localization. In this regard anion radical 2^- is of special interest, because the spectrum expected from a localized electronic structure with rapid hopping can be simulated using parameters measured for 7^-. The spectrum of 7^- consists of the six-line pattern expected if the splitting is by three individual protons with a_H = 2.50, 2.70, and 1.10 G. Rapid hopping of the electron between two phenanthraquinone fragments of 2^- would then be expected to give a spectrum with twice as many splittings each with half the value (three pairs of protons a_H = 1.25, 1.35, and 0.55 G). These values are close to those observed, reinforcing the concern that ESR cannot distinguish delocalized structures from localized ones if there is a small barrier to electron hopping.

Conclusions

Reduction potentials and the near-IR and ESR spectra of 1–6^- are consistent with the hypothesis that these anion radicals, unlike the linear analog, 9^-, are delocalized. This delocalization is not only around the helix but also across the gap between the ends of the molecule. The evidence is particularly compelling for the five-ringed radical anion 1^-, which exhibits a large separation in reduction potentials, a calculable electronic transition energy, a fairly intense and solvent independent near-IR band, and a calculable temperature independent ESR spectrum with high electron density on the non-quinone bridge hydrogens. For the larger helicene–bisquinones, all the data are consistent with delocalization, and the near-IR spectra strongly support helically delocalized structures. Such structures are unique and impart unusual physical properties, the most remarkable of which are the π^*–π^* bands occurring at wavelengths from 1.4 to 2.2 μm.

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Probing Ergot Alkaloid Biosynthesis: Intermediates in the Formation of Ring C

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Abstract: The mode of C-ring formation in ergot alkaloid biosynthesis was probed by synthesizing two potential intermediates, compounds **6** and **7**, in deuterated form from the prenylated indole **8**. Both compounds were incorporated into the ergot alkaloid elymoclavine by washed mycelia of *Claviceps* sp., strain SD 58, but only the formation of **7**, and not **6**, could be demonstrated in the cultures. Hence it is proposed that only **7** is an intermediate in ergot alkaloid biosynthesis, whereas **6** is not on the pathway but can be converted into **7** when added to the cultures. A pathway is proposed for the formation of ring C involving epoxidation of **7** at the terminal double bond and cyclization of the epoxide with simultaneous decarboxylation.

The biosynthesis of the clinically important ergot alkaloids both in the ergot fungus[1,2] and in higher plants[3] proceeds from the building blocks L-tryptophan, L-methionine, and an isoprene unit derived from mevalonic acid. Much has been learned from tracer studies in fermentations with *Claviceps* species about the assembly of the tetracyclic ergoline ring system from these basic building blocks.[1,2] From these studies the pathway shown in Scheme I has emerged for the formation of elymoclavine (**1**), the precursor of the commercially important lysergic acid derivatives. However, one notable gap in our understanding of this pathway concerns the mode of closure of ring C, i.e., the formation of the tricyclic intermediate, chanoclavine-I (**2**), from its last established precursor,[4] *N*-methyl-4-(γ,γ-dimethylallyl)tryptophan (*N*-methyl-DMAT, **3**).

The formation of **2** proceeds stereospecifically with retention of the original hydrogen from the chiral center of L-tryptophan as H-5[5] and of the *pro-R* hydrogen from C-10 of DMAT as H-10[6] in the final product, **1**. It must involve a cis–trans isomerization at the allylic double bond, since an isotopic label from C-2 of mevalonate, which labels the *E*-methyl group of γ,γ-dimethylallyl pyrophosphate (DMAPP),[7] appears in the methyl and not the hydroxymethyl group of **2**,[8] whereas DMAT labeled in the *Z*-methyl group labels exclusively the hydroxymethyl group of **2**.[9] The oxygen atom of the hydroxymethyl group originates from molecular oxygen[10] and must be introduced prior to ring closure, since deoxychanoclavine-I was not incorporated into agroclavine or **1**.[11] Both *E*- and *Z*-4-(4-hydroxy-3-methyl-2-butenyl)tryptophan were incorporated into **1**,[12,13] but a detailed analysis of

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(1) Floss, H. G. *Tetrahedron* **1976**, *32*, 873.
(2) Floss, H. G.; Anderson, J. A. In *The Biosynthesis of Mycotoxins—A Study in Secondary Metabolism*; Steyn, P. S., Ed.; Academic Press: New York, 1980; pp 17–67.
(3) Gröger, D.; Mothes, K.; Floss, H. G.; Weygand, F. *Z. Naturforsch.* **1963**, *18B*, 1123.
(4) Otsuka, H.; Quigley, F. R.; Gröger, D.; Anderson, J. A.; Floss, H. G. *Planta Med.* **1980**, *40*, 109 and references therein.
(5) Floss, H. G.; Mothes, U.; Günther, H. *Z. Naturforsch.* **1964**, *19B*, 784.
(6) Shibuya, M.; Chou, H.-M.; Fountoulakis, M.; Hassam, S.; Kim, S.-U.; Kobayashi, K.; Otsuka, H.; Rogalska, E.; Cassady, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1990**, *112*, 297 and references therein.
(7) Popjak, G.; Cornforth, J. W. *Biochem. J.* **1966**, *101*, 553.
(8) Fehr, T.; Acklin, W.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1966**, 801.
(9) Pachlatko, P.; Tabacik, C.; Acklin, W.; Arigoni, D. *Chimia* **1975**, *29*, 526.
(10) Kobayashi, M.; Floss, H. G. *J. Org. Chem.* **1987**, *52*, 4350.
(11) Fehr, T. Ph.D. Dissertation No. 3967, Eidgenössische Technische Hochschule, Zürich, 1967. Arigoni, D. *Symposium on Organic Chemical Approaches to Biosynthesis*; London, 1965.
(12) Plieninger, H.; Wagner, C.; Immel, H. *Liebigs Ann. Chem.* **1971**, *743*, 95.

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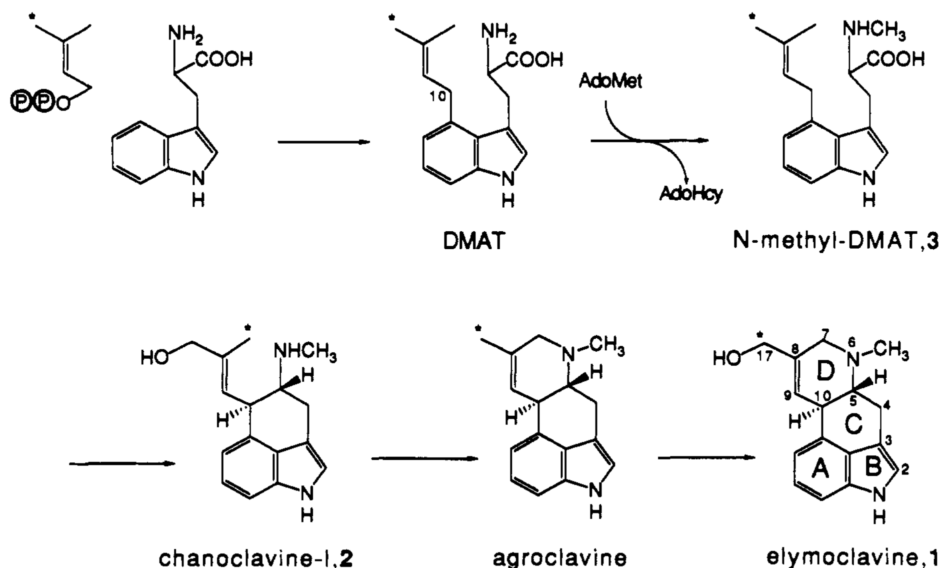
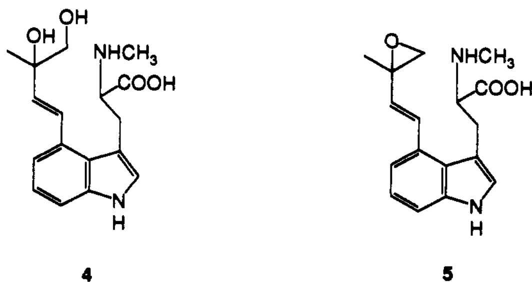
Scheme I. Biosynthesis of the Ergot Alkaloid Elymoclavine from Tryptophan and γ,γ-Dimethylallyl Pyrophosphate[a]



