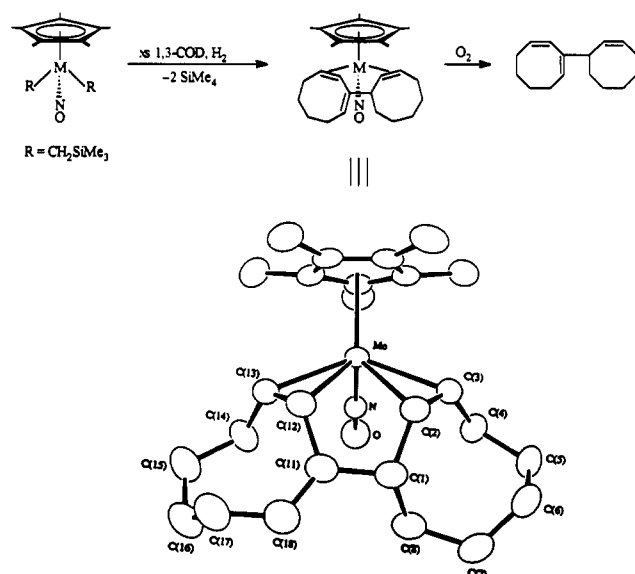


Scheme I



actions depicted in Scheme I do not permit an unambiguous assignment of their molecular structures. Consequently, we have subjected $\text{Cp}^*\text{Mo}(\text{NO})(\text{C}_{16}\text{H}_{24})$ to a single-crystal X-ray crystallographic analysis.⁷

The carbon-carbon bond lengths within the $C_{16}H_{24}$ ligand of $Cp^*Mo(NO)(C_{16}H_{24})$ indicate the existence of three $C=C$ linkages as shown in Scheme 1, namely, $C(2)-C(3)$ [$1.392(3) \text{ \AA}$] and $C(12)-C(13)$ [$1.383(3) \text{ \AA}$], each of which is involved in η^2 - π -bonding to Mo with an average $Mo-C = 2.34 \text{ \AA}$, and $C(11)-C(18)$ [$1.340(4) \text{ \AA}$].⁸ In solutions, the $Cp^*M(NO)(C_{16}H_{24})$ complexes display relatively complicated 1H NMR spectra which contain complex coupling patterns for the CH and CH_2 protons of the cyclooctenyl-1,3-cyclooctadiene ligand.³ $^{13}C\{^1H\}$ and APT data, however, prove to be more useful during structure elucidation. Thus, in addition to Cp^* signals, the APT spectra exhibit the expected nine peaks assignable to CH_2 carbons, six peaks assignable to CH carbons, and one peak attributable to the lone quaternary carbon in the $C_{16}H_{24}$ ligand. The free 2-cyclooct-2-en-1-yl-1,3-cyclooctadiene displays similar spectral features.⁹

The mechanistic details of how the triene ligand is formed during the conversions shown in Scheme I are unclear at present. SiMe_4 has been identified by GC and ^1H NMR spectroscopy as a byproduct in both reactions. However, the use of D_2 instead of H_2 in both conversions does not result in any incorporation of deuterium into the final organometallic products. These coupling reactions represent a novel example of the ability of a transition-metal center to promote a dimerization which would not occur without metal mediation.¹⁰ We are currently extending this work

(7) Crystals of $\text{p}^*\text{Mo}(\text{NO})(\text{C}_{16}\text{H}_{24})$ are triclinic, space group $P\bar{1}$; $a = 8.772(1) \text{ \AA}$, $b = 8.898(1) \text{ \AA}$, $c = 16.137(2) \text{ \AA}$, $\alpha = 103.26(1)^\circ$, $\beta = 103.98(1)^\circ$, $\gamma = 94.58(1)^\circ$, $V = 1177.4 \text{ \AA}^3$, $Z = 2$, $D_{\text{calc}} = 1.347 \text{ g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 5.6 \text{ cm}^{-1}$; diffractometer, Enraf-Nonius CAD-4 θ ; radiation, Mo K α , graphite monochromator ($\lambda(\text{K}\alpha_1) = 0.70930 \text{ \AA}$); $4^\circ \leq 2\theta \leq 49^\circ$; $n_{\text{obsd}} = 3452$ ($I_0 \geq 2.5\sigma(I_0)$); $N_{\text{var}} = 279$; $R_F = 0.023$; $R_{wF} = 0.031$; maximum residual peak $0.37(5) \text{ e \AA}^{-3}$.

