A Revision of the Structures of 17-*epi*-Aristoteline and Aristolasicone, the First Two Examples of Inverted Indole Alkaloids

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A reinvestigation of aristolasicone and 17-*epi*-aristoteline, two alkaloids previously isolated from *Aristotelia australasica*, has led to a revision of their structures. These two compounds **5** and **6** belong to the same allo series, and are the first reported indole alkaloids from natural sources possessing an inverted indole unit. The structure of **5** was determined by X-ray diffraction. The use of fast atom bombardment ionization combined with tandem mass spectrometry (MS/MS) allowed a distinction between the two series.

In 1988 we reported the isolation of two new indole alkaloids from *Aristotelia australasica* called aristolasicone and 17-*epi*-aristoteline,[1a] to which structures **1** and **3** were attributed, respectively[1b] (Chart I).

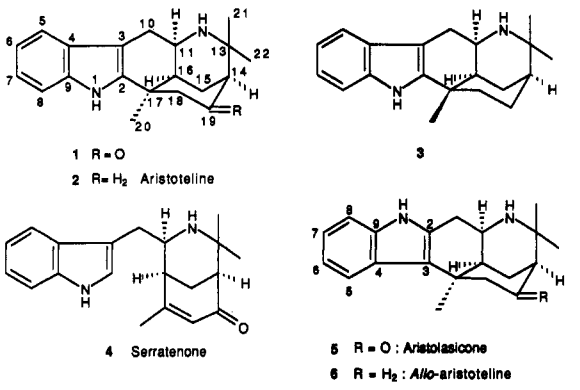
Despite its strained conformation, structure **3** seemed the only one possible for this alkaloid, by comparison of its ^1H and ^{13}C NMR spectra with those of aristoteline (**2**).

The structure 19-oxoaristoteline (**1**) for aristolasicone likewise was suggested on the basis of NMR spectral data and a possible biogenetic relationship with aristone.[2]

However, synthetic work undertaken by two of us (S.B. and H.-J.B.) showed that (±)-19-oxoaristoteline (**1**) obtained as expected by treatment of (±)-serratenone (**4**) with BF_3 was not the same as the natural product.[3] The identities of the two new alkaloids were therefore questioned. In this paper we report further structural studies on alkaloids **5** and **6**, for which a total synthesis has recently been achieved.[4]

An X-ray analysis (Figure 1) showed that aristolasicone had the inverted indole structure **5**, which we term allo[5] and which is also a feature of the second alkaloid, now called *allo*-aristoteline (**6**). Compounds **5** and **6** are the first inverted indole alkaloids isolated from natural sources. However, such derivatives have been obtained previously by acid rearrangement of dihydropseudoindoxyls in the ibogaine,[6] yohimbine,[7] and more recently the deformyl-3-isogeissoschizine series.[8]

Chart I



The X-ray analysis does not define the absolute configuration, and the enantiomer shown represents an arbitrary choice corresponding to the aristoteline configuration. It will be observed that the hydrogen atom bonded to the nitrogen N-12 appears in the axial position. Energy minimization by the semiempirical molecular orbital method at the AM1 level[9] (MOPAC),[10] establishes that the axial position is favored by 3.0 kcal/mol and shows that this conformation is not induced by packing.

A careful examination of the ^1H and ^{13}C NMR spectra of natural aristolasicone **5** and synthetic (±) 19-oxo-aristoteline (**1**) revealed some significant differences. The chemical shift of the Me-20 protons (Table I) appeared at lower field for aristolasicone **5** (δ = 1.62 ppm) than for

(1) (a) 11-*epi*-Aristoteline would have to be named 17-*epi*-aristoteline according to the biogenetic numbering system: Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 2555. (b) Kan-Fan, C.; Quirion, J.-C.; Bick, I. R. C.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 1651.

(2) Zabel, V.; Watson, W. H.; Bittner, M.; Silva, M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2842.

(3) Burkard, S.; Borschberg, H.-J. *Helv. Chim. Acta* **1991**, *74*, 275.

(4) (a) Güller, R.; Dobler, M.; Borschberg, H.-J. *Helv. Chim. Acta* **1991**, *74*, 1636. (b) Güller, R.; Borschberg, H.-J. *Helv. Chim. Acta* **1991**, *74*, 1643.