[a] Asterisks indicate the position of an isotopic label from C-2 of mevalonic acid.

the pattern of their incorporation revealed that neither can be an intermediate on the normal biosynthetic pathway.[9,13,14]

In light of these results, two possible structures were proposed for the active species undergoing cyclization to **2**, a vicinal diol[15] and an epoxide.[9] Modified to include the *N*-methyl group, these would be structures **4** and **5**; either one could cyclize with simultaneous decarboxylation via an S_N2' mechanism. We have previously synthesized labeled **4** and shown that it is not at all incorporated into **1**.[16] We now report results which identify one of the intermediates in the conversion of **3** into **2** and which indirectly support the intermediacy of **5**. Some of this work has been communicated in preliminary form.[17]



Results

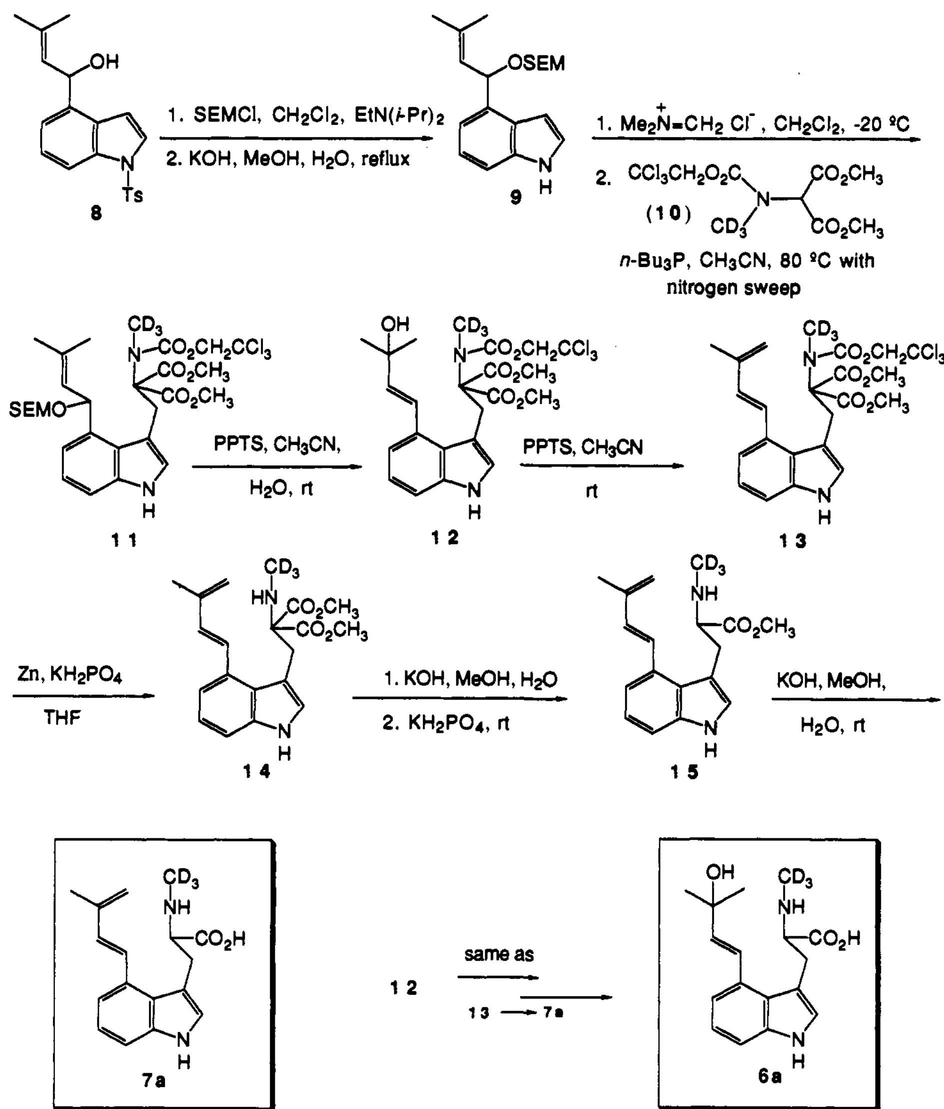
The conversion of **3** into **2** formally requires two two-electron oxidations, one to close ring C and one to hydroxylate the methyl group. The first oxidation cannot be a hydroxylation at the methyl group, on the basis of the earlier results,[9,13,14] leaving attack at the allylic–benzylic position C-10 as a likely alternative. Oxidation at that carbon may lead either to the 10-hydroxy compound or to its allylic rearrangement product, **6**. Since the latter was expected to be the more stable compound, we decided to test its role in the biosynthesis first. A plausible precursor of the epoxide, **5**, would be the diene, **7**, and on the basis of the results with **6**, this became our second target compound. For isotopic labeling we followed the same strategy as in our earlier work of installing a trideuterated methyl group on the side-chain nitrogen of the precursors.

Synthesis of Labeled Precursors 6a and 7a. The synthesis of both target compounds was accomplished by a common approach, deriving **6a** from an intermediate in the route to **7a**. The synthesis of the dienyltryptophan **7** was undertaken initially with considerable circumspection, for prior experience had taught us that 4-(1,3-butadienyl)-substituted indoles are unstable molecules, which undergo decomposition within several days even when stored at refrigerator temperatures. Thus extreme care had to be exercised in selecting a pathway to the ultimate product. In particular, it was most desirable to carry out a minimum number of synthetic operations subsequent to the generation of the 1,3-butadienyl moiety. We therefore decided to prepare a fully elaborated 3,4-disubstituted indole first in which the diene was temporarily disguised as an allylic ether, and then to process this ether by a dehydration protocol to reveal a diene intermediate which could be transformed in a small number of additional steps to **7**. Selection of functional group protection during the intermediary stages of the synthesis would have to be based upon the removability of such groups under nearly neutral or basic reaction conditions.

