The reaction was allowed to stir overnight at room temperature and then was quenched with water (50 mL). The mixture was partitioned between diethyl ether and water (200 mL), and the resulting organic layer was washed with additional water (3 × 100 mL) and with brine (3 × 100 mL). The organic extract was dried and evaporated to yield the crude diphenylphosphine oxide *Z* olefin **6**.

Acetate **6a** was purified by Kugelrohr distillation, bp 230 °C (1.0 mm), to yield 18.5 g (45 mmol, 90%) as a yellow oil: NMR 7.30–8.10 (m, 10 H), 5.20–5.50 (m, 2 H), 4.10 (t, 2 H, J = 7 Hz), 2.10 (s, 3 H), 1.0–2.5 (m, 16 H); IR (film) 2925, 1730, 1435, 1360, 1240, 1180, 1120, 1030, 720; ^{13}C NMR 131.825, 131.695, 131.370, 131.110, 130.687, 128.997, 128.477, 128.347, 64.628, 30.851 and 27.665 (J_1PC), 29.518, 28.900, 28.575, 27.893 (allylic carbons), 27.210, 25.844, 21.618 and 21.456 (J_2PC), 21.001; mass spectrum, m/e 412 (M^+), 369, 353, 298, 277, 255, 229, 215, 202, 201, 183, 180, 152, 125, 107, 77, 61, 43, 32; exact mass (high-resolution mass spectrum) calcd for $C_{25}H_{33}O_3P$ 412.2167, found 412.2166.

THP ether **6b** was purified by filtration through silica gel with 3:1 EtOAc–CH_2Cl_2 to yield 22.30 g (49.1 mmol, 98%) as an oil: NMR 7.10–8.20 (m, 10 H), 5.25–5.65 (m, 2 H), 4.60 (m, 1 H), 3.30–4.25 (m, 6 H), 1.0–2.60 (m, 20 H); IR (film) 2950, 2870, 1440, 1350, 1200, 1120, 1040; ^{13}C NMR 131.793, 131.663, 131.553, 131.110, 130.687, 128.964, 128.447, 128.184, 98.958, 67.684, 62.418, 30.818, 29.746, 29.616, 29.290 and 27.633 (J_1PC), 29.160, 28.510, 27.860, 27.242 (allylic carbons), 26.170, 25.519, 21.586 and 21.423 (J_2PC), 19.733; mass spectrum, m/e 454 (M^+), 370, 369, 353, 340, 298, 277, 255, 229, 215, 202, 201, 183, 155, 152, 125, 104, 85, 77, 67, 55, 47; exact mass (high-resolution mass spectrum) calcd for $C_{28}H_{39}O_3P$ 454.2637, found 454.2642.

Conversion of Acetate 6a to THP Ether 6b. A solution of acetate **6a** (16.5 g, 40 mmol) and KOH (34 g, 60 mmol) in methanol (100 mL) and water (50 mL) was stirred at room temperature until TLC showed complete disappearance of starting material. The methanol was evaporated, and the resulting aqueous layer was extracted with ether (5 × 50 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and evaporated to give an oil. The oil was dissolved in CH_2Cl_2 (100 mL), and to it was added dihydropyran (4.6 mL, 50 mmol) and *p*-toluenesulfonic acid (0.4 g). The reaction mixture was stirred at room temperature until TLC showed complete disappearance of the intermediate alcohol, approximately 2 h. The organic layer was extracted with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and evaporated to yield 17.7 g (39 mmol, 97%) as a thick yellow syrup, identical with THP ether **6b** produced by the alternate method in all respects.

Gossyplure (9b and 10b). To a cooled solution of phosphine oxide **6b** (0.45 g, 1 mmol) in dry solvent (10 mL) was added *n*-butyllithium (0.75 mL, 1.6 M in hexane, 1.2 mmol) dropwise via syringe. After 15 min, *n*-valeraldehyde (0.132 mL, 1.3 mmol) was added via syringe, and the resulting solution was stirred for 30 min and then allowed to warm to room temperature. Alcoholates **7a** and **8a** could then be decomposed by either of two methods, both monitored by TLC.

