Alkaloids of *Andrachne aspera*

Sibel Mill and Claude Hootelé*

Organic Chemistry Department (CP 160/06), University of Brussels, 50 Avenue F. D. Roosevelt, B-1050 Brussels, Belgium

Received October 15, 1999

Two new 2,6-disubstituted piperidine alkaloids andrachcinine (**1**) and andrachcinidine (**5**) have been isolated from *Andrachne aspera* along with andrachamine and andrachcine (**2**). The absolute configurations of **1**, **2**, and **5** were established. (+)-Allosedridine and the new alkaloids (−)-8-epi-8-ethylnorlobelol I (**4**) and (−)-8-epihalosaline (**7**) were also identified as constituents of *A. aspera*. Structures were determined by MS and NMR techniques and by chemical conversions.

Andrachne aspera Spreng. (Euphorbiaceae) was previously shown to contain piperidine alkaloids, and the two alkaloids andrachamine and andrachcine were isolated from this species.[1,2] Recently, we corrected[3] the structure initially attributed to andrachamine; however, a sample of the original alkaloid was no longer available and a reisolation of the alkaloid from *A. aspera* was therefore undertaken. Andrachamine appeared as a minor constituent of this species in which a number of 2-substituted and 2,6-disubstituted piperidine derivatives were identified. The structure elucidations of these new piperidine alkaloids are discussed in the present communication.

Results and Discussion

The spectral properties of andrachcinine (**1**) ($C_{15}H_{27}NO_2$ by HRMS) clearly established that it was a *trans*-2,6-disubstituted *N*-methylpiperidine derivative with a C_4 chain ($CH_2-CO-C_2H_5$) and a C_5 chain ($CH_2-CHOH-nC_3H_7$). The MS of **1** exhibited intense fragment ions at *m*/*z* 182 and *m*/*z* 166 arising from loss of the C_4 and the C_5 chains, respectively, from the molecular ion. The position of the double bond in the piperidine ring was deduced from the ^{1}H NMR and COSY spectra: the proton at δ 3.56 (H-2) showed coupling to a vinylic proton (δ 5.61) and to the two methylene protons (double doublets at δ 2.59 and 2.81) next to the propanoyl group. The second vinylic proton (δ 5.78) was coupled to the first one and to protons appearing between δ 1.6 and 2.1. The signal of the $N-CH_3$ protons appeared as a singlet at δ 2.31. The two side-chain methyl groups gave rise to two triplets (δ 0.92 and 1.06); the latter showed couplings to the two methylene protons adjacent to the carbonyl group at δ 2.44. The H-6 proton (triple triplet at δ 3.14) was coupled with H-5 and H-7 with two large (J = 11 Hz) and two small (J = 3.5 Hz) identical coupling constants; thus H-6 is axial on the half-chair piperidine ring and on the pseudo-cycle formed by intramolecular hydrogen bonding between the OH group and the nitrogen atom (Figure 1). On the basis of this favored conformation, the half-height width of H-8 (δ 3.79, $W_{1/2}$ = 23 Hz) is consistent with the axial orientation of this proton. The ^{1}H and ^{13}C NMR spectra of **1** resembled the spectra of the *Sedum* alkaloid sedacrine[4] and indicated that the two compounds were structurally (and conformationally) closely related. Particularly, the chemical shifts observed for C-2 (δ 57.8), C-6 (δ 53.7), and the NCH_3 group (δ 34.6) in **1** were similar to those observed in the spectrum of sedacrine for the corresponding carbon atoms (δ 57.5, 53.5, and 34.4, respectively); these values are characteristic

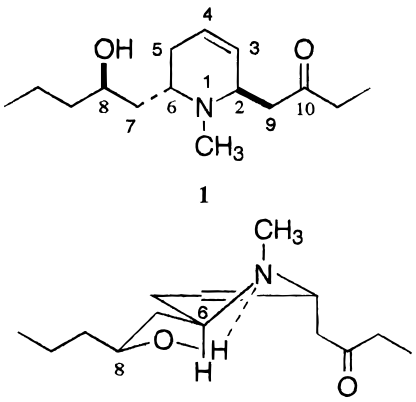

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Figure 1. The favored conformation of andrachcinine (**1**).

of *trans*-2,6-disubstitution of the piperidine ring.[4] The relative configuration of andrachcinine is, therefore, as depicted in **1**.