The successful synthesis of the labeled dienyltryptophan **7a** is depicted in Scheme II. The synthesis was accomplished starting from the indole **8**, a compound available by procedures described previously by us.[18] The hydroxyl group of **8** was protected as its SEM ether, and the *N*-tosyl group was removed by hydrolysis with potassium hydroxide.[16] Next, intermediate **9** was converted to the corresponding 4-substituted gramine derivative by reaction with *N,N*-dimethylmethyleneammonium chloride,[19] and the gramine derivative was reacted in turn with the amidomalonate **10**[16] using tri-*n*-butylphosphine as catalyst. The resulting indole **11** was then stirred with pyridinium *p*-toluenesulfonate (PPTS) to furnish the deprotected and allylically rearranged alcohol **12**.[17] Further treatment of alcohol **12** with PPTS in acetonitrile at room temperature resulted in dehydration with formation of the unstable diene **13**. Since this diene was found to decompose within two days when kept at room temperature, all of the reaction steps carried out subsequent to the preparation of **12** were performed without undue delay. The nitrogen-protecting group was now cleaved employing zinc and potassium dihydrogen phosphate. A two-step protocol entailing potassium hydroxide treatment followed

(13) Pachlatko, P. Ph.D. Dissertation No. 5481, Eidgenössische Technische Hochschule, Zürich, 1975.
(14) Plieninger, H.; Immel, H.; Wagner, C. *Abh. Dtsch. Akad. Wiss. Berlin* **1971**, 423.
(15) Abou-Chaar, G. C.; Günther, H. F.; Manuel, M. G.; Robbers, J. E.; Floss, H. G. *Lloydia* **1972**, *35*, 272.
(16) Kozikowski, A. P.; Okita, M.; Kobayashi, M.; Floss, H. G. *J. Org. Chem.* **1988**, *53*, 863.
(17) Kozikowski, A. P.; Wu, J.-P.; Shibuya, M.; Floss, H. G. *J. Am. Chem. Soc.* **1988**, *110*, 1970.
(18) Kozikowski, A. P.; Ishida, H.; Chen, Y. Y. *J. Org. Chem.* **1980**, *45*, 3350.
(19) Kozikowski, A. P.; Ishida, H. *Hetrocycles* **1980**, *14*, 55.

Scheme II. Synthesis of Prenylated Tryptophan Derivatives for Ergot Alkaloid Biosynthetic Feeding Experiments



by stirring with potassium dihydrogen phosphate yielded the mono-decarbomethoxylated product **15**. Lastly, the ester was saponified with aqueous potassium hydroxide in methanol at room temperature to furnish the desired D,L-dienyltryptophan **7a**. Surprisingly, this compound was found to be remarkably stable in comparison to diene **13**, and it was found to undergo little decomposition when kept as an NMR sample in CD_3OD for a two-week period.

The allylic alcohol **6a** was prepared by the same reaction sequence from the intermediate **12**, but the dehydration step[17] was omitted.

Feeding Experiments. The incorporation of the labeled precursors into **1** was evaluated in 50-mL replacement cultures of *Claviceps* sp., strain SD 58[20] in phosphate buffer as described earlier[16] with the modification that the filtered mycelia were resuspended and shaken for 2 h in buffer before the final filtration and suspension in the incubation buffer. This reduced considerably the amount of preformed **1** remaining in the cells. In the initial experiments the amount of mycelium in the replacement cultures was the same as in the original fermentations, i.e., one-half the mycelium from one 100-mL production culture was used for each 50-mL replacement culture. It was subsequently found that substantial reduction of the amount of mycelium gave higher enrichments in the product; hence in the feeding experiments with **7a** only 4% and 10% of the amounts of mycelium, respectively, were used per volume of buffer.

(20) Gröger, D. *Arch. Pharm.* (*Weinheim, Ger.*) **1959**, *292*, 389.

To evaluate the incorporation of **6a**, a 9-mg sample was incubated in one culture with shaking at 25 °C for two days. The alkaloids were then extracted and chromatographed on alumina, and the fraction containing **1** was analyzed by GC–MS, all as previously described.[16] The EI mass spectrum of the biosynthesized **1** (Table I), after correction for the strong M − 1 peak in **1**, showed the presence of only unlabeled and M + 3 species in a ratio corresponding to 33% specific incorporation of **6a** into **1**. A parallel experiment with L-tryptophan (5 mg), D,L-mevalonic acid (10 mg), and L-[$^{13}C^2H_3$]methionine (99% ^{13}C and ^2H, 5 mg) instead of **6a** as precursors gave 49% specific incorporation into **1**. Repetition of the experiment with a separately synthesized sample of **6a** (5 mg) gave 9% specific incorporation into **1**.

We next carried out a trapping experiment in order to probe whether **6** is also formed in cultures of *Claviceps*. To a replacement culture containing unlabeled L-tryptophan (1 mg), D,L-mevalonic acid (2 mg), and L-methionine (1 mg) was added **6a** (10 μg). After a 1-h incubation with shaking, **6a** was reisolated by filtration and 1-butanol extraction of the filtrate, methylated with diazomethane, and analyzed by GC–MS. An authentic sample of **6a** methylated in the same way showed two GC peaks of t_R 22.1 and 21.7 min, identified by their mass spectra as the methyl esters of *N*-methyl-**6a** (M^+ at m/z 333) and *N*-methyl-**7a** (M^+ at m/z 315), respectively. The GC–MS of the reisolated **6a** showed the same two peaks. The spectrum of the methyl ester of **6a** showed no dilution of the deuterium label, as evidenced by the absence of a peak at m/z 116, the unlabeled counterpart of the base peak of the deuterated species at m/z 119. This fragment

Table I. Incorporation of Labeled Precursors into Elymoclavine by Replacement Cultures of *Claviceps* sp., Strain SD58

expt no.	sample	rel int of ion[a]							
		M − 1 253[b]	M 254[b]	M + 1 255[b]	M + 2 256[b]	M + 3 257[b]	M + 4 258[b]	M + 5 259[b]	% sp incorporation
1	unlabeled **1**	100	50.4	7.4	0.5				
2	**1** from **6a** (9 mg)	100	57.6	10.3	48.3	26.1	4.2		32.6
3	control: **1** from $^{13}C^{2}H_3$-methionine (5 mg)	100	55.8	16.9	2.2	96.8	49.8	7.9	49.2
4	**1** from **6a** (5 mg)	100	89.4	14.6	10.4	6.1	0.6		9.4

expt no.	sample	rel int of ion[a]							
		M − 1 325[b]	M 326[b]	M + 1 327[b]	M + 2 328[b]	M + 3 329[b]	M + 4 330[b]	M + 5 331[b]	% sp incorporation
5	**1** from **7a** (2 mg), 4% mycelia	16.8	10.4	3.2	100	51.2	13.9	2.7	85.6
6	control: **1** from $^{13}C^{2}H_3$-methionine (5 mg), 4% mycelia	88.2	47.3	13.5	5.2	100	53.2	12.5	53.1
7	**1** from **7a** (2 mg), 10% mycelia	23.8	14.2	3.2	100	55.8	14.2	2.7	80.8
8	control: **1** from $^{13}C^{2}H_3$-methionine, 10% mycelia	100	46.3	13.2	1.4	32.9	15.7	2.7	24.8

[a] Samples of **1** biosynthesized from stable-isotope-labeled precursors were analyzed by GC–MS either as such (M = 254) or as their TMS derivatives (M = 326). [b] *m/z*. [c] Specific incorporation = 100 × (enrichment of product/enrichment of precursor) [%].

arises from loss of the indole moiety by benzylic cleavage and corresponds to the amino acid side chain less C-3. The spectrum of the t_R 21.7 min peak, however, indicated dilution of the labeled **7a** with 19% unlabeled material (intensity ratio *m/z* 116:119 = 27:113). Hence, while there is no evidence for the presence of **6** in the culture, the presence of **7** is clearly indicated. This was confirmed by working up replacement cultures (2 × 100 mL) incubated for 3 h with buffer without addition of **6a** in the same way. After methylation with excess diazomethane, GC–MS with selective ion monitoring demonstrated the presence of a peak at t_R 21.8 min corresponding to the methyl ester of the *N*-methyl derivative of **7**.