(a) Via heating in HMPA. Addition of HMPA (5 mL) followed by warming for 2 h at 70 °C effected decomposition to dienes **9a** and **10a**.

(b) Via NaH in DMF. Isolation of alcohols **7b** and **8b** by aqueous extraction, followed by dissolution in DMF (5 mL) and addition of sodium hydride (0.120 g, 5 mmol) effected decomposition to dienes **9a** and **10a** in approximately 30 min.

In both cases, the reaction mixture was partitioned between ether and water, filtered, and evaporated to give crude THP dienes **9a** and **10a**.

Crude THP dienes **9a** and **10a** were dissolved in glacial acetic acid (2 mL) and to the solution was added acetyl chloride (1 mL). The reaction mixture was stirred at room temperature for 30 min, at which time TLC showed complete conversion to diene acetates **9b** and **10b**. The mixture was partitioned between ether and water, and the acetic acid carefully quenched by cautious portionwise addition of solid $NaHCO_3$. The organic layer was washed with saturated aqueous bicarbonate and brine, dried (Na_2SO_4), filtered, and evaporated to give an amber oil, which was chromatographed on silica gel in CH_2Cl_2 to yield gossyplure mixture **9b** and **10b**, 180 mg (0.64 mmol, 64%), as a clear colorless oil. The ratio was determined by gas chromatography (see Table I). On a preparative scale, the mixture **9b** and **10b** can be isolated by distillation: bp 150 °C (0.5 mm, Kugelrohr) [lit.[3] bp 80 °C (0.025 mm)]; NMR 5.45 (m, 4 H), 4.05 (t, J = 6 Hz, 2 H), 2.0 (m, 11 H), 1.33 (m, 12 H), 0.90 (t, J = 6 Hz, 3 H); IR 2930, 2850, 1730, 1450, 1355, 1230, 1030, 960, 720; mass spectrum, m/s 280 (M^+), 220, 96, 81, 67, 61, 55, 43.

Acknowledgment. We are very grateful to Drs. C. A. Henrick and R. J. Anderson, Zoecon Corp., Palo Alto, for providing us with generous amounts of the pure gossyplure components. The ^{13}C NMR spectral and GLC measurements were made by Dr. M. Maddox and Mr. J. Nelson of this Institute, whose valuable assistance in this regard is gratefully acknowledged.

Registry No. 3, 43017-36-3; **5a**, 29425-54-5; **5b**, 34335-17-6; **6a**, 75812-59-8; **6b**, 75812-60-1; **9a**, 53155-17-2; **9b**, 52207-99-5; **10b**, 53155-14-9; **10b**, 53042-79-8; (4-hydroxybutyl)diphenylphosphine, 7526-70-7; 7-hydroxyheptanal, 22054-13-3; 4-(dimethylamino)-pyridine, 1122-58-3; *n*-valeraldehyde, 110-62-3.

Synthesis of Hexahydrophosphindole Oxides with Oxygen Functions at C-6[1]

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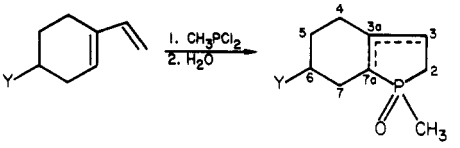
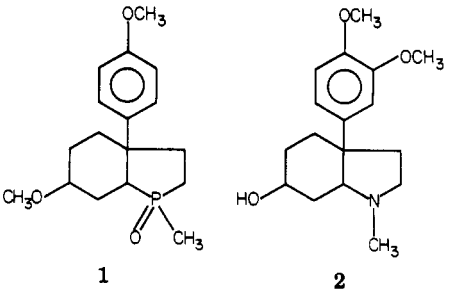
Hexahydrophosphindole 1-oxides are readily obtained by the McCormack cycloaddition of 1-vinylcyclohexene with phosphorus(III) halides.[2] We have now extended the scope of this reaction to include the use of 1-vinylcyclohexenes bearing ketal or ether functionality at the 4-position. The resulting hexahydrophosphindole products in