Three 2,6-disubstituted piperidine alkaloids were previously isolated from *Lobelia berlandieri* and structures were proposed.[8] However, inspection of the published NMR data for the $C_{14}H_{25}NO_2$ alkaloid[8]—i.e., the ^{13}C chemical shifts attributable to C-2 (δ57.5), C-6 (δ 53.3), and the NCH_3 group (δ 34.2)—clearly indicates that the base is a *trans*- (not a *cis*-[8]) 2,6-piperidine derivative with two C_4 side chains. On the basis of its NMR properties this compound appears to be a lower homologue of **1** possessing the same relative configuration.

The second alkaloid obtained from *A. aspera* was andrachcine (**2**), previously isolated from this species and tentatively identified[2] as a *trans*-2,6-disubstituted *N*-methylpiperidine derivative with a C_4 chain ($CH_2-CHOH-C_2H_5$) and a C_5 chain ($CH_2-CHOH-nC_3H_7$). In the ^{13}C NMR spectrum we observed that the chemical shifts of C-2 (δ 63.1), C-6 (δ 49.4), and $N-CH_3$ (δ 34.8) were close to those reported for sedinine[4] (δ 62.6, 49.3, and 34.7, respectively), indicating that **2** was a related *trans*-2,6-disubstituted *N*-methylpiperidine derivative. [5]

At this stage, **2** was correlated with andrachcinine: reduction of the carbonyl group in andrachcinine (**1**) with sodium borohydride in MeOH led to two epimeric alcohols, of which the major isomer appeared to be identical with **2**. This established the position of the double bond in **2** and established that **1** and **2** have the same configuration at C-2, C-6, and C-8. On the other hand, catalytic hydrogenation of andrachcine yielded dihydroandrachcine. This *trans*-2,6-disubstituted derivative contained a C_2-symmetric moiety as indicated by the observation that the C-3/C-5 and C-2/C-6 pairs only gave rise to two signals in the ^{13}C NMR

* To whom correspondence should be addressed. Tel.: 32-2-650 30 40. Fax: 32-2-650 27 98. E-mail: chootele@ulb.ac.be.

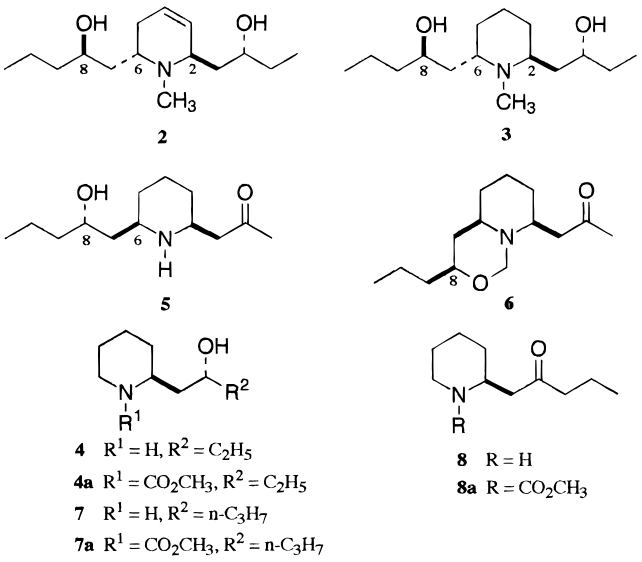
10.1021/np9905214 CCC: $19.00
Published on Web 04/25/2000

spectrum. Dihydroandrachcine was therefore assigned structure **3**. The absolute configuration of dihydroandrachcine was unambiguously established by synthesis from (−)-8-*epi*-8-ethylnorlobelol I (**4**)[7] through our general procedure for the synthesis of *trans*-2,6-disubstituted piperidine derivatives.[3] The spectral and chiroptical properties of our synthetic sample of **3** were identical with those of dihydroandrachcine obtained above through reduction of andrachcine. The absolute configuration of andrachcinine and andrachcine are therefore established as depicted in **1** and **2**, respectively, and the stereochemistry initially attributed[2] to andrachcine must be altered.

