temperature. Treatment by di-*tert*-butyl dicarbonate gave the amino BOC derivative **23** as shown by TLC.

Hydrolysis of the *t*-BOC derivative **23** (0.020 mmol) in 50 μL of 1 M HCl in acetic acid was complete in less than 1 min. The product was precipitated with ethyl ether (2 mL), centrifuged, washed with ethyl ether, and dried in vacuo to give TLC pure amine **19** as a salt (dec >177 °C). Mass spectral peaks were observed in the CI mode with ammonia at *m/e* 404 (MH^+ 40%), 386 (100%), 315 (35%); IR (KBr) 3430, 3200–3000 (shoulder), 1690, 1665, 1610 cm^{-1}.

Deoxycorticosterone-21-S$(CH_2)_5NH_2$ (20) and Deoxycorticosterone-21-S$(CH_2)_5$NH-*t*-BOC (24). The reaction of 0.082 mmol of deoxycorticosterone-21-mesylate and 0.160 mmol of 5-amino-1-pentanethiol in 2.1 mL of DMF was complete in less than 30 min at room temperature. Di-*tert*-butyl dicarbonate (150 μL, 0.750 mmol) was added with triethylamine (120 μL, 0.840 mmol) to the reaction solution, which was added to 5 mL of ethyl acetate after 2 min and washed with water containing HCl (700 μmol). The organic phase was extracted with dilute HCl, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by preparative TLC with benzene–ethyl acetate (4:1) to give the TLC pure amino *t*-BOC derivative **23** in 77% yield as an oil. Mass spectral peaks were obtained in the CI mode with ammonia at *m/e* 532 (MH^+, 40%), 476 (100%), 432 (65%), 315 (22%); IR (KBr) 3380, ~1690 cm^{-1} (br).

The same product (**24**) was obtained from deoxycorticosterone-21-chloride (0.020 mmol) with 5-amino-1-pentanethiol (0.040 mmol) in 500 μL of DMF at room temperature in less than 30 min. Treatment with di-*tert*-butyl dicarbonate (30 μL) and triethylamine (20 μL) gave the same amino *t*-BOC derivative **24** as shown by TLC.

Hydrolysis of **24** and purification of the amine **20** as a salt were accomplished as for **19** to give a TLC pure oil. Mass spectral peaks were obtained in the CI mode with ammonia at *m/e* 432 (MH^+, 100%), 391 (20%), 315 (26%), 237 (24%), 120 (19%); IR (KBr) 3430, ~3100 (shoulder), 1690, 1660, 1610 cm^{-1}.

Deoxycorticosterone-21-aminopropane (21). The reaction of deoxycorticosterone-21-chloride (0.066 mmol) and 16 equiv of *n*-propylamine in 1 mL of DMF at 62 °C was complete after 25 min, as determined by TLC. The reaction solution was added to 10 mL of cold aqueous saturated NaCl. Extraction with ethyl acetate (3 × 10 mL) followed by drying over $MgSO_4$ and removal of solvent under reduced pressure gave the crude amine. Preparative TLC (90:10 $CHCl_3$–MeOH on silica gel) gave >85% pure product (by high-pressure LC) in 67% yield, mp 197–201 °C. A mass spectral peak was observed in the CI mode with ammonia at *m/e* 372 (MH^+, 100%); IR (KBr) ~3420, ~3050 (shoulder), 1720, 1670, 1610, 1450, 1230 cm^{-1}.

The reaction of deoxycorticosterone-21-mesylate (0.070 mmol) with 16 equiv of *n*-propylamine in 1 mL of DMF at 65 °C was over in 30 min but also gave several byproducts. After purification, deoxycorticosterone-21-aminopropane was obtained in 15% yield (mp 196–199 °C). A mass spectral peak was observed in the CI mode with ammonia at *m/e* 372 (MH^+, 100%).

The same reaction in acetone at room temperature with deoxycorticosterone-21-mesylate and -chloride gave many byproducts and less than 10% of deoxycorticosterone-21-aminopropane after 66 h.