Y = OCH_2CH_2O, $OCH_2C_6H_5$, OCH_3

turn serve as precursors of 6-keto and 6-hydroxy derivatives of this ring system. The former may prove useful as substrates for annelations to produce multicyclic structures. Both functionalities are frequently found in alkaloids bearing reduced indole moieties. In another report,[3] we show that the 6-methoxy derivative can be converted to perhydrophosphindoles such as **1**, which bear resemblance to the mesembrine family of alkaloids from *Sceletium* (e.g., mesembranol, **2**).

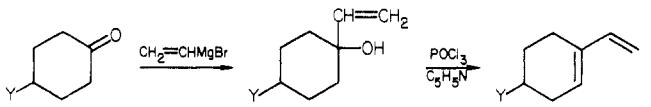


1 **2**

(1) Taken from the Ph.D. Dissertation of J. E. MacDiarmid, Duke University, Durham, NC, 1980.
(2) Symmes, C., Jr.; Quin, L. D. *J. Org. Chem.* **1976**, *41*, 238.
(3) MacDiarmid, J. E.; Quin, L. D. *J. Org. Chem.*, submitted for publication.

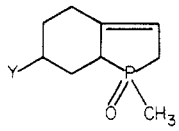
0022-3263/81/1946-0461$01.00/0

The requisite dienes **9–11** were prepared by the two-step process of addition of vinyl Grignard reagent to the corresponding ketones (**3–5**) and then dehydration of the vinyl carbinols (**6–8**) by the $POCl_3$–pyridine method. Overall yields of the distillable dienes were in the 45–65% range.



3	Y = OCH_2CH_2O	**6**	**9**
4	Y = $OCH_2C_6H_5$	**7**	**10**
5	Y = OCH_3	**8**	**11**

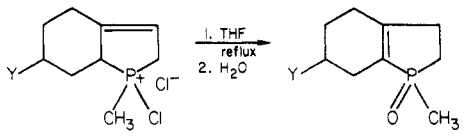
When the McCormack cycloaddition is conducted at room temperature with CH_3PCl_2, and the cycloadduct hydrolyzed with the pH controlled at neutrality or on the basic side, the phospholene oxides formed have the 3,4-position for the double bond. This procedure led to the isolation of phospholene oxides **12** and **13** from dienes **9** and **10**, respectively. The ketal derivative **12** is capable



12, Y = $O(CH_2)_2O$
13, Y = $OCH_2C_6H_5$

of existence as two cis,trans isomers, and both were present in 1:1 ratio as revealed by ^{31}P and ^1H NMR spectroscopy. The benzyloxy derivative **13** can have four diastereoisomeric forms; all were detected by ^{31}P NMR spectroscopy, which showed separate shifts in the range δ +62.6 to +71.3. It will be seen in another report[4] that a 4-methyl group leads to greater specificity in the cycloaddition, and only two of the four isomers are formed. The mixture of the isomers of **12** was separated by crystallization from acetone, from which a pure sample of the isomer with the relatively upfield ^{31}P NMR signal was obtained. Its exact structure has not yet been assigned. No effort was made to separate the more complex mixture of isomers of **13**.

In two cases, the McCormack cycloadducts were isomerized thermally to the substituted 2-phospholene structure and on hydrolysis provided the corresponding oxides **14** and **15**. No cleavage of the ether groups by the thermal



14, Y = $OCH_2C_6H_5$
15, Y = OCH_3

treatment was detected. Again stereoisomerism is present, and the two possible isomers were formed for both **14** and **15**. Only subtle differences existed in their spectral properties; neither ^1H nor ^{31}P NMR revealed their presence, but some doubling of ^{13}C signals (e.g., for C-6 as recorded in Table I) provided evidence for their existence.