(8) Other metrical parameters of interest are C(11)–C(12) = 1.492(3) Å, C(1)–C(2) = 1.521(3) Å, C(1)–C(8) = 1.498(3) Å, C(12)–C(11)–C(18) = 121.9(2)°, C(8)–C(1)–C(2) = 118.5(2)°.

(9) Anal. Calcd for $C_{16}H_{24}$: C, 88.80; H, 11.20. Found: C, 88.48; H, 11.71. IR (neat): 3007, 2926, 2849, 1639, 1446, 1261, 920, 846, 817, 763, 704 cm^{-1} . Low-resolution mass spectrum (probe temperature 120 $^{\circ}C$): m/z 216 [P^{+}], 1H NMR (C_6D_6): δ 5.94–5.52 (m, 5 H, CH), 3.52 (s, 1 H, CH), 2.29–1.95 (m, 6 H, 3 CH_2), 1.68–1.27 (m, 12 H, 6 CH_2). $^{13}C\{^1H\}$ NMR: δ 141.69 (C_{quat}), 133.45, 132.26, 128.53, 127.08, 125.05, 43.92 (6 CH), 35.67, 29.90, 29.02, 28.05, 26.92, 26.71, 26.30, 24.77, 23.25 (9 CH_2).

(10) A recent example of metal-facilitated dimerization involves the reductive activation of benzene in $[\text{Mn}(\eta^6\text{-C}_6\text{H}_6)(\text{CO})_3]^+$ to obtain $[\{\text{Mn}(\text{CO})_3\}_2\mu\text{-(}\eta^4\text{-C}_6\text{H}_6\text{:}\eta^4\text{-C}_6\text{H}_6\text{)}]^{2-}$ in which the Mn centers are bridged by the newly formed tetrahydrobiphenylene ligand.¹¹

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to establish which other dienes display the same dimerization behavior as 1,3-COD and to determine which functional groups may be tolerated during such metal-mediated coupling processes.

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Supplementary Material Available: Experimental procedures and characterization data for all complexes and full details of the crystal structure analyses including associated tables for $\text{Cp}^*\text{Mo}(\text{NO})(\text{C}_{16}\text{H}_{24})$ (14 pages); tables of measured and calculated structure factor amplitudes for $\text{Cp}^*\text{Mo}(\text{NO})(\text{C}_{16}\text{H}_{24})$ (18 pages). Ordering information is given on any current masthead page.

Biosynthesis of the *Ephedra* Alkaloids: Evolution of the C₆-C₃ Skeleton

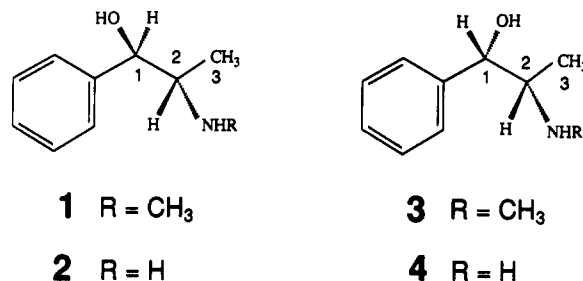
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The skeleton of the *Ephedra* alkaloids, (1*R*,2*S*)-(-)-ephedrine (1), (1*R*,2*S*)-(-)-norephedrine (2), (1*S*,2*S*)-(+)-pseudoephedrine (3), and (1*S*,2*S*)-(+)-norpseudoephedrine (4), originates by union of a C₆-C₁ unit with a C₂ unit. The latter is derived from the intact CH₃CO group of pyruvic acid.^{1,2} The C₆-C₁ unit is supplied by the benzylic C₆-C₁ fragment of phenylalanine,³⁻⁵ which presumably cleaves by the ammonia lyase route,⁶ since the C₆-C₁ unit of cinnamic acid⁵ is incorporated and since benzaldehyde and benzoic acid^{4,5} also serve as precursors. It has not been determined which of these two C₆-C₁ compounds reacts with pyruvate, nor have the C₆-C₃ intermediates on the route from the two fragments C₆-C₁ plus C₂ into the noralkaloids been identified.