The spectral properties of the new alkaloid andrachcinidine (**5**) indicated that this base was a *cis*-2,6-disubstituted piperidine with a C_3 chain ($CH_2-CO-CH_3$) and a C_5 chain ($CH_2-CHOH-nC_3H_7$); the MS of **5** exhibited intense fragment ions at *m*/*z* 170 and 140 corresponding to the loss of these two chains. The ^{1}H NMR spectrum showed three multiplets centered at δ 3.80 (H-8), 3.01, and 2.80 (H-2 and H-6); a singlet at δ 2.13; and two multiplets at δ 2.65−2.40 (CH_3COCH_2). A triplet was centered at δ 0.91 (CH_3CH_2). In the ^{13}C NMR spectrum, C-4 appeared at δ 24.5; this value is characteristic of a *cis*-2,6-disubstituted piperidine derivative.[6] The C-6/C-8 configuration rests on the transformation of **5** into the corresponding tetrahydrooxazine **6**: comparison of the ^{1}H NMR spectrum of **6** (chemical shifts of H-8 and of the $N-CH_2-O$ protons) with those of model compounds[7] demonstrated the equatorial orientation of the *n*-propyl chain at C-8; the relative configuration of **5** is therefore established. The absolute configuration of **5** was established by synthesis; a sample of **5** unambiguously prepared from (+)-8-epihalosaline (**7**)[9] was found to be identical with natural (−)-andrachcinidine.

(+)-Allosedridine,[9,10] (−)-8-*epi*-8-ethylnorlobelol I (**4**), and (−)-8-epihalosaline (**7**) were also isolated from *A. aspera*. As the homologue derivatives **4** and **7** were difficult to separate, their mixture was treated with methyl chloroformate, and the two corresponding carbamates were obtained as pure compounds. Both derivatives exhibited negative optical rotations in MeOH and appeared to be identical with the synthetic carbamates **4a** and **7a** prepared from synthetic samples of **4**[7] and **7** of established (2*S*,8*R*)-configuration.

Synthetic (−)-8-epihalosaline (**7**) was prepared through highly stereoselective reduction with $LiAl(O\text{-}tBu)_3H$ of the carbamate **8a** (derived from the corresponding secondary aminoketone **8**[11]) followed by basic hydrolysis of the carbamate function and decarboxylation.



Experimental Section

General Experimental Procedure. Mass spectral data were obtained on a Micromass 7070 spectrometer or a Fisons Autospec spectrometer (high-resolution measurements). NMR spectra were recorded on a Bruker WM 250 (^{1}H, 250 MHz; ^{13}C, 62.8 MHz) apparatus in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Bruker IFS 25 spectrometer in CCl_4 solution. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Analytical TLC were performed on Polygram Sil G/UV_{254} plates and on Merck aluminum sheets (aluminum oxide 60 F_{254} neutral, type E). Visualization was accomplished either by ethanolic phosphomolybdic acid solution followed by heating or by iodine followed by Dragendorff reagent.

Plant Material. The vegetal material (aerial parts) was collected near the campus of the University of Karachi (Pakistan)[3] and identified by Professor S. I. Ali (Department of Botany, University of Karachi).

Isolation of the Alkaloids of *Andrachne aspera*. The crude alkaloids were obtained from dried plants of *A. aspera* (870 g) as described previously[3] and were submitted to a flash chromatography over Si gel ($CHCl_3$−isopropylamine 50:1) to give five fractions. Repeated chromatography of fraction I (Si gel; hexane−acetone 1:1; Al_2O_3, hexane−EtOAc 3:1) led to the isolation of andrachcinine (**1**) (55 mg) and andrachcine (**2**) (50 mg). Chromatography of fraction II (Al_2O_3, EtOAc−EtOH 95:5) gave andrachcinidine (**5**) (40 mg). Andrachamine (3.5 mg), (+)-allosedridine (2 mg), and a mixture of (−)-8-*epi*-8-ethylnorlobelol I (**4**) and (−)-8-epihalosaline (**7**) (13.4 mg) were obtained from fraction IV after further chromatographies over Si gel ($CHCl_3$−isopropylamine 50:1) and Al_2O_3 ($CHCl_3$ − isopropylamine 100:1).

