Structure of Alkaloid 275A, a Novel 1-Azabicyclo[5.3.0]decane from a Dendrobatid Frog, *Dendrobates lehmanni*: Synthesis of the Tetrahydrodiastereomers

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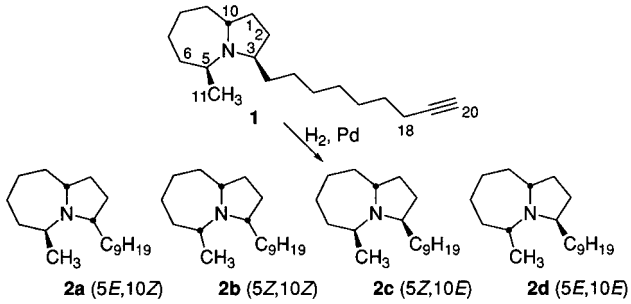
The principal alkaloid **275A** in skins of the Colombian poison frog *Dendrobates lehmanni* has been identified as the pyrrolo[1,2-*a*]azepane (**1**), the first occurrence in nature of this "izidine" system. Tetrahydro-**1** proved identical to one of the four synthetic diastereomers, **2a**−**2d**, thereby establishing that **1** has the 5*Z*,10*E* relative stereochemistry. Alkaloid **1** is often accompanied by other congeners, in particular a 5*Z*,10*Z* diastereomer **15**, a dihydro analogue **16**, and a ketone **17**. Such izidines in frogs may arise from dietary ants, as do other classes of izidines.

Dendrobatid frogs of Central and South America have been a rich source of a wide variety of biologically active alkaloids, comprising over 20 structural classes; code names for the over 500 alkaloids found in frog skins are provided in a recent review.[1] In 1976, a C_{19} alkaloid of molecular weight 275, which was code-named **275A** (**1**), was found to be a major alkaloid in skin extracts of a red and black-banded dendrobatid frog, *Dendrobates lehmanni* Myers and Daly, 1976, collected in montane forest near Cali, Colombia.[2] The frog, known previously only from street markets in Cali, had been considered another populational variant of the extremely variable species *Dendrobates histrionicus* Berthold, 1845.[3] The frog was described as a new species, *D. lehmanni*,[2] primarily on the basis of the lack of histrionicotoxins, a class of alkaloids present in all examined populations of *D. histrionicus*.[4] Analysis of mating calls now supports the validity of *D. lehmanni* as a separate species and was also the basis for separation of the *D. histrionicus* complex into *D. histrionicus* and *D. sylvaticus* Funkhauser, 1956.[5]

A gross structure (**1** with stereochemistry undefined) was presented for alkaloid **275A**, based upon unpublished results in a recent review.[1] Alkaloid **1** was later one of a group of mono- and bicyclic alkaloids studied with GC-CI (NH_3)-MS/MS and collision-activated dissociation.[6] The relative stereochemistry of **1** has now been established as that of **2c** by comparison of tetrahydro-**1** with the four synthetic diastereomers **2a**−**2d** (Scheme 1).

Alkaloid **1** has been found as a major alkaloid only in *D. lehmanni*, even in populations separated by over 100 km (unpublished results). It has been detected by GC−MS, but only rarely, as a trace alkaloid in populations of *D. speciosus* Schmidt, 1857; *D. pumilio* Schmidt, 1858; *D. granuliferus* Taylor, 1958; and *D. auratus* Girard, 1855 from Panama and Costa Rica (ref 4 and unpublished results). We presume that **1** originates in frogs from an alkaloid-containing small arthropod, on the basis of ongoing studies of dendrobatid frogs, where other izidines and decahydroquinolines have been shown to come from dietary ants (ref 7 and references therein). The occurrence of **1** as a significant alkaloid only in populations of *D. lehmanni* poses interesting questions as to the distribution of the putative alkaloid-containing arthropod. Montane forest (850−1200 m) is the habitat for *D. lehmanni*, while most populations of *D. histrionicus* occur at lower elevations (<600 m). Thus, the putative arthropod containing **1** may also be a montane species. Conversely, the arthropod(s) containing the histrionicotoxins, also mainly C_{19} alkaloids, which are in all populations of *D. histrionicus*, may not be abundant at high elevations where *D. lehmanni* occurs but only at lower elevations where *D. histrionicus* occurs. However, a population of *D. histrionicus* from Altos de Buey, Colombia, at 800 m, contained histrionicotoxins but not **1**.[8] Feeding experiments indicated that *D. lehmanni* readily accumulated histrionicotoxin into skin when fed alkaloid-dusted fruit flies (unpublished results). Of the other dendrobatid frogs found to contain **1**, albeit in trace amounts, only the Panamanian *D. speciosus* was from montane forest (1250−1410 m).[9]

Scheme 1. Frog Skin Alkaloid **275A** (**1**) and Four Synthetic Tetrahydro Diastereomers (**2a**−**2d**)[a]



[a] Diastereomer **2c** results from hydrogenation of **1**.

Results and Discussion

Alkaloid **1** possessed a molecular formula of $C_{19}H_{33}N$ (HREIMS) and had a nine-carbon side-chain containing a terminal acetylene as shown by EIMS and GC−FTIR. Figure 1 shows clearly the terminal acetylene with a $\nu_{C\equiv C}$ at 2119 cm^{-1}, the $\nu_{\equiv CH}$ as a split absorption at 3328 cm^{-1}, and very weak Bohlmann bands (ca. 2800 cm^{-1}).

