was reduced by one half. Saturated sodium bicarbonate solution was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). After drying over anhydrous $MgSO_4$, the solution was concentrated to ~5 mL, then tosyl chloride (209 mg, 1.1 mmol) and triethylamine (0.21 mL, 1.5 mmol) were added, and the resulting solution was stirred for 48 h. The mixture was washed with water, then dried over $MgSO_4$, and concentrated to give a yellow solid. Flash chromatography on silica gel (ethyl acetate–hexanes, 9:1) gave **37a** (351 mg, 86%) as a colorless solid. Recrystallization from ether–ethyl acetate (4:1) afforded colorless needles: mp 121 °C; IR (KBr) 3.14, 3.50, 5.78, 6.24, 6.90 μm; ^{1}H NMR δ 1.20–1.90 (m, 8 H), 1.90–2.32 (m, 4 H), 2.39 (s, 3 H), 2.66 (dt, 1 H, *J* = 11, 4 Hz), 3.55 (br t, 1 H), 3.57 (m, 1 H), 3.83 (s, 3 H), 3.94 (m, 1 H), 4.54 (dd, 1 H, *J* = 8, 4 Hz), 5.44 (br s, 1 H), 7.30 (d, 2 H, *J* = 8 Hz), 7.77 (d, 2 H, *J* = 8 Hz); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{20}H_{28}NO_5S$: C, 58.82; H, 6.90. Found: C, 58.92; H, 6.92.

(1*S*,2*S*,6*S*)-2-(*N*-Tosylamino)-6-methyl-1-[((2*S*)-2-carbomethoxy-pyrrolidinyl)carbonyl]cyclohexane (38b). Subjecting **25** to the conditions described for the preparation of **37a**, followed by flash chromatography on silica gel (EtOAc–hexane, 4:1), gave **37b** (321 mg, 76%) as a light yellow gum: IR (film) 3.06, 3.38, 5.75, 6.14 μm; ^{1}H NMR δ 0.80 (d, 3 H, *J* = 8 Hz), 1.16–2.01 (m, 11 H), 2.34 (s, 3 H), 2.78 (t, 1 H), 3.46 (m, 2 H), 3.78 (m, 1 H, 3.78, overlapping singlet, 3 H), 4.41 (m, 1 H), 5.20 (m, 1 H), 7.32 (d, 2 H, *J* = 8 Hz), 7.78 (d, 2 H, *J* = 8 Hz); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). An acceptable analysis could not be obtained.

(1*S*,2*S*)-2-(*N*-Tosylamino)cyclohexanecarboxylic Acid (39a). A mixture of **38a** (408 mg, 1 mmol) in 2 mL of 6 N sulfuric acid was heated to 100 °C for 12 h; after several hours, a precipitate appeared. The mixture was cooled to room temperature and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Filtration and evaporation of solvent gave **39a** (255 mg, 86%) as a colorless solid; recrystallization from ether–methylene chloride (4:1) afforded colorless needles: mp 180 °C; IR (KBr) 3.06, 3.40, 5.87, 8.65 μm; ^{1}H NMR δ 1.24–1.78 (m, 5 H), 1.98 (br d, 2 H), 2.32 (dt, 1 H, *J* = 12, 4 Hz), 2.42 (s, 3 H), 3.45 (m, 1 H), 5.26 (d, 1 H, *J* = 8 Hz), 7.30 (d, 2 H, *J* = 8 Hz), 7.76 (d, 2 H, *J* = 8 Hz); $[\alpha]^{20}_D$ +35.0° (*c* 0.50, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) 298 (M + 1, 30), 280 (100). Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.56; H, 6.44. Found: C, 56.60; H, 6.42.

