New Quinolizidine Alkaloids from *Lupinus argenteus* and Its Hosted Root Parasite *Castilleja sulphurea*. Stereochemistry and Conformation of Some Naturally Occurring Cyclic Carbinolamides

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At one Colorado location, *Castilleja sulphurea* (Scrophulariaceae) is a root parasite on *Lupinus argenteus* subsp. *rubricaulis* (Fabaceae). The new carbinolamide quinolizidine alkaloids 2(*S*),9(*R*)-dihydroxyaphyllidine, **1**; 2(*R*),9(*R*)-dihydroxyaphyllidine, **2**; 2(*R*)-hydroxyaphyllidine or (−)-argyrolobine, **4**; and 2(*S*)-hydroxyaphyllidine, **5**, and the known (+)-aphyllidine, **6**, were isolated from both plant species. The alkaloids are inherent to the *Lupinus* and are transferred via root parasitism to the *Castilleja*. The pairs **1**–**2** and **4**–**5** are interconvertible epimers of each other, although they can be isolated pure either as such or as ester derivatives. NMR and X-ray crystal data reveal that each of the four carbinolamides (or ester derivatives) adopts a conformation placing the functional group perpendicular to the plane of the conjugated amide bond system. Subspecies of the *L. argenteus* complex apparently differ in quinolizidine alkaloid patterns because of a differing order in the timing of ring-oxidation steps.

Species of *Castilleja* (Scrophulariaceae; common name: Indian paintbrush) from the western United States were reported[1-4] to contain pyrrolizidine or quinolizidine alkaloids. We recently showed[5a] that these alkaloids are not inherent to the *Castilleja*, but are transferred from an alkaloid-containing hostplant into the *Castilleja* via root parasitism. Preliminary evidence[5a] indicated that quinolizidine alkaloids in one Colorado population of *C. sulphurea* were being obtained from *Lupinus argenteus* subsp. *rubricaulis*. We report here the results of structural and chemical studies on these alkaloids, two of which possess functional groups present individually or partially in some other quinolizidines, but whose total array in a single compound is unprecedented. The alkaloids were isolated as a mixture of diastereomers containing epimeric carbinolamide groups. We also isolated and characterized (−)-argyrolobine, whose enantiomorph was previously known, but incompletely characterized. Again, this alkaloid occurred as interconvertible epimeric carbinolamides. (+)-Aphyllidine, the presumed biosynthetic precursor of the carbinolamides, was isolated and characterized spectrally in detail.

Results

Extraction of a multiplant collection of *C. sulphurea* and subsequent isolation of a crude base fraction yielded a residue which showed the presence of three alkaloids by TLC. When individual plants were analyzed, some were found to contain the three alkaloids, while others were alkaloid-free. This population of *C. sulphurea* was growing interspersed with plants of *L. argenteus* subsp. *rubricaulis* (Fabaceae). TLC analysis of a crude base fraction from *L. argenteus* showed alkaloid spots of identical R_f value to those shown by the crude base fraction from *C. sulphurea*. The major alkaloid and one of the minor alkaloids were isolated from both plant sources and were shown to indeed be the same from either source. Near the same location, *L. argenteus* was growing with a second paintbrush species, *C. flava*. The same three alkaloids were found to be present in *C. flava* as well. Large-scale isolation, separation, and characterization work was accomplished on alkaloids isolated from *L. argenteus*, the most convenient source in terms of plant size and numbers.

Si gel TLC of a column chromatography isolate showed a single alkaloidal spot, but a doubling of resonances occurred in the ^{13}C NMR spectrum of the isolate. The presence of two very closely related substances, in the ratio 1:1.2, seemed likely. HPLC of the mixture gave two base-line separated peaks in approximately the same ratio. Each peak was collected, making conservative cuts, but reinjection of each isolate gave a two-component system identical with that of the original injection. One of the components could be obtained nearly pure and characterized spectrally if the solvent from a conservative cut was immediately evaporated at less than 40 °C. Eventually, one component crystallized pure from ether/methanol. Diacetates of each compound were separated after acetylation of the alkaloid mixture. The diacetates were characterized spectrally. Detailed NMR studies and a single-crystal X-ray diffraction experiment allowed us to assign structures **1** and **2** (without absolute stereochemistry) to the alkaloids. Microcrystalline bis-4-bromobenzoates were obtained from both **1** and **2**, and the absolute configurations were established as indicated by the exciton chirality method.[6]

A second chromatography isolate similarly proved to be a mixture of two closely related substances, one of which, along with its monoacetate, was obtained pure and characterized spectrally and by optical rotation. Spectral data for the second substance could be obtained from an isolate contaminated by the first. The spectral data, in comparison to those for **1** and **2** and chemical degradation to (+)-sparteine, **3**, resulted in assignment of structures **4** and **5** for these alkaloids. Compound **4** is (−)-argyrolobine, the enantiomer of a known alkaloid whose stereochemistry at C2 was previously undetermined.[7] Presence of the epimer corresponding to **5** was not noted in the previous work.[7]

Finally, one additional isolate (also minor) proved to be a single substance, the known[8] compound (+)-aphyllidine, **6**, which was characterized by optical rotation, mass spectrum, ^1H and ^{13}C NMR spectra (considered in themselves and in comparison with spectral data from the other isolates) and by conversion to **3**. Previous work[8] on **6** and on its enantiomer (−)-aphyllidine[7] included only incomplete spectral characterization.

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Table I. ^{1}H NMR Spectral Chemical Shift Assignments (ppm) for Quinolizidine Isolates 1, 4, and 6 and Acetate Derivatives 1Ac, 2Ac, and 4Ac

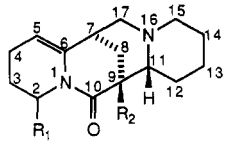
proton	1	1Ac	2Ac	4	4Ac	6
H2ax	–	–	–	–	–	3.68
H2eq	5.95	6.99	7.16	6.14	7.17	3.81
H3ax	2.02	2.12	2.14	1.91	2.19	1.77
H3eq	1.54	1.82	1.69	1.75	1.68	1.77
H4ax	2.32	2.21	2.16	2.31	2.14	2.08
H4eq	1.93	2.06	1.98	1.95	1.96	2.08
H5	4.83	4.75	4.77	4.82	4.78	4.70
H7	2.71	2.73	2.77	2.65	2.65	2.59
H8ax	1.75	1.88	1.80	1.71	1.76	1.71
H8eq	1.97	2.69	2.65	1.95	1.76	1.85
H9	–	–	–	2.47	2.48	2.46
H11	2.90	3.17	3.10	3.06	3.05	3.03
H12ax	1.51	1.69	1.66	1.97	1.82	1.84
H12eq	1.48	1.45	1.43	1.17	1.10	1.24
H13ax	1.40	1.51	1.47	1.55	1.48	1.50
H13eq	1.87	1.91	1.90	1.91	1.83	1.86
H14ax	1.59	1.64	1.63	1.71	1.58	1.60
H14eq	1.10	1.14	1.17	1.18	1.12	1.18
H15ax	2.75	2.84	2.81	2.77	2.72	2.74
H15eq	2.75	2.78	2.74	2.77	2.72	2.74
H17ax	3.21	3.32	3.29	3.38	3.27	3.26
H17eq	2.46	2.55	2.43	2.45	2.41	2.39
H2′(OAc)	–	2.04[a]	2.04[b]	–	2.03	–
H9′(OAc)	–	2.01[a]	2.01[b]	–	–	–

[a,b] Interchangeable assignments.