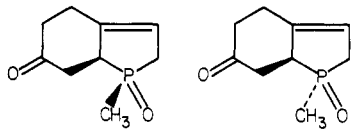
The ketal group of **12** (cis,trans mixture) was readily hydrolyzed (50% yield) by warm dilute acid, giving the ketone **16** also as a mixture of stereoisomers. Cis,trans structure was readily assigned from their ^{13}C NMR spectra, using the same criterion (steric compression of P–CH_3 in the cis isomer causing an upfield shift) as used in the original work on hexahydrophosphindoles.[2] No tendency

(4) MacDiarmid, J. E.; Quin, L. D., unpublished results.

Table I. Spectral Properties[a]

	^{31}P	^1H NMR		^{13}C NMR								
compd	NMR	PCH_3	=CH or CHO	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	PCH_3
12[b]	+69.3	1.52 (13)	5.78 (29)[c]									
	+62.1	1.68 (13)	5.52 (29)[c]									
14[d]	+67.2	1.55 (12.5)		24.4 (70.2)	31.3 (8.5)	155.4 (29.9)			72.5 (8.6)		127.0 (97.1)	15.4 (67.1)
	+67.5	1.55 (12.5)										
15[d]	+68.1	1.58 (13)	3.55[e]	24.3 (65.3)	31.2 (7.9)	155.4 (29.9)	25.7 (4.3)	26.8 (s)[f]	74.5 (8.6)	26.3 (s)[f]	127.2 (97.1)	15.4 (66.5)
	+68.1	1.58 (13)	3.55[e]	24.3 (65.3)	31.2 (7.9)	155.5 (29.9)	25.7 (4.3)	26.8 (s)[f]	74.6 (8.5)	26.3 (s)[f]	127.2 (97.1)	15.4 (66.5)
16a[g]	+72.7	1.62 (13	5.90 (32)[c]	34.2 (64.5)	120.2 (6.8)	139.3 (11.7)	28.6 (8.8)		209.7 (11.7)	39.1 (4.9)	42.1 (68.4)	11.6 (63.5)
16b[g]	+64.4	1.73 (13)	5.76 (29)[c]	34.2 (64.5)	120.2 (6.8)	139.3 (11.7)	29.8 (9.8)	40.4 (s)	209.7 (11.7)	39.1 (4.9)	42.1 (68.4)	16.3 (63.5)
17[d]	+68.2	1.61 (13)	4.05 (m)[e]	24.5 (70.8)	*h*	155.0 (29.9)	*h*	*h*	65.3 (8.6)	*h*	127.1 (90.9)	15.4 (66.5)
	+68.2	1.61 (13)	4.05 (m)[e]	24.5 (70.8)	*h*	155.5 (29.9)	*h*	*h*	65.0 (7.9)	*h*	129.8 (84.2)	15.4 (66.5)

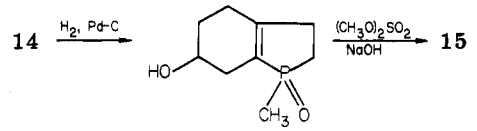
[a] Conditions are given in ref 5. [b] Cis,trans isomers. Data for the isomer with downfield ^{31}P signal were obtained on an isomer mixture; data for the other isomer were obtained on a pure sample. [c] For =CH. [d] Cis,trans isomers. Data obtained on a mixture. [e] For CHO. [f] May be reversed. [g] IR $\nu_{C=O}$ 1695, $\nu_{C=C}$ 1640 cm^{-1}. [h] Unassigned, in region δ 21.2–31.5.



cis-16a *trans*-16b

for double bond migration was evident in the hydrolysis. The purification of the ketone was somewhat difficult but was facilitated by formation of the bisulfite addition product and regeneration of the ketone.

The benzyloxy group of **14** was cleaved in 80% yield by hydrogenolysis over palladium on charcoal forming **17**. Methylation with dimethyl sulfate and NaOH gave the same methoxy compound **15** as prepared directly by the McCormack route.