Andrachcinine (1): oil, $[\alpha]^{22}_D$ −108° (*c* 2.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3335, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.78 (1H, m, H-4), 5.61 (1H, m, H-3), 3.79 (1H, m, H-8), 3.56 (1H, m, H-2eq), 3.14 (1H, tt, J = 11, 3.5 Hz, H-6ax), 2.59 and 2.81 (2H, 2 dd, J = 16, 7 Hz, CH_2-CO), 2.43 and 2.46 (2H, 2m, CH_2-CO), 2.31 (3H, s, $N-CH_3$), 1.95 (1H, m, H-5), 1.28−1.75 (8H, m), 1.06 (3H, t, J = 7 Hz, CH_3), 0.92 (3H, t, J = 7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 209.3 (C-10), 127.7 (C-4), 125.9 (C-3), 73.6 (C-8), 57.8 (C-2), 53.7 (C-6), 47.5 (C-9), 40.3 (C-13), 37.0, 36.9 (C-7 and C-11), 34.5 (NCH_3), 25.2 (C-5), 18.9 (C-14), 14.4 (C-15), 7.9 (C-12); EIMS *m*/*z* 253 [M]$^+$ (3), 238 (7), 210 (6), 196 (21), 182 (53), 166 (21), 152 (23), 138 (9), 110 (24), 96 (36), 94 (100); HREIMS *m*/*z* 253.2035 (calcd for $C_{15}H_{27}NO_2$, 253.2042).

Andrachcine (2): oil, $[\alpha]^{22}_D$ −84° (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz)[5] δ 5.79 (1H, m, H-4), 5.57 (1H, m, H-3), 3.69 (2H, m, H-8 and H-10), 3.31 (1H, m, H-6a), 3.16 (1H, m, H-2e), 2.32 (3H, s, $N-CH_3$), 2−1.85 (2H, 2m, H-5), 1.80−1.30 (ca 12H, m), 0.93 (3H, t, J = 7 Hz, CH_3), 0.92 (3H, t, J = 7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 127.9 (C-4), 125.5 (C-3), 74.1 (C-8), 70.6 (C-10), 63.1 (C-2), 49.4 (C-6), 40.9, 40.4, 38.8 (C-7, C-9, and C-13), 34.8 (NCH_3), 31.0 (C-11), 24.6 (C-5), 19.0 (C-14), 14.3 (C-15), 10.0 (C-12); EIMS *m*/*z* 255 [M]$^+$ (3), 240 (3), 226 (7), 212 (8), 196 (3), 182 (100), 168 (38), 130 (9), 110 (15), 96 (42), 94 (28); HREIMS *m*/*z* 255.2194 (calcd for $C_{15}H_{29}NO_2$, 255.2198).

Andrachcinidine (5): oil, $[\alpha]^{22}_D$ −20° (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz), δ 3.80 (1H, m, H-8), 3.01 and 2.80 (2H, 2m, H-2 and H-6), 2.65−2.4 (2H, 2m, CH_2CO),

2.13 (3H, s, CH_3CO), 0.91 (3H, t, $J = 7$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 207.2, 72.3, 58.1, 53.0, 50.5, 43.1, 40.4, 33.5, 32.4, 30.5, 24.5, 18.5, 14.0; EIMS *m/z* 227 $[M]^+$ (9), 184 (18), 170 (40), 154 (19), 152 (19), 140 (100), 126 (18), 112 (14), 98 (14), 96 (38), 84 (28), 83 (29), 82 (82); HREIMS *m/z* 227.1887 (calcd for $C_{13}H_{25}NO_2$, 227.1885).

Andrachcinidine (5) from (−)-8-Epihalosaline (7). Andrachcinidine **(5)** was obtained from (-)-8-epihalosaline by the procedure described for the synthesis of related compounds.[3] Compound **5**: oil, $[\alpha]^{22}_D$ −16° (*c* 1.7, $CHCl_3$,); ^1H NMR, ^{13}C NMR, and MS were virtually identical with those of the natural sample.

(+)-Allosedridine: oil; spectral properties (MS, ^1H and ^{13}C NMR spectra) in agreement with those reported;[9] $[\alpha]^{22}_D$ +12° (*c* 0.16, EtOH).