The acetylenic side-chain underwent facile α-cleavage on EIMS. A weaker methyl loss was also detected, presumably

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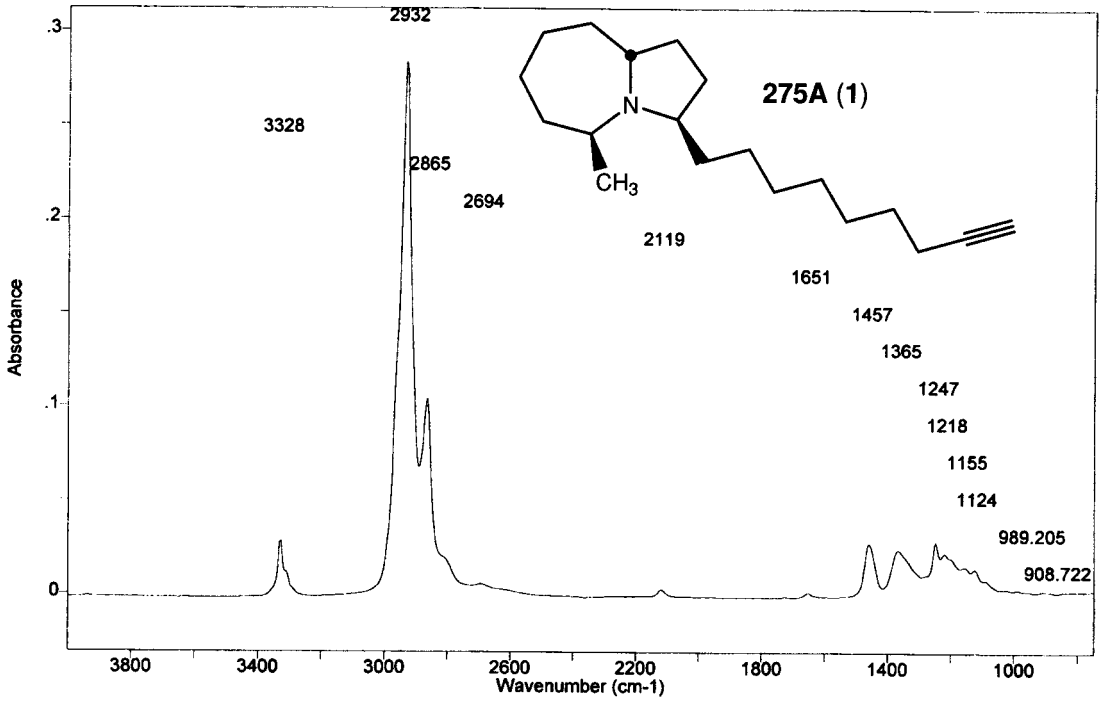
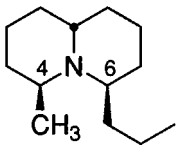


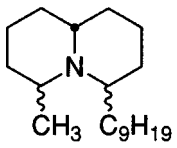
Figure 1. GC−FTIR spectrum of the alkaloid **275A** (**1**) from the colombian frog *Dendrobates lehmanni*.

also from α-cleavage. Since the only unsaturation resided in the acetylene moiety as proved by the uptake of four hydrogens, **1** must have a bicyclic ring system. These observations and the detection of no labile hydrogen exchanges on CIMS with ND_3, as well as very weak Bohlmann bands, led us to propose initially a 6*Z*,10*E*[10] 4,6-disubstituted quinolizidine structure for this alkaloid.[11] After this proposal, a (6*Z*,10*E*)-4-methyl-6-*n*-propyl quinolizidine, **3**, was detected in a Madagascan frog and also a Brazilian ant;[7] it had very weak Bohlmann bands, similar to those observed with **1**.



3

Using the same 2-methylpiperidine-6-*n*-butanal acetal previously used in the synthesis of **3**[7] and an *n*-nonyl Grignard reagent, a mixture of four diastereomeric 4-methyl-6-*n*-nonyl quinolizidines (**4a**−**4d**) was synthesized. However, despite very close similarities of tetrahydro-**1** and one diastereomer, **4d**, in MS and IR properties and GC behavior, their retention times differed on co-injection. EIMS/MS data also confirmed significant differences between tetrahydro-**1** and the two major diastereomers of **4** (see Supporting Information).

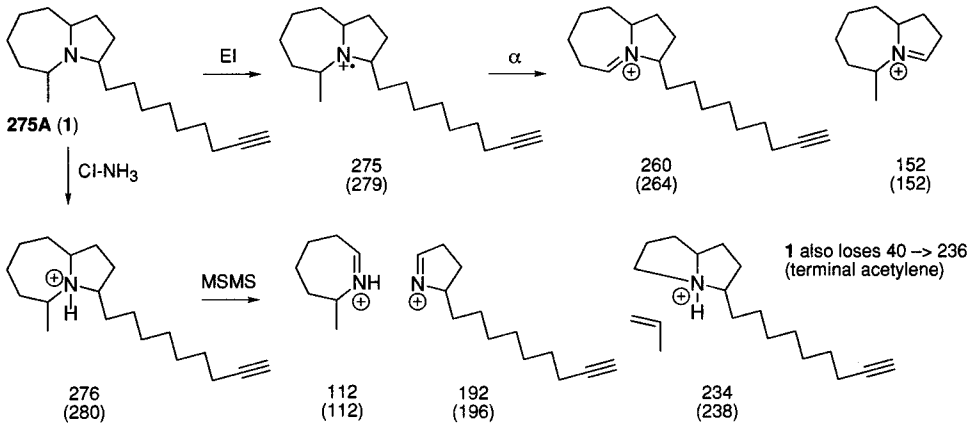


4a, 4b, 4c, 4d

We briefly considered branching in the nonyl chain as a possible reason for the discrepancy between tetrahydro-**1** and the synthetic quinolizidines **4a**−**4d**. However, analysis of ^{1}H NMR spectra obtained for **1** confirmed our earlier conclusion of only one methyl group (d, $J = 6.8$), assignable to an α-methyl group (δ 1.45). We then began to study the application to alkaloids of a seldom used MS technique based upon collision-activated dissociation of the protonated molecular ion, created by CI with NH_3 reagent gas. We found this tandem mass spectral technique particularly useful when applied to the study of "izidine" alkaloids where the separate rings and their attached substituents are detected as major fragments.[6] When applied to quinolizidine **3**, GC-CI (NH_3)-MS/MS produced the even mass fragments of *m*/*z* 98 and 126. When this technique was applied to **1**, however, we found not the ions observed (*m*/*z* 98, 210) with the synthetic 4,6-disubstituted quinolizidine isomers **4a**−**4d**, i.e., protonated six-membered piperideines with a methyl or nonyl substituent attached, but rather a pyrroline carrying a nonynyl side-chain (*m*/*z* 192) and a seven-membered dehydroazepane ring having a methyl substitutent (*m*/*z* 112) (Scheme 2, cf. ref 6). This tandem mass spectrometry technique revealed not only the nature of each fused ring but also its substituent.

