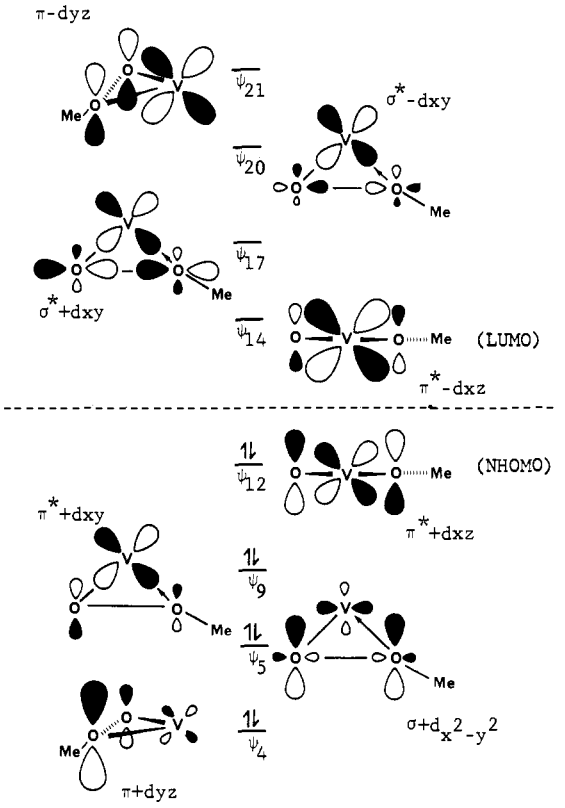

Figure 2. Frontier molecular d orbitals for vanadium complex **2**.

(NHOMO) has π^* symmetry and exemplifies how a metal, using an empty diffuse p orbital, has the proper symmetry to migrate from the distal oxygen (O2) to the "metal-bearing" oxygen. The next two lower lying occupied MOs of LiOOH constitute the σ_{O-O} ($\psi_{8'}$) and the π_{O-O} ($\psi_{7'}$) orbitals.

We have superimposed a set of d orbitals on the metal center and defined their role in epoxidation. The successful utilization of a vanadium cation with low-energy empty d orbitals (d^0) becomes immediately evident upon examination of the FMOs for complex **2** (Figure 2).[13] Since the ground-state π and π^* orbitals of an O–O bond are both occupied, a unique opporunity exists for d orbital participation. The NHOMO (ψ_{12}) and ψ_4 in **2** represent $d\pi-p\pi$ bonding MOs of the d_{xz} and d_{yz} orbitals with the π^* and π O–O bonds, respectively. The LUMO (ψ_{14}) and ψ_{21} are the antibonding (empty) combinations of these MOs. The occupied in-plane orbitals that are responsible for the "σ-type" bonding in this complex utilize the d_{xy} (ψ_9) and $d_{x^2-y^2}$ (ψ_5) orbitals. These metal d orbitals are ideally situated to facilitate a symmetry allowed 1,2 migration of the metal across the O–O bond in both the σ and π planes.

The principal axis of reaction in alkene epoxidation involves a "backside" attack by the alkene π-bond on both the σ (ψ_5) and σ^* (ψ_{17}) orbitals of the O–O bond. The electrophilic nature of the peroxo moiety is attributable to the steep descent in energy of the σ^* O–O orbital resulting from the perturbation of the σ O–O bond mediated by its molecular collision with the alkene. The net effect of this stabilizing, four-electron three-MO electronic interaction is to lower the enthalpy of activation for oxygen transfer to the alkene.[12b]

In summary, successful metal catalysts possess low-lying empty d orbitals that can facilitate an oxygen transfer with a simultaneous 1,2 metal migration without disruption of metal–oxygen bonding. The metal atom in bridged species like **1** provides a source of "internal solvation" that reduces the amount of desolvation that this nucleophilic oxy anion would require relative to a simple hydroperoxy anion. For example, the gas-phase activation barrier for transferring oxygen from HOO^- to ethylene (+38.9 kcal/mol, STO-3G) is lower than that for LiOOH (+43.6 kcal/mol, spiro geometry).[12b,14] The order in reactivity would be reversed in solution due to solvation that lowers the energy of a "naked" anion.

