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A Total Synthesis of Racemic and Optically Active Ibogamine. Utilization and Mechanism of a New Silver Ion Assisted Palladium Catalyzed Cyclization

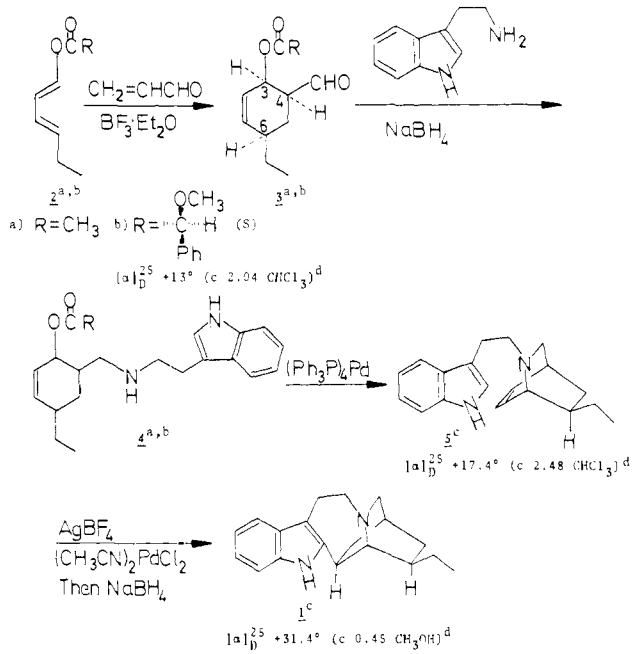
Sir:

The potential for partial synthesis of the clinically important antitumor alkaloid vinblastine[1] provides stimulus for the creation of more efficient synthetic approaches to the iboga alkaloid family.[2-4] We wish to report (a) a short, stereocontrolled synthesis of ibogamine, (b) the discovery of a new silver–palladium catalyzed olefin arylation, (c) the potential of this approach as a chiral synthesis of this alkaloid family, and (d) mechanistic insight into the nature of the olefin arylation.

Scheme I outlines the synthesis of racemic ibogamine (**1**). The boron trifluoride etherate catalyzed Diels–Alder reaction of 1-acetoxy-1,3-hexadiene (**2**) and acrolein ($PhCH_3$, −10 °C, 18 h, 90%) yielded only the desired regio- and stereoisomer of the cyclohexene **3**.[6] Formation of the Schiff base of **3** with tryptamine ($PhCH_3$, $MgSO_4$, −10 to −5 °C) followed by workup with $NaBH_4$ (MeOH, 0 °C) gave the desired aminoacetate **4** in 93% yield. Palladium catalyzed cyclization of **4** $[Pd(PPh_3)]_4$[7] (CH_3CN, 70 °C, 3–6%) produced the isoquinuclidine **5** (45%) after chromatography (preparative TLC, silica gel, 9:1:0.1 EtOAc–MeOH–NEt_2, R_f 0.6). The critical cyclization was effected by the reaction of **5** with bis(acetonitrile)palladium chloride,[8,9] silver tetrafluoroborate, and triethylamine (CH_3CN, 1 h at room temperature, 12 h at 70–75 °C) followed by a $NaBH_4$ workup (0 °C, MeOH, 1 h) to reduce the intermediate palladium species. Medium-pressure liquid chromatography[10] gave **1** in 40–45% yield (mp 126–128 °C, cf. ref 3a,d). ^1H NMR (270 MHz), mass spectra, and ^{13}C NMR (60 MHz)[11] of synthetic material were identical with those obtained from natural ibogamine.[12]