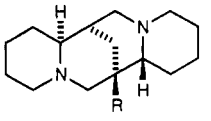
Our new isolates are probably best named as follows: **1**, 2(*S*),9(*R*)-dihydroxyaphyllidine; **2**, 2(*R*),9(*R*)-dihydroxyaphyllidine; **4**, 2(*R*)-hydroxyaphyllidine = (–)-argyrolobine; **5**, 2(*S*)-hydroxyaphyllidine.

Of particular interest is the fact that the 2-OH group in **1**, **2**, **4**, and **5** (and the 2-OAc group in their acetate derivatives) is, in every case, axial (perpendicular to the C5, C6, N1, C10, O19 plane). This is evident from the X-ray crystal structure for **1** and from analysis of the solution NMR spectra of all four compounds and their acetate derivatives.

An attempted degradation of **1** and **2** to (+)-sparteine was successful only to the intermediate (+)-9-hydroxysparteine, **7**, a previously unknown substance. **7** was characterized physically and spectrally.



1: R_1 = β-OH; R_2 = OH
2: R_1 = α-OH; R_2 = OH
4: R_1 = α-OH; R_2 = H
5: R_1 = β-OH; R_2 = H
6: R_1 = R_2 = H



3: R = H
7: R = OH

Detailed Structural Results. Ultimately, the structure of **1** was established by X-ray diffraction, but prior spectral and chemical studies independently indicated the same structure. Thus, HRMS and elemental analysis established the molecular formula, the UV and IR spectra indicated the presence of an enamide, and formation of a diacetate suggested a diol. The MS, IR, and UV data are given in the Experimental Section. The NMR data are worthy of special mention since they were important in making structural assignments for the other isolates and derivatives and in assuring that conformations seen in the crystal structure reflected those in solution.

Complete ^{13}C and ^{1}H NMR spectral assignments were made for **1**, its diacetate (**1Ac**), and the diacetate of **2** (**2Ac**) (Tables I–III). Assignments were aided by DEPT, ^{1}H–^{13}C HETCOR, and ^{1}H–^{1}H COSY for each and extensive NOE experiments on **2Ac**. One key starting point for the analyses and functional group placements was the H5 vinyl resonance. Connectivities could be shown from it to the H4 protons, thence to the H3 protons, and finally to the H2 resonances. This established the presence of one OH group at C2. A typical deshielding shift was noted for the H2 proton in the acetates. The second OH group was on a tertiary carbon as evidenced by the quaternary ^{13}C resonances at 71.41 ppm for **1** and 77.80 or 78.19 for the acetates. The OH had to be at either C9 or C7 since, if it was at C11, the carbon would have been much more deshielded because of the neighboring nitrogen. An NOE experiment on **2Ac** established that the C5 vinyl proton was in the vicinity of a methine H resonance, and the COSY spectrum showed that the carbon bearing this methine H was neighbor to two methylene groups. Such an arrangement was only possible if the methine H was at C7. The second OH must therefore be at C9. Problems with the isolation of **2** made it difficult to obtain complete spectral data on the pure epimer, but the data for **2Ac** were in complete accord with the assignment of **2** as the C2 epimer of **1**.

Table II. ^{1}H NMR Spectral Coupling Constants (*J*, Hz) for Quinolizidine Isolates and Derivatives

protons	1	1Ac	2Ac	4[a]	4Ac	6
2ax, 2eq	–	–	–	–	–	13.2
2ax, 3ax	–	–	–	–	–	8.3
2ax, 3eq	–	–	–	–	–	4.1
2eq, 3ax	2.7	2.8	2.9	2.8	2.8	4.2
2eq, 3eq	2.7	2.8	2.9	2.8	2.8	6.8
2eq, 4eq			1.0		0.8	
3ax, 3eq				13.4		
3ax, 4ax	13.9			13.4		
3eq, 4ax	5.3			5.6		
4ax, 4eq	18.7			16.9	11.9	
4ax, 5	2.0	1.7		2.1		4.0
4eq, 5	5.4	5.8	6.2	5.9	6.2	4.0
7, 8ax	3.4	2.8	3.2			
7, 8eq	3.5	3.3	3.6			
7, 17ax	2.7	2.5	2.7	2.9	3.0	3.5
7, 17eq	2.7	2.0	2.4	3.0	2.6	3.2
8ax, 8eq	12.3	11.4	11.9			
8ax, 9	–	–	–	2.5		
8eq, 9	–	–	–	2.5		
9, 11	–	–	–	4.7	5.3	2.4
11, 12ax	11.9	12.0	12.0	12.3	12.0	11.9
11, 12eq	3.0	2.4	2.3			
12ax, 12eq	12.7	12.0	10.4			
12ax, 13ax	12.8	12.0	12.6	12.7	13.2	13.0
12ax, 13eq		3.5				
12eq, 13ax	3.7	3.5	3.5	3.7	3.5	
13ax, 13eq	12.8	12.0	12.6	12.7	13.2	13.0
13ax, 14ax	12.8	12.0	12.6	12.7	13.2	13.0
13ax, 14eq	3.7	3.5	3.5	3.7	3.5	3.6
14ax, 14eq	13.1	11.8	12.8			
17ax, 17eq	10.8	10.7	10.8	10.9	10.6	10.7

[a] CD_3OD solvent.

Similarly, NMR spectral data for **4** and **4Ac** (Tables I–III) were directly comparable to those for the **1**–**2** series, with the exception of changes expected for a structure lacking the C9 OH. An incorrect assignment of the two key proton resonances was made in the orginal work[7] on (+)-**4** and its acetate. Thus, a 6.0 ppm resonance (here 6.14 ppm) observed for (+)-**4** and a 7.21 ppm (here 7.17 ppm) resonance observed for **4Ac** were erroneously assigned to H5 rather than H2.