Finally, we conclude that the bonding of a filled in-plane orbital with "π^*-type" symmetry on the peroxide with an empty d orbital on the metal (ψ_9) is the single most important bonding characteristic of these bridged peroxo epoxidizing agents. The direction of electron flow is the antithesis of that of the Dewar–Chatt model[15] for the π-complexation of alkenes with metals, where electron density flows from a filled metal d oribtal to the empty π^* oribtal of an alkene.

Acknowledgment. We are grateful to Wayne State University Computing Center for generous amounts of computational time and to Professors H. Bernhard Schlegel and K. Barry Sharpless for their helpful discussions.

Registry No. 2, 91842-63-6; **3**, 91842-64-7; LiOOH, 23594-83-4; H_2O_2, 7722-84-1.

(13) The bonding characteristics in vanadium complex **2** were examined by using extended Hückel calculations where ab initio (STO-3G) methods were employed on **3**. Both methods afforded d orbitals of remarkable similarity. The d orbitals shown are those of complex **2**. The calculated relative energies of these MOs were also the same with the exception of one reversed order in the higher lying empty orbitals. The basis set for vanadium was taken from: Tatewaka, H.; Huzinaga, S. *J. Chem. Phys.* **1979** *71*, 4339.

(14) The calculated barriers (4-31G) for oxygen transfer from LiOOH to ethylene are 22.8 and 23.6 kcal/mol for a spiro and a planar orientation of reactants.

(15) (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C79. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939.

(±)-Linaresine and (±)-Dihydrolinaresine. The Possible Conversion of Protoberberinium Salts into Cularine Alkaloids

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Polycarpine (**3**) is an unusual amide first obtained from a member of the Annonaceae.[1] In 1979, it was recognized that the biogenesis of this pseudobenzylisoquinoline alkaloid probably proceeds from the known protoberberinium salt palmatine (**1**). Indeed, in vitro oxidation of **1** with *m*-chloroperbenzoic acid was found to afford polycarpine (**3**), and similar oxidation of the common protoberberinium salt berberine (**2**) led to the hitherto unknown polyberbine (**4**).[2]

As a result of a detailed investigation of the alkaloids of *B. valdiviana* Phil. (Berberidaceaɛ),[3] we have now obtained amorphous polyberbine (**4**), $C_{20}H_{19}NO_6$, for the first time from a natural source, where it is accompanied by berberine (**2**).[4]

But the more significant finding was in our subsequent isolation from the same source of the two novel, colorless, and alcoholic alkaloids (±)-linaresine (**9**) and (±)-dihydrolinaresine (**8**), both

(1) Jossang, A.; Leboeuf, M.; Cavé, A.; Damak, M.; Riche, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1977**, *284*, 467.

(2) Murugesan, N.; Shamma, M. *Tetrahedron Lett.* **1979**, 4521.

(3) Guinaudeau, H.; Elango, V.; Shamma, M.; Fajardo, V. *Chem. Commun.* **1982**, 1122.

(4) A total of 20 kg of *B. valdiviana* gave 25 mg of polyberbine (**4**): λ_{max} MeOH 216, 332 nm (log ε 4.51, 4.17); ν_{max} $CHCl_3$ 1610, 1660, 3500 cm^{-1}; MS, *m/z* 369 (M^+, 100), 352 (33), 341 (34), 326 (39), 324 (37), 308 (57), 294 (23). Ethereal diazomethane O-methylation of **4** furnished *O*-methylpolyberbine, identical with semisynthetic material.[2]