(1*S*,2*S*,3*S*)-2-(*N*-Tosylamino)-6-methylcyclohexanecarboxylic Acid (39b). Following the procedure described for preparation of **39a**, **39b** was obtained (280 mg, 90%) as a colorless solid. Recrystallization from ethyl acetate gave colorless needles: mp 198–199 °C; IR (KBr) 2.98, 3.05, 5.80, 8.61 μm; ^{1}H NMR δ 0.92 (d, 3 H, *J* = 8 Hz), 1.26 (m, 1 H), 1.50 (m, 4 H), 2.02 (m, 1 H), 2.26 (m, 1 H), 2.44 (s, 3 H), 2.56 (dd, 1 H, *J* = 9, 4 Hz), 3.60 (m, 1 H), 5.02 (br d, 1 H), 7.32 (d, 2 H, *J* = 8 Hz), 7.80 (d, 2 H, *J* = 8 Hz); $[\alpha]^{22}_{365}$ −27.1° (*c* 0.80, MeOH); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (30), 294 (100). Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 57.87; H, 6.79. Found: C, 57.86; H, 6.79.

(5a*R*,6*S*,9a*S*,11a*S*)-6-Methylperhydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (40). A solution of **14b** (and its minor diastereomer, 234 mg, 1 mmol) in dry CH_2Cl_2 (3 mL) and $[Ir(cod)PyPCy_3]PF_6$ (40 mg, 0.05 mmol) was subjected to hydrogenation at atmospheric pressure for 6 h. The reaction mixture was concentrated and redissolved in MeOH (2 mL); addition of ether (2 mL) caused precipitation of the catalyst which was removed by filtration through Celite. Concentration gave **40** and its hydrogenated epimer as a light yellow foam (236 mg, quantitative). Fractional crystallization from ethyl acetate–hexane (3:2, twice) gave a sample of pure **40** as colorless crystals, mp 176–177 °C; ^{1}H NMR δ 1.04 (d, 3 H, *J* = 7 Hz), 1.12–2.20 (m, 9 H), 2.62 (m, 1 H), 2.80 (t, 1 H, *J* = 4 Hz), 3.57 (m, 3 H), 3.86 (br s, 1 H), 4.42 (dd, 1 H, *J* = 9, 6 Hz), 5.85 (br s, 1 H); $[\alpha]^{23}_D$ −86.4° (*c* 0.02, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Except for preparation of the analytical sample, the crude reaction mixture was carried on to the next experimental step, after which the diastereomers could be easily separated. Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.08; H, 8.52. Found: C, 66.22; H, 8.46.

(1*R*,2*S*,6*S*)-2-(*N*-Tosylamino)-6-methyl-1-[((2*S*)-2-carbomethoxy-pyrrolidinyl)carbonyl]cyclohexane (41). Prepared as described for **38a**; flash chromatography on silica gel (EtOAc–hexane, 4:1) gave **41** as a colorless solid (352 mg, 86%). Recrystallization from ethyl acetate–hexane (3:2) gave colorless needles: mp 110–111 °C; IR (KBr) 3.12, 3.42, 5.75, 6.18 μm; ^{1}H NMR δ 0.68–2.30 (m, 11 H, overlapping doublet 0.78, 3 H, *J* = 6.5 Hz), 2.16 (dd, 1 H, *J* = 12, 4 Hz), 2.39 (s, 3 H), 3.04 (m, 1 H), 3.26 (br s, 1 H), 3.48 (br t, 1 H), 3.67 (s, 3 H), 3.95 (t, 1 H, *J* = 6 Hz), 6.07 (br s, 1 H), 7.32 (d, 2 H, *J* = 8 Hz), 7.69 (d, 2 H, *J* = 8 Hz); $[\alpha]^{20}_D$ +13.5° (*c* 2.03, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (100). Anal. Calcd for $C_{21}H_{30}NO_5S$: C, 59.71; H, 7.15. Found: C, 59.96; H, 7.11.