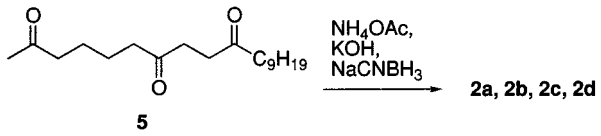
Thus, **1** was proved not a quinolizidine but rather an isomeric "izidine" with fused five- and seven-membered rings commonly referred to as a 1-azabicyclo[5.3.0]decane, although a pyrrolo[1.2-*a*]azepine nomenclature is also accepted.[12] We propose that such "5-7-izidines" be named "lehmizidines" to emphasize their unique occurrence, as yet in nature only in skin extracts of dendrobatid frogs, chiefly from the Colombian dendrobatid frog *D. lehmanni*, and to honor the late F. Carlos Lehmann Valencia for whom that frog was named.[2] CI (NH_3)-MS/MS of tetrahydro-**1** generated ions at *m*/*z* 112 and 196, proving the unsaturation to be associated with the side-chain attached to the five-membered pyrroline ring. For quick comparison purposes, a mixture of the four diastereomers (**2a**−**2d**) of tetrahydro-**1** was prepared by reductive amination of the triketone **5** (Scheme 3, unpublished work of T. H. Jones and J. S. T. Gorman; see Supporting Information for the characterization of **5**).

Scheme 2. EIMS and CI-MS/MS Fragmentation Pathways Proposed for Alkaloid **275A** (**1**) and Tetrahydro-**1**[a]



[a] Fragment ion masses from tetrahydro-**1** are in parentheses.

Scheme 3. Lehmizidines from Reductive Amination of Triketone **5**



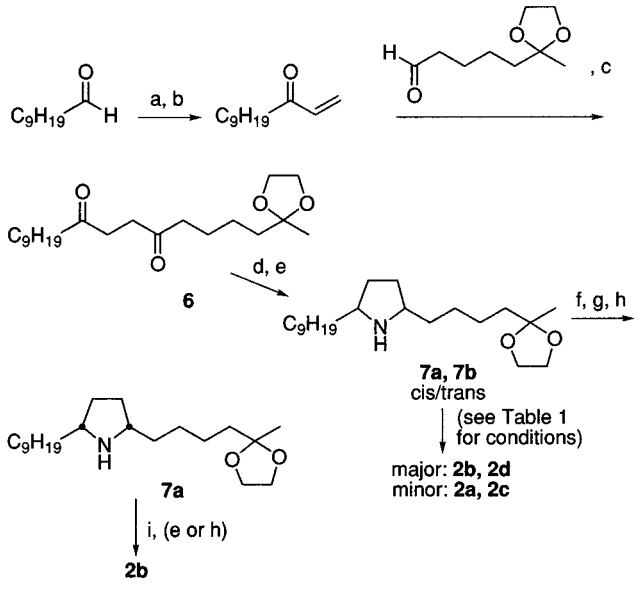
Gas chromatography of this mixture gave a separation showing the four expected diastereomers and indicated that the third-eluting component (**2c**) was identical in its GC retention time, EIMS and CI (NH_3)-MS/MS, and GC−FTIR spectrum with tetrahydro-**1**. The EIMS fragmentations of these diastereomers are virtually identical with one slight difference noted; **2a** and **2d** show a slightly greater α-cleavage of the C-5 methyl than do the other two isomers (see Supporting Information).

We then set about designing efficient syntheses to determine the relative stereochemistry of **2c**. Two routes were selected, one commencing from 2,5-disubstituted pyrrolidines and the other from 2,7-disubstituted azepanes, and, taken together, we were confident such syntheses would prove the stereochemistry of **2c**. A similar approach was recently employed by us in the determination of the relative stereochemistry of **3**.[7] First we prepared from **6** the *cis and trans* pyrrolidine ketals **7a** and **7b** (Scheme 4), which were then cyclized by reductive amination after deprotection. The major products from the *cis*/*trans* mixture were **2b** and **2d**. When nearly pure *cis* **7a** was treated in a similar manner, the major product was **2b**, proving that the pyrrolidine ring in **2b** was *cis* and thus *trans* in diastereomer **2d**.

Since pure *trans* pyrrolidines are difficult to obtain by reductive methods[13] and since this route did not provide useful amounts of **2c**, we next devised a complementary route (Scheme 5) through the appropriate azepanes based on cyanoamine methodology. The requisite cyanoazepane **10** would require the cyclization of a protected seven-carbon aldehyde with an amine at C-6. The precursor for this compound, ketoacetal **8**, was obtained in one step from commercial starting materials using a Ni^0-mediated conjugate addition.[14] The aminoacetal **9** was produced nearly quantitatively by reductive amination of **8** with benzylamine in the presence of titanium isopropoxide.[15]

The aminoacetal **9** was deprotected in the presence of cyanide ion, and the resulting cyanoamine **10** was treated with the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane to provide the *N*-benzylazepanes **13**. Debenzylation gave a nearly 1:1 mixture of the isomeric dioxanyl azepanes **14a/14b**. Deprotection of **14a/14b** in the presence