17

Experimental Section

Preparation of 4-Substituted Cyclohexanones. 4,4-(Ethylenedioxy)cyclohexanone (**3**) was prepared from 1,4-cyclohexanedione and ethylene glycol according to the procedure of Courtot.[6] 4-(Benzyloxy)cyclohexanone (**4**) resulted from the monosodio derivative of 1,4-cyclohexanediol and benzyl bromide, as described by Prins,[7] and on oxidation with CrO_3–acetic acid gave 4-(benzyloxy)cyclohexanone, bp 128–135 °C (0.07 mm) [lit.[7] bp 118–120 °C (0.14 mm)]. 4-Methoxycyclohexanone (**5**)[8] was formed similarly from the cyclohexanol.

Preparation of 4-Substituted 1-Vinyl-1-cyclohexanols. The same general procedure was applied to several 4-substituted cyclohexanones. That for the 4,4-ethylenedioxy compound[9] (**3**) is typical. The vinyl Grignard reagent prepared from 75.5 g (0.71 mol) of vinyl bromide and 15.6 g (0.64 mol) of magnesium in 500 mL of THF was treated slowly with a solution of 77.1 g (0.49 mol) of **3** in 300 mL of THF. The mixture was stirred at room temperature for several hours and then hydrolyzed with saturated aqueous NH_4Cl. The aqueous solution was extracted with four 100-mL portions of ether, and the combined ether fractions were dried ($MgSO_4$), concentrated, and distilled [84–90 °C (0.04 mm)] to yield 86.0 g (94.5%) of 4,4-(ethylenedioxy)-1-vinylcyclohexanol (**6**). 4-(Benzyloxy)cyclohexanone (**4**) similarly gave the vinyl carbinol **7** and 4-methoxycyclohexanone (**5**) gave **8**; both carbinols were used in crude form for dehydration to the vinylcyclohexenes (see below).

Preparation of 4-Substituted 1-Vinylcyclohexenes. The general procedure is illustrated by the synthesis of 4,4-(ethylenedioxy)-1-vinylcyclohexene (**9**).[9] The vinyl carbinol **6** (86 g, 0.47 mol) was dissolved in 350 mL of pyridine and treated slowly at −5 °C with a solution of 98.7 g (0.64 mol) of $POCl_3$ in 275 mL of pyridine. The mixture was allowed to warm to 15–20 °C and held there for 16 h. While being maintained at this temperature, the mixture was hydrolyzed slowly with ice water and the diene extracted with hexane (six 200-mL portions). The extract was washed with 10% HCl to remove pyridine and then dried ($MgSO_4$). Distillation gave 35.8 g (46.1%) of diene **9**, Y = OCH_2CH_2O, bp 48–52 °C (0.03 mm). Diene **10** was similarly prepared from vinyl carbinol **7** (63.5% yield overall from ketone **4**): bp 76–78 °C (0.05 mm); ^1H NMR δ 3.7 (m, HC-4), 4.58 (s, CH_2OR), 4.8–5.3 (m, CH_2=C), 5.65 (t, J = 2 Hz, HC-2), 6.2–6.5 (m, H_2C=CH).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.08; H, 8.47. Found: C, 84.01; H, 8.29.

Diene **11** prepared from vinyl carbinol **8** (65% from ketone **5**) was collected at 95–100 °C (12–14 mm) and used without further purification in the McCormack cycloaddition; ^1H NMR δ 3.45 (s, OCH_3), 3.60 (m, HC-4), 4.9–5.3 (m, C=CH_2), 5.73 (br s, HC-2), 6.25–6.6 (m, CH=CH_2).

6,6-(Ethylenedioxy)-1-methyl-Δ³-2,4,5,6,7,7a-hexahydro-1*H*-phosphindole 1-Oxide (12). A hexane solution (50 mL) of diene **9** (20 g, 0.12 mol) and freshly distilled CH_3PCl_2 (18.3 g, 0.156 mol) was allowed to stand at room temperature for 5 days. Copper stearate (0.4 g) was employed as a polymerization inhibitor. The cycloadduct precipitated as a solid and was recovered by filtration. The filtrate was preserved and allowed to continue with the formation of cycloadduct for 27 days. The first crop of cycloadduct was hydrolyzed with aqueous $NaHCO_3$, and the phospholene oxide extracted continuously with $CHCl_3$. Concentration gave an oil, which was purified by extraction into hot ether (leaving some dark insolubles); the residue from stripping the ether was purified by reprecipitation from acetone with hexane. The product (10.1 g, a mixture of stereoisomers) seldom crystallized from this state. However, crystallization from a concentrated acetone solution did occur and provided a sample that proved to be a single isomer, mp 156–157 °C. NMR data for both isomers are given in Table I. The second crop of cycloadduct provided an additional 10.6 g, total yield 72.7%. The single isomer was used for elemental analysis.