Ring A conformations were deduced from the coupling constants observed between the H2 and H3 protons in the epimeric pairs **1**–**2** and **4**–**5** or their acetates and the bis-4-bromobenzoates of **1** and **2**. H2 was coupled to both H3

Table III. ^{13}C NMR Spectral Assignments for Quinolizidine Isolates 1, 4, and 6 and Acetate Derivatives 1Ac, 2Ac, and 4Ac

carbon	1	1Ac	2Ac	4	4Ac	6
C2	72.24	73.16	73.32	72.84	73.42	40.22
C3	26.46	24.78	24.90	25.55	24.91	21.23
C4	16.51	17.04	16.62	16.93	16.93	22.13
C5	103.97	101.89	101.73	102.96	101.98	102.39
C6	136.46	137.26	137.56	136.84	138.36	139.27
C7	36.46	36.84	36.87	35.59	35.68	35.40
C8	28.02	25.88	25.13	21.53	21.19	21.66
C9	71.41	77.80	78.19	44.50	44.27	44.07
C10	174.68	169.59	169.60	172.90	171.97	171.20
C11	64.09	62.49	61.62	58.49	58.37	59.00
C12	16.31	16.76	16.65	23.18	22.41	23.26
C13	25.14	25.19	25.02	26.89	25.54	25.15
C14	18.81	18.94	18.87	19.30	18.94	19.22
C15	53.64	53.75	53.85	54.33	54.28	54.16
C17	51.57	52.13	52.35	53.57	53.57	53.32
C2′	-	21.09[a]	21.08[c]	-	21.19	-
C2″	-	169.50[b]	169.12[d]	-	169.66	-
C9′	-	21.28[a]	21.29[c]	-	-	-
C9″	-	169.27[b]	168.82[d]	-	-	-

[a-d] Interchangeable assignments.

protons with small coupling constants (2.7–2.9 Hz) in each of the alkaloids and derivatives. No diaxial couplings were observed, and hence the H2 proton must be equatorial in each compound. In the spectrum of **6**, which lacks an OH at C2, there are indeed larger coupling constants (8.3 and 6.8 Hz) between the H2 and H3 protons (Table III). Since **6** lacks a substituent at C2, there is no preference for either conformer of ring A (see below), and the coupling constants observed probably result from a time average. If the H2 protons in **1**–**2** and **4**–**5** (and their derivatives) are equatorial, then the C2 OH and OAc groups must be axial. ^1H NMR spectroscopy was used to qualitatively follow epimerization at C2 in **1**. **1** was stable in MeOH at room temperature for 12 h but was converted to a mixture of **1** and **2** under the same conditions in 1:1 MeOH/H_2O.

Single-Crystal X-ray Diffraction and Absolute Configuration Studies. These studies were conducted to confirm the relative and absolute stereochemistries and ring conformations. Single-crystal X-ray diffraction data for **1** are given in the Experimental Section, and a structure of one possible enantiomer from these data is given in Figure 1. Both **1** and **2** formed bis-4-bromobenzoate derivatives, whose CD spectra (**1BrBz**, $\Delta\epsilon_{255}$ +5.70, $\Delta\epsilon_{240}$ −7.45; **2BrBz**, $\Delta\epsilon_{253}$ −40.26, $\Delta\epsilon_{234}$ +13.18) showed that Figure 1 also represents the absolute configuration of **1**. Since **1** and **2** are interconvertible by epimerization at C2, the absolute configuration is established for **2** as well.

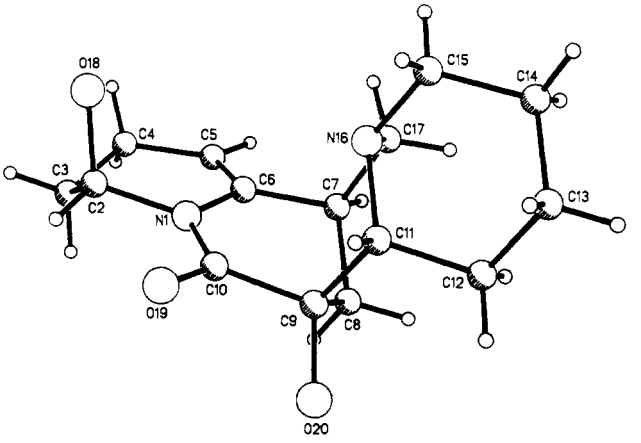
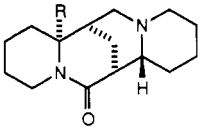


Figure 1. X-ray structure of 2(*S*),9(*R*)-dihydroxyaphyllidine, **1**.

Discussion

General Botanical and Structural Relationships. This work continues to extend our observation[5a] that *Castilleja* root parasitism on leguminous plant species results in quinolizidine alkaloid transfer. Such transfer to a *Pedicularis* species has also recently been found.[5b] As in the present case, an array of alkaloids present in the host roots appears to be transferred directly as such to the parasite without any selectivity.

In spite of the hundreds of quinolizidine alkaloid-containing species known,[9] only a few taxa contain alkaloids related to aphyllidine, **6**. No previously known quinolizidines contain a C10 OH and only one a C2 OH. Early work focused on *Anabasis aphylla* (Chenopodiaceae), from which (+)-aphyllidine and (+)-aphylline, **8**, were identified[10] and later 6-hydroxyaphylline,[11a] **9**, without stereochemistry assigned, and 17-oxoaphyllidine.[11b] (−)-Monspessulanine, from *Cytisus monspessulanus*,[12] was much later shown[13] to be 11-epiaphyllidine. Two of 21 American *Lupinus* species studied (*L. aduncus* and *L. greenei*) were shown by GCMS to contain aphyllidine.[14]



8: R = H
9: R = OH

More closely related to our work was the isolation from *Argyrolobium megarhizum* (Leguminosae) of (−)-aphyllidine and (+)-argyrolobine.[7] Here we have shown that (+)-argyrolobine must be the enantiomer of **4** and have established the structures of the previously unknown alkaloids **1**, **2**, and **5**. The relatively facile interconversions

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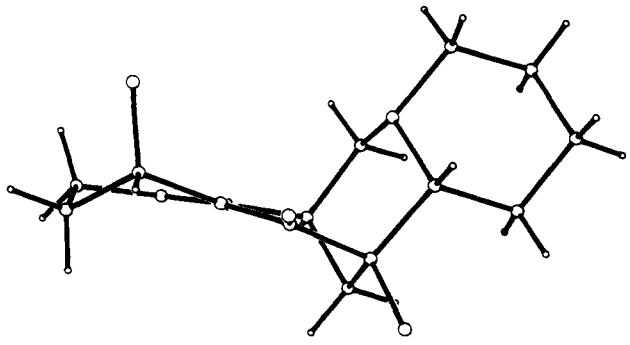


Figure 2. X-ray structure of 1, viewed down N1–C6 bond.