(5) To avoid confusion in the future, we propose to designate all *Aristotelia* alkaloids containing an inverted indole unit by the prefix "allo". The more obvious prefixe "iso" is already reserved for tetracyclic *Aristotelia* alkaloids having axially oriented (indol-3-yl) methyl side chains at C-11.

(6) Bartlett, M. F.; Dickel, D. F.; Maxfield, R. C.; Paszek, L. E.; Smith, A. F. *J. Am. Chem. Soc.* **1959**, *81*, 1932.

(7) Finch, N.; Gemenden, C. W.; Hsu, I. H.-C.; Kerr, A.; Sim, G. A.; Taylor, W. I. *J. Am. Chem. Soc.* **1965**, *87*, 2229.

(8) Wenkert, E.; Shi, Y. J. *Synth. Commun.* **1989**, *19*, 1071.

(9) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 7822.

(10) MOPAC. A General Orbital Molecular Package. QCPE 455.

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Table I. ^{1}H NMR for Synthetic 19-Oxoaristoteline (1), Aristoteline (2), Aristolasicone (5), and *allo*-Aristoteline (6) (δ in ppm from TMS)

	5	6	7	8	10	10′	11	14	15	15′	16	18	18′	19	19′	20	21	22
1	7.46	7.09	7.13	7.32	3.14	2.61	3.77	2.16	2.23	2.30	1.85	3.28	2.51	–	–	1.44	1.38	0.94
2	7.45	7.08	7.13	7.30	3.07	2.62	3.62	1.39	1.96	2.06	1.70	2.30	1.60	1.60	1.92	1.45	1.29	1.06
5	7.62	7.03	7.09	7.28	3.25	2.53	3.74	2.13	2.22	2.29	1.79	3.06	2.93	–	–	1.62	1.34	0.93
6	7.74	7.10	7.15	7.33	3.23	2.57	3.62	1.45	2.10	2.10	1.66	2.10	2.10	1.77	1.93	1.70	1.33	1.12

Table II. ^{13}C NMR Data for Synthetic 19-Oxoaristoteline (1), Aristoteline (2), Aristolasicone (5), and *allo*-Aristoteline (6) (δ in ppm from TMS)

	2	3	4	5	6	7	8	9	10	11	13	14	15	16	17	18	19	20	21	22
1	139.6	105.2	127.8	118.2	119.4	121.6	110.8	136.2	28.9	49.8	51.4	54.9	26.8	39.3	37.1	54.7	212.8	25.7	29.2	26.5
2	142.7	104.5	128.3	118.3	119.3	121.3	110.6	136.5	28.6	50.8	54.5	36.0	25.5	39.5	33.4	36.1	27.8	25.4	29.0	27.5
5	129.7	117.4	125.8	119.3	119.8	121.0	110.9	136.8	31.1	54.8	51.8	50.2	26.9	40.0	37.8	55.1	213.5	26.0	29.2	27.7
6	129.4	119.8	126.3	119.0	120.2	120.8	110.8	139.7	30.8	51.0	54.1	35.8	25.7	40.2	33.9	36.4	28.3	26.2	29.0	27.7

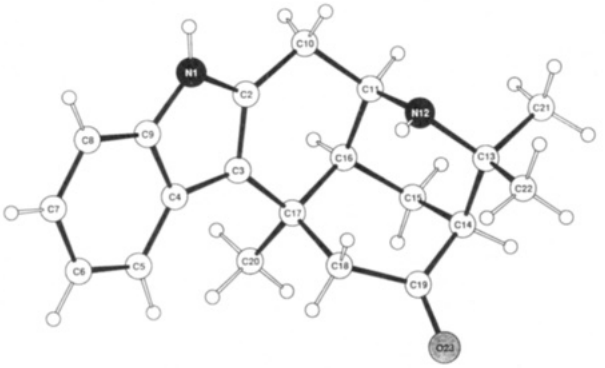

Figure 1. X-ray crystal structure of aristolasicone (**5**).

compound **1** (δ = 1.44 ppm). More diagnostic was a comparison of the ^{13}C NMR data for **1** and **5** where the most important differences ($\Delta\delta > 10$ ppm) appeared in the case of C-2 and C-3 (Table II). These differences can be explained by a rotation of the indole subunit through 180°.