Anal. Calcd for $C_{11}H_{17}O_2P$: C, 57.98; H, 7.51; P, 13.57. Found: C, 58.01; H, 7.56; P, 13.71.

6-(Benzyloxy)-1-methyl-Δ³-2,4,5,6,7,7a-hexahydro-1*H*-phosphindole 1-Oxide (13). By the same procedure as described for **12**, the benzyloxy compound **13** was obtained in 49.6% yield after a 12-day cycloaddition of **10** g (0.047 mol) of diene **10** and CH_3PCl_2 (6.55 g, 0.056 mol). The product, an isomer mixture, could not be crystallized: ^1H NMR ($CDCl_3$) δ 1.52, 1.60, and 1.62 (all d, $^2J_{PH}$ = 13 Hz, PCH_3 groups), 3.80, (m, CHOR), 4.55 (s, $C_6H_5CH_2$), 5.41 (d, $^3J_{PH}$ = 30 Hz, =CH); ^{31}P NMR δ +71.3, +70.5, +64.3, +62.6.

6-Methoxy-1-methyl-Δ$^{3a(7a)}$-2,3,4,5,6,7-hexahydro-1*H*-phosphindole 1-Oxide (15). The cycloadduct formed after 3 days from 10.1 g (0.073 mol) of diene **11** and 10.3 g (0.088 mol) of CH_3PCl_2 in 10 mL of pentane was collected by filtration and refluxed in 50 mL of sodium-dried THF for 6 h. Hydrolysis and isolation by the usual procedure, and then Kugelrohr distillation, gave 3.1 g (21.2% from **11**) of **15**. An additional crop of adduct formed after 14 days raised the yield to 7.9 g (54%). The oil did not crystallize but could be Kugelrohr distilled at 100 °C (0.1 mm). Spectral data are recorded in Table I. The spectra were identical with those of an analyzed sample prepared by methylation of hydroxy derivative **17** (vide infra).

6-(Benzyloxy)-1-methyl-Δ$^{3a(7a)}$-2,3,4,5,6,7-hexahydro-1*H*-phosphindole 1-Oxide (14). By the same procedure as for the preparation of **15**, the cycloadduct from diene **10** was refluxed in THF for 20 h. The product (yield about 80% from the adduct) was a noncrystallizing isomer mixture; spectral data are given in Table I.

1-Methyl-6-oxo-Δ³-2,4,5,6,7,7a-hexahydro-1*H*-phosphindole 1-Oxide (16). A solution of 3.2 g (0.014 mol) of ketal **12** (pure isomer) in 30 mL of acetone and 15 mL of 10% aqueous HCl was heated at 50 °C for 27 h. It was then treated with about 50 mL of saturated NaCl and neutralized with solid $NaHCO_3$. The product was extracted with four 50-mL portions of $CHCl_3$; the extracts were evaporated to dryness. The ketone was converted to its $NaHSO_3$ addition product to facilitate separation from impurities. This was accomplished by extracting a benzene solution of the product with three 30-mL portions of 20% $NaHSO_3$. Addition of K_2CO_3 to the aqueous layer regenerated the ketone, which was extracted into $CHCl_3$ (5 × 50 mL). Evaporation after drying ($MgSO_4$) gave 1.3 g (50%) of **16** as a slightly yellow oil, still contaminated with ethylene glycol. Continuous extraction ($CHCl_3$) of the remaining aqueous solution, followed by evaporation of the extract, provided a crystalline sample of ketone **16**, free of glycol; it was recrystallized from acetone, mp 75 °C. NMR data are given in Table I. The sample appeared to contain 0.5