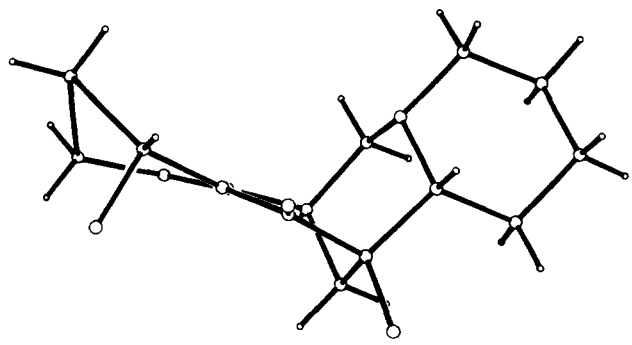
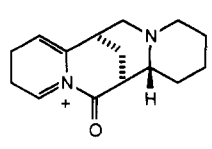


Figure 3. Structure of 2(*R*),9(*R*)-dihydroxyaphyllidine, 2, viewed down N1–C6 bond. Redrawn from Figure 2 by changing the configuration at C2 and ring conformation based upon NMR analysis.

$1 \rightleftarrows 2$ and $4 \rightleftarrows 5$, which most likely proceed through the acyliminium ion **10**, would be easily achieved under our isolation conditions, and hence it is not possible to absolutely determine if both members of a pair are actually present in the living plant. It does seem likely in view of the facile interconversion in aqueous medium. Since the biosynthesis of quinolizidine alkaloids proceeds from the reduced compounds (such as **3**; see below) to the more oxidized ones, the alkaloids of *L. argenteus* subsp. *rubricaulis* all represent late biosynthetic products. The three legume genera containing these highly oxidized quinolizidines are all in the tribe Genistae of the subfamily Papillionoidae. *L. argenteus* is a complex taxon, with numerous subspecies and varieties having been described.[15] The chemistry of subspecies *rubricaulis* is novel within this group, since subspecies *stenophyllum* contains[16] a typical array of common quinolizidines (sparteine, β-isosparteine, lupanine, α-isolupanine, anagyrine, and thermopsine), while subspecies *spathulatus* has α-isolupanine as its major component, with only traces of other quinolizidines (G. H. Harris, unpublished results).

Bridgehead hydroxylation is extremely rare. The only previous occurrence among the quinolizidines as far as we are aware was in *L. sericeus* where 7-hydroxy-β-isosparteine, 11, was found.[17]



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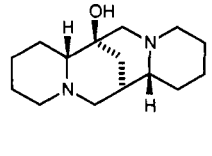

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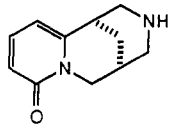

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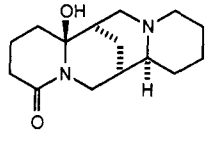

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Detailed Structure and Conformational Analyses. The X-ray crystal and solution NMR studies both led to the same structural relationships. The ring A conformation of **1** can be seen in another view from the X-ray data (Figure 2), looking down the N1–C6 bond. This shows the axial orientation of the C2 hydroxyl and also that there is a slight twist about the N1–C6 bond so that complete coplanarity of the C5/C6/N5/C10/O20 conjugated system is not achieved. The NMR evidence shows that **1Ac** has essentially the same conformation in solution. NMR data extractable for **2** from the mixture with **1** and obtained on pure **2Ac** shows that **2** must have the conformation depicted in Figure 3 (drawn by modifying the **1** structure in accordance with Dreiding models and the ^{1}H NMR data). There is a known general preference for electronegative substituents next to an sp^2 center to adopt a perpendicular conformation,[18] and this has been treated as an anomeric effect as well.[19] Carbinolamine epimers are more common than epimeric carbinolamides and occur in the biologically active pyrrolo[1,4]benzodiazepine antibiotics, for example. The relative importance of individual carbinolamine epimers for bioactivity have been studied for tomamycin[20] and anthramycin.[21]

The X-ray structure showed that the C and D rings are both in chair conformations and the extensive 2D and, particularly, NOE NMR experiments resulted in a similar conclusion for solution conformations. Total NMR assignments and conformation determinations have recently also been completed for sparteine, **3**, and its lactams,[22] calpaurine[23] (a hydroxylated and esterified lupanine), and cytisine,[24] **12**. In the last case, a single-crystal X-ray structure was also obtained, and both the crystal and solution work gave the same conformational results.

One oddity was observed in the ^{1}H NMR spectra of **1Ac** and **2Ac**. In the spectra of the other quinolizidines (including **4Ac** and **5Ac**), H8eq is in the 1.9 ppm region, while H8ax is around 1.7 ppm. The H8eq is, however, at 2.69 ppm in **1Ac** and at 2.65 ppm in **2Ac**, while H8ax remains near its more usual position. This large deshielding effect on H8eq must come from an orientation of the 9Ac carbonyl so that the deshielding part of the π-bond cone is in proximity to H8eq, but not H8ax. Dreiding models suggest that the 9Ac rotamer with an orientation for shielding H8ax may be destabilized by interference between the carbonyl oxygen and H12ax. No interactions

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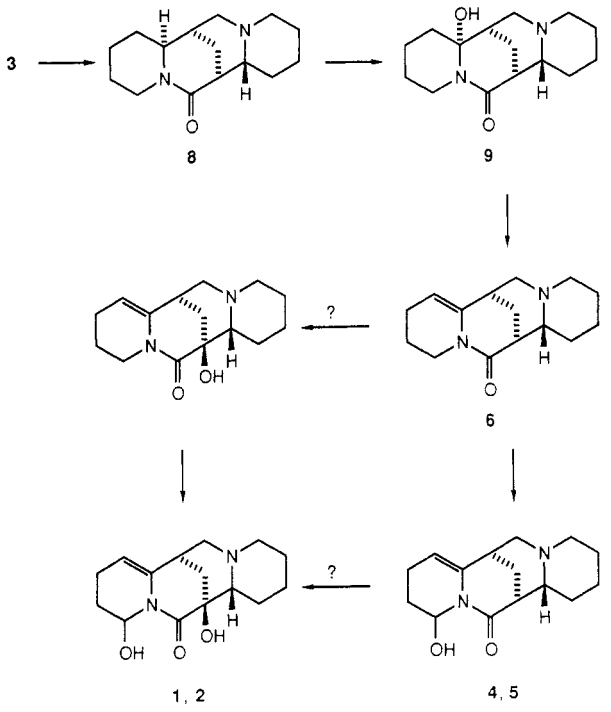
Scheme I



which might favor the observed rotamer are readily discernible.