Registry No. **4**, 2265-22-7; **5**, 73816-20-3; **7**, 73816-21-4; **8**, 73816-22-5; **9**, 73816-23-6; **10**, 73816-24-7; **11**, 1177-87-3; **12**, 73816-25-8; **13**, 73816-26-9; **14**, 20576-45-8; **15**, 73816-27-0; **16**, 73816-28-1; **17**, 58958-14-8; **18**, 73816-29-2; **19**, 73816-30-5; **20**, 73816-31-6; **21**, 73816-32-7; **22**, 26987-64-4; **23**, 73816-33-8; **24**, 73816-34-9; dexamethasone, 50-02-2; deoxycorticosterone, 64-85-7; methyl mercaptoacetate, 2365-48-2; β-mercaptoethanol, 60-24-2; cysteamine hydrochloride, 52-89-1; 2-*t*-Boc-amino-1-ethanethiol, 67385-09-5; 1,4-butanedithiol; ethanethiol, 75-08-1; 3-aminopropanethiol, 462-47-5; 5-amino-1-pentanethiol, 58657-85-5.

Conformation of Epi-α-cyperone and Related Enones

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The conformations of epi-α-cyperone (10-epieudesma-4,11-dien-3-one, **2**) and its dihydro and 14-nor analogues (**4** and **15**, respectively) have been investigated by a combination of lanthanide induced shift reagent ^1H NMR, ^{13}C NMR, and high-field ^1H NMR techniques. Comparison of these spectral data with those of the normal eudesmane derivatives, α-cyperone (**1**), dihydro-α-cyperone (**3**), and 14-noreudesm-4-en-3-one (**14**) clearly shows that the conformations of all six enones are similar with a half-chair conformation for ring A and a chair conformation for ring B. 11-Methyl-10-epieudesm-4-en-3-one (**5**) was prepared either from 5α-hydroxy-10-epieudesm-11-en-3-one (**6**) or by the Robinson annulation of 2-methyl-5-*tert*-butylcyclohexanone with ethyl vinyl ketone. 14-Nor-11-methyl-10-epieudesm-4-en-3-one (**15**) was prepared by the annulation of 2-methyl-5-*tert*-butylcyclohexanone with methyl vinyl ketone. The ^{13}C lanthanide induced shift and high-field ^1H NMR spectra of enones **5** and **13** indicate that these molecules are not conformationally homogeneous. An X-ray structure determination of the oxime of enone **5** showed that in the solid state ring A exists in a envelope conformation and ring B in a twist conformation with a ψ-equatorial *tert*-butyl group. Crystals of the oxime of **5** belong to the triclinic system, space group $P\bar{1}$, with a = 6.290 (3) Å, b = 12.010 (5) Å, c = 10.341 (5) Å, α = 85.20 (2)°, β = 95.56 (2)°, γ = 101.09 (2)°, and Z = 2. Atomic positional and thermal parameters were refined by least-squares calculations to R = 0.068 over 1609 observed reflections measured by a diffractometer.

Experiments directed toward the elucidation of the structure and stereochemistry of the eudesmanoid sesquiterpene α-cyperone (eudesma-4,11-dien-3-one, **1**) have shown that the Robinson annulation of dihydrocarvone with ethyl vinyl ketone or the equivalent afforded not the expected product (**1**) but a stereoisomer, epi-α-cyperone (7-epieudesma-4,11-dien-3-one, **2**).[2] A coincident investigation of the ORD properties of unsaturated ketones, including α-cyperone (**1**), epi-α-cyperone (**2**), and dihydroepi-α-cyperone (**4**), led Djerassi et al. to conclude that α-cyperone (**1**) had the expected conformation in which ring B was a chair with an equatorial isopropenyl sub-

(1) (a) Clemson University. (b) Tulane University. (c) Duke University.