Methyl (1*R*,2*S*,6*S*)-2-(*N*-Tosylamino)-6-methylcyclohexanecarboxylate (42a). A solution of **41** (410 mg, 1 mmol) in 6 N sulfuric acid (2 mL) was heated to 100 °C for 48 h. The solution was cooled, diluted with 1 mL of water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. Addition of ether, esterification with diazomethane, and flash chromatography on silica gel (EtOAc–hexane, 4:1) gave **42** (200 mg, 68%) as a light yellow oil. An analytical sample was prepared by distillation in a Kugelrohr apparatus to give a colorless oil: bp 100–102 °C (0.5 mmHg); IR (film) 3.05, 3.42, 5.83, 7.50, 8.60 μm; ^{1}H NMR δ 0.79 (d, 3 H, *J* = 7 Hz), 0.82–2.00 (m, 10 H), 2.04 (dd, 1 H, *J* = 10, 4 Hz), 2.38 (s, 3 H), 3.50 (m, 1 H), 5.30 (br d, 1 H), 7.32 (d, 2 H, *J* = 8 Hz), 7.75 (d, 2 H, *J* = 8 Hz); $[\alpha]^{22}_D$ +34.9° (*c* 1.17, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) M + 1 (60), 293 (100). Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.07; H, 7.12. Found: C, 59.09; H, 7.18.

(1*S*,2*R*,3*S*)-2-(Hydroxymethyl)-3-methyl-*N*-tosylcyclohexylamine (42b). To a slurry of lithium aluminum hydride (60.7 mg, 1.6 mmol) in 3 mL of THF was added a solution of **42a** (294 mg, 1 mmol) in THF (2 mL) over 5 min. The reaction mixture was stirred for 12 h at room temperature and quenched with 20% aqueous KOH solution. The precipitated salts were removed by filtration; concentration of the filtrate gave **42b** (226 mg, 85%) as a colorless solid. Recrystallization from ether gave colorless crystals: mp 101–102 °C; IR (KBr) 2.84, 3.05, 3.41, 6.95, 7.54 μm; ^{1}H NMR δ 0.90 (d, 3 H, *J* = 6 Hz), 0.96 (m, 1 H), 2.54 (s, 3 H), 2.85 (t, 1 H, *J* = 7 Hz), 3.68 (br t, 3 H), 4.82 (br d, 1 H), 7.31 (d, 2 H, *J* = 8 Hz), 7.78 (d, 2 H, *J* = 8 Hz); $[\alpha]^{20}_D$ +23.2° (*c* 1.22, $CHCl_3$); electron impact mass spectrum, *m/z* (rel intensity) M + (7), 210 (16), 155 (58), 142 (97), 91 (100). Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.59; H, 7.79. Found: C, 60.47; H, 7.75.

(1*S*,2*R*,3*S*)-2-(Hydroxymethyl)-3-methyl-*N*-((*tert*-butyloxy)-carbonyl)cyclohexylamine (43c). To a solution of **42b** (1.229 g, 4.60 mmol) in THF (3 mL) was distilled ~50 mL of ammonia. Sodium (635 mg, 27.6 mmol) was added until a blue coloration persisted for 25 min, after which the solution was quenched with solid NH_4Cl. Ammonia was evaporated, and the resulting residue was partitioned between water (2 mL) and CH_2Cl_2 (10 mL). The water layer was washed with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give **43a**. This material was redissolved in a solution of triethylamine (606 mg, 6.00 mmol) and di-*tert*-butyl dicarbonate (1.39 g, 5.06 mmol) in CH_2Cl_2 (5 mL). After 12 h stirring at room temperature, the reaction mixture was diluted with 5 mL of CH_2Cl_2, washed with 5% citric acid, and dried over anhydrous $MgSO_4$. Flash chromatography on silica gel (EtOAc–hexane, 1:1) gave **43c** (754 mg, 71%) as a colorless solid. Recrystallization from ether gave colorless needles: mp 124 °C; IR (KBr) 2.98, 3.05, 3.39, 6.03, 6.53 μm; ^{1}H NMR δ 0.78 (d, 3 H, *J* = 6 Hz), 0.94–1.90 (m, 8 H, 1.47, overlapping singlet, 9 H), 3.18 (t, 1 H, *J* = 12 Hz), 3.70 (dt, 1 H, *J* = 12, 4 Hz), 4.08 (br d, 1 H), 4.76 (br d, 1 H); $[\alpha]^{22}_{365}$ −4.1° (*c* 0.54, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) 188 (100), 144 (77). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.17; H, 10.35. Found: C, 64.11; H, 10.35.