Biosynthetic Implications. The present extension of aphyllidine alkaloid structures, along with those previously known, provides a sequence so that the genesis of this group can now be suggested (Scheme I). This pathway is related to that proposed[25] for the quinolizidine alkaloids of *Bolusanthus speciosus*. The suggested early intermediacy of 6-hydroxyaphylline, **9**, found in the *A. aphylla* work[11] is supported by the occurrence of the related 6β-hydroxylupanine, **13**, in *B. speciosus*, and the report that it dehydrates readily (even during hot methanol extraction of the plant material) to 5,6-dehydrolupanine.[25] The key sequence which leads to the array of aphyllidine alkaloids would then be the early oxidation at C10, followed by a later oxidation at C2. The more common pathway among quinolizidine-alkaloid plants would involve oxidation only at C2. Hence, an early oxidation at C10 would be the step which differentiates *L. argenteus* subsp. *rubricaulis* from the other *L. argenteus* subspecies so far studied.

Experimental Section

Instrumentation and General Procedures. NMR spectra were recorded on Bruker ACE-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C) or Bruker-IBM WP-270 (270 MHz for ^1H and 63 MHz for ^{13}C) spectrometers. The 2D ^1H–^1H COSY and ^1H–^{13}C HETCOR experiments were carried out on the ACE-300. Spectra were obtained in $CDCl_3$ unless otherwise noted and are reported as ppm from TMS. For ^1H NMR spectra, the $CHCl_3$ resonance was set at 7.24 ppm and at 77.0 ppm for the ^{13}C spectra. UV spectra were obtained on Perkin-Elmer 320 or Varian DMS 80 instruments. EIMS and CIMS (NH_3) were measured on a VG Micromass 16F spectrometer with a Systems Industries interface and a Digital PDP-8A computer. Exact mass spectra were obtained by the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. IR spectra were recorded on a Beckman 4240 spectrophotometer. Optical rotations were measured on an Autopol III polarimeter. TLC was accomplished on 0.25-mm precoated plates of Si gel 60 F-254 (Merck), reverse-phase octadecylsilane (C_{18}) F-254 (Whatman), or aluminum oxide Type T F-254 (Merck) and visualized by UV absorption or iodoplatinic acid spray. HPLC was carried out on a Beckman 110B solvent delivery module with a Beckman 163 variable-wavelength detector using an Altex Ultrasphere-ODS, semipreparative, reverse-phase Si gel column.

Plant Collections and Alkaloid Isolations. *Castilleja sulphurea* Rydb. was collected in an aspen grove along the south side of State Highway 14, 1.9 miles east of County Road 30, Jackson County, Colorado (voucher specimens GH103 and GH137) and identified by L. R. Heckard, Jepson Herbarium, University of California, Berkeley, CA. *Lupinus argenteus* Pursh. subsp. *rubricaulis* (Greene) Hess and Dunn was collected at the same site (voucher specimen GH171) and identified by D. B. Dunn, Department of Biology, Univeristy of Missouri, Columbia, MO. Some *C. flava* Watson was present at the same site, but only along the north side of the highway. A large population of *C. flava* (FRS 72, identified by D. M. Wilken, Department of Biology, Colorado State University) occurs with *L. argenteus* subsp. *rubricaulis* in a sagebrush area 13 miles east of Walden, CO, also along Highway 14, and about 5 miles west of the above site. Voucher specimens are in the Colorado State University Herbarium.

Dried and powdered above-ground *C. sulphurea* (GH103;87.4 g) was wet with 150 mL of 10% aqueous Na_2CO_3, and 400 mL of 1:1 toluene/*n*-BuOH was added. The mixture was filtered after standing for 24 h, and the organic layer was washed with three 50-mL portions of 1 M H_2SO_4. The combined acidic solutions were extracted once with 200 mL of $CHCl_3$ and then made basic to pH 9 with NH_4OH. The solution was extracted with two 200-mL portions of $CHCl_3$. The $CHCl_3$ solutions were combined, dried over Na_2SO_4, and evaporated to yield 48 mg of a crude base residue. TLC (Al_2O_3, 2.5% MeOH/ether) showed three alkaloid spots: R_f 0.19 (major), 0.67 (minor), and 0.95 (minor). CIMS (NH_3)[9] of the residue showed m/z +1 peaks at 279, 263, 247, 245, indicating the presence of alkaloids of even molecular weight, typical of quinolizidines. The ^1H NMR spectrum of the mixture was also similar to that of quinolizidine-containing isolates.[2]

Dried and powdered above-ground *L. argenteus* (342 g) was treated similarly and yielded 1.22 g of a crude alkaloid mixture, which showed the same three alkaloid spots on TLC and a ^1H NMR spectrum essentially identical with that of the residue from the *C. sulphurea* extraction. Five individual *C. sulphurea* plants growing within a few centimeters of *L. argenteus* and five isolated plants not growing near *L. argenteus* were analyzed for alkaloid content. Four of the five plants growing near the lupine had alkaloid profiles similar to that of the lupine, while one was negative for alkaloids. None of the five isolated *C. sulphurea* plants contained alkaloids. Plants of *C. sulphurea* and *L. argenteus* growing together were dug up, the root masses washed, and haustorial connections between roots of the two plants were identified.

Individual plants of *C. flava* growing near *L. argenteus* yielded an alkaloid mixture identical by TLC to that from *L. argenteus*.

Alkaloid Separations. A crude alkaloid mixture (3.29 g) from *L. argenteus* was separated by flash chromatography on a basic Al_2O_3 (Merck, Type T) column by elution with ether (1000 mL), 10% MeOH in ether (500 mL), 50% MeOH/ether (300 mL), and finally MeOH (200 mL). Approximately 50-mL fractions were taken and yielded: Fractions 6–8, **6**, 0.13 g; Fractions 25–27, a mixture of **1**, **2**, **4**, and **5**, 0.99 g; Fractions 28–43, a mixture of **1** and **2**, 0.83 g. The fractions 25–27 mixture was similarly rechromatographed to yield fractions containing mainly **4** and **5** (along with **1** and **2**) and fractions containing 0.60 g of only **1** and **2**.

The HRMS of the **1** and **2** mixture showed m/z 278.1625 (19), calc for $C_{15}H_{22}N_2O_3$ 278.1623. The ^{13}C NMR spectrum of the isolate showed a doubling of essentially all the resonances. HPLC analysis (0.3% aqueous NH_3 in 1:1 H_2O/MeOH, 3400 psi, 240-nm monitoring) showed two peaks of retention times 7.9 and 9.4 min, intensity ratio 1:1.2. Each peak was collected, making conservative cuts, but reinjection of each again produced two peaks in the same intensity ratio. Solvent was quickly evaporated from a collectin of the 7.9-min peak and was shown by NMR to be mainly **1**, which was finally obtained pure by recrystallization of the **1**, **2** mixture from ether/methanol. NMR spectral data for **2** were obtained by difference from spectra of the mixture.