(2) (a) McQuillin, F. J. *J. Chem. Soc.* **1955**, 528. (b) Howe, R.; McQuillen, F. J. *J. Chem. Soc.* **1955**, 2423. These workers carried out this annulation using (−)-dihydrocarvone to afford the enantiomer of enone **2**.

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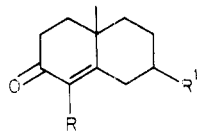
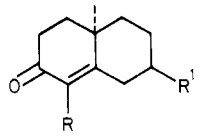
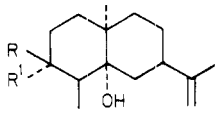


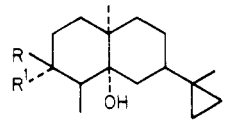
1, R = CH_3; R^1 = CH_2=CCH_3
3, R = CH_3; R^1 = $CH(CH_3)_2$
14, R = H; R^1 = $CH(CH_3)_2$
16, R = CH_3; R^1 = H
17, R = R^1 = H



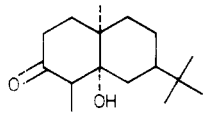
2, R = CH_3; R^1 = CH_2=CCH_3
4, R = CH_3; R^1 = $CH(CH_3)_2$
5, R = CH_3; R^1 = $C(CH_3)_3$
13, R = H; R^1 = $C(CH_3)_3$
15, R = H; R^1 = $CH(CH_3)_2$



6, R, R^1 = O
8, R = OH; R^1 = H
9, R = H; R^1 = OH
10, R = H; R^1 = OAc



7, R, R^1 = O
11, R = H; R^1 = OH



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stituent at C-7 but that compounds in the epi series (2 and 4) had a preferred conformation in which ring B exists in a boat (twist) conformation.[3] Prior to 1956, this conclusion seemed logical, since the conformational free-energy for an axial isopropyl group was considered to be greater than 3 kcal/mol.[4] However, subsequent studies by a number of groups[5,6] showed that this value was too high, and a revised value of 2.1 kcal/mol was determined. In addition, the chair conformation of enone 4, in which the isopropyl group is axial, has an sp^2-hybridized carbon (C-5) β to the axial substituent. By analogy to a 3-alkyl ketone effect, the conformational free energy for an axial isopropyl group in enone 4 is reduced to ca. 1.6 kcal/mol.[7] Although there appear to be no data available for the chair to twist interconversion of alkylidene cyclohexanes (e.g., ring B of enone 4), the free energy for this interconversion in cyclohexanone is approximately 3.3 kcal/mol.[8] Assuming that the energetics of the chair–twist interconversion in an alkylidene cyclohexane and a cyclohexanone are comparable, one must conclude that enone 4, and presumably enone 2, should exist predominently in that conformation in which ring B is in a chair conformation, with the alkyl substituent at C-7 being axial.[9]

Although an approximation of the relative energetics for the chair to boat interconversion of ring B in enone 4 indicates that this ring should not adopt a twist conformation, the differences in the ORD curves of enones 1 and 3 compared with those of 2 and 4 indicate that there must be some differences in the conformations of these pairs of compounds. In an attempt to clarify this question we undertook the preparation of a closely related compound, the *tert*-butyl analogue of enones 2 and 4 (5) in which it would be predicted that ring B would be forced into a twist conformation. It was felt that a detailed comparison of the chiroptical and spectral properties of enones 1–5 could resolve the problem of the conformation of epi-α-cyperone and its dihydro derivative.