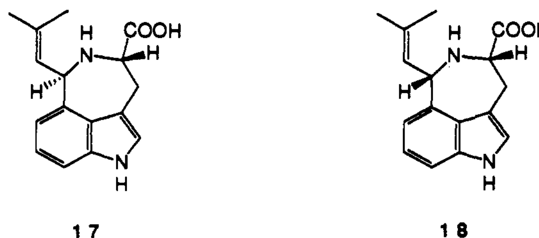
The precursor role of **7** was further probed by incubating synthetic **7a** (2 mg) with 25-mL replacement cultures of *Claviceps* sp., strain SD 58, containing either 4% or 10% of the mycelium of the corresponding volume of production culture. With each experimental culture a control containing L-tryptophan (1 mg), D,L-mevalonic acid (2 mg), and L-[$^{13}C^{2}H_3$]methionine (1 mg) was run. Following extraction and chromatographic separation of the alkaloids, the **1** in this case was derivatized by silylation prior to GC–MS analysis. As shown in Table I, the silyl derivative of **1** showed 81% enrichment in the experiment with 10% mycelium (control 25%) and 86% enrichment in the experiment with 4% mycelium (control 53%).

Discussion

The experiments described above provide strong evidence for a role of **7** as an intermediate in the biosynthesis of ergot alkaloids. It meets the two most important criteria of a biosynthetic intermediate: The trapping experiment and the detection of **7** in the culture fluid demonstrate that the compound is formed in *Claviceps*; and the high efficiency of conversion of **7a** into **1**, 81–86%, leaves little doubt about its specific precursor role. On the other hand, although **6a** was also appreciably incorporated into **1**, 9–33%, the failure to detect formation of **6** in the trapping experiment under conditions of formation of **7** strongly suggests that **6** is not on the normal biosynthetic pathway to the ergot alkaloids. More likely, **6** is channeled into the pathway by dehydration to the true intermediate, **7**. Whether this conversion is purely nonenzymatic, as demonstrated during the derivatization of authentic material, or enzyme-catalyzed cannot be decided from the available data.

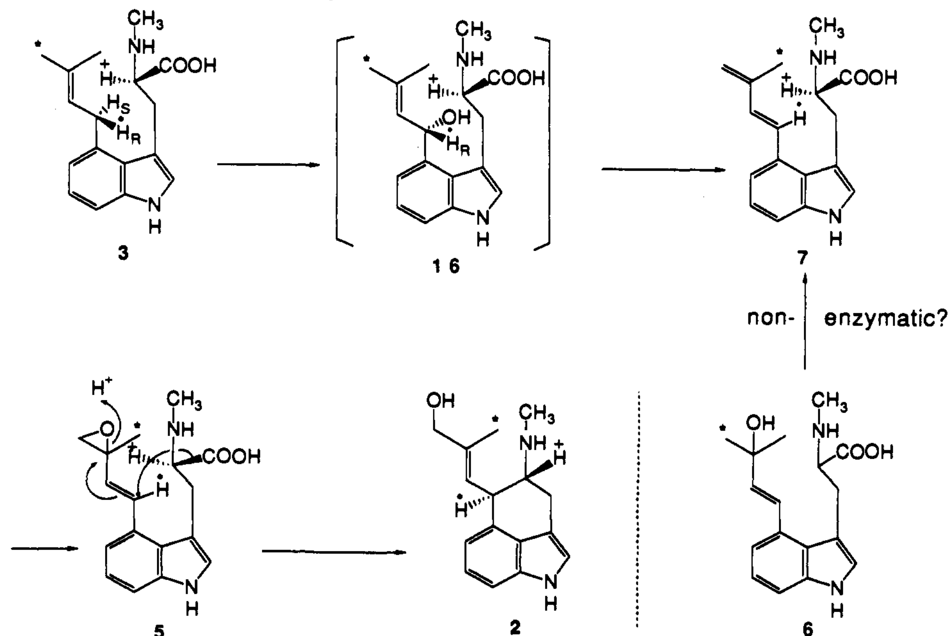
Several mechanisms can be envisioned for the oxidative conversion of **7** into **2**. The compound may first undergo an oxidative decarboxylation to give the 5,6-imine; this species could then cyclize by a process, initiated by protonation at N-6, in which the C ring is closed by nucleophilic attack of C-10 on C-5. The reaction sequence would be terminated by addition of OH^- to the terminal methylene group of the isoprenoid side chain to give **2**. This mechanism can be excluded because it would require that the oxygen of **2** come from water, whereas it has been shown[10] that molecular oxygen is the source of this oxygen atom. The hypothetical diene–5,6-imine could conceivably also cyclize directly to agroclavine in a hetero-Diels–Alder reaction. However, the ample evidence pointing to the tricyclic **2** as an intermediate in the pathway[1,2] argues strongly against such a mechanism. This leaves as the most plausible route conversion of **7** to the epoxide **5**, which can then cyclize in a process involving decarboxylation and attack of the resulting C-5 anion on C-10 followed by epoxide ring opening to give **2** (Scheme III). The decarboxylation may be promoted by formation of an iminium ion between N-6 and a carbonyl group in the enzyme active site, although in view of the steric constraints imposed by a methylated amino group, this carbonyl compound in the enzyme is not likely to be the common decarboxylation cofactor, pyridoxal phosphate.[4,10] Whether decarboxylation is concerted with ring closure, as seems most plausible, or occurs as a separate prior step remains open. However, if the latter were the case, the hydrogen introduced in the decarboxylation must also be the one removed from C-5 in the subsequent carbanion formation, since the original H-5 of L-tryptophan is completely retained throughout the biosynthesis.[5] In either case, bond formation must occur on the *Re* face at C-10 of **5** (or its decarboxylation product), which must approach C-5 on the face opposite the departing carboxyl group. This follows from the configurations of substrate and product and from the retention of H-5.

The epoxide **5**, in its unmethylated form, had been suggested earlier by Arigoni and co-workers as a plausible species to undergo cyclization to close ring C. However, its formation was postulated to proceed directly from DMAT via a hydroperoxide intermediate.[13] The present work points to a different origin, by epoxidation of the diene **7**. The latter, in turn, is apparently not generated via **6**, because this compound, although incorporated into **1**, does not seem to be formed by the ergot fungus. Quite plausibly, **7** may be formed from **3** by hydroxylation at the benzylic carbon of the isoprenoid moiety followed by a 1,4-dehydration (Scheme III). Whether the initial hydroxylation product, compound **16**, is stable enough to have an appreciable lifetime or even to be isolated is not clear. In the synthetic work it has not been possible to isolate the unrearranged alcohol expected from deprotection of an oxygen function at that position, e.g., in **11** (Scheme II). Particularly relevant in this context are the clavicipitic acids, a pair of diastereomeric compounds, **17** and **18**,



formed in ergot cultures in which alkaloid synthesis is inhibited with ethionine and detected in small quantities also in normal cultures of *Claviceps* sp., strain SD 58.[21] These compounds are

Scheme III. Proposed Mechanism of Formation of Ring C of Ergot Alkaloids



dead-end side products of the pathway, which are not convertible into the normal alkaloids, e.g., **1**.[22] Their structures,[22,23] presumed to be epimeric at C-10, suggest that they may be formed non-enzymatically by cyclization of a 10-hydroxylated DMAT. Such a species may be formed by "erroneous" 10-hydroxylation of DMAT, particularly when DMAT accumulates due to inhibition of the subsequent methylation step, by the enzyme normally hydroxylating **3**.[22]

The results presented here thus shed considerable light on the mode of ring C formation, the least understood part of the ergot alkaloid biosynthetic pathway. They lend strong credence to the sequence of events depicted in Scheme III for this process. However, confirmation at the enzymatic level will be necessary to validate this hypothetical pathway for the conversion of **3** into **2**.