(1*S*,2*R*,3*S*)-2-Formyl-3-methyl-*N*-((*tert*-butyloxy)carbonyl)cyclohexylamine (44a). To a solution of oxalyl chloride (140 mg, 1.1 mmol)[27] in 2 mL of CH_2Cl_2 cooled to −60 °C was added a solution of dimethyl sulfoxide (185 mg, 2.2 mmol) in CH_2Cl_2 (2 mL) over several min. After stirring for 2 min, **43c** (231 mg, 1.0 mmol) in 3 mL of CH_2Cl_2 was added. The mixture was stirred at −60 °C for an additional 20 min. Triethylamine (505 mg, 5 mmol) was then added, and the mixture was allowed to warm to room temperature. Water was added, and the resulting solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give a yellow oil. Chromatography on silica gel (EtOAc–hexane, 1:1) gave **44a** (197 mg, 86%) as a colorless solid. Recrystallization from ether gave colorless needles: mp 109.5–110.5 °C; IR (KBr) 3.03, 3.42, 5.85, 5.95 μm; ^{1}H NMR δ 1.00 (d, 3 H, *J* = 7 Hz), 1.08 (m, 1 H), 1.26–1.82 (m, 5 H, 1.41, overlapping singlet, 9 H), 2.10 (br m, 1 H), 2.31 (br m, 1 H), 4.18 (br s, 1 H), 5.06 (br d, 1 H), 9.65 (s, 1 H); $[\alpha]^{23}_D$ −2.2° (*c* 0.81, $CHCl_3$); chemical ionization mass spectrum, *m/z* (rel intensity) 186 (100), 142 (95). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.71; H, 9.60. Found: C, 64.77; H, 9.63.

(1*S*,2*R*,3*S*)-2-(*trans*-3-Oxohex-1-enyl)-3-methyl-*N*-((*tert*-butyloxy)carbonyl)cyclohexylamine (44b). Following the procedure of Ov-

erman,[20a] dimethyl 2-oxopentylphosphonate[30] (388 mg, 2 mmol) in 2 mL of THF was added to a rapidly stirred suspension of sodium hydride (45.6 mg, 1.9 mmol) in THF (5 mL) at −10 °C. The resulting suspension was stirred at −10 °C for 30 min, and then **44a** (229 mg, 1 mmol) in THF (5 mL) was added over 5 min. After stirring an additional 10 min at −10 °C, the mixture was allowed to warm to room temperature and then refluxed for 1 h. The reaction mixture was partitioned between ether (20 mL) and 1 M NaOH (10 mL), after which the aqueous layer was washed with ether (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. Chromatography on silica gel (EtOAc–hexane, 1:1) gave **44b** (278 mg, 90%) as a colorless solid. Recrystallization from ether–hexane (3:7) gave coloriess needles: mp 74–75 °C; IR (KBr) 2.94, 5.86, 6.05, 6.66 μm; ^{1}H NMR δ 0.81 (d, 3 H, J = 6.4 Hz), 0.90 (t, 3 H, J = 7.3 Hz), 0.98–1.84 (m, 9 H, 1.43, overlapping singlet, 9 H), 2.02 (br t, 1 H), 2.53 (t, 2 H, J = 7 Hz), 3.94 (br m, 1 H), 4.74 (br d, 1 H), 6.08 (d, 1 H, J = 16 Hz), 6.68 (dd, 1 H, J = 16, 9 Hz); $[\alpha]^{24}_D$ +53.2° (c 0.43, $CHCl_3$); chemical ionization mass spectrum, m/z (rel intensity) M + 1 (22), 209 (100), 265 (26). Anal. Calcd for $C_{18}H_{30}NO_3$: C, 70.10; H, 9.80. Found: C, 69.93; H, 9.65.