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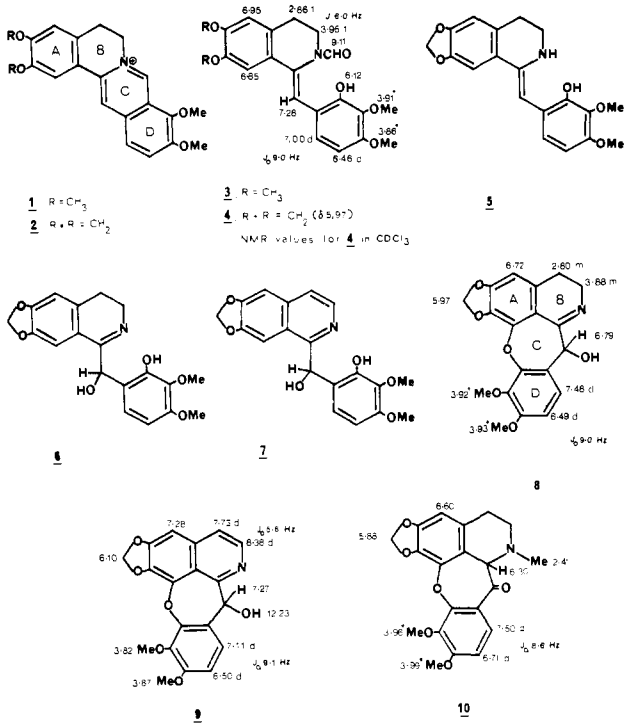
of which incorporate a dihydrooxepine system and can thus be assigned to the cularine group of isoquinoline alkaloids.[5]



(±)-Linaresine,[6] $C_{19}H_{15}NO_6$, mp 215 °C (methanol–benzene–ether), ν_{max} $CHCl_3$ 3000 and 3680 cm^{-1}, exhibits a well-defined 360-MHz ^1H NMR spectrum in CD_3CN which has been summarized around expression **9**. Two methoxyl singlets are present at δ 3.82 and 3.87, as well as a methylenedioxy singlet at δ 6.10. A set of two doublets at δ 6.50 and 7.11, with J_o = 9.1 Hz, denotes two vicinal benzenoid protons, while another set of two doublets at δ 7.73 and 8.38, but this time with a smaller coupling constant, J_o = 5.6 Hz, can be assigned to the vicinal protons of a substituted-pyridine system. Two remaining absorptions are also present, at δ 7.27 and 7.28, one due to the proton geminal to the alcoholic group (J_{vic} = 0.6 Hz), and the other to the aromatic proton on ring A. A downfield peak at δ 12.23 (J_{vic} = 0.6 Hz) which disappeared upon D_2O exchange is due to the alcoholic proton.

These spectral assignments were confirmed by means of NMR NOEDS which interrelated most of the protons in the molecule.[7] A telling observation is that irradiation of the δ 8.38 aromatic doublet effected an 18.1% NOE of the adjacent aromatic proton at δ 7.73, as well as a −3.1% NOE of the aromatic singlet at δ 7.28. These three protons must, therefore, be situated in a triangular or near-linear relationship.[8] Similarly, irradiation of the methoxyl singlet at δ 3.87 led to a 26.9% NOE of the aromatic doublet at δ 6.50 and to a −5.0% NOE of the proton doublet at δ 7.11, which represents a more remote aromatic hydrogen.[9]

The 360-MHz $CDCl_3$ ^1H NMR spectrum of the accompanying alkaloid (±)-dihydrolinaresine,[10] $C_{19}H_{17}NO_6$, mp 170 °C (methanol–benzene–ether), ν_{max} $CHCl_3$ 3000 and 3660 cm^{-1}, is presented around expression **8**. In this instance, the set of two aromatic doublets due to the vicinal protons on the pyridine ring have been replaced by a two-proton multiplet at δ 2.80 and another two-proton multiplet centered at δ 3.88, pointing to the dihydro nature of the compound.

N-Methylation of dihydrolinaresine (**8**) using methyl iodide in methanol[11] furnished mainly *N*-methyldihydrolinaresinone (**10**), $C_{20}H_{19}NO_6$, mp 84 °C (methanol), which exhibited a conjugated ketone absorption, ν_{max} $CHCl_3$ 1710 cm^{-1}. The key characteristic of the 360-MHz $CDCl_3$ spectrum of this derivative was the one-proton singlet at δ 6.30 assigned to the benzylic hydrogen α to the carbonyl function, as shown in expression **10**.