We reinvestigated all the data of Aristotelia alkaloids and observed similar differences for 17-*epi*-aristoteline for which the Me-20 protons resonated at 1.70 ppm. In the ^{13}C spectrum the C-2 and C-3 resonances were similar to those of aristolasicone (δ = 129.4 and 119.8 ppm). These data suggest that the previously described 17-*epi*-aristoteline belongs to the same allo series as aristolasicone and possesses the inverted structure **6**.

With a view to distinguishing between the two series, the possibilities offered by modern mass spectrometry (MS) techniques were also explored. Conventional EI mass spectra of aristolasicone **5** and 19-oxoaristoteline (**1**) did not show any significant difference. This result prompted us to apply fast atom bombardment (FAB) ionization combined with tandem mass spectrometry (MS/MS), whose efficiency in the structural differentiation of isomers or stereoisomers has been previously demonstrated.[11] In particular, recent studies have shown that the influence of isomerism (positional or skeletal) or stereochemistry may show up in the low-energy collisionally activated dissociation (CAD) spectra of protonated molecules generated either under CI or FAB conditions.[12] Also, since the initial internal energy of the precursor protonated molecules is of significance in this context, the CAD spectra of protonated **1** and **5** alkaloids were recorded in a 3 eV–30 eV collision energy range (E_{lab}). Under "single collision" conditions, MH$^+$ ions (m/z 309) prepared by FAB from

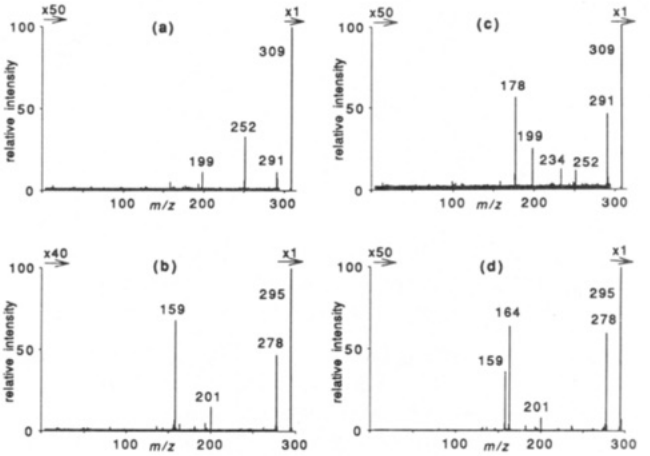

Figure 2. CAD spectra of MH$^+$ ions formed under FAB (matrix: glycerol; E_{lab} = 6 eV) from: (a) 19-oxoaristoteline (**1**), (b) aristoteline (**2**), (c) aristolasicone (**5**), and (d) *allo*-aristoteline (**6**).

both compounds showed similar fragmentation pathways leading to a limited number of fragment (also called "daughter") ions (Figure 2). Loss of water from the protonated molecules gave daughter ions at m/z 291. Further loss of a neutral species comprising the *gem*-dimethyl group and the adjacent N-12 nitrogen (57 amu) yielded a common daughter ion at m/z 252 accompanied, in the case of aristolasicone (**5**), by a signal (m/z 234) corresponding to subsequent loss of a water molecule. A third decomposition pathway also generated a daughter ion at m/z 199. Following the variation of the collision energy, the relative intensities of these different daughter ions changed from one spectrum to another. The only difference between the two compounds under investigation appeared clearly in the CAD spectra of protonated aristolasicone (**5**), which displayed a very intense daughter ion peak at m/z 178. This ion, which originates by loss of a molecule of 2-methyl indole (131 amu) from the protonated molecule was absent from the corresponding spectra of the protonated 19-oxoaristoteline (**1**). The high reproducibility of the spectra obtained under such CAD-MS/MS conditions has led us to regard the intense signal due to loss of 131 amu from the protonated aristolasicone as a diagnostic fragment of this compound, useful for the characterization of the "allo" skeleton.