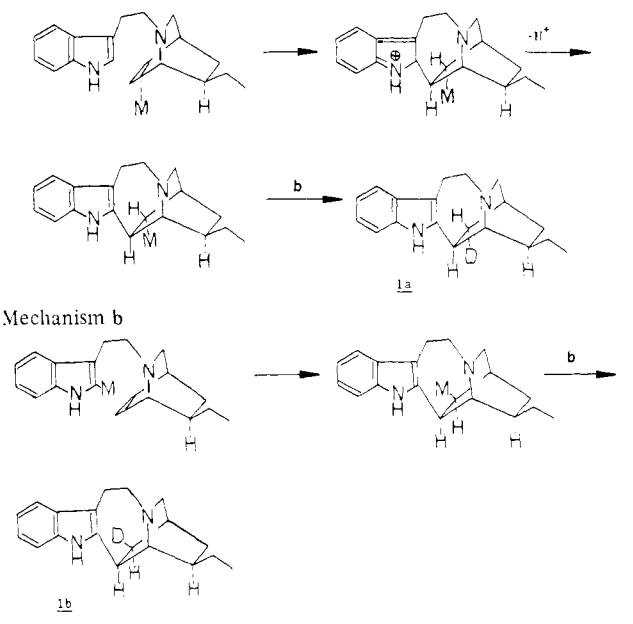
Of the possible mechanisms for the cyclization of the isoquinuclidine **5** to give **1**, two seemed most likely (Scheme II).[13] ^1H NMR (270 MHz) spectra of material obtained using $NaBD_4$–MeOD[14] reductive workup in the cyclization reaction showed the disappearance of the resonance at δ 1.63 (nondeuterated, ddd, J = 13.5, 7.5, 4.0 Hz) assigned to C(17) exo H and collapse of the signal at 2.06 (nondeuterated, dddd, J = 13.5, 11.5, 3.0, 3.0 Hz) to a doublet of multiplets (J = 11.5 Hz) assigned to C(17) endo H. Identification of the product as deuterioibogamine (**1b**) provided strong evidence for mechanism b.

Scheme I. Synthesis of Ibogamine



[a] In a series, compound is racemic. [b] In b series, only major enantiomer, 3*R*,4*S*,6*R*, is depicted. [c] In series derived from **3a**, this compound is racemic. In series derived from **3b**, this represents major enantiomer (**5**, 7*S*; **1**, 16*S*,20*R*) obtained. [d] These represent the directly observed rotations, uncorrected for the optical purity of the mandelate unit.

Scheme II. Two Possible Mechanisms of Cyclization[a]



[a] M is either a silver–palladium mixed salt complex or a partially ionized palladium salt. [b] $NaBD_4$, CH_3OD.

Since the chirality of the product is established in the initial cycloaddition, this approach lends itself to a chiral synthesis. Indeed, (*E*,*E*)-1-(*S*-2′-phenyl-2′-methoxyacetoxy)-1,3-hexadiene (**2b**)[15] and acrolein (10% boron trifluoride etherate, $PhCH_3$, −10 °C, 48 h, 92%)[16] gave 80% (3*R*,4*S*,6*R*)-**3b** and 20% 3*S*,4*R*,6*S* isomer. The use of the *O*-methylmandeloyl group as the chiral inducing agent also has the advantage of allowing direct determination of the optical purity by NMR spectroscopy[16,17] (see Scheme I). Reductive amination of **3b** with tryptamine and $NaBH_4$, followed by $Pd(PPh_3)_4$ catalyzed cyclization and palladium–silver catalyzed olefin arylation

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(conditions similar to racemic synthesis throughout) produced an 80:20[18] mixture of (+)-**1**-(−)-**1**[19] (mp 140–142 °C).

The availability of ibogamine in 17% overall yield in four steps from diene **2** without yield optimization as well as in chiral form demonstrates the efficiency of this approach to this exciting class of compounds. The generality and further application of the newly described cyclization reaction is under further investigation.