(5) Melting points were taken on a Mel-Temp apparatus and are corrected; boiling points are uncorrected. Spectra were taken as follows: ^1H, JEOL MH-100 spectrometer, internal Me_4Si reference, $CDCl_3$ solutions; ^{31}P, Bruker HFX-10 at 36.43 MHz, FT proton decoupled, 85% H_3PO_4 external reference with positive signs downfield, negative upfield, $CDCl_3$ solutions; ^{13}C, JEOL FX-60 at 15.0 MHz, FT proton decoupled, internal Me_4Si as reference in $CDCl_3$ solutions as lock.

(6) Courtot, P. *Ann. Chim., Ser. 13* **1963**, *8*, 197.

(7) Prins, D. A. *Helv. Chim. Acta* **1957**, *40*, 1621.

(8) Helfer, L. *Helv. Chim. Acta* **1924**, *7*, 950.

(9) Vig, O. P.; Sharma, S. D.; Kad, G. L.; Sharma, M. L. *Indian J. Chem.* **1975**, *13*, 764.

mol of water from the analysis.

Anal. Calcd for $C_9H_{13}O_2P \cdot 0.5H_2O$: C, 55.95; H, 7.31; P, 16.03. Found: C, 56.12; H, 7.37; P, 16.21.

6-Hydroxy-1-methyl-$\Delta^{3a(7a)}$-2,3,4,5,6,7-hexahydro-1*H*-phosphindole 1-Oxide (17). The isomer mixture of 14 (10 g, 0.036 mol) was dissolved in 150 mL of glacial acetic acid and hydrogenated over 3.0 g of 10% Pd on charcoal at 50 psi for 19 h. The oil that remained from concentration of the solution was converted to crystalline form (2.4 g, 35.6%) by mixing with a small amount of acetone. The residual material was Kugelrohr distilled to give an additional 4.2 g (62.3%, total yield of 17 87.9%) of oil that later solidified. A sample vacuum sublimed for analysis had mp 145 °C. Spectral data are in Table I.

Anal. Calcd for $C_9H_{13}O_2P$: C, 58.06; H, 8.12; P 16.64. Found: C, 58.16; H, 8.33; P, 16.96.

O-Methylation of Hydroxyphosphindole 17. A solution of 1 g (0.0054 mol) of alcohol 17 in 1 mL of water was mixed with a solution of 1 g (0.025 mol) of NaOH in 1.5 mL of water. It was slowly treated with 4 g (0.03 mol) of dimethyl sulfate (caution), and the mixture stirred for 3 h at room temperature. The solution was determined to be acidic and was made basic with NaOH. During the next 20 h, the mixture was treated with two 1-mL portions of dimethyl sulfate and NaOH to keep the solution basic. The solution was then made slightly acidic and continuously extracted with $CHCl_3$. Evaporation of the extract and then distillation (Kugelrohr) at 100 °C (0.1 mm) gave 0.8 g (75%) of 15 as an oil. NMR properties were identical with those of the sample of 15 prepared by the cycloaddition of diene 11.

Anal. Calcd for $C_{10}H_{17}O_2P$: C, 59.99; H, 8.56; P, 15.47. Found: C, 59.89; H, 8.59; P, 15.67.

Registry No. 3, 4746-97-8; 4, 2987-06-6; 5, 13482-23-0; 6, 57707-01-4; 7, 75802-42-5; 8, 75802-43-6; 9, 57707-02-5; 10, 75802-44-7; 11, 75802-45-8; 12 (isomer 1), 75802-46-9; 12 (isomer 2), 75802-47-0; 13, 75802-48-1; 14 (isomer 1), 75802-49-2; 14 (isomer 2), 75802-50-5; 15 (isomer 1), 75802-51-6; 15 (isomer 2), 75802-52-7; 16a, 75802-53-8; 16b, 75802-54-9; 17, 75802-55-0; vinyl bromide, 593-60-2.