The biogenesis of (±)-linaresine (**9**) and (±)-dihydrolinaresine (**8**) could prove a matter of some moment within the realm of the isoquinoline alkaloids. Since both berberine (**2**) and polyberbine (**4**) are also found in *B. valdiviana*, it is likely that hydrolysis of polyberbine (**4**), derived from berberine (**2**), yields enamine **5**, which can suffer ready oxidation to the racemic pseudobenzylisoquinolines **6** and **7**. Intramolecular oxidative coupling of their diphenolic analogues would then lead eventually to (±)-dihydrolinaresine (**8**) and (±)-linaresine (**9**), respectively. Such an in vivo process would amount to a new biogenetic route to the cularine alkaloids.[12]

The evidence so far accumulated concerning phenolic oxidative coupling is that two phenoxy radicals are involved in the coupling reaction,[13] and such is almost certainly the case in the present instance. However, since berberine (**2**), polyberbine (**4**), linaresine (**9**), and dihydrolinaresine (**8**) all bear the identical oxygenated substituents in rings A and D, there is, at least a priori, also a slight possibility that it is monophenolic intermediates **6** and **7** that supply directly dihydrolinaresine (**8**) and linaresine (**9**). The significant feature in such a biogenetic pathway would be enzyme-induced loss of an electron from the appropriate methylenedioxy oxygen in **6** or **7** to supply a radical cation which can then condense with the neighboring phenoxy radical. A relevant observation is that intramolecular oxidative coupling of a phenolic moiety through attack at a site ortho to an aromatic ether has been achieved in vitro using vanadium oxytrifluoride,[14] so that such a process could also occur enzymatically.[15]

The characterization of linaresine (**9**) and dihydrolinaresine (**8**) throws an interesting beam of light into some of the biogenetic transformations prevailing in nature. It is conceivable that protoberberinium salts may be oxidized to pseudobenzylisoquinolines,

(5) For a complete listing of the cularine alkaloids, together with their physical and spectral properties, see: Gözler, B.; Shamma, M. *J. Nat. Prod.*, in press.

(6) (±)-Linaresine (**9**), 2 mg: λ_{max} MeOH 236, 298, 334 nm (log ε 4.71, 4.27, 4.09); λ_{max} MeOH–H_3O^+ 245, 312, 346 nm (log ε 4.61, 4.23, 4.11); MS, *m/z* 353 (M^+, 85), 336 (5), 324 (16), 310 (11), 294 (100), 172 (78).

(7) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.

(8) Mersh, J. D.; Sanders, J. K. M. *Org. Magn. Reson.* **1982**, *18*, 122.

(9) Molecular models indicate that linaresine (**9**) is V-shaped. The C-α alcoholic function is at the base or trough of the V and is quasi-equatorial, while the geminal C-α hydrogen (δ 7.27) is quasi-axial. An NMR NOE would have been observed between the C-α hydrogen (δ 7.27) and one of the methoxyl signals if the methoxyl groups had been situated at C-2′ and C-3′ rather than at C-4′ and C-5′. Additionally, the positioning of the methoxyls at C-2′ and C-3′ instead of at C-4′ and C-5′ does not lend itself to any rational biogenetic scheme.

(10) (±)-Dihydrolinaresine (**8**), 2 mg: λ_{max} MeOH 230, 299, 325 nm (log ε 4.37, 4.23, 4.07); λ_{max} MeOH H_3O^+ 238, 250, 260, 307, 381 nm (log ε 4.22, 4.22, 4.06, 4.14, 3.86); MS, *m/z* 355 (M^+, 52), 338 (4), 326 (18), 312 (5), 296 (100), 280 (9), 181 (13), 176 (12).

(11) Dihydrolinaresine (**8**) (0.75 mg) was allowed to react with methyl iodide in methanol in the presence of a little potassium carbonate. The mixture was refluxed gently on a steam bath near 45 °C for 1 h. The product, **10**, was purified by TLC on silica gel: λ_{max} MeOH 235, 295, 337 nm (log ε 4.09, 4.11, 3.36); λ_{max} MeOH–H_3O^+ 238, 253, 309, 369 nm (log ε 4.09, 4.10, 4.08, 3.72); MS, *m/z* 369 (M^+, 54), 368 (5), 354 (17), 341 (22), 340 (100), 338 (7).

(12) It is generally accepted that classical-type cularine alkaloids are formed by intramolecular phenolic oxidative coupling of diphenolic 7,8,3′,4′-tetraoxygenated tetrahydrobenzylisoquinolines. Lately, it has been pointed out that the unusual cularine base gouregine is very probably biosynthesized via oxidation of the accompanying aporphine melosmine; see: Leboeuf, M.; Cortes, D.; Hocquemiller, R.; Cavé, A.; Chiaroni, A.; Riche, C. *Tetrahedron* **1982**, *38*, 2889. The present biogenetic route to the cularines, which originates with protoberberinium salts, may therefore represent a third natural avenue to the cularines.