We now report results which identify benzoic acid as the immediate precursor of the C₆-C₁ unit and which show that 1-phenylpropane-1,2-dione (6) and (S)-(-)-2-amino-1-phenylpropan-1-one (cathinone) (7) are the penultimate intermediates in the evolution of the C₆-C₃ skeleton of the noralkaloids.

In four experiments, solutions of (i) sodium [carboxyl- ^{13}C]benzoate (99% ^{13}C), (ii) [carbonyl- ^{13}C , ^2H]benzaldehyde (99% ^{13}C , 99.6% ^2H), (iii) [1,2,3- $^{13}\text{C}_3$]-1-phenylpropane-1,2-dione (6) (98% $^{13}\text{C}_3$), and (iv) [1,2,3- $^{13}\text{C}_3$]-(*S*)-2-amino-1-phenylpropan-1-one (7) (97% $^{13}\text{C}_3$) were applied to growing shoots of *Ephedra*

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(1) Grue-Sørensen, G.; Spenser, I. D. *J. Am. Chem. Soc.* **1988**, *110*, 3714-3715.

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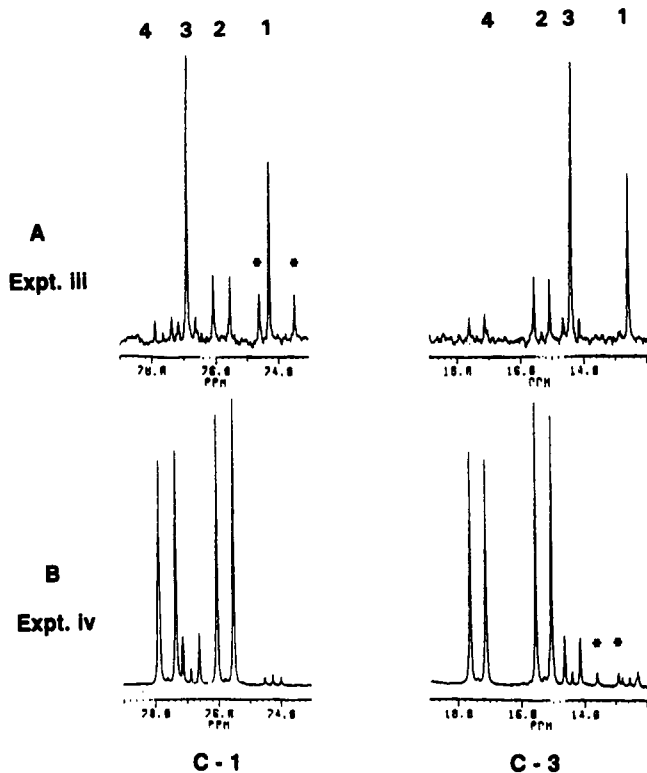


Figure 1. C-1 and C-3 regions of the 75.47-MHz proton noise decoupled ^{13}C NMR spectra of the mixture of *Ephedra* alkaloids isolated from plants to which the following ^{13}C -labeled substrates had been administered: (A) [1,2,3- $^{13}\text{C}_3$]-1-phenylpropane-1,2-dione (6) (experiment iii); (B) [1,2,3- $^{13}\text{C}_3$]-(*S*)-2-amino-1-phenylpropan-1-one (7) (experiment iv). The signals marked with an asterisk (*) are due to unidentified contaminants in the alkaloid mixture.

gerardiana. After 7 days the aerial parts were worked up¹ to yield a mixture (14–31 mg) of the alkaloids 1–4 as hydrochlorides. The 75.47-MHz proton noise decoupled ^{13}C NMR spectrum of the product mixture (in $^2\text{H}_2\text{O}$) from each of the experiments showed signals due to ^{13}C -enriched carbon atoms.