Mechanism of Amino Acid α-Hydroxylation and Formation of the Lysergyl Moiety in Ergotamine Biosynthesis

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The formation of the modified peptide portion of peptide ergot alkaloids, e.g., ergotamine (I), involves the conversion of an α-amino acid, e.g., alanine in the case of I, into the corresponding α-hydroxy α-amino acid moiety. This transformation is thought to occur after the assembly of the entire lysergyl-tripeptide, possibly at the stage of an N^1-(lysergylalanyl)prolylphenylalanyl lactam (II).[1] In a previous communication[2] we were able to rule out one of three possible mechanisms for this conversion, dehydrogenation to the 2,3-dehydro amino acid followed by addition of water, by showing that deuterium at the 3-position of this amino acid is completely retained during the conversion to the α-hydroxy α-amino acid moiety. We now report results which allow us to distinguish between the remaining two mechanisms, (a) dehydrogenation to the imine followed by addition of water and (b) direct hydroxylation at the α-position, in favor of the latter. The data also shed some light on the mode of formation of the lysergyl moiety from its precursor, elymoclavine (III).

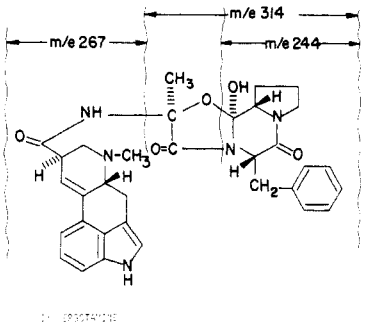
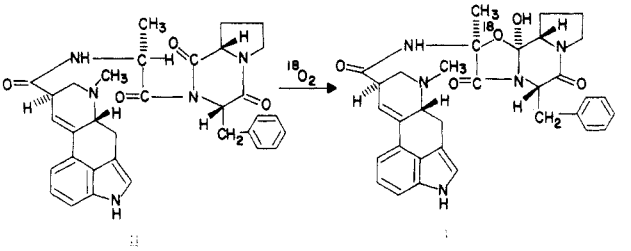


Figure 1.

Scheme I



Results and Discussion

A distinction between the two remaining mechanisms a and b for the amino acid α-oxidation should be possible by determining whether the oxygen in the cyclol ring of I is derived from water (mechanism a) or from molecular oxygen (mechanism b). Consequently, we carried out fermentations of the ergotamine-producing *Claviceps purpurea* strain PCCE1[3] in an atmosphere of 91.7% ^{18}O-enriched oxygen. The ergotamine formed was extracted, purified by preparative thin-layer chromatography, and subjected to EI and CI mass spectrometry. Three mass spectral fragments were analyzed for their isotopic composition, the ions at m/e 244 or 245 and 314 or 315 and, in the case of the EI spectra, also the one at m/e 267. In the CI spectra this ion was too weak for quantitative evaluation. The origin of these fragments,[4] which is supported by high-resolution data, is shown in Figure 1.

The results of two independent experiments are listed in Table I. The fragment of mass 244 clearly shows no significant isotopic enrichment. Thus, as one would expect, ^{18}O from molecular oxygen is not incorporated into the carboxyl groups of amino acids. The fragment of mass 314 contains ^{18}O at an average enrichment of about 43.8 atom %. On the basis of the enrichment of 91.7 atom % of the $^{18}O_2$ used, this indicates the incorporation of 0.48 atoms of oxygen from O_2 into this fragment. This figure reflects the fact that the cultures were only exposed to $^{18}O_2$ starting on day 8, at which time some I was already present. In view of the nonincorporation of ^{18}O into the carboxyl groups of amino acids, as indicated by the absence of labeling in fragment m/e 244, it seems justified to conclude that the ^{18}O in fragment m/e 314 is located in the cyclol oxygen. The results thus support mechanism b, a direct oxygenation, for the conversion of the α-amino to the α-hydroxy α-amino acid moiety (Scheme I). The stereochemistry of this process, replacement of H by OH in a retention mode, as deduced from the configurations of

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