Scheme 4. Lehmizidines from 2,5-Disubstituted Pyrrolidines

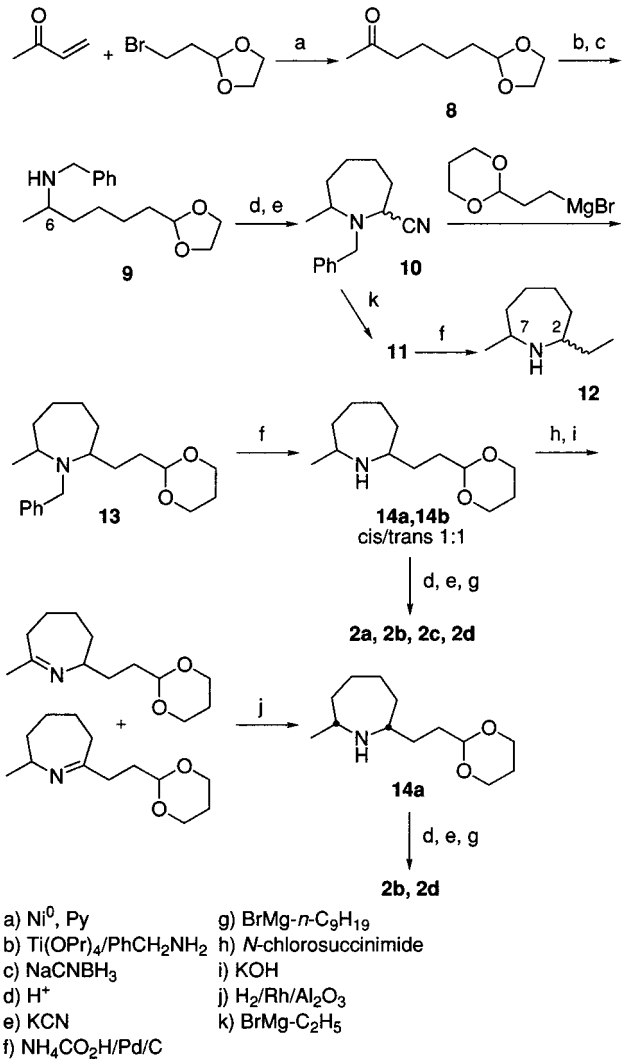


a) CH_2=CHMgBr
b) PCC
c) thiazolium salt, Et_3N
d) NH_4OAc
e) $NaCNBH_3$
f) *N*-chlorosuccinimide
g) KOH
h) H_2, Rh/Al_2O_3
i) H^+

of cyanide ion and treatment with *n*-nonylmagnesium bromide gave **2a**, **2b**, **2c**, and **2d** in a 45:13:11:31 ratio. Similar treatment of a nearly pure sample of *cis* azepane **14a**, obtained by the methodology used to provide the *cis* pyrrolidine **7a**, produced **2b** and **2d**, indicating the azepane ring in these isomers to be *cis* and thus the azepane ring in **2a** and **2c** to be *trans*.

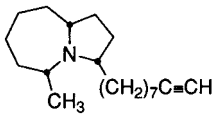
These results allowed the assignment of *cis* pyrrolidine and *cis* azepane rings to isomer **2b**, i.e., a 5*Z*,10*Z* relative stereochemistry. This is reflected in its slightly more intense and broader Bohlmann bands relative to the other diastereomers (see Figure 2, Supporting Information). Diastereomer **2d** then had a *trans* pyrrolidine ring and a *cis* azepane ring or a 5*E*,10*E* stereochemistry. The stereochemistry of the other two isomers, **2a** and **2c**, was deduced by examining the material balances of **2a**−**2d** resulting from various mixtures of *cis* and *trans* pyrrolidine ketals **7a/7b** (see Scheme 4 and also Table 1 in Supporting Information), in turn prepared by various reductants on an intermediate pyrroline created from the *N*-chloro compound with base (see Experimental Section).

Scheme 5. Lehmizidines from 2,7-Disubstituted Azepanes

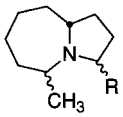


The proportion of **2a** in the cyclized mixtures rises paralleling the increased percentage of *cis* pyrrolidine (**7a**) in the starting mixture, proving that **2a** has a *cis* pyrrolidine, while the azepane cyclizations proved **2a** to have a *trans* azepane ring. Thus **2a** must have the 5*E*,10*Z* stereochemistry, and finally by difference, **2c**, the tetrahydro derivative of the naturally occurring alkaloid, must have a *trans* pyrrolidine and *trans* azepane ring, i.e., the 5*Z*,-10*E* stereochemistry. This assignment is secured by the observation that **2c** increases with increases in the percentage of *trans* pyrrolidine, **7b** in the starting **7a**/**7b** mixture (see Table 1, Supporting Information). Thus, the first two isomers to elute from the GC column derive from a *cis* pyrrolidine, and the pair to elute last arise from a *trans* pyrrolidine. FTIR absorbance spectra of the four synthetic diastereomers **2a**−**2d** are presented in the Supporting Information. A mixture of *cis* and *trans* 2-ethyl-7-methyl azepanes (**12**) was also synthesized from **10**, via the *N*-benzyl intermediates **11** (Scheme 5), and GC−FTIR spectra indicate these isomers can be distinguished by the weak Bohlmann band shoulder evident in the *cis* isomer but not the *trans* (see Figure 3, Supporting Information), as is the case with piperidines and *N*-methylpyrrolidines.[16] The elution order on our GC columns is the same as α,α′-disubstituted-pyrrolidines and -piperidines with the *cis* isomer eluting first.

In most extracts of *D. lehmanni*, there were detected along with major amounts of **1**, minor amounts of a diastereomer **15**, a dihydro derivative **16**, shown by EIMS to have a molecular ion at *m*/*z* 277 with fragments at *m*/*z* 262 and 152 and by GC−FTIR to have a terminal olefin and the same Bohmann band pattern as **1**, a ketone congener **289A** (**17**: $x = 1-5$), $C_{19}H_{31}NO$, and, tentatively, a diene isomer of **1**, **275G** (**18**). A significant ion at *m*/*z* 165, seen with ketone **17** using the JEOL mass spectrometer (see Experimental Section), indicates the carbonyl group in the side-chain is not adjacent to the ring, and the FTIR spectrum indicates it is not conjugated with the terminal acetylene.



275A' (15)



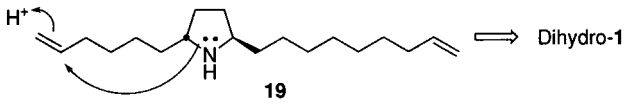
277A (16) R = $(CH_2)_7CH{=}CH_2$
289A (17) R = $(CH_2)_xCO(CH_2)_{6-x}C{\equiv}CH$
275G (18) R = $(CH_2)_5CH{=}CHCH{=}CH_2$

The major natural alkaloid **1** after hydrogenation corresponded on co-injection to the synthetic **2c**, while the minor isomer **15** after hydrogenation corresponded with **2b**, exhibiting identical retention times and EIMS and CI (NH_3)-MS/MS spectra (major fragments at *m*/*z* 112, 196 of the same relative intensities; see Experimental Section) and identical GC−FTIR spectra in the case of **2c** and tetrahydro-**1** (insufficient material was available for an IR spectrum on tetrahydro-**15**).