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Rechromatography (flash, Al_2O_3, 5% MeOH/ether) of the residues containing **4** and **5** yielded 190 mg, which was still contaminated by **1** and **2**. This was again rechromatographed (flash, Al_2O_3, 1% MeOH/ether) to yield 52 mg of a mixture consisting only of the **4** and **5** epimers. The mixture was dissolved in a minimum of EtOH and refrigerated for several weeks. An amorphous powder precipitated, which was characterized by optical rotation and NMR spectral data as **4**. Spectral data for **5** were obtained by difference from spectra of the epimeric mixture.

Derivative Formation. A mixture of **1** and **2**, 0.35 g, was allowed to stand at 25 °C in 2 mL of Ac_2O, 0.25 mL of triethylamine, and 0.025 g of DMAP. At the end of 72 h, dilute aqueous NaOH was added, and the solution was extracted with CH_2Cl_2. Evaporation of the organic layer left a residue, which was separated by HPLC (C_{18} Si gel, 7:3 MeOH/H_2O) to yield 0.059 g of **1Ac** (R_f 0.43, Si gel, CH_2Cl_2/MeOH, 19:1) and 0.084 g of **2Ac** (R_f 0.32). A similar acetylation of pure **1** yielded only the R_f 0.43 component, assuring its identity as **1Ac**. A mixture of **4** and **5** was acetylated, yielding a separable mixture of **4Ac** (R_f 0.30) and **5Ac** (R_f 0.36). A small amount of pure **4** yielded only **4Ac**.

To a mixture (300 mg) of **1** and **2** and 200 mg of DMAP in 50 mL of pyridine was added 2.7 g of 4-bromobenzoyl chloride dissolved in 2 mL of benzene. The solution was stirred for 72 h at 25 °C, an equal volume of water was then added along with $NaHCO_3$ until the solution was saturated. The suspension was evaporated in vacuo, and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the bromobenzoates were separated by PLC to yield 28 mg of **1BrBz** (R_f 0.90, 9:1 CH_2Cl_2/MeOH; mp 124 °C dec) and 167 mg of **2BrBz** (R_f 0.65; mp of solid from EtOH 174–177 °C dec). Pure **1** was treated similarly to yield only the R_f 0.90 compound, assuring its identity as **1BrBz**.

Alkaloid and Derivative Characterizations. 2(*S*),9(*R*)-Dihydroxyaphyllidine (1): prisms, mp 122–123 °C from Et_2O/MeOH; X-ray diffraction data given below; $[\alpha]^{26}_D$ + 53.6° (*c* 1.48, $CHCl_3$); IR 3410, 2910, 2835, 2780, 1665, 1630, 1435, 1395, 1365, 1340, 1300, 1155, 1145, 1090, 1080 cm^{-1} (NaCl plate); UV (EtOH) λ_{max} 239 nm (ϵ 8040); NMR, Tables I–III. Anal. ($C_{15}H_{22}N_2O_3 \cdot CH_3OH$) C, H, N.

2(*S*),9(*R*)-Diacetoxyaphyllidine (1Ac): oil; $[\alpha]^{26}_D$ + 10.0° (*c* 1.14, $CHCl_3$); UV, λ_{max} 240 nm (EtOH); IR ($CHCl_3$) 3000, 2924, 2850, 2795, 1735, 1690, 1655, 1365, 1136, 1104, 1066, 1030, 1000, 954, 938, 918, 898, 858, 837, 812 cm^{-1}; NMR, Tables I–III. Purity established by ^{13}C and ^1H NMR (see the supplementary material).

2(*S*),9(*R*)-Bis(4-bromobenzoxy)aphyllidine (1BrBz): CD (CH_3CN), $\Delta\epsilon_{255}$ +5.70, $\Delta\epsilon_{240}$ −7.45; ^{13}C NMR 17.08, 17.24, 18.87, 24.74, 25.16, 25.78, 36.81, 52.77, 53.95, 62.76, 74.15, 78.34, 102.32, 127.76, 128.25, 128.98, 129.49, 131.24 (2 C), 131.35 (2 C), 131.45 (2 C), 131.62 (2 C), 137.22, 164.24 (2 C), 169.09; ^1H NMR 7.4–8.0 (aromatic H's), 7.24 (br s, H2), 4.82 (d, J = 6 Hz, H5); HRFABMS 643.0258 (calc for $C_{29}H_{28}N_2O_5Br_2$ 643.0267).

2(*R*),9(*R*)-Dihydroxyaphyllidine (2): ^{13}C NMR (by difference from a mixture with **1**) 16.12, 16.38, 19.10, 25.36, 26.78, 28.24, 37.04, 52.31, 53.95, 63.36, 71.48, 72.93, 103.67, 137.52, 174.99.

2(*R*),9(*R*)-Diacetoxyaphyllidine (2Ac): oil; $[\alpha]^{26}_D$ +38.5° (*c* 0.62, $CHCl_3$); UV (EtOH) λ_{max} 240; IR ($CHCl_3$) 3000, 2925, 2850, 2790, 1735, 1685, 1660, 1363, 1164, 1132, 1102, 1063, 1028, 1005, 995, 952, 936, 915, 895, 836 nm; NMR, Tables I–III. Purity established by ^1H and ^{13}C NMR (see the supplementary material).

2(*R*),9(*R*)-Bis(4-bromobenzoxy)aphyllidine: oil; CD (CH_3CN) $\Delta\epsilon_{253}$ −40.26, $\Delta\epsilon_{234}$ +13.18; ^{13}C NMR 16.63, 17.20, 18.84, 25.04, 25.12, 25.43, 37.04, 52.30, 53.93, 61.88, 75.12, 79.03, 102.22, 127.74, 127.98, 129.12, 129.48, 131.19 (2 C), 131.42 (2 C), 131.47 (2 C), 131.56 (2 C), 137.68, 163.61, 164.94, 169.16; ^1H NMR 7.5–7.8 (aromatic H's), 7.29 (s, H2), 4.86 (d, J = 6.0 Hz, H5); HRFABMS 643.0262 (calc for $C_{29}H_{28}N_2O_5Br_2$ 643.0267).

2(*R*)-Hydroxyaphyllidine or (−)-argyrolobine (4): solid, mp 150–155 °C; $[\alpha]^{26}_D$ −15° (*c* 0.20, $CHCl_3$) [lit.[7] for the enantiomer +13.3°]; NMR, Tables I–III.