Experimental Section

General Materials and Methods. THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. Benzene and toluene were distilled from CaH_2 prior to use. CH_2Cl_2 was dried by passage through a column of activity I neutral alumina and stored over 4-Å molecular sieves. Solvents used for chromatography were purchased in 50-gal drums, redistilled in an all-glass apparatus, and stored in glass bottles. Silica gel 60 (Merck, 70–230 mesh, or 230–400 mesh for flash chromatography) was used for column chromatography. TLC was performed on Merck silica gel 60F-254 (0.25 mm, precoated on glass). Other reagents were used as supplied or purified as noted. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75.47 MHz on a Bruker AC-300 NMR spectrometer, respectively, with $CDCl_3$ or C_6D_6 as the internal standard. Infrared spectra were obtained on a Mattson 2020 FT-IR; low-resolution mass spectra, on a Hewlett-Packard 5971A spectrometer; and high-resolution mass spectra, on a VG 70-SE double focusing magnetic sector spectrometer. Elemental analyses were obtained from Oneida Research Services, Inc., Whitesboro, NY. GC–MS analyses were carried out on a Hewlett-Packard 5790/5970A gas chromatograph–mass spectrometer as described previously.[10]

Synthesis of Labeled Precursors. (±)-1-[(4-Methylphenyl)sulfonyl]-α-(2methyl-1-propenyl)-1*H*-indole-4-methanol (8). Under nitrogen at room temperature, 1-bromo-2-methylpropene (1.7 mL, 16 mmol) was added to a mixture of magnesium turnings (0.6 g, 24.7 mmol) and several drops of 1,2-dibromoethane in THF (5 mL). The reaction was slightly exothermic, and the mixture was heated at 50 °C for 1 h. The resulting brownish mixture was then cooled to −10 °C in an ice–salt bath and diluted with 5 mL of THF. A solution of *N*-tosylindole-4-carboxaldehyde (1.58 g, 5.3 mmol) in 5 mL of THF was added slowly. The reaction mixture was stirred at −10 °C for 1 h, quenched with saturated ammonium chloride, and extracted with ether (3 × 10 mL). The combined ethereal extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel with 25% ethyl acetate–hexane as eluent to afford alcohol **8** (1.81 g) in 96% yield: IR (neat) 3546, 3399, 3121, 2977, 2917, 1734, 1670, 1597, 1527, 1424, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88–7.91 (m, 1 H), 7.76 (d, 1 H, J = 8.4 Hz), 7.57 (d, 1 H, J = 3.7 Hz), 7.20–7.26 (m, 4 H), 6.84 (d, 1 H, J = 3.6 Hz), 5.70 (d, 1 H, J = 9.0 Hz), 5.50 (d, 1 H, J = 8.9 Hz), 2.34 (s, 3 H), 1.83 (s, 3 H), 1.73 (s, 3 H); mass spectrum, m/z 355 (M^+), 377, 322, 298, 284, 272, 258, 200, 182, 167 (base); HRMS calcd for $C_{20}H_{21}NO_3S$ 355.1242, found 355.1242.

(±)-1-[(4-Methylphenyl)sulfonyl]-4-[3-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-butenyl]-1*H*-indole. To a solution of alcohol **8** (0.48 g, 1.35 mmol) in dry methylene chloride (15 mL) was added *N,N*-diisopropylethylamine (1.5 mL, 8.6 mmol) followed by SEM-Cl (1 mL, 5.5 mmol). The solution was heated at 35–40 °C for 3 h. The mixture was then cooled to room temperature, diluted with 50 mL of methylene chloride, washed with brine, dried with magnesium sulfate, and concentrated. Chromatography of the residue on silica gel with 5% ethyl acetate–hexane as eluent gave 0.63 g (96%) of the title compound: IR (neat) 3121, 1597, 1527, 1480, 1424, 1374, 1021, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.89 (d, 1 H, J = 7.4 Hz), 7.78 (d, 2 H, J = 8.3 Hz), 7.57 (d, 1 H, J = 3.7 Hz), 7.21–7.29 (m, 4 H), 6.84 (d, 1 H, J = 3.6 Hz), 5.64 (d, 1 H, J = 9.3 Hz), 5.44 (d, 1 H, J = 9.4 Hz), 4.71 (d, 1 H, J = 6.9 Hz), 4.55 (d, 1 H, J = 6.9 Hz), 3.51–3.68 (m, 2 H), 2.35 (s, 3 H), 1.82 (s, 3 H), 1.72 (s, 3 H), 0.87–0.92 (m, 2 H), −0.03 (s, 9 H); mass spectrum, m/z 412 ($M^+ - SiMe_3$), 384, 339, 184, 155.

(±)-4-[3-Methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-butenyl]-1*H*-indole (9). A 5% solution of KOH in CH_3OH–H_2O (9:1, 10 mL) was added to a solution of the above indole (2.19 g) in THF (10 mL) at room temperature. The solution was refluxed for 7 h. After removal of the solvent under reduced pressure, the residue was extracted with ether, and the ether layer was washed with brine, dried over magnesium sulfate, and evaporated. Purification of the residue by chromatography on silica gel with 10% ethyl acetate–hexane as eluent gave 1.27 g (85%) of the deprotected indole **9**: IR (neat) 3413, 3326, 3045, 2952, 1693, 1613, 1584, 1156, 1096, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (br, s, 1 H), 7.32 (d, 2 H, J = 6.7 Hz), 7.13–7.21 (m, 3 H), 6.72 (m, 1 H), 5.76 (d, 1 H, J = 9.3 Hz), 5.62 (d, 1 H, J = 9.2 Hz), 4.76 (d, 1 H, J = 7.0 Hz), 4.64 (d, 1 H, J = 6.8 Hz), 3.56–3.76 (m, 2 H), 1.88 (s, 3 H), 1.83 (s, 3 H), 1.74 (s, 3 H), 0.92–0.97 (m, 2 H), −0.02 (s, 9 H); mass spectrum, m/z 331 (M^+), 258, 184 (base), 163; HRMS calcd for $C_{19}H_{29}NO_2Si$ 331.1968, found 331.1968.

Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.84; H, 8.82; N, 4.22. Found: C, 69.18; H, 8.95; N, 4.13.

(±)-*N,N*-Dimethyl-[4-[3-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-butenyl]-1*H*-indol-3-yl]methylamine. To a solution of indole **9**

(21) Robbers, J. E.; Floss, H. G. *Tetrahedron Lett.* **1969**, 1857.
(22) Robbers, J. E.; Otsuka, H.; Floss, H. G.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1117.
(23) King, G. S.; Mantle, P. G.; Szczyrbak, C. A.; Waight, E. S. *Tetrahedron Lett.* **1973**, 215; King, G. S.; Waight, E. S.; Mantle, P. G.; Szczyrbak, C. A. *J. Chem. Soc., Perkin Trans 1* **1977**, 2099.