We had purified approximately 1 mg of **1** by HPLC and obtained 1D and 2D proton NMR spectra. These data, reported in Table 2 (Supporting Information), confirmed the terminal acetylene and showed three downfield protons (C-3, C-5, C-10) corresponding to C*H*N signals, one coupled with the single methyl group, but were ambiguous regarding the ring sizes and stereochemistry. In retrospect, we saw connectivity in the five-membered ring in the COSY spectrum of **1** but not in the seven-membered ring. Only a single H-1- -H-2 cross-peak was detectible and was quite weak and normally would have been ignored, were it not that the structure became known in the interim. Initial NMR work was attempted in $CDCl_3$ but gave poor results. Much better spectra were obtained in D_2O, and from the better separation of H-3, H-5, and H-10, we concluded that a tertiary amine deuteriochloride had formed on exposure to $CDCl_3$. When the 11-methyl was decoupled, the signal assigned to H-5 changed to a doublet (J = 7.5 Hz), indicating only one H-6- -H-5 coupling. We observed the acetylenic hydrogen at δ 2.33 (J = 2.7) coupled with the H-18 methylene at δ 2.20. The latter signal on standing in D_2O for several days gradually changed from a triplet of doublets (J = 7.0, 2.7) to a triplet as the long-range coupling to the acetylenic hydrogen (H-20) disappeared when that hydrogen slowly exchanged with deuterium. Acetylenic hydrogen exchange under neutral or slightly acidic conditions is very unusual and so far as we know has only been reported to occur via metal ion π-complexes.[17] Our results suggest an intramolecular general base deuteriochloride catalysis.

Other "izidines", namely, 3,5-disubstituted pyrrolizidines and indolizidines and 4,6-disubstituted quinolizidines, found in frog skin appear to derive from dietary ants,[7] and thus it appears likely that lehmizidines will have an ant origin. However, at this time no simple lehmizidines, such as **1** from dendrobatid frogs, have been detected in ants nor anywhere else in nature. The common occurrence of the C_{19} *trans* pyrrolidine **19** in myrmicine ants indigenous

Scheme 6. Possible Biosynthetic Conversion of Ant Pyrrolidine **19** to a Lehmizidine System



19

to the western hemisphere[18] suggests that **19** in ants might share the same biosynthetic pathway as **1** or even be its biosynthetic precursor (see Scheme 6). The bicyclic analogues of monocyclic ant venom alkaloids are well known, and indeed, pyrrolidine **19** occurs along with analogous pyrrolizidines in other *Monomorium* species.[19] A *cis* pyrrolidine isomer (present as a trace accompanying **19**, *cis*:*trans* ≈ 1:100) might lead to a dihydro-**15**. Acetylenic groups have not been detected in ant pyrrolidines.

Although simple lehmizidines represent a new alkaloid class, the *Stemona* alkaloids contain this ring system (cf. ref 20 and references therein) as do the *Cephalotaxus* alkaloids.[21] Several recent syntheses of the simple lehmizidine system have been reported.[22] Earlier work was undertaken chiefly in the context of an abnormal Clemmensen reduction product encountered by Clemo.[23] We chose to develop different stereoselective routes from pyrrolidines and azepanes (Schemes 3 and 4) to allow the unambiguous and efficient determination of diastereomer structures.

Experimental Section

General Experimental Procedures. Vapor phase FTIR spectra were obtained using a Hewlett-Packard (HP) model 5965B detector interfaced with an HP 5890 gas chromatograph fitted with either a J&W 15 m × 0.25 mm DB-1 column or a 30 m × 0.25 mm Restek Rtx-5 Amine column. An HP ChemStation was used to process the data. Mass spectra were obtained in the EI mode using a Shimadzu QP-5000 GC−MS equipped with a 30 m × 0.32 mm Rtx-5 column. A Finnigan GCQ mass spectrometer with the same column was used for EI-MS/MS and CI (NH_3)-MS/MS and a Finnigan Ion Trap Model 7 for some earlier EIMS data on various extracts. High-resolution mass spectrometry (HREIMS) used a JEOL SX102 instrument equipped with a 15 m × 0.20 mm HP-5 column for GC−EIMS and GC−HREIMS. Direct probe work with the same instrument was done in the FAB^+ mode with xenon gas and a poly(ethylene glycol) reference and glycerol matrix.

Source of Biological Materials. Specimens of *D. lehmanni* were originally purchased from street vendors of Cali, Colombia, and later collected in montane forest of the Río Anchicayá drainage nearby in the department of Cauca in the 1970s.[2] Voucher specimens are in the American Museum of Natural History (New York City). A subsequent collection in 1983 was from steep slopes in the same general area near Río Clara, since most of the higher forest had been destroyed (unpublished data). Further specimens of unknown locales have come through the pet trade or were provided to us after confiscation by the U.S. Fish and Wildlife Service. We are indebted to Volker Ennenbach for specimens from the Río Anchicayá drainage and from the Río Daqua drainage a few kilometers to the north and to Dr. Jack Frankel for specimens from the Río Tápare drainage near San José de Palmar, Choco, Colombia, some 150 kilometers to the north. Such specimens were obtained in the early 1990s.

Characterization of Alkaloids. The profiles of alkaloids in skin extracts of different specimens of *D. lehmanni* obtained in different years and different locations in Western Colombia were assessed by GC−MS analysis. The profile and amounts of alkaloids differed considerably in these extracts, suggesting variability in alkaloid prey items. The original extract from the Río Anchicayá drainage collected in January 1973[4] was characterized as follows: Alkaloid **275A** (**1**) was a major alkaloid and was accompanied by **15**, **16**, and **17** with the proportions of **1**:**15**:**16**:**17** ≈ 10:1:1:2 based on GC−MS chromatograms. The extract also contained several pumiliotoxins (alloPTX **253A**, alloPTX **267A**, PTX **307A**, PTX **323A**) and a number of trace alkaloids. The alkaloid fraction from skins of a yellow and black morph of *D. lehmanni* collected in the Río Anchicayá drainage in 1992 contained large amounts of **1** and also minor amounts of **15** in a ratio of 9:1. A variety of other alkaloids were present, but in relatively small amounts. Alkaloid fractions from two such frogs were combined and purified by HPLC using an HP 1090 with flow rate of 1 mL/min and a gradient of H_2O−CH_3CN with an HP Asahipak column (4.6 mm × 25 cm) to provide approximately 1 mg of **1**.