2(*R*)-Acetoxyaphyllidine (4Ac): noncrystalline solid; mp 59–63 °C [lit.[7] mp 61 °C]; $[\alpha]^{26}_D$ +9.0° (*c* 0.54, $CHCl_3$); NMR, Tables I–III.

2(*S*)-Hydroxyaphyllidne (5): ^{13}C NMR (by difference from mixture with **4**) 16.72, 19.02, 21.70, 22.92, 25.40, 26.70, 35.08, 44.02, 53.00, 54.12, 59.54, 71.97, 102.69, 137.69, 173.38.

Table IV. Details of the X-ray Diffraction Study on 2(*S*),3(*R*)-Dihydroxyaphyllidine, 1

molecular formula	$C_{15}H_{22}N_2O_3 \cdot CH_3OH$
molecular weight	310.4
crystal system	monoclinic
space group	$P2_1$
unit cell	
a, Å	8.836 (3)
b, Å	10.934 (1)
c, Å	8.920 (2)
b, deg	116.52 (2)
unit cell vol, Å^3	771.1
Z	2
calcd density, g cm^{-1}	1.33
min, max cryst dimens, mm	0.21, 0.40 (irregular shape)
data collcn temp, °C	−140
radiation (1, Å)	Mo Kα (0.710 73)
monochromator	graphite
abs coeff, cm^{-1}	0.90
2*q* range, deg	4–50
index restrictions	$\pm h,k \geq 0, l \geq 0$
no. of reflcns with $\lvert F_o\rvert > 2.55s(\lvert F_o\rvert)$	2296
total no. of reflcns measd	3910
scan type	*W*
scan speed, deg min^{-1}	variable (4–30)
data/param	11.37
R^a	0.0389
$R_w{}^b$	0.0446
GOF^c	1.128
g	0.0019 (refined)
slope of normal probability plot	1.019

$^aR = (S|(F_o - F_c|)/(SF_o)$. $^bR_w = (Sw^{1/2}|F_o - F_c|)/(Sw^{1/2}F_o)$. ^{c}GOF = error in an observation of unit wt = $\{(Sw(|F_o - F_c|)^2)/(N_{data} - N_{params})\}^{1/2}$.

2(*S*)-Acetoxyaphyllidine (5Ac): ^1H NMR 3.22 (H15ax), 4.75 (H5), 7.00 (H2) (sample decomposed before additional characterization was possible).

(+)-Aphyllidine (6): oil; $[\alpha]^{26}_D$ +7.3° (*c* 2.18, EtOH) [lit.[8] +9°]; UV λ_{max} 240 nm (EtOH); EIMS *m/z* (rel intensity) 246 (37), 245 (27), 218 (8), 190 (6), 189 (6), 163 (14), 150 (6), 149 (10), 148 (7), 136 (13), 135 (11), 134 (12), 109 (14), 108 (9), 99 (8), 98 (100); NMR Tables I–III.

Conversion of 2(*R*)-Acetoxyaphyllidine (Argyrolobine Acetate), 4Ac, to (+)-Sparteine. 4Ac (5 mg) was dissolved in 10 mL of 10% HCl and hydrogenated (prereduced PtO_2, 25 °C, 4 atm) for 12 h. The mixture was filtered, made basic to pH 9 with K_2CO_3, and extracted twice with CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and evaported to leave 2 mg of yellow oil, $[\alpha]^{26}_D$ +8° (*c* 0.2, EtOH), whose ^1H NMR spectrum (300 MHz) was superimposable with that of authentic sparteine.

Conversion of Dihydroxyaphyllidines to 9-Hydroxysparteine (7). PtO_2 (980 mg) was prereduced with H_2 in 20 mL of 10% HCl. To this solution was added 270 mg of a mixture of **1** and **2**, and the resultant mixture was hydrogenated while stirring at room pressure and temperature for 48 h. The residue after filtration and evaporation was subjected to VLC (Si gel; gradient elution with 25, 30, and 35% MeOH in CH_2Cl_2) to yield 72 mg of **7**·HCl (R_f 0.65, C_{18} Si gel, 6:4 MeOH/$CHCl_3$). The HCl salt was converted with base to **9-hydroxysparteine**: $[\alpha]^{26}_D$ +27.3° (*c* 1.65, $CHCl_3$); mp 112 °C dec; HRMS 250.2048 (calc for $C_{15}H_{26}N_2O$ 250.2047); ^{13}C NMR spectrum (sparteine standard) multiplicites established by DEPT: C4 24.61 t (24.8 t), C13 24.80 t (24.9 t), C14 25.29 t (25.8 t), C3 25.56 t (26.0 t), C8 26.27 t (27.7 t), C5 28.61 t (29.5 t), C7 33.73 d (33.2 d), C12 36.51 t (34.4 t), C17 53.12 t (53.5 t), C15 55.71 t (55.5 t), C2 55.98 t (56.4 t), C6 65.37 d (66.6 d), C11 68.26 d (64.6 d), C10 68.78 t (62.1 t), C9 68.97 s (36.2 d).

Crystallographic Studies. A colorless crystal of $C_{15}H_{22}N_2O_3 \cdot CH_3OH$ was centered on a Nicolet R3m diffractometer. Centering of 25 reflections allowed least-squares calculation[26] of

(26) Calculations for diffractometer operations were performed by using software supplied with the Nicolet R3m diffractometer. All structural calculations were performed with the SHELXTL program library written by Professor G. M. Sheldrick and supplied by NICOLET XRD Corp.

Table V. Atomic Coordinates (×10⁴) and Isotropic Thermal Parameters (Å² × 10³)[a] for 1, 2(*S*),9-Dihydroxyaphyllidine (Methanol)

atom	x	y	z	U_{iso}[b]
N1	4311 (2)	2523 (1)	1960 (2)	19 (1)*
C2	6016 (2)	2188 (2)	2200 (2)	24 (1)*
C3	5896 (3)	1567 (2)	638 (3)	31 (1)*
C4	4813 (3)	419 (2)	254 (3)	32 (1)*
C5	3235 (3)	663 (2)	411 (2)	27 (1)*
C6	3006 (2)	1633 (2)	1192 (2)	21 (1)*
C7	1380 (2)	1894 (2)	1276 (2)	22 (1)*
C8	960 (2)	3249 (2)	828 (2)	22 (1)*
C9	2278 (2)	3978 (2)	2269 (2)	19 (1)*
C10	4075 (2)	3613 (2)	2584 (2)	17 (1)*
C11	2125 (2)	3726 (2)	3902 (2)	18 (1)*
C12	452 (2)	4148 (2)	3851 (2)	24 (1)*
C13	411 (3)	3876 (2)	5500 (3)	29 (1)*
C14	770 (3)	2522 (2)	5950 (2)	28 (1)*
C15	2406 (2)	2136 (2)	5924 (2)	24 (1)*
N16	2515 (2)	2421 (1)	4350 (2)	19 (1)*
C17	1413 (2)	1599 (2)	2973 (2)	21 (1)*
O18	6783 (2)	1347 (1)	3540 (2)	30 (1)*
O19	5251 (2)	4317 (1)	3371 (2)	22 (1)*
O20	2043 (2)	5233 (1)	1844 (2)	23 (1)*
O(s)	3993 (2)	7061 (1)	3984 (2)	23 (1)*
C(s)	3251 (3)	8110 (2)	2978 (2)	25 (1)*

[a] Estimated standard deviations in the least-significant digits are given in parentheses. [b] For values with asterisks, the equivalent isotropic U is defined as one-third of the trace of the U_{ij} tensor.