When compared to the other daughter ions, the relative intensity of the m/z 178 daughter ion increased with collision energy from almost 0 to 6–10 eV and then decreased in a regular manner on increasing the collision energy up to 30 eV. For this reason, the CAD spectra of MH$^+$ ions (m/z 295) produced from both aristoteline (**2**) and *allo*-aristoteline (**6**) were recorded at 6 eV under the same conditions of ionization and collision gas pressure and

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(12) Laprévote, O.; Bui, A.-M.; Das, B. C.; Charles, B.; Tabet, J.-C. *Org. Mass Spectrom.* **1991**, *26*, 621 and references cited therein.

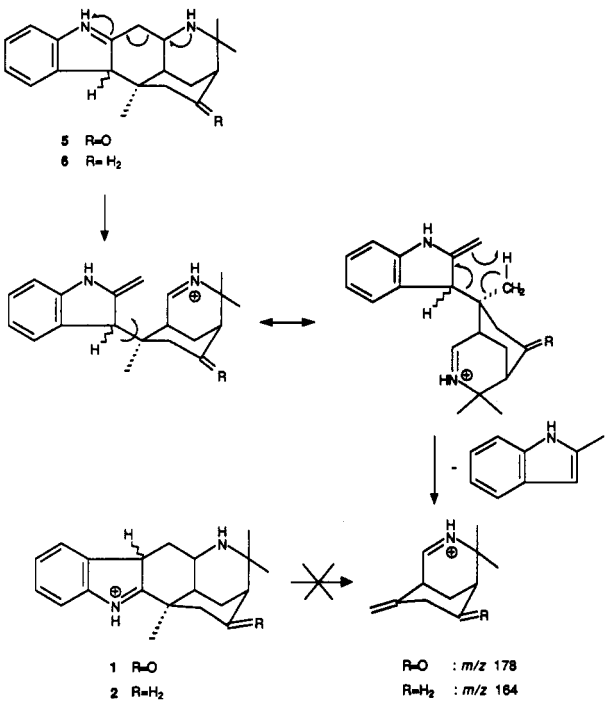

Figure 3. Fragmentation pathway of alkaloids **5** and **6** leading to fragment ions at m/z 178 and 164 after protonation at C-3.

without changing the focusing setting of the mass spectrometer. The CAD spectra so obtained were remarkably different with an intense daughter ion at m/z 164 in the CAD spectrum of protonated *allo*-aristoteline (**6**); this ion was negligible in the corresponding spectrum of protonated aristoteline **2** (Figure 2). The loss of 131 amu from the protonated alkaloid **6**, similar to that observed from protonated aristolasicone (**5**), confirmed unambiguously that both compounds belong to the same allo series as inferred previously.

The typical fragmentation process of the "allo" skeleton, yielding the m/z 178 and 164 daughter ions from protonated alkaloids **5** and **6** respectively (Figure 3) can be summarized as follows: (i) two C–C bond ruptures (C-10–C-11 and C-2–C-17 bonds) occurred under collisional activation, (ii) two protons were transferred to the neutral methylindole species, and (iii) the charge was retained on the secondary N-12 atom. In order to rationalize this fragmentation pathway, we have recorded the CAD spectrum of aristolasicone using glycerol-d_3 as FAB matrix in place of standard glycerol. The complete exchange of the protons located on both secondary amino groups and the deuteriation of the molecule by an additional D^+ ion shifted the molecular ion from m/z 309 (in glycerol) to m/z 312. The CAD spectrum of this $[M\text{-}d_2 + D]^+$ ion exhibited the diagnostic daughter ion at m/z 179, shifted by only one mass unit. It was therefore concluded that the proton involved in the ionization of the molecule was retained by the neutral methylindole released during fragmentation. Among the possible protonation sites present in the molecule, the N-12 atom would appear to be more nucleophilic than the indole nitrogen. In that case, the rupture of the C-10–C-11 bond might occur by the transfer of a proton from the N-12 ammonium group to the methylene at position 10, followed by another transfer from the methyl-20 to C-2. This process would not explain either the very high intensity of the daughter ion in question or its complete absence from the CAD spectra of the aristoteline-type isomers whose structure also seemed to be compatible with such a fragmentation pathway. The evidence suggests the existence of an alternative protonation site such as the C-3 enamine position, which is the favored site for protonation and for electrophilic attack of an indole molecule in solution.[13] Such protonated molecules could decompose easily owing to the three-carbon chain between the two nitrogen atoms of the molecule which would allow a charge transfer from the first (indole nitrogen) to the second atom with a simultaneous rupture of the C-10–C-11 bond (Figure 3). A proton could be easily transferred via a six-membered ring from the methyl-20 to the methylene group thus formed at position 10, leading to the rupture of the C-2–C-17 bond. This second fragmentation scheme, whose driving force is the location of the charge on the indole nitrogen, seems much more appropriate than the former one. Furthermore, the specificity of such a process for the "allo-type" compounds is apparent, since the aristoteline-type alkaloids possess a four-carbon bridge between the two nitrogen atoms which prevents any charge transfer from one site to the other.