Catalytic Hydrogenation of 1. Tetrahydro-**1** was obtained from an estimated 50 μg of **1** in a 1 mL screw cap vial fitted with a Mayo-type Teflon adaptor cap and containing 100 μL of MeOH, a 7 mm Teflon stirring bar, and a trace of 5% Pd/C (Degussa) catalyst. After reduction at room temperature for 2 h under 2 atm pressure of H_2 (generated using an Alltech electrolytic generator), the H_2 atmosphere was replaced with N_2 and the solution was filtered through a 4 mm syringe filter (Alltech, #2092). The filter was then rinsed with another 100 μL of methanol in portions and the combined filtrate concentrated to 50 μL for GC−FTIR and GC−EIMS.

2-Methyl-2-(5,8-dioxoheptadecyl)-1,3-dioxolane (6). A mixture containing 2.52 g (13.9 mmol) of 1-dodecen-3-one,[24] 2.32 g of 2-methyl-2-(5-oxopentyl)-1,3-dioxolane[25] (13.9 mmol), 0.8 mL of triethylamine, and 0.38 g of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride was stirred and heated under argon overnight. The mixture was taken up in 50 mL of diethyl ether and filtered through a short Florisil column. The solvent was removed in vacuo, and the residue was recrystallized from methanol to provide 2.78 g (56.5% yield) of **6** as a waxy solid, mp 34−36 °C: FTIR 2934, 1723, 1457, 1216, 1125, 1065 cm^{-1}; EIMS *m*/*z* 354 (M^+, 0.5), 339 (2), 321 (1), 249 (2), 199 (3), 165 (1), 128 (11), 111 (2), 99 (3), 87 (100), 55 (11), 43 (38); HREIMS *m*/*z* 353.2693 (calcd for $C_{21}H_{37}O_4$, $(M - H)^+$, 353.2692); 355.2857 (calcd for $C_{21}H_{39}O_4$ $(M + H)^+$, 355.2848).

***cis*- and *trans*-2-Methyl-2-[4-(5-*n*-nonyl-2-pyrrolidyl)-butyl]-1,3-dioxolane (7a/7b).** A solution containing 0.358 g (1.01 mmol) of **6** in 8 mL of methanol was treated sequentially with 20 mg of KOH, 0.27 g of $NaCNBH_3$, and 0.092 g of NH_4-OAc. The mixture was stirred overnight, and 40 mg of $NaBH_4$ was added. After 1 h, the solvent was removed in vacuo and the residue partitioned between 10% NaOH and diethyl ether. The ether layer was dried over anhydrous K_2CO_3, and the solvent was removed in vacuo to provide 0.3 g (90%) of an oily residue that contained two major components in a 51:49 ratio having identical EIMS: EIMS *m*/*z* 339 (M^+, 1), 324 (4), 294 (3), 213 (4), 212 (45), 197 (11), 196 (84), 182 (8), 168 (13), 152 (7), 126 (9), 99 (8), 87 (77), 82 (20), 69 (17), 68 (18), 55 (19), 43 (100); HREIMS *m*/*z* 340.3200 (calcd for $C_{21}H_{42}NO_2$ $(M + H)^+$, 340.3216).

***cis*-2-Methyl-2-[4-(5-*n*-nonyl-2-pyrrolidyl)butyl]-1,3-dioxolane (7a).** A solution containing 0.36 g of a mixture of **7a** and **7b** in 10 mL of anhydrous CH_2Cl_2 was treated with 0.2 g of *N*-chlorosuccinimide and stirred for 2 h. The solvent was removed in vacuo, and the residue was taken up in 10 mL of ethanol, treated with 1.0 g of NaOH, and heated at reflux for 2 h. After cooling, the solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. GC−MS analysis of the ether layer showed only two isomeric 1-pyrrolines. EIMS: *m*/*z* 336 ($(M - H)^+$, 1), 322 (4), 294 (11), 292 (17), 250 (8), 222 (13), 209 (30), 180 (3), 166 (19), 124 (20), 110 (10), 97 (15), 96 (28), 87 (100), 83 (42), 82 (61), 55 (20), 43 (96), 41 (40), and *m*/*z* 336 ($(M - H)^+$, 1), 322 (3), 294 (5), 292 (9), 250 (14), 238 (8), 194 (6), 183 (8), 182 (70), 180 (18), 87 (100), 83 (35), 55 (15), 43 (79), 41 (34). Hydrogenation of this mixture over 5% Rh/Al_2O_3 in ethanol provided an 83:17 ratio of **7a** and **7b**. Treatment of similarly prepared pyrroline mixtures with a slight excess of DIBAL under argon at −15 °C provided **7a** and **7b** in an 89:11 ratio on one occasion and a 93:7 ratio on another (Table 1, Supporting Information).

2-(5-Oxohexyl)-1,3-dioxolane (8). A solution containing 25 mL of pyridine, 50 mL of THF, 7 g of Zn dust, 8 mL (98

mmol) of methyl vinyl ketone, and 5 g of nickel(II) chloride was heated and stirred under argon until the mixture became reddish-brown (0.5 h). A solution containing 9.05 g (50.0 mmol) of 2-(2-bromoethyl)-1,3-dioxolane in 2 mL of pyridine was added dropwise, and the mixture was refluxed overnight. After cooling, it was diluted with 200 mL of diethyl ether and filtered through Celite. The solvent was removed in vacuo, and the residue was filtered through a short silica gel column with diethyl ether to provide, after evaporation of the solvent, 8.35 g (97.0%) of **8**. A sample had bp 73−77 °C (0.3 mmHg): EIMS *m/z* 171 ($(M - H)^+$, 1), 154 (1), 139 (1), 129 (1), 114 (2), 99 (2), 84 (4), 73 (100), 55 (4), 43 (44); HREIMS *m/z* 173.1191 (calcd for $C_9H_{17}O_3$ $(M + H)^+$, 173.1178); 171.1023 (calcd for $C_9H_{15}O_3$ $(M - H)^+$, 171.1021).