(13) For excellent discussions of phenolic oxidative dimerization, see: "Oxidative Coupling of Phenols"; Taylor, W. I., Battersby, A. R., Eds.; Marcel Dekker: New York, 1967.

(14) Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K. *J. Org. Chem.* **1976**, *41*, 4049.

(15) It has recently been established that methylenedioxy substituents may be reduced enzymatically to *o*-methoxyphenols; see: Beecher, C. W. W.; Kelleher, W. J. *Tetrahedron Lett.* **1983**, *24*, 469. Rueffer, M.; Ekindaya, O.; Nagakura, N.; Zenk, M. H. *Tetrahedron Lett.* **1983**, *24*, 2643. However, in the case of intermediates **6** and **7**, the expected reduction products on the basis of the above precedents would be (6-hydroxy-7-methoxybenzyl)isoquinolines which are still not properly substituted for classical-type intramolecular phenolic oxidative coupling.

which in turn may be converted into cularine- or turkiyenine[16]-type alkaloids, depending upon the enzymatic systems available in the plant.

Acknowledgment. This research was supported by NSF Grant CHE-8210699 and by NSF Latin American Cooperative Grant INT-8213104. S.F. is the recipient of a Fulbright fellowship from C.I.E.S.

(16) Gözler, T.; Gözler, B.; Weiss, I.; Freyer, A. J.; Shamma, M. *J. Am. Chem. Soc.*, following paper in this issue.

(+)-Turkiyenine: An Unusual Extension of the Biogenetic Sequence for the Isoquinoline Alkaloids

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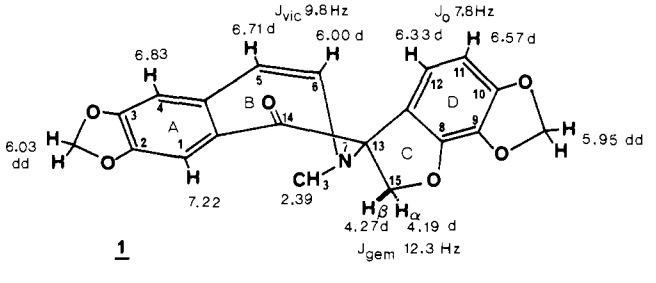
The amorphous base turkiyenine (**1**) was originally isolated by us 2 years ago, shortly following collection of the plant *Hypecoum procumbens* L. (Papaveraceae) in April 1982, near the village of Fethiye, in the province of Muğla, in south central Anatolia. Our original studies indicated that the alkaloid $C_{20}H_{15}NO_6$ ($[\alpha]^{23}_D$ +72° (*c* 0.053, $CHCl_3$); ν_{max} $CHCl_3$ 1663, 1710 cm^{-1}; λ_{max} MeOH 218 sh, 258, 281 sh, 352 nm (log ϵ 4.42, 4.62, 4.11, 3.55))[1] incorporated an *N*-methyl group, a ketonic function, a cis-disubstituted double bond as part of a seven-membered ring, and a spiro linkage—an amalgam of structural features hitherto unknown among the recognized isoquinoline- or isoquinoline-derived alkaloids.

In order to confirm the authenticity of (+)-turkiyenine (**1**) as an alkaloid, *H. procumbens* was collected again in 1983, on the same day and the same location where it had been gathered the previous year.[2] Extraction again provided (+)-turkiyenine, at which point a detailed structural study became warranted.