Table VI. Bond Lengths (Å)[a] for 1, 2(*S*),9-Dihydroxyaphyllidine (Methanol)

N1–C2	1.470 (3)	N1–C6	1.429 (2)
N1–C10	1.369 (2)	C2–C3	1.511 (3)
C2–O18	1.418 (2)	C3–C4	1.521 (3)
C4–C5	1.487 (4)	C5–C6	1.333 (3)
C6–C7	1.499 (3)	C7–C8	1.535 (3)
C7–C17	1.536 (3)	C8–C9	1.518 (2)
C9–C10	1.537 (3)	C9–C11	1.547 (3)
C9–O20	1.413 (2)	C10–O19	1.230 (2)
C11–C12	1.530 (3)	C11–N16	1.481 (2)
C12–C13	1.517 (3)	C13–C14	1.529 (3)
C14–C15	1.517 (3)	C15–N16	1.482 (3)
N16–C17	1.482 (2)	O(s)–C(s)	1.424 (2)
C(s)–HA	0.960	C(s)–HB	0.960
C(s)–HC	0.960		

[a] Estimated standard deviations in the least-significant digits are given in parentheses.

the cell constants given in Table IV. Other experimental parameters are also listed in this table.

The intensities of the control reflections [100, 040, 004] monitored every 97 reflections showed no significant trend during the course of the data collection. Lorentz and polarization corrections were applied to the data.

The structure was solved by the direct methods program SOLV.[27] Anisotropic thermal parameters were employed for all non-hydrogen atoms. Hydrogen atoms were included in calculated positions (C-H = 0.96 Å, U(H) = 1.2U_{iso}(C)). Neutral-atom scattering factors (including anomalous scattering) were taken from the *International Tables for X-ray Crystallography*.[28] The

(27) Sheldrick, G. M. SHELXTL, revision 5. Nicolet XRD Corp.: Madison, WI 1985.

(28) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham (present distributor Kluwer Academic Publishers: Dordrecht), 1974; Vol. IV, pp 55, 99, 149.

Table VII. Bond Angles (deg)[a] for 1, 2(*S*),9-Dihydroxyaphyllidine (Methanol)

C2–N1–C6	117.1 (2)	C2–N1–C10	119.3 (1)
C6–N1–C10	123.4 (2)	N1–C2–C3	109.4 (1)
N1–C2–O18	110.9 (2)	C3–C2–O18	107.2 (2)
C2–C3–C4	110.9 (2)	C3–C4–C5	110.6 (2)
C4–C5–C6	124.1 (2)	N1–C6–C5	120.9 (2)
N1–C6–C7	115.6 (2)	C5–C6–C7	123.4 (2)
C6–C7–C8	107.3 (2)	C6–C7–C17	114.4 (1)
C8–C7–C17	110.8 (2)	C7–C8–C9	106.3 (1)
C8–C9–C10	111.0 (2)	C8–C9–C11	110.3 (2)
C10–C9–C11	107.4 (1)	C8–C9–O20	108.5 (1)
C10–C9–O20	108.5 (2)	C11–C9–O20	111.1 (2)
N1–C10–C9	119.0 (1)	N1–C10–O19	122.2 (2)
C9–C10–O19	118.8 (2)	C9–C11–C12	114.1 (1)
C9–C11–N16	108.6 (2)	C12–C11–N16	113.8 (2)
C11–C12–C13	110.7 (1)	C12–C13–C14	110.7 (2)
C13–C14–C15	110.6 (2)	C14–C15–N16	114.9 (1)
C11–N16–C15	110.7 (2)	C11–N16–C17	111.9 (1)
C15–N16–C17	111.2 (2)	C7–C17–N16	114.0 (2)
O(s)–C(s)–HA	108.8 (1)	O(s)–C(s)–HB	114.3 (1)
HA–C(s)–HB	109.5	O(s)–C(s)–HC	105.2 (1)
HA–C(s)–HC	109.5	HB–C(s)–HC	109.5

[a] Estimated standard deviations in the least-significant digits are given in parentheses.

weighted least-squares refinement converged (weights calculated as $(s^2(F) + (g)F_o^2)^{-1}$) with the average shift/esd <0.019 over the last three cycles). In the final difference Fourier map, the maximum and minimum electron densities were 0.77 e Å^{-3} (near O(S)) and −0.30 e Å^{-3}. Analysis of variance as a function of Bragg angle, magnitude of F_o, reflection indices, etc., showed no significant trends.

Table V contains a list of atomic positional parameters and equivalent isotropic thermal parameters for all non-hydrogen atoms. Table VI contains a list of bond distances, and Table VII contains a list of bond angles.

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Registry No. **1**, 124125-77-5; **1 Ac**, 124125-79-7; **1 BrBz**, 124125-80-0; **2**, 124125-78-6; **2 Ac**, 124125-81-1; **2 BrBz**, 124125-82-2; **4**, 124223-06-9; **4 Ac**, 111665-37-3; **5**, 124223-07-0; **5 Ac**, 124222-28-2; **6**, 124223-08-1; **7**, 124262-84-6; (+)-sparteine, 492-08-0; 4-bromobenzoyl chloride, 586-75-4.

Supplementary Material Available: NMR spectra for **1** (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HETCOR), **1Ac** (^{1}H, ^{13}C, ^{1}H–^{13}C HETCOR), **1BrBz** (^{13}C), **2Ac** (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HETCOR), **2BrBz** (^{13}C), **4** (^{1}H, ^{13}C), **4Ac** (^{1}H, ^{13}C, ^{1}H–^{13}C HETCOR), and **5Ac** (^{1}H) and tables of anisotropic thermal parameters, hydrogen coordinates, and thermal parameters (23 pages); observed and calcualted structure factors for X-ray structure of **1** (14 pages). Ordering information is given on any current masthead page.