2-(5-Benzylaminohexyl)-1,3-dioxolane (9). The keto-acetal **8** prepared above was treated with 5.46 mL (50.0 mmol) of benzylamine and 18.4 mL (1.3 equiv) of titanium(IV) isopropoxide for 2 h. After the addition of 50 mL of anhydrous ethanol and 2.1 g of $NaCNBH_3$, the mixture was stirred overnight. The mixture was diluted with 250 mL of diethyl ether and treated with 4 mL of 10% NaOH and 8 mL of water followed by 20 g of anhydrous K_2CO_3. The mixture was filtered through Celite, and after the solvent was removed in vacuo, the residue was filtered through a short Florisil column with ether. Subsequent evaporation of the solvent provided 7.64 g (59.9%) of nearly pure **8**. A sample purified by Kugelrohr distillation had bp 130−140 °C (0.15 mmHg): EIMS *m/z* 262 ($(M - H)^+$, 1), 248 (2), 218 (1), 206 (1), 186 (1), 172 (1), 160 (1), 146 (1), 134 (73), 106 (7), 91 (100), 73 (25), 65 (9), 45 (16); HREIMS *m/z* 264.1954 (calcd for $C_{16}H_{26}NO_2$ $(M + H)^+$, 264.1964).

***N*-Benzyl-2-methyl-7-[3-(1,3-dioxan-2-yl)propyl]-azepane (13).** A solution containing 3.21 g (12.2 mmol) of 2-(5-benzylaminohexyl)-1,3-dioxolane **9** in 5 mL of THF was cooled in an ice bath and treated with 20 mL of 10% HCl and 2.5 mL of 70% $HClO_4$ and stirred at room temperature for 12 h. A small aliquot was neutralized with 10% NaOH, and analysis of the organic phase showed that the starting material was completely hydrolyzed. The mixture was then diluted with 50 mL of H_2O, and after the addition of 70 mL of CH_2Cl_2, the two-phase mixture was adjusted to a methyl orange end-point by the careful addition of solid KCN and stirred for 5 h. The mixture was made slightly basic by the careful addition of excess KCN, the organic phase was separated and dried over anhydrous K_2CO_3, and the solvent was removed in vacuo. The residue **10**, was dissolved in 10 mL of anhydrous THF and added under argon to a 1.8-fold excess of the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane.[26] The mixture was worked up by the addition of 150 mL of diethyl ether and 3 mL of 10% NaOH, followed by anhydrous K_2CO_3. The mixture was filtered through Celite, and the solvent was removed in vacuo to provide 4.1 g of residue, 80% of which consisted of **13**, present as a pair of isomers: FTIR (mixture of both isomers) 3068, 3030, 2973, 2961, 2931, 2853, 2732, 1600, 1492, 1456, 1378, 1280, 1243, 1216, 1148, 1097, 1023, 1005, 928, 892, 854, 799 cm^{-1}; EIMS *m/z* 317 (M^+, 1), 302 (2), 274 (1), 260 (1), 240 (1), 226 (4), 216 (1), 203 (16), 202 (100), 186 (1), 174 (5), 160 (2), 146 (4), 127 (7), 106 (5), 91 (93), 69 (9), 55 (11), 41 (27); HREIMS *m/z* 318.2427 (calcd for $C_{20}H_{32}NO_2$ $(M + H)^+$, 318.2433); 316.2273 (calcd for $C_{20}H_{30}NO_2$ $(M - H)^+$, 316.2277).

***cis*- and *trans*-2-Methyl-7-[3-(1,3-dioxan-2-yl)propyl]-azepane (14a/14b).** A solution containing 4.1 g of **13**, 4.0 g of 10% Pd/C, and 4.2 g of ammonium formate in 100 mL of MeOH was heated at reflux for 5 h. Analysis of an aliquot showed that none of the starting material remained. Occasionally when repeating this step, there would be no reaction, then the mixture would be filtered, new catalyst and ammonium formate added, and the reflux resumed. When all the starting material had reacted, the mixture was filtered through Celite, the solvent was removed in vacuo, and the residue was partitioned between diethyl ether and 10% NaOH. Evaporation of the solvent provided 2.5 g (85%) of a mixture, 70% of which was **14a**/**14b**, which were analyzed together: FTIR (broad GC peak) 2960, 2931, 2852, 1379, 1148, 1003 cm^{-1}; EIMS *m/z* 227 (M^+, 0.5), 226 (2), 212 (1), 198 (2), 184 (1), 170 (2), 152 (2), 138 (4), 126 (7), 113 (11), 112 (100), 96 (4), 87 (11), 84 (18), 70 (18), 56 (13), 41 (36); HREIMS *m/z* 228.1966 (calcd for $C_{13}H_{26}NO_2$ $(M + H)^+$, 228.1964).

***cis*-2-Methyl-7-[3-(1,3-dioxan-2-yl)propyl]azepane (14a).** A 0.1 g sample of *cis* and *trans* **14a/14b** was treated sequentially with *N*-chlorosuccinimide and NaOH as described for the synthesis of **7a** to provide a 1:1 mixture of the isomeric 1-dehydroazepane acetals: EIMS *m/z* 225 (M^+, 2), 224 (4), 210 (2), 197 (2), 139 (20), 124 (60), 111 (62), 110 (80), 96 (46), 87 (90), 83 (17), 82 (20), 68 (30), 67 (33), 55 (40), 42 (50), 41 (100) and *m/z* 225 (2), 224 (2), 149 (12), 148 (10), 138 (30), 125 (100), 124 (36), 110 (54), 97 (15), 87 (14), 84 (14), 82 (15), 80 (15), 44 (42), 41 (100). Hydrogenation of this mixture over 5% Rh/Al_2O_3 provided a 98:2 mixture of the azepanes **14a/14b**.

Cyclizations to 3-*n*-Nonyl-5-methyllehmizidines (2a−2d). A. From Dioxanyl Azepanes (14a/14b). A solution containing 0.1 g of a 1:1 mixture of **14a/14b** in 5 mL of THF, 5 mL of 10% HCl, and 0.5 mL of 70% $HClO_4$ was stirred overnight. The THF was evaporated, 20 mL of CH_2Cl_2 was added, and the mixture was carefully brought to a methyl orange end-point with KCN and stirred for 20 h. The mixture was then made basic by the addition of a slight excess of KCN, and the organic layer was separated and dried over anhydrous K_2CO_3. The solvent was removed in vacuo, and the residue was taken up in 10 mL of THF and treated with an excess of *n*-nonylmagnesium bromide to provide after the usual workup **2a**, **2b**, **2c**, and **2d** in a 45.2:13.4:10.5:30.9 ratio. HREIMS: *m/z* 280.3013 (calcd for $C_{19}H_{38}N$ $(M + H)^+$, 280.3004); *m/z* 278.2859 (calcd for $C_{19}H_{36}N$ $(M - H)^+$, 278.2848). When a 98:2 mixture of **14a/14b** was treated under similar conditions, a 1.4:25:0.2:74 mixture of **2a**, **2b**, **2c**, and **2d** was obtained. HREIMS: *m/z*, 280.3014 (calcd for $C_{19}H_{38}N$ $(M + H)^+$, 280.3004); 278.2859 (calcd for $C_{19}H_{36}N$ $(M - H)^+$, 278.2848).