(0.447 g, 1.35 mmol) in dry methylene chloride (25 mL) at −20 °C was added *N,N*-dimethylmethyleneammonium chloride (0.5 g, 5.3 mmol). After being stirred for 1 h in a stoppered flask, the reaction mixture was treated with a sufficient amount of 5% NaOH solution to make the aqueous phase basic, and the resulting mixture was extracted with methylene chloride. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by chromatography ($CHCl_3$–CH_3OH–NH_4OH, 94:5:1) on silica gel to afford 0.43 g (93%) of the title gramine derivative as a slightly brownish oil: IR (neat) 3409, 3314, 3056, 2948, 2811, 2768, 1667, 1619, 1551, 1441, 1250, 1017, 835, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06 (br, s, 1 H), 7.11–7.33 (m, 4 H), 6.37 (d, 1 H, J = 8.7 Hz), 5.59 (d, 1 H, J = 8.8 Hz), 4.75 (d, 1 H, J = 6.8 Hz), 4.68 (d, 1 H, J = 6.8 Hz), 3.56–3.75 (m, 2 H), 2.26 (s, 6 H), 1.90 (s, 3 H), 1.76 (s, 3 H), 0.90–0.96 (m, 2 H), −0.01 (s, 9 H); mass spectrum, m/z 343 (M^+), 313, 285, 270, 196, 180, 154, 73 (base); HRMS calcd for $C_{20}H_{29}O_2NSi$ 343.1968, found 343.1967.

(±)-2-[Methyl-*d*$_3$-[(2,2,2-trichloroethoxy)carbonyl]amino]-2-[[4-[3-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]-2-butenyl]-1*H*-indol-3-yl]methyl]propanedioic Acid Dimethyl Ester (11). To a solution of the above gramine derivative (1.06 g, 2.73 mmol) and amidomalonate **10** (1.39 g, 4.10 mmol) in dry acetonitrile (40 mL) at 78 °C was added tri-*n*-butylphosphine (0.14 mL, 0.55 mmol) with vigorous nitrogen gas bubbling. The reaction mixture was stirred at 78 °C with continuous nitrogen bubbling for 20 h, cooled to 0 °C, stirred at 0 °C for 30 min, and concentrated. The residue was chromatographed with 17% ethyl acetate–hexane on silica gel to give compound **11** (0.86 g, 46%) as a colorless thick oil: IR (neat) 3400, 2955, 1747, 1730, 1435, 1413, 1321, 1091, 837, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (br s, 1 H), 7.18–7.29 (m, 4 H), 5.97 (d, 1 H, J = 8.6 Hz), 5.49 (d, 1 H, J = 8.6 Hz), 4.78 (s, 2 H), 4.70 (d, 1 H, J = 7.0 Hz), 4.61 (d, 1 H, J = 7.0 Hz), 3.95 (d, 1 H, J = 14 Hz), 3.82 (s, 6 H), 3.71 (s, 2 H), 3.56 (dd, 1 H, J = 9.6, 17.8 Hz), 1.86 (s, 3 H), 1.75 (s, 3 H), 0.93 (m, 2 H), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 168.8, 166.5, 155.2, 137.5, 136.5, 134.8, 126.3, 124.9, 123.9, 122.3, 118.7, 110.7, 108.9, 95.1, 91.8, 75.7, 75.5, 71.3, 65.4, 62.2, 53.2, 32.5, 18.4, 3.0.

Anal. Calcd for unlabeled compound $C_{29}H_{41}Cl_3N_2O_8Si$: C, 51.22; H, 6.08; N, 4.12. Found: C, 50.91; H, 6.18; N, 4.09.

(*E*)-2-[[4-(3-Hydroxy-3-methyl-1-butenyl)-1*H*-indol-3-yl]methyl]-2-[methyl-*d*$_3$-[(2,2,2-trichloroethoxy)carbonyl]amino]propanedioic Acid Dimethyl Ester (12). The indole derivative **11** (0.92 g, 1.35 mmol) was dissolved in acetonitrile (12 mL) and H_2O (2.4 mL) and stirred under argon in the presence of a catalytic amount of PPTS for 4 h. The mixture was then extracted with ethyl acetate (20 mL), and the extract was washed with brine, dried over magnesium sulfate, and concentrated. Chromatography of the residue on silica gel with 33% ethyl acetate–hexane gave the desired compound **12** (0.51 g, 68%) as a white foam: IR (neat) 3398, 3051, 2972, 1745, 1714, 910, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (br s, 1 H), 7.08–7.29 (m, 5 H), 6.18 (d, 1 H, J = 15.8 Hz), 4.74 (s, 2 H), 4.01 (s, 2 H), 3.69 (s, 6 H), 2.30 (br s, 1 H), 1.46 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.3, 155.4, 140.1, 136.2, 131.6, 125.4, 125.3, 124.3, 122.2, 118.8, 110.6, 109.5, 95.1, 75.6, 73.8, 71.0, 53.2, 33.0, 31.5, 29.8; mass spectrum, m/z 553 (M^+ + 2), 537 (M^+ − 18), 535; HRMS calcd for $C_{23}H_{24}Cl_3D_3N_2O_7$ 551.1067, found 551.1080.

(*E*)-2-[[4-(3-Methyl-1,3-butadienyl)-1*H*-indol-3-yl]methyl]-2-[methyl-*d*$_3$-[(2,2,2-trichloroethoxy)carbonyl]amino]propanedioic Acid Dimethyl Ester (13). The indole derivative **12** (0.352 g, 0.637 mmol) was dissolved in acetonitrile (20 mL) and stirred at room temperature in the presence of a catalytic amount of PPTS for 3 h. After concentration, the residual oil was submitted to flash chromatography over silica gel using 20% ethyl acetate–hexane as eluent to give 0.229 g (67%) of compound **13**: IR (thin film) 3399, 2953, 1746, 1713, 1396, 1090, 1057, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (s, 1 H), 7.30 (d, 1 H, J = 16.1 Hz), 7.11–7.24 (m, 4 H), 6.79 (d, 1 H, J = 16.1 Hz), 5.11 (d, 2 H, J = 10.8 Hz), 4.71 (s, 2 H), 4.00 (s, 2 H), 3.71 (s, 6 H), 2.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.3, 155.3, 142.6, 136.4, 133.4, 131.6, 127.4, 125.2, 124.7, 122.2, 118.3, 117.1, 110.8, 109.3, 95.2, 75.5, 73.4, 53.1, 32.0, 18.7; mass spectrum, m/z 539 (M^+, 3 − ^{37}Cl), 537, 535; HRMS calcd for $C_{23}H_{22}{}^{35}Cl_3D_3N_2O_6$ 533.0962, found 533.0938.