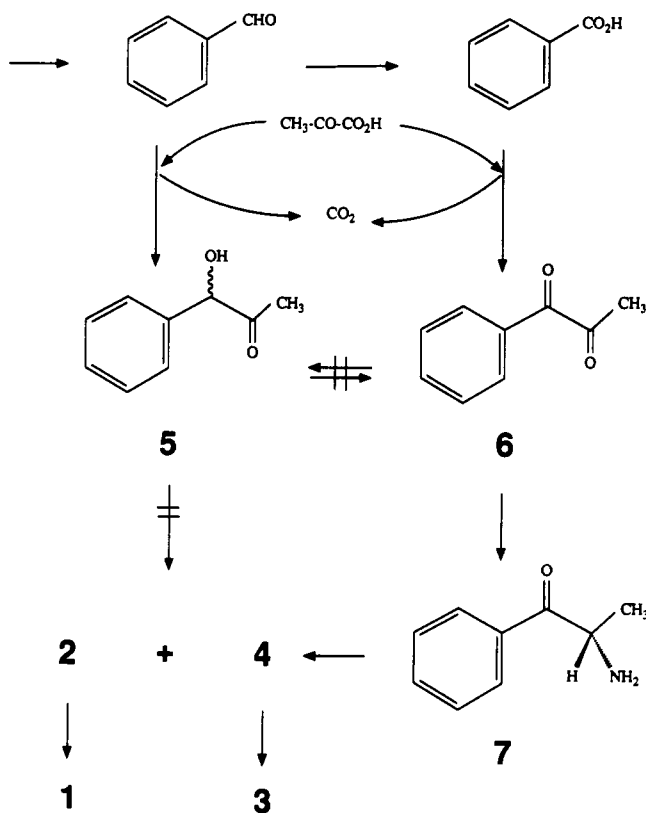
The spectra of the alkaloid mixture from the experiments with benzoic acid (experiment i) and with benzaldehyde (experiment ii) showed enhancement of the signals due to the carbinol carbon atoms (C-1) (δ 74.15–77.55 ppm)² of each of the four alkaloids, compared to those of the methyl (C-3) (δ 12.49–17.36 ppm)² and amino carbons (C-2) (δ 54.90–62.68 ppm).²

The incorporation of label⁷ into 1, 2, 3, and 4 was calculated to be 1.3, 6.0, 0.3, and 3.5%, respectively, for benzoic acid and 0.2, 0.9, 0.2, and 1.5%, respectively, for benzaldehyde. The molar composition of the alkaloid mixture, calculated from the natural abundance signals due to nonenriched carbon atoms, was 1:2:3:4 = 32:~1:60:7% in the case of benzoic acid and 27:1:64:8% in the case of benzaldehyde.

There was no trace of deuterium/ ^{13}C coupling in the carbinol signals of the alkaloid sample from [carbonyl- ^{13}C , ^2H]benzaldehyde. Intact incorporation of the ^{13}C , ^2H -labeled benzaldehyde would have delivered deuterium to the carbinol carbon of the propanoid chain, giving rise to multiplicity of the carbinol signals in the ^{13}C NMR spectrum. It follows that benzaldehyde is not the immediate precursor but that it is oxidized to benzoic acid prior to incorporation.

Further experiments corroborate this conclusion: If benzaldehyde were the immediate precursor, its condensation with the pyruvate-derived C_2 unit would yield 1-hydroxy-1-phenylpropan-1-one (5).⁸ Attempts to demonstrate incorporation of

Scheme 1



(*RS*)-5 into the *Ephedra* alkaloids have been unsuccessful.^{9,10} If, on the other hand, benzoic acid (or its CoA thioester) were the immediate precursor, its condensation with the pyruvate-derived C_2 unit would lead to 1-phenylpropane-1,2-dione (6) as the first C_6 – C_3 intermediate. This compound has not been detected in *Ephedra* species but occurs in *Catha edulis*,^{11,12} a plant that also contains (*S*)-(-)-2-amino-1-phenylpropan-1-one (cathinone) (7), 4, and 2.^{11,12}