Cyclizations to 3-*n*-Nonyl-5-methyllehmizidines (2a−2d). B. From Pyrrolidine Ketals (7a/7b). Solutions containing ca. 50 mg of **7a/7b** in 5 mL of THF were treated with 1 mL of 10% HCl and 3 drops of 70% $HClO_4$ and stirred overnight. The mixture was made basic with 10% NaOH and partitioned between diethyl ether and water. The ether layer was evaporated, and the residue was taken up in 10 mL of MeOH, then treated with a few drops of 10% NaOH and a slight excess of $NaCNBH_3$, and stirred for 6 h. The mixture was carefully acidified with 10% HCl and made basic with 10% NaOH, and after concentration in vacuo, the residue was partitioned between diethyl ether and water. Gas chromatographic analysis of the ether layers showed the presence of 3-*n*-nonyl-5-methyllehmizidines **2a**−**2d** in the ratios shown in Table 1 (Supporting Information).

Characterization of lehmizidine 275A (1): EIMS *m/z* 275 (1), 260 (4), 152 (100), 124 (3), 110 (2), 96 (1), 82 (1), 67 (3); EIMS/MS (on *m/z* 260) 138 (100); (on *m/z* 152) 124 (58), 110 (67), 96 (27), 70 (100); (on *m/z* 138) 110 (24), 96 (17), 84 (100), 70 (30); CIMS (NH_3) 276; CIMS (ND_3): 277; CI (NH_3)-MS/MS *m/z* 192 (43), 112 (100), 109 (43), 95 (60), 81 (18); FTIR (see Figure 1) 3328, ca. 2800, 2119, 1457, 1364, 1247 cm^{-1}; ^1H NMR (see Table 2, Supporting Information); HREIMS *m/z*, 275.2621 (calcd for $C_{19}H_{33}N$, 275.2613); 274.2171 (calcd for $C_{19}H_{32}N$, 274.2164); 260.2380 (calcd for $C_{18}H_{30}N$, 260.2378).

Characterization of tetrahydro-275A: FTIR (identical to **2c**, see Figure 2, Supporting Information) 2932, 2865, ca. 2800, 1460, 1365, 1212 cm^{-1}; EIMS *m/z* 279 (2), 278 (2), 264 (8), 250 (2), 236 (2), 222 (3), 153 (8), 152 (100), 138 (6), 124 (3), 110 (3), 96 (2), 82 (2); EIMS (direct probe) *m/z* 279 (3), 264 (5), 250 (5), 222 (3), 180 (3), 152 (100), 138 (5), 124 (5), 110 (6), 96 (5), 83 (12), 70 (22), 55 (13); CIMS (*i*-C_4H_{10}, direct probe) 289 (100), 294 (35), 268 (52); CI (NH_3)-MS/MS *m/z* 196 (44), 112 (100), 109 (23), 95 (61), 81 (18).

Characterization of lehmizidine 275A′ (15): FTIR 3328, 2865, ca. 2800 (broader than for **1** above, resembling that of **2b**, see Figure 2, Supporting Information), ca. 2110, 1457, ca. 1360, ca. 1250−1150 cm^{-1}; EIMS *m/z* 275 (6), 274 (9), 260 (17), 246 (4), 232 (3), 218 (3), 194 (3), 178 (3), 166 (2), 152 (100), 138 (3), 136 (3), 124 (5), 110 (4), 95 (3), 81 (4), 67 (6), 55 (6);

H_4-**5**, CI (NH_3)-MS/MS *m*/*z* 196 (28), 112 (100), 109 (33), 95 (71), 81 (23); GC peak overlaps that of **16** below (**15**:**16** ≈ 1.6:1)

Characterization of lehmizidine 277A (16): FTIR 3085, 2864, ca. 2800, 1643, 991, 912 cm^{-1}; EIMS *m*/*z* 277 (5), 276 (6), 262 (12), 248 (2), 234 (3), 220 (4), 194 (2), 178 (3), 162 (3), 152 (100), 124 (5), 110 (4), 96 (4), 82 (4), 67 (7), 55 (10).

Characterization of lehmizidine 289A (17): FTIR 3328, ca. 2800, ca. 2120, 1723, 1452, 1360, 1249, 1214, 1120 cm^{-1}; HREIMS *m*/*z* 289.2399 (calcd for $C_{19}H_{31}NO$ (M^+), 289.2406); 288.2306 (calcd for $C_{19}H_{30}NO$ ($M^+ - 1$), 288.2327); 274.2177 (calcd for $C_{18}H_{28}NO$ ($M^+ - CH_3$) 274.2171); 152.1436 (calcd for $C_{10}H_{18}N$, ($M^+ - C_9H_{13}O$), 152.1439); EIMS *m*/*z* 289 (1), 274 (6), 208 (2), 178 (2), 165 (4), 152 (100), 124 (4), 110 (3), 82 (3), 67 (3); EIMS (JEOL instrument) *m*/*z* 289 (10), 288 (10), 274 (50), 260 (6), 246 (6), 232 (6), 208 (10), 193 (6), 180 (10), 165 (26), 152 (100), 124 (16), 110 (10), 96 (10), 81 (10); CIMS (NH_3) 290; CIMS (ND_3) 291.

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Supporting Information Available: The compositions of mixtures of **2a**−**2d** from cyclizations of pyrrolidines **7a**/**7b** (Table 1), the ^1H NMR data on **1** (Table 2), the spectral characterization of 4-methyl-6-*n*-nonylquinolizidines (**4a**−**4d**) and the triketone **5**, the synthesis of *cis*- and *trans*-2-ethyl-7-methylazepanes (**12**) via the *N*-benzyl intermediates (**11**), the FTIR spectra of **2a**−**2d** (Figure 2) and *cis* and *trans* **12** (Figure 3), and the MS characterization of the four synthetic diastereomers of tetrahydro-**1** (**2a**−**2d**) are available free of charge via the Internet at http://pubs.acs.org.

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