(+)-Pumiliotoxin C (45). A solution of **44b** (145 mg, 0.47 mmol) in 2 mL of ethanol was treated with hydrogen (1 atm) in the presence of 5% palladium carbon (20 mg) until the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration through Celite, and the resulting solution was concentrated. The residue was treated with 1 mL of 90% trifluoroacetic acid (TFA) at room temperature for 1 h. After removal of the excess TFA under reduced pressure, the residue was made basic with 1 N NaOH and washed with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give the $\Delta^{1,2}$ imine, which was immediately dissolved in 5 mL of ethanol and several drops of concentrated HCl solution. Hydrogenation in the presence of 5% palladium on carbon (50 mg) for 6 h, removal of the catalyst by filtration through Celite, and concentration gave essentially pure (+)-pumiliotoxin C (109 mg, 72%) as the amine hydrochloride. Recrystallization from 2-propanol afforded the hydrochloride as colorless needles: mp 285–286 °C (sealed capillary); lit. mp 286–288 °C; ^{1}H NMR δ ($CDCl_3$) 0.87 (d, 3 H), 0.89 (t, 3 H), 0.90–2.54 (m, 16 H), 2.98 (br m, 1 H), 3.32 (br d, 1 H), 8.46 (br m, 1 H), 9.62 (br m, 1 H); ^{13}C NMR ($CDCl_3$) δ 60.2, 58.2, 41.1, 35.0, 34.5, 29.2, 27.3, 25.3, 23.3, 20.6, 19.7, 19.2, 13.7; $[\alpha]^{24}_D$ +16.1°, $[\alpha]^{24}_{435}$ +28.8° (c 0.50, MeOH); lit. $[\alpha]^{20}_D$ +16.4°, $[\alpha]^{20}_{436}$ 28.1° (c 1.00, MeOH); chemical ionization mass spectrum, m/z (rel intensity) 194 (100), 152 (88). The spectral data were in agreement with those reported for the natural product.[28]

(30) Prepared from methyl butyrate by the procedure described in Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5653.

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Supplementary Material Available: Tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates for **5** and **18** (6 pages). Ordering information is given on any current masthead page.

Communications to the Editor

Modelling the Photosynthetic Water Oxidation Center: Preparation and Physical Properties of a Tetranuclear Oxide Bridged Mn Complex Corresponding to the Native S_2 State

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Elucidating the precise structure and mode of action of the Mn aggregate responsible for photosynthetic water oxidation/oxygen evolution represents an area of intense research at the present time. It is generally believed that four Mn atoms per photosystem II (PS II) reaction center are essential for activity.[2] The Mn aggregate is capable of cycling between five oxidation levels (S_0–S_4) during the catalytic cycle[3] but can also adopt an additional "super-reduced" oxidation level, labeled S_{-1}, under certain conditions.[4] We have been seeking inorganic model complexes of this biological unit to assist in elucidation of the precise structural changes and concomitant substrate transformations during turnover. We recently reported the synthesis of complexes containing the $[Mn_4O_2]$ core with structural features similar to the enzyme and isolable in three oxidation levels corresponding to the native S_{-1}, S_0, and S_1 levels.[5] Since the EPR active S_2 level has allowed the most detailed study of the biological unit to date, we have turned our attention to the synthesis of an Mn_4 complex in this important oxidation level (3 Mn^{III}, Mn^{IV}) and herein report the successful attainment of this objective.

A stirred slurry of brown "manganic acetate" (0.54 g)[6] in degassed MeCN (25 mL) was treated dropwise with Me_3SiCl (0.66 mL). To the resulting solution was added imidazole (HIm, 0.25 g) in MeCN (15 mL), followed by $NaClO_4$ (0.29 g) in MeCN (10 mL). The final red-brown solution was stirred for a further 10 min, filtered, and left undisturbed for 2 days at ambient temperature. The resulting dark brown crystals were collected by filtration, washed with MeCN, and dried; yield ~ 20%. The product was identified by analysis[7] and crystallographic

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(6) Prepared by a slight modification to the standard reaction of $Mn(OAc)_2$ with $KMnO_4$ in hot glacial acetic acid, as described by Lis, T. *Acta Crystallogr. Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *B36*, 2042. Full details, together with a more detailed discussion of the preparation of **1**, will be provided in the full report of this work.

(7) Anal. Calcd for $C_{18}H_{27.5}N_{7.5}O_9Cl_6Mn_4$: C, 23.36; H, 3.00; N, 11.35; Cl, 22.98; Mn, 23.75. Found: C, 22.96; H, 3.06; N, 11.48; Cl, 22.98; Mn, 23.17.

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