[1,2,3- $^{13}\text{C}_3$]-1-Phenylpropane-1,2-dione (6) is incorporated into the alkaloids. The ^{13}C NMR spectrum (Figure 1A) of the alkaloid mixture (molar composition 1:2:3:4 = 36:2:61:1%) from experiment iii showed the characteristic coupling pattern ($^1J_{1,2} = 39$ Hz, $^1J_{2,3} = 37$ Hz¹) for the presence of a $^{13}\text{C}_3$ unit in the signals from three of the alkaloids. The incorporation of label¹³ into 1, 2, 3, and 4 was 0, >25, 0.15, and 10%, respectively. A trace (<1%) of triply enriched cathinone (7) (incorporation >25%)¹³ (C-2 54.76 ppm, C-3 19.45 ppm, $^1J_{1,2} = 42$ Hz, $^1J_{2,3} = 33$ Hz) was also present. This is the first report of the presence of cathinone in *Ephedra*.

Reduction of the C-1 oxo group and stereospecific transamination at the C-2 oxo group are required to convert 1-phenylpropane-1,2-dione (6) into the noralkaloids. The negative outcome of the experiment¹⁰ with (*RS*)-1-hydroxy-1-phenylpropan-2-one (5) and the observed presence of cathinone suggest that transamination¹⁵ precedes reduction and that cathinone (7) is an intermediate.

The result of the feeding experiment with [1,2,3- $^{13}\text{C}_3$]cathinone (7) (experiment iv) shows that this is indeed the case. The ^{13}C

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(13) Specific incorporation = % enrichment above natural abundance = $1.1\% \times (\text{peak height of enriched C-1 signal} - \text{peak height of natural abundance C-1 signal}) / (\text{peak height of natural abundance C-1 signal})$.

(14) Cf.: al-Meshal, I. A.; al-Rashood, K. A.; Nasir, M.; el-Ferally, F. S. *J. Nat. Prod.* 1987, 50, 1138–1140.

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(7) Specific incorporation = % enrichment above natural abundance = $1.1\% \times (\text{peak height of enriched C-1 signal} - \text{peak height of natural abundance C-1 signal}) / (\text{peak height of natural abundance C-1 signal})$.

(8) Cf.: Crout, D. H. G.; Dalton, H.; Hutchinson, D. W.; Miyagoshi, M. *J. Chem. Soc., Perkin Trans. 1* 1991, 1329–1334.

NMR spectrum (Figure 1B) showed $^{13}\text{C}_3$ enrichment in all four alkaloids (molar composition 1:2:3:4 = 28:17:41:14%). The incorporation into the four alkaloids, 1, 2, 3, and 4, calculated from the relative intensities of the singlet and doublet signals due to C-3, was 2, 98, 8, and 97%, respectively. The high efficiency of incorporation of label from cathinone into the noralkaloids explains why cathinone had not hitherto been detected in *Ephedra*.

Scheme I shows the biosynthetic sequence that is now established for the route to the *Ephedra* alkaloids.

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The Electronic Structure of $\text{Sc}_3@C_{82}$

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Soon after the discovery of C_{60} in 1985, researchers found that metal atoms could be trapped not only in C_{60} but in higher fullerenes as well.¹⁻⁸ Since the development of the carbon-arc method of fullerene preparation,⁹ many of the higher fullerenes have proven to be capable of encapsulating more than one metal atom, as in the recently reported $\text{La}_2@C_{80}$,⁴ $\text{Y}_2@C_{82}$,⁶ and $\text{Sc}_3@C_{82}$.^{8,10} Although a number of metal fullerene species have been reported, the nature of the cluster-fullerene interaction within the cage has received limited attention.¹¹⁻¹³ Work by Manolopoulos and Fowler has shown that a C_{3v} symmetry isomer of C_{82}^{2-} is a particularly stable species.¹³ Kikuchi and co-workers have shown from NMR results that one isomer of C_{82} does indeed have C_{3v} symmetry.¹⁴ $\text{Sc}_3@C_{82}$ has been studied by EPR spectroscopy, and results indicate that the molecule either has C_{3v} symmetry or is fluxional.⁸ Although no further conclusions were drawn as to the geometry of this molecule or to the position of the Sc_3 triangle, it seems likely that the C_{82} cage in $\text{Sc}_3@C_{82}$ has C_{3v}