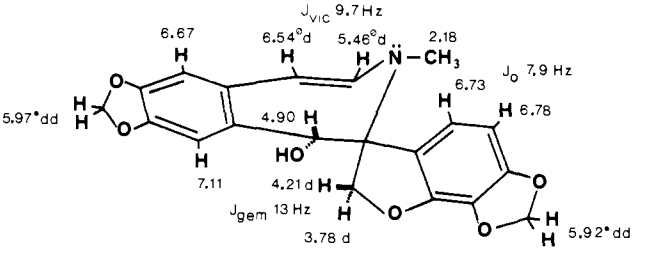


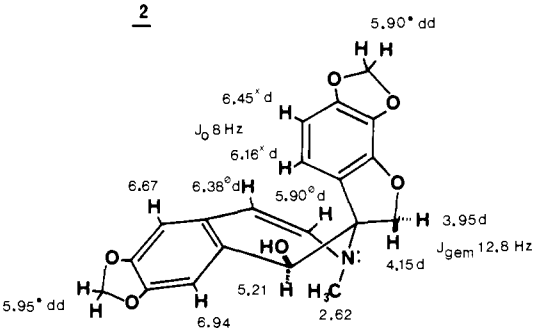
1

The 360-MHz (CD_3CN) ^1H NMR spectrum of turkiyenine has been summarized around expression **1** of relative configuration.[3] One *N*-methyl singlet is present at δ 2.39. Two methylenedioxy groups appear each as closely packed doublets of doublets, one set at δ 6.03 and the order at 5.95. The vinylic protons of the cisoid double bond are found at δ6.00 and 6.71, each as a doublet with J_{vic} = 9.8 Hz. A particularly informative feature of the spectrum was the two-proton methylene doublets at δ 4.19 and 4.27, J_{gem} = 12.3 Hz. A coupling of this magnitude is characteristic of a five-membered ring containing an oxygen atom.[4]

NMR NOEDS[5] proved to be particularly effective not only in the gross structural elucidation but also in the establishment of the favored conformation. The seven-membered ring is in a quasi-boat conformation. Irradiation of the *N*-methyl singlet (δ 2.39) caused enhancements of three signals, namely, H-1 (δ 7.22) by 3.0%, H-6 (δ 6.00) by 15%, and H-15α,β (δ 4.19–4.27) by ~5%. Irradiation of the methylenedioxy protons at δ 6.03 resulted in a 2.6% NOE of the H-1 (δ 7.22) singlet which has a long T_1 since no other proton is situated in its immediate vicinity. It follows that the alternate methylenedioxy absorption at δ 5.95 can be assigned to the substituent on ring D. A significant negative NOE of 2.6% was recorded for H-4 (δ 6.83) upon irradiation of the H-6 signal (δ 6.00).[6] This is a counterpoint to the strongly positive NOE of 19.4% observed for H-5 (δ 6.71) upon irradiation of H-6. Finally, by use of Gaussian multiplication, long-range coupling through five bonds could be detected between H-1 (δ 7.22) and H-5 (δ 6.71).

Reduction of (+)-turkiyenine (**1**) with sodium borohydride in methanol provided two amorphous alcohols, **2** and **3**, $C_{20}H_{17}NO_6$, in a 2:1 ratio. In both alcohols, the C-14 hydroxyl prefers to adopt





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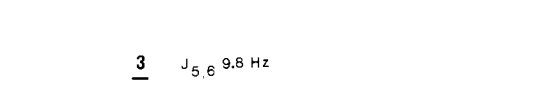

3

a pseudoequatorial position. For the major compound **2**, $[\alpha]^{23}_D$ −28° (*c* 0.001, $CHCl_3$), two NMR NOE's were observed upon irradiation of the pseudoaxial H-14 at δ 4.90, viz., H-1 (δ 7.11)

(1) Turkiyenine: mass spectrum, *m/z* 364 $(M-1)^+$ (0.9), 363 (6), 362 (18), 350 (14), 349 (59), 332 (54), 320 (100); CD Δε (nm) (MeOH) +1.2 (403), −9.5 (353), −2.4 (290), +22.4 (258), −10.1 (239).

(2) Plant collection dates were April 8, 1982 and 1983. The dried plant material (1.35 kg) was extracted with ethanol at room temperature. The usual acid–base workup, followed by silica gel chromatography, provided 30 mg of turkiyenine.

(3) We have found that CD_3CN is generally a superior solvent to $CDCl_3$ for recording the NMR spectra of alkaloids. The aromatic proton peaks are better separated, and the solvent is not as destructive of alkaloids as chloroform.

(4) Rozwadowska, M. D.; ApSimon, J. W. *Tetrahedron* **1972**, *28*, 4125.

(5) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.

(6) Mersh, J. D.; Sanders, J. K. M. *Org. Magn. Reson.* **1982**, *18*, 122.

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