(−)-8-epi-8-Ethylnorlobelol I (4) and (−)-8-Epihalosaline (7). The mixture of **4** and **7** (13.4 mg) from *A. aspera* was treated with methyl chloroformate (0.03 mL) in a 2% aqueous K_2CO_3 solution (5 mL). After 15 h at room temperature, the solution was extracted with $CHCl_3$. Evaporation of the solvent and flash chromatography of the residue (Si gel; hexane−EtOAC 2:1) yielded (−)-*N*-carbomethoxy-8-epi-8-ethylnorlobelol I (**4a**) (1.4 mg) and (−)-*N*-carbomethoxy-8-epihalosaline (**7a**) (7.7 mg).

Compound 4a: negative rotation between 589 and 312 nm (MeOH, ca. 0.1); ^1H NMR ($CDCl_3$, 250 MHz) δ 4.39 (1H, m, H-2), 3.98 (1H, m, H-6e), 3.69 (3H, s, CO_2CH_3), 3.56 (1H, m, H-8), 2.89 (1H, m, H-6a), 1.4−1.8 (11H, m), 0.95 (3H, t, $J = 7.5$ Hz, CH_3); EIMS *m/z* 215 $[M]^+$ (2), 186 (1), 156 (2), 142 (100), 84 (3).

Compound 7a: $[\alpha]^{22}_D$ −40° (*c* 0.8, MeOH); ^1H NMR ($CDCl_3$, 250 MHz) δ 4.39 (1H, m, H-2), 3.99 (1H, m, H-6e), 3.69 (3H, s, CO_2CH_3), 3.64 (1H, m, H-8), 2.88 (1H, td, $J =$ 14, 2 Hz, H-6a), 1.3−1.8 (13 H, m), 0.93 (3H, t, $J = 7$ Hz, CH_3); EIMS *m/z* 229 $[M]^+$ (2), 186 (1), 170 (2), 142 (100), 84 (3). The above samples of **4a** and **7a** were found to be identical with those prepared by acylation with methyl chloroformate of synthetic (−)-8-epi-8-ethylnorlobelol I (**4**) $[\alpha]^{22}_D$ −15.7° (*c* 2.1, MeOH)[7] and (−)-8-epihalosaline (**7**) (see below), respectively.

Synthetic 4a: $[\alpha]^{22}_D$ −40° (*c* 4, MeOH).

Synthetic 7a: $[\alpha]^{22}_D$ −36° (*c* 2.3, MeOH); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 156.5, 69.9, 52.5, 48.9, 39.8, 39.6, 38.2, 29.1, 25.5, 19.0, 18.9, 14.0.

Preparation of (−)-8-epihalosaline (7). The carbamate **8a** was prepared by acylation of the corresponding secondary synthetic aminoketone **8**[11] ($[\alpha]^{22}_D$ −21° (*c* 1.8, MeOH) with methyl chloroformate. To a stirred solution of **8** (0.37 g) in THF (20 mL) was added $LiAl(O\text{-}tBu)_3H$ (1.2 g). After 1 h, water was added, and the mixture was filtered through Celite. The solvent was then evaporated under reduced pressure, and the residue (homogeneous on TLC) was refluxed for 2 h in ethanolic 10% KOH (10 mL). After dilution with water and extraction with $CHCl_3$ (30 mL) evaporation of the organic solvent furnished a solid residue that was sublimed to give pure **7**: mp 32 °C, $[\alpha]^{22}_D$ −8° (*c* 3.7, MeOH), $[\alpha]^{22}_D$ +29° (c 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 4−2.5 (1H, OH), 3.80 (1H, m, H-8), 3.02 (1H, m), 2.70 (1H, tt, $J = 10.5$, 2.5 Hz, H-2), 2.58 (1H, m), 1.82 (1H, m), 1.67−1.05 (12H, m), 0.91 (3H, t, $J = 7$ Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 73.4, 58.9, 46.7, 43.3, 41.1, 35.2, 28.1, 25.2, 19.3, 14.8; EIMS *m/z* 171 $[M]^+$ (2), 128 (5), 84 (100).