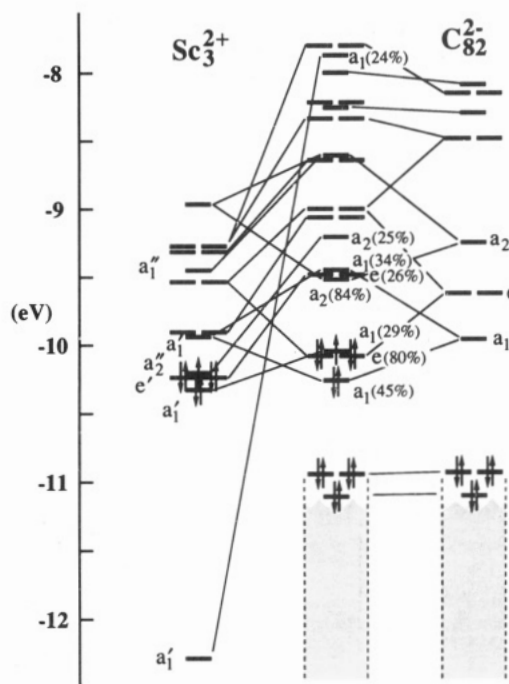


Figure 1. Molecular orbital diagram from an extended Hückel calculation on $\text{Sc}_3@C_{82}$ for the proposed C_{3v} geometry (1). The shaded area indicates the dense region of occupied orbitals of primarily C_{82} character. C_{82} contributions are indicated in parentheses. Correlation lines indicate the primary orbital parentage from the two fragments, some of which are described in the text. The lowest lying a_1' orbital of the naked Sc_3^{2+} fragment is shown without two electrons in order to make clear the orbital occupancy of the neutral Sc_3 cluster, not to indicate the ground state of the dication.

symmetry and that reasonable placement of the Sc_3 triangle within the carbon cage will enable us to use extended Hückel calculations to examine the electronic structure of the $\text{Sc}_3@C_{82}$ molecule. (There is no reason to assume that the C_{82} framework of $\text{Sc}_3@C_{82}$ is the same as the empty fullerene.)

Starting with the C_{3v} symmetry C_{82} connectivity suggested by previous workers,^{14,15} we used MM2 calculations with the CAChe system (Computer Aided Chemistry, Tektronix Inc., Beaverton, OR) to obtain a model input geometry of the C_{82} molecule for subsequent extended Hückel calculations. The molecular mechanics parameters were set so that all atoms were sp^2 hybridized. This C_{3v} isomer of C_{82} is built up of 12 pentagons and 31 hexagons, and the bottom of the molecule can be thought of as the carbon framework of the coronene molecule. Placing the Sc_3 trimer ($d(\text{Sc}-\text{Sc}) = 2.98 \text{ \AA}$) inside the cage with its center 2.5 \AA above the center of the coronene unit centers the Sc_3 fragment within reasonable bonding distance of the carbon framework ($d(\text{Sc}-\text{C}) = 2.15 \text{ \AA}$). 1a shows a view of $\text{Sc}_3@C_{82}$ from the top, with the coronene unit directly below the metal cluster; 1b is a side view of the molecule showing the vertical positioning of the cluster within the cage.

We obtain energy levels for the naked Sc_3 cluster that are consistent with Knight and co-workers' EPR results for a Sc_3 cluster in a cryogenic matrix,¹⁶ though our energy level scheme is different from either of the possible schemes put forward by those investigators. The lowest occupied orbital of the Sc_3 is mostly an a_1' bonding combination of Sc 4s orbitals, as suggested by Knight and co-workers. The remaining four closely spaced occupied levels of the Sc_3 triangle are consistent with the low-lying configurations studied by Walch and Bauschlicher for the free Sc_3 and Sc_3^+ species using ab initio theory.¹⁷ Consistent with

*To whom correspondence should be addressed.

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