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(11) ^{13}C NMR was obtained in $CD_3C(=O)CD_3$ using a 1.7-mm tube, sample size ~5 mg (0.018 mol). Tentative assignments were based on a model constructed from indole ^{13}C resonance of epiibogamine and isoquinuclidine ^{13}C resonances of ibogaine obtained from E. Wenkert, D. W. Cochran, H. E. Gottlieb, E. W. Hagaman, R. B. Filho, F. J. Matos, and M. Madruga, *Helv. Chim. Acta*, **59**, 2437 (1976). 1: C(2), quaternary carbon not observed; C(3), 55.1; C(5), 50.7; C(6), 21.4; C(7), 101.1; C(8), quaternary carbon not observed; C(9), 118.2; C(10), 119.0; C(11), 120.9; C(12), 110.9; C(13), quaternary carbon not observed; C(14), 27.5; C(15), 33.0; C(16), 41.7; C(17), 35.0; C(18), 12.1; C(19), 28.6; C(20), 42.7; C(21), 58.3 ppm.
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(15) The diene was prepared from tricyclo[4.2.1.0^{2,5}]non-7-en-3-one by ethylation, carbonyl reduction, acylation with *S,O*-methylmandeloyl chloride (from 97% optically pure acid[21]) and pyrolysis as described in B. M. Trost, J. Ippen, and W. C. Vladuchick, *J. Am. Chem. Soc.*, **99**, 8116 (1977); M. E. Jung, *J. Chem. Soc., Chem. Commun.*, 956 (1974).
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(19) Although the vast majority of ibogamine (**1**) that has been isolated from natural sources has the (−)-16(*R*),20(*S*) configuration opposite to that of the ibogamine synthesized here, racemic ibogamine has been isolated from *Tabernaemontana retusa* (LAM.) PICHON. 2. M. J. Holzey, L. Oliver, M. DeBray, M. Quirin, J. Lemen, and K. So, *Ann. Pharm. Fr.*, **28**, 127 (1970). In addition (−)-ibogamine could be prepared by our route by simply substituting the *R* isomer of mandelic acid *O*-methyl ether in the synthesis.
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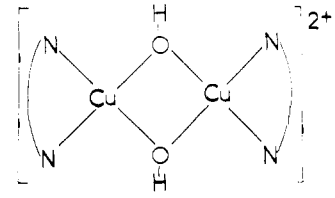
Interaction between Orthogonal Magnetic Orbitals in a Copper(II)–Oxovanadium(II) Heterobinuclear Complex

Sir:

In the last few years, several orbital models have been proposed to describe the mechanism of the exchange interaction in binuclear paramagnetic complexes.[1-7] In most of these models, the exchange interaction parameter J, which appears in the Heisenberg-Dirac-Van Vleck phenomenological Hamiltonian $-J\hat{S}_A\cdot\hat{S}_B$ whatever its sign may be, is interpreted as resulting from an antiferromagnetic component J_{AF} and a ferromagnetic component J_F. Several recent attempts to determine semiquantitiatively J_{AF} attest that the mechanism of the antiferromagnetic coupling *is* now rather well understood.[2,8,9] In contrast, it does not yet appear possible to predict the magnitude of the exchange interaction parameter in binuclear complexes when the metallic centers are ferromagnetically coupled. The main difficulty apparently arises because, as soon as the magnetic orbitals centered on the transition ions are no longer rigorously orthogonal, the J_{AF} component becomes important and very quickly dominates J_F. We recall that a magnetic orbital is defined as a singly occupied orbital, centered on a transition ion and partially delocalized toward the ligands surrounding this ion. Such a magnetic orbital may be considered as a molecular orbital of the monomeric part of the binuclear complex constituted by a transition ion surrounded by its terminal and bridging ligands.

So far, to our knowledge, no binuclear complex in which all the magnetic orbitals are rigorously orthogonal has been synthesized. To make this situation clear, let us consider the hydroxo-bridged copper(II) dimers of the type studied by Hatfield, Hogdson, and coauthors.[10,11] In these complexes the



copper(II) ions are located in C_{2v} sites, and the magnetic orbitals built from each of the metallic $d_{x^2-y^2}$ orbitals pointing along the Cu–N and Cu–O bonds have b_1 symmetry. The overlap integral $\langle b_1|b_1\rangle$ between these magnetic orbitals is in principle different from zero, except for a particular value of the bridging angle $\angle$ CuOCu which cannot be known exactly a priori.

Strict orthogonality of the magnetic orbitals for reasons of symmetry can occur in heterobinuclear complexes. We have synthesized one of the first such complexes, of the formula $CuVO(fsa)_2en\cdot CH_3OH$ where $(fsa)_2en^{4-}$ denotes the bichelating ligand derived from the Schiff base bis(2′-hydroxy-3′-

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