(*E*)-2-(Methyl-*d*$_3$-amino)-2-[4-(3-methyl-1,3-butadienyl)-1*H*-indol-3-yl]propanedioic Acid Dimethyl Ester (14). To a vigorously stirred mixture of zinc dust (0.6 g) and compound **13** (0.112 g, 0.210 mmol) in THF (6 mL) was added 1 mL of a 1 M aqueous solution of KH_2PO_4. After being stirred for 17 h, the mixture was filtered, and the residue was washed thoroughly with THF. The filtrate was dried over $MgSO_4$. After concentration, the residual oil was submitted to flash chromatography over silica gel using 33% ethyl acetate–hexane as eluent to give 66 mg (88%) of compound **14**: IR (thin film) 3403, 2951, 1734, 1435, 1242, 1209, 966, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (s, 1 H), 7.56 (d, 1 H, J = 15.8 Hz), 7.09 (m, 4 H), 6.82 (d, 1 H, J = 15.8 Hz), 5.10 (d, 2 H, J = 12.1 Hz), 3.75 (s, 2 H), 3.68 (s, 6 H), 2.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.1, 142.9, 136.4, 132.9, 131.8, 128.2, 125.3, 124.0, 122.0, 117.5, 116.5, 110.5, 109.8, 71.8, 52.7, 28.8, 18.8; mass spectrum, m/z 360 (MH^+), 304, 197, 157, 155, 130, 126; HRMS calcd for $C_{20}H_{21}D_3N_2O_4$ 359.1919, found 360.2001 (MH^+).

(*E*)-*N*-(Methyl-*d*$_3$)-4-(3-methyl-1,3-butadienyl)-DL-tryptophan Methyl Ester (15). A 5% solution of KOH in CH_3OH–H_2O (9:1, 0.4 mL) was added dropwise to a solution of diester **14** (24.5 mg, 0.069 mmol) in THF (0.2 mL) at 0 °C. The solution was allowed to warm to room temperature and kept at this temperature for 18 h. After removal of most of the solvent under reduced pressure, H_2O (0.5 mL) was added, and the mixture was neutralized at 0 °C by adding sufficient KH_2PO_4 (1 M) to cause the solution to become cloudy. Additional THF (0.5 mL) was added, and the mixture was stirred for 1.5 h. The solution was extracted with ethyl acetate and dried over $MgSO_4$. After concentration, the residual oil was submitted to flash chromatography over silica gel using ethyl acetate as eluent to give 14.5 mg (70%) of compound **15**: IR (thin film) 3402, 3310, 3153, 3055, 2949, 2856, 1732, 1448, 1342, 1211, 962, 833, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (s, 1 H), 7.35 (d, 1 H, J = 15.8 Hz), 7.02–7.31 (m, 4 H), 6.89 (d, 1 H, J = 15.8 Hz), 5.12 (d, 2 H, J = 14.0 Hz), 3.68 (s, 3 H), 3.58 (dd, 1 H, J = 8.2, 6.1 Hz), 3.37 (dd, 1 H, J = 14.5, 6.1 Hz), 3.13 (dd, 1 H, J = 14.5, 8.2 Hz), 2.09 (s, 3 H), 1.56 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 175.4, 142.6, 137.4, 133.5, 131.7, 127.1, 124.6, 124.4, 122.4, 117.3, 111.7, 110.6, 64.1, 51.7, 31.8, 18.6; mass spectrum, m/z 301 (M^+), 246; HRMS calcd for $C_{18}H_{19}D_3N_2O_2$ 301.1865, found 301.1865.

(*E*)-*N*-(Methyl-*d*$_3$)-4-(3-methyl-1,3-butadienyl)-DL-tryptophan (7a). A 5% solution of KOH in CH_3OH–H_2O (9:1, 0.2 mL) was added dropwise to a solution of compound **15** (18 mg, 0.060 mmol) in THF (0.3 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 6 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel with 1:1 MeOH–EtOAc as eluent to afford 16 mg (93%) of the desired product **7a**: IR (KBr) 3408, 3190, 2957, 1626, 1444, 1404, 1334, 1118, 960, 752 cm^{-1}; ^1H NMR (CD_3OD) δ 7.35 (d, 1 H, J = 15.6 Hz), 7.07–7.30 (m, 4 H), 6.86 (d, 1 H, J = 15.6 Hz), 5.08 (d, 2 H, J = 14.7 Hz), 3.79 (m, 2 H), 3.23 (m, 1 H), 2.12 (s, 3 H); ^{13}C NMR (CD_3OD) δ 173.1, 144.3, 139.4, 134.6, 132.4, 128.6, 126.2, 125.7, 123.2, 118.1, 117.2, 112.1, 110.0, 65.7, 33.6, 23.1, 19.2; mass spectrum, m/z 312 (MH^+ + 23), 302, 288, 256, 243; HRMS calcd for $C_{17}H_{17}D_3N_2O_2$ 287.1709, found 288.1809 (MH^+).

(*E*)-*N*-(Methyl-*d*$_3$)-4-(3-hydroxy-3-methyl-1-butenyl)-DL-tryptophan (6a). The preparation of compound **6a** followed steps identical to those used in the preparation of **7a** with the exception that the PPTS-promoted dehydration step (i.e., **12** to **13**) was omitted. Complete spectral data for the nondeuterated compound, **6**, together with the ^1H NMR data of the deuterated product, **6a**, follow: IR (KBr) 3500–2000 (strong, broad), 2969, 1628, 1395, 1354, 1132, 1048, 967, 750 cm^{-1}; ^1H NMR (CD_3OD) δ 7.28 (d, 1 H, J = 15.7 Hz), 7.17 (d, 1 H, J = 7.3 Hz), 7.09 (s, 1 H), 6.90–7.02 (m, 2 H), 6.12 (d, 1 H, J = 15.7 Hz), 3.64–3.70 (m, 2 H), 3.04 (dd, 1 H, J = 11.3, 16.2 Hz), 2.35 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H); FABMS 303 (M^+ + 1), 285, 217 (base), 198, 181, 126, 109; ^1H NMR of d_3 product (CD_3OD) δ 7.28 (d, 1 H, J = 15.7 Hz), 7.17 (d, 1 H, J = 7.3 Hz), 7.09 (s, 1 H), 6.90–7.02 (m, 2 H), 6.12 (d, 1 H, J = 15.7 Hz), 3.64–3.70 (m, 2 H), 3.04 (dd, 1 H, J = 11.3, 16.2 Hz), 1.32 (s, 3 H), 1.31 (s, 3 H).

Feeding Experiments. *Claviceps* sp., strain SD 58,[20] was grown for 5 days in shake culture at 25 °C in 500-mL Erlenmeyer flasks containing 100 mL of medium NL 406.[24] The cultures were then filtered and washed with water aseptically. The mycelia were resuspended in 100 mL of 1/15 M phosphate buffer, pH 7.3, and placed back on the shaker for 2–3 h. The mycelia were then again filtered, washed, and resuspended in 1/15 M phosphate buffer, pH 7.3. For most experiments the mycelium from one culture was distributed over two 250-mL Erlenmeyer flasks, each containing 50 mL of buffer. In the feeding experiments with **7a** the original mycelia were shaken with buffer for 12 h, and then 1/100 or 1/25 of the mycelia from one 100-mL culture was placed in each 125-mL flask containing 25 mL of buffer. The replacement cultures were incubated with the labeled precursors for 2 days at 25 °C with rotary shaking at 300 rpm (3/4-in. stroke) and then filtered. The alkaloids were extracted from the culture filtrate, purified, and analyzed by GC–MS as described before.[16] In the feeding experiments with **7a** and the corresponding controls the crude alkaloid extracts were silylated with SIGMA-SIL-A, following the manufacturer's instructions, prior to GC–MS analysis.