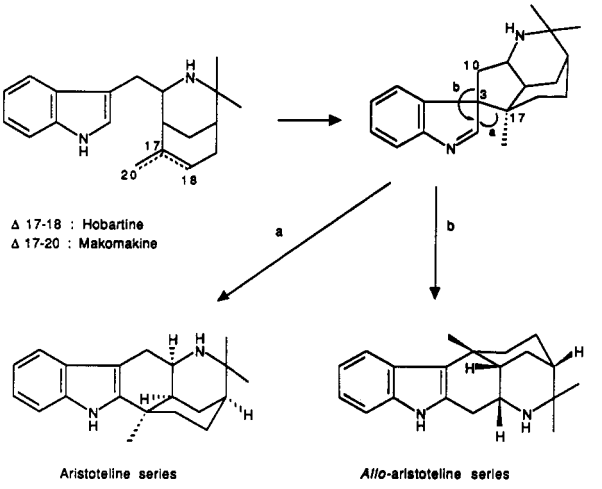

Figure 4. Aristoteline and *allo*-aristoteline alkaloids biogenetic pathway.

Even though different protonated species (i.e., on the N-12 site or on the indole nitrogen) may be produced in admixture in the FAB matrix, the protonation at position 3 of part of the alkaloids under investigation is unexpected. However, further studies on other pairs of isomeric indole alkaloids such as dregamine (four carbons between the two nitrogen atoms) and *epi*-ervatamine (five-carbon bridge) have confirmed this hypothesis.[14]

The formation of the allo series alkaloids can be explained by the biogenetic pathway presented in Figure 4.

It is known[15] that the precursors of the aristoteline alkaloids are makomakine or hobartine, which give the natural spiro compound aristoserratenine on cyclization. This alkaloid and its 3-epimer have been isolated from *A. australasica*.[1b] Classical rearrangement (path a) furnishes the alkaloids of the aristoteline series, but when migration of the less substituted C-3–C-10 bond takes place, *allo*-aristoteline alkaloids are obtained. It has been generally accepted that migration of the more substituted center is preferred, and the isolation of the *allo*-aristotelines suggest that rearrangement of the kind involved in their formation could be encountered in other indole series, prompting a reinvestigation of previously known structures and a

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(14) Laprévote, O.; Girard, C.; Bui, A.-M.; Das, B. C. Unpublished results.
(15) Bick, I. R. C., Hai, M. A. In The *Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. XXIV.

careful examination of new compounds.

Experimental Section

X-ray Crystallography. $C_{20}H_{24}N_2O$, M_w = 308.43. Crystals obtained by slow evaporation of a solution in acetone–ether; orthorhombic, $P2_12_12_1$, a = 6.535 (1) Å, b = 12.484 (2) Å, c = 20.039 (5) Å, V = 1634.8 Å^3, d_c = 1.25 g cm^{-3}, Z = 4, I (Cu Kα) = 1.5418 Å, F(000) = 664, m, 5.3 cm^{-1} (absorption ignored). Data collected from a small crystal (0.3 × 0.3 × 0.4 mm) on a Cad-4 Nonius diffractometer, using graphite monochromated Cu Kα radiation and the q – 2q scan technique up to q = 68°. From the 3071 (hkl and $-hkl$) measured reflections, of which 1732 were unique (R_{sym} = 0.037), 1680 were considered as observed having $I > 3s(I)$, $s(I)$ from counting statistics, and kept in refinement calculations. The structure was solved by direct methods[16] and refined by full-matrix least-squares methods, minimizing the function $S(F_o - F_c)^2$.[17] Difference Fourier maps showed all the hydrogen atoms. They were refined and affected an isotropic thermal factor equivalent to that one of the bonded atom, plus 10%. Convergence was reached at R = 0.038, R_w = 0.039 (with $R_w = [Sw(F_o - F_c)^2/SWF_o^2]^{1/2}$ and $w = 1/s^2(F_o)$). No residual was higher than 0.22 e Å^{-3} in the final difference map. In the crystal, the molecules are linked by hydrogen bonds established between the hydrogen atom HN1 of one molecule and the oxygen atom O23 of another (d N1···O23 = 2.985 (19) Å, angle N1–H1–O23 = 145°).