Hydrogenation of Andrachcine (1). Andrachcine (8 mg) was dissolved in MeOH (1 mL) with one drop of aqueous HCl and was then hydrogenated over Pt at room temperature for 1 h at 4 atm. After filtration, water and NH_4OH were added, and the solution was extracted with chloroform; evaporation of the organic phase yielded quantitatively dihydroandrachcine (**3**): oil, $[\alpha]^{22}_D$ −27° (*c* 0.8, MeOH); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.7−3.6 (2H, m, H-8 and H-10), 3.16 (2H, m, H-2 and H-6), 2.41 (3H, s, NCH_3), 1.90−1.10 (18H, m), 0.93 and 0.92 (6H, 2t, $J = 7$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 72.9, 71.3, 56.1, 40.5, 38.7, 38.1, 35.1, 30.9, 23.0, 20.8, 18.7, 14.1, 9.8; EIMS *m/z* 257 $[M]^+$ (5), 228 (19), 214 (22), 184 (55), 170 (100), 156 (11), 140 (12), 130 (9), 112 (22), 110 (13), 98 (60), 96 (30).

Synthetic Dihydroandrachcine (3) from (−)-8-Epi-8-ethylnorlobelol I (4). Dihydroandrachcine (**3**) was obtained from (−)-8-epi-8-ethylnorlobelol I (**4**) by the procedure described for the synthesis of related compounds.[3]

Compound 3: oil, $[\alpha]^{22}_D$ −26° (*c* 1, MeOH); ^1H NMR, ^{13}C NMR, and MS (HREIMS *m/z* 257.2362 (calcd for $C_{15}H_{31}NO_2$, 257.2355) virtually identical with those of the sample of **3** obtained above by hydrogenation of natural andrachcine.

Preparation of the Tetrahydrooxazine 6. To a solution of **5** (6 mg) in MeOH (1 mL) was added a 1.5% methanolic formaldehyde solution (0.4 mL). After 30 min at room temperature, the MeOH was evaporated, and the residue chromatographed over a short column of Al_2O_3 ($CHCl_3$) to give quantitatively the tetrahydrooxazine **6**: ^1H NMR ($CDCl_3$, 250 MHz) δ 4.36 and 3.53 (2H, 2d, $J = 8$ Hz, NCH_2O), 3.41 (1H, m, H-8), 2.82 and 2.36 (2H, 2dd, $J = 6$, 17 Hz, $J = 5$, 17 Hz, CH_2CO), 2.61 (1H, m, H-2), 2.14 (4H, m + s, H-6 + CH_3CO), 1.90−1.20 (12H, m), 0.90 (3H, t, $J = 7$ Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 206.7, 84.1, 77.2, 60.8, 53.0, 48.9, 38.8, 37.8, 33.1, 32.6, 30.4, 23.8, 18.3, 13.9; EIMS *m/z* 239 $[M]^+$ (5), 238 (7), 199 (8), 196 (8), 182 (100), 181 (9), 168 (11), 152 (38), 140 (8), 124 (6), 111 (8), 110 (10).

$NaBH_4$ Reduction of Andrachcinine (1). To a methanolic solution (5 mL) of andrachcinine (**1**) (43 mg) $NaBH_4$ (50 mg) was added at room temperature. After 30 min the MeOH was evaporated, H_2O was added, and the solution was extracted with $CHCl_3$. After evaporation of the organic phase, the residue was flash chromatographed over Si gel (acetone−hexane 1:1) to yield andrachcine (**2**) ($[\alpha]^{22}_D$ −84° (*c* 0.9, MeOH), TLC, MS, ^1H and ^{13}C NMR) as the major compound (30 mg).

Acknowledgment. One of us (S.M.) wishes to thank the Fonds pour la Recherche dans l'Industrie et dans l'Agriculture (FRIA, Belgium). C.H. is a Research Associate of the National Fund for Scientific Research (FNRS, Belgium).

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(5) The spectral and chiroptical properties of our sample of **2** are consistent with those reported[2] for andrachcine; the small downfield differences of ^1H chemical shifts affecting the H-2, H-6, and the N−CH_3 signals in ref 2 are probably attributable to traces of acid in the deuterated chloroform; we found no indication for the presence of a diastereoisomer of **2** in *Andrachne aspera*.
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NP9905214