In the trapping experiment a 50-mL replacement culture was incubated for 1 h with 1 mg of L-tryptophan, 1 mg of L-methionine, 2 mg of D,L-mevalonic acid, and 10 μg of **6a**. The culture was then filtered, and the filtrate was extracted with 1-butanol. The extract was evaporated

(24) Floss, H. G.; Gröger, D. *Z. Naturforsch.* **1963**, *18B*, 519.

to dryness, and the residue was taken up in a small volume of methanol and treated with diazomethane in ether. Following evaporation of the solvent, the residue was subjected to GC-MS analysis.

The natural occurrence of **7** was demonstrated by incubating the washed mycelia from two 100-mL cultures of *Claviceps* sp., SD 58 in 2 × 100 mL 1/15 M phosphate buffer, pH 7.3, with shaking for 3 h, removing the mycelia by filtration, and extracting the filtrate with 1-butanol. The residue from the butanol extract was then treated with excess diazomethane in ether and analyzed by GC-MS. Selective ion monitoring at m/z 116 revealed the presence of a peak at t_R 21.8 min corresponding to **7**: mass spectrum, m/z (rel. intensity, %) 312 (24), 253 (8), 196 (71), 181 (42), 168 (46), 116 (100).

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Synthesis, Reactions, and Crystal Structure of a Stable 10-I-4 Periodonium Ion[1a]

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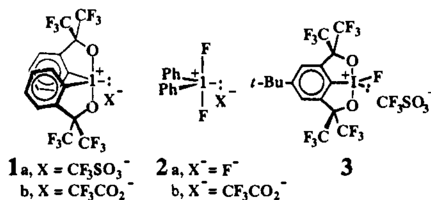
Abstract: The structure of the 10-I-4 periodonium ion of bis[α,α-bis(trifluoromethyl)benzenemethanolato(2−)-C^2,O^α]iodine(1+) triflate, salt **1a**, was confirmed by an X-ray crystallographic structure determination. The periodonium ion of **1a** was the first example of a stable cationic 10-I-4 species lacking fluorine ligands. In contrast to other periodonium ions, that of **1a** is not hydrolyzed by atmospheric moisture nor by water in neutral or acidic media. It does not react with weak nucleophiles such as pyridine or methanol. The unreactivity of **1a** is attributed to the stabilizing effects of its spirobicyclic ligand system with electronegative apical oxygen ligands and electropositive equatorial carbon ligands designed to stabilize a pseudo-trigonal-bipyramidal hypervalent species. The periodonium ion of **1a** reacts with stronger nucleophiles by attack at iodine. Treatment of the 10-I-3 tetra-*n*-butylammonium 2-[3,3-bis(trifluoromethyl)-1,2-benziodoxol-1(3H)-yl]-α,α-bis(trifluoromethyl)-benzenemethanolate (**6**) with bromine gave the 12-I-5 bis[α,α-bis(trifluoromethyl)benzenemethanolato(2−)-C^2,O^α]bromoiodine (**8b**), the first example of a stable 12-I-5 bromoperiodinane. Treatment of alkoxydiaryliodinane **6** with chlorine gave 12-I-5 chloroperiodinane **8a**. Treatment of **8b** with trifluoromethanesulfonic (triflic) anhydride gave the very stable 10-I-4 periodonium salt **1a**. Treatment of **8b** with trifluoroacetic acid gave nearly equal amounts of iodinane **9** and 10-I-4 periodonium trifluoroacetate **1b**, with oxidation of the bromide to bromine. Reaction with excess hydroxide ion is postulated to produce the 12-I-5 periodinanide oxide anion **10a**. Reaction with excess *tert*-butylamine provides the analogous 12-I-5 adduct **11a**. Reaction with phenyllithium gives the 10-I-4 adduct **12**, isolable as a crystalline solid. Addition of triflic acid to a solution of **10a**, **11a**, or **12** regenerates the periodonium ion of **1a**.

Introduction

Prior to the synthesis and isolation of **1a**,[2] the periodonium ion of **2a,b**[3] was the only reported isolable pseudo-trigonal-bipyramidal (Ψ-TBP) 10-I-4 organoiodine species. The highly reactive inorganic salt $IF_4^+SbF_6^-$ was isolated in 1950,[4] and its structure was determined by X-ray crystallography.[5] Since the first report of **1a**,[2] periodonium salt **3** and related species stabilized by this tridentate ligand have been isolated.[6] Other less stable periodonium ions such as $C_6F_5IF_3^+$ have been observed in solution.



(1) (a) The *N*-X-*L* system is applicable when *N* electrons are involved in the bonding of *L* ligands to main group element X: Perkins, C. W.; Martin, J. C.; Arduengo, A. J., III; Lau, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753. (b) Current address of J.C.M.: 5031 Lakeview Dr., Nashville, TN 37220.

(2) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 902.

(3) Lyalin, V. V.; Ordu, V. V.; Olekseeva, L. A.; Yagupolski, L. M. *J. Org. Chem. USSR* (*Engl. Transl.*) **1972**, *8*, 215.

(4) Woolf, A. A. *J. Chem. Soc.* **1950**, 3678.

(5) Gibler, D. D. *Nucl. Sci. Abstr.* **1973**, *28*, 26892.

(6) Nguyen, T. T. Ph.D. Thesis, University of Illinois, 1982. Weclas-Henderson, L.; Nguyen, T. T.; Hayes, R. A.; Martin, J. C. *J. Org. Chem.* **1991**, *56*, 6565.

(7) Bardin, V. V.; Furin, G. G.; Yakobson, G. G. *Zh. Org. Khim.* **1980**, *16*, 1256.

The study of periodonium ions (10-I-4 species) may be approached from either of two important avenues. Periodonium ions may be viewed in the context of the study of high-coordinate iodine species[8] or in the more general setting of the study of hypervalent 10-X-4 species in which X is a nonmetal.[9] The study of this type of organo-nonmetallic[9b] compound has attracted much attention in recent years. This paper uses both approaches.

Experimental Section

General Procedures. Chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard for ^1H and ^{13}C NMR spectra and $CFCl_3$ as an internal standard for ^{19}F NMR spectra. Elemental analysis values were within 0.4% of calculated values for the indicated elements, unless otherwise noted. The X-ray crystallographic structure determination was done by Dr. Scott Wilson of the X-ray Crystallography Laboratory of the University of Illinois at Urbana-Champaign.

Tetrabutylammonium 2-[3,3-Bis(trifluoromethyl)-3*H*-1,2-benziodoxol-1-yl]-α,α-bis(trifluoromethyl)benzenemethanolate (6). A solution of chloroiodinane **5**[9a] (40.5 g, 0.102 mol) in THF (80 mL) was slowly added to a solution of dilithio species **4**[9a] (0.1 mol) in hexane (95 mL), THF (16 mL), and tetramethylethylenediamine (TMEDA, 3 mL) at 0 °C over a 45-min period. The solvent was removed under vacuum to give a viscous brown oil. Addition of 20 mL of 12 N HCl to the oil gave vigorous bubbling. The mixture was diluted with CH_2Cl_2 and extracted

(8) (a) For reviews, see: Banks, D. F. *Chem. Rev.* **1966**, *66*, 243. (b) Koser, G. F. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons Ltd.: New York, 1983; Chapter 18.

(9) (a) Perozzi, E. F.; Michalak, R. S.; Figuly, G. D.; Stevenson, W. H., III; Dess, D. B.; Ross, M. R.; Martin, J. C. *J. Org. Chem.* **1981**, *46*, 1049. (b) Martin, J. C. *Science* **1983**, *221*, 1049.

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