Mass Spectrometry. Tandem mass spectrometry experiments were carried out on a triple quadrupole R-30-10 Nermag mass spectrometer. Ionization conditions: bombardment gas = xenon; FAB gun voltage = 9 kV; FAB matrix = glycerol. Collisionally activated dissociation (CAD) conditions: collision gas = argon; collision gas pressure = 4 × 10^{-6} Torr; collision energy (E_{lab}) between 0 and 30 eV. The values of lens potentials were optimized for obtaining maximum intensity of the MH$^+$ ion peaks before introduction of the collision gas.

Acknowledgment. We thank Professor J.-C. Tabet and Professor J. Bedin (Université Pierre et Marie Curie, Paris) for allowing us access to instrumental facilities for the mass spectrometry.

Registry No. (±)-1, 134779-80-9; 2, 57103-59-0; 5, 117611-47-9; 6, 117678-03-2.

Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, bond lengths, and selected bond and torsion angles (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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On the Mechanism of Lewis Acid Promoted Ene Cyclizations of ω-Unsaturated Aldehydes

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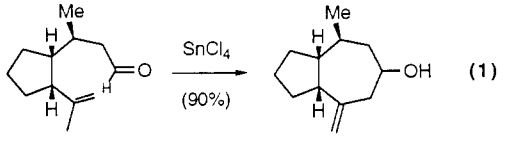
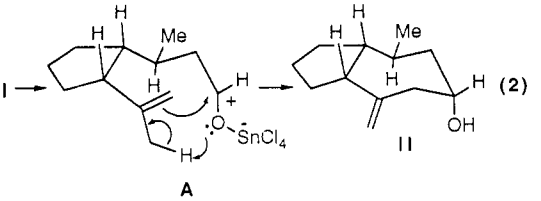
The diastereomerically labeled d_1 enals **1** and **2** were prepared from (*S*)-3-bromo-2-methylpropanol **5** by a sequence involving homologation to the allylic alcohol **13** and Sharpless epoxidation to either the α- or the β-epoxide diastereomers **14** or **15**. Reduction with $LiAlD_4$ afforded the diastereomerically deuterated diols **16** and **20**, respectively. Deoxygenation of the thionocarbonate derivatives **17** and **21** followed by THP ether cleavage and Swern oxidation afforded aldehydes **1** and **2**. The undeuterated aldehyde **28** was similarly prepared. Cyclization of **1** and **2** with Me_2AlCl afforded the *cis*-(*E*)-ethylidenecyclohexanols **3** and **4**, respectively, as the major products in accord with a mechanism involving internal proton or deuteron transfer from the vinylic CHD grouping to the aldehyde carbonyl. Product ratios (*E*:*Z*, cis:trans) from the two aldehydes were significantly different, indicative of a substantial isotope effect.

Some years ago we described a stereoselective synthesis of hydroazulenes through cyclization of ω-unsaturated aldehydes such as **I** (eq 1).[1] To account for the predominance of the trans product **II** and the absence of endocyclic double bond isomers we suggested a mechanism involving internal proton transfer as formulated for the ene reaction (eq 2). Subsequent studies by Snider and co-workers on Lewis acid cyclizations of 5-hexenals were consistent with this proposal.[2]



I II α-OH (major) III β-OH (minor)



A II

While transition state **A** nicely accounts for the stereochemistry and regiochemistry of these cyclizations, the alternative pathway **B** involving external proton transfer is also possible (eq 3).[3] In the case of aldehyde **I** only the

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