In order to obtain an enantiomer of known configuration and to assure the correct stereochemistry at both chiral centers, we employed the ketol derived from (+)-dihydrocarvone and ethyl vinyl ketone (6)[2b,10] as the starting material for the preparation of *tert*-butyl enone 5. Reaction of ketol 6 under standard Simmons–Smith conditions gave a poor yield of ketol 7 with much apparent dehydration. In an attempt to circumvent this undesired side reaction, we reduced ketol 6 to the 3β,5α-diol (8) with lithium aluminum hydride; however, the Simmons–Smith reaction again led predominantly to dehydrated products. Lithium–ammonia–*tert*-butyl alcohol reduction of ketol 6 afforded the 3α,5α-diol (9) which also underwent dehydration under Simmons–Smith conditions. The 3-acetate (10) of diol 9 afforded good yields of diol 11 after cyclopropanation and reductive deesterification. Oxidation of diol 11 gave ketol 7, catalytic hydrogenation of which, followed by reoxidation of the partially reduced 3-carbonyl group, gave ketol 12, the precursor to enone 5. Ketol 12 proved somewhat resistant to dehydration under the moderately basic conditions or with *p*-toluenesulfonic acid in refluxing benzene; however, when the mixture was heated to reflux with *p*-toluenesulfonic acid in toluene, dehydration to enone 5 proceeded smoothly. Following the completion of much of this synthetic work, House reported the preparation of a racemic, desmethyl analogue of enone 5 (13) by the Robinson annulation of 2-methyl-5-*tert*-butylcyclohexanone with methyl vinyl ketone.[11] Repetition of this procedure with ethyl vinyl ketone afforded racemic ketol 12, dehydration of which gave the racemate of enone 5.

The other bicyclic enones used in this study were prepared by known procedures or variations thereof. Dihydroepi-α-cyperone (4) was prepared from ketol 6 by a modification of the published procedure.[12] Reduction of α-cyperone (1), prepared by Caine's method,[13] using a homogeneous catalyst gave dihydro-α-cyperone (3).

Since House had suggested a preferred conformation for the 14-norenone 13,[11] it was felt that our study should be expanded to include the 14-nor analogues of enones 3 and 4.[14] 14-Nordihydroepi-α-cyperone (14-noreudesm-4-en-3-one, 14) and its C-10 epimer (14-nor-10-epieudesm-4-

(3) Djerassi, C.; Riniker, R.; Riniker, B. *J. Am. Chem. Soc.* **1956**, *78*, 6362, 6377.
(4) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.
(5) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Interscience: New York, 1965 (pp 41 ff summarize this work).
(6) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J.; VanCatledge, F. A. *J. Am. Chem. Soc.* **1968**, *90*, 1199.
(7) Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 777. These authors have found a value of 0.5 kcal/mol for the 3-alkyl ketone effect. See also: Allinger, N. L.; Freiberg, L. A. *J. Am. Chem. Soc.* **1962**, *84*, 2836.
(8) Allinger, N. L.; Blatter, H. M.; Freiberg, L. A.; Karkowski, F. M. *J. Am. Chem. Soc.* **1966**, *88*, 2999.
(9) An alternative conformation, analogous to the nonsteroidal conformation of a *cis*-decalone, is a formal possibility for these enones. This conformation for enone 4 would have ring B in a chair conformation with an equatorial substituent at C-7. The attempted construction of a Dreiding model of this conformation leads to the conclusion that the planarity of the enone system would be severely disrupted, which should result in anamolous ultraviolet spectra for these enones, which are not observed.
(10) Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501.
(11) House, H. O.; Lusch, M. J. *J. Org. Chem.* **1977**, *42*, 183. These authors suggest, without comment, a nonsteroidal conformation for enone 13 (see ref 9).
(12) Hikino, H.; Kohana, T.; Takemoto, T. *Tetrahedron* **1969**, *25*, 1037.
(13) (a) Caine, D.; Gupton, J. T. *J. Org. Chem.* **1974**, *39*, 2654. (b) It was found that the preparation of 2-carone by the procedure of Dauben and Deviny (Dauben, W. G.; Deviny, E. J. *J. Am. Chem. Soc.* **1970**, *92*, 6273) led to much dehydrochlorination. Good yields were obtained by using the modified procedure described in the Experimental Section.
(14) Not only was this study necessary for clarification of the conformation of enone 13 but the possibility also existed that at least some of the differences in the ORD curves of enones 3 and 4 are caused by steric interaction of the 14-methyl group with the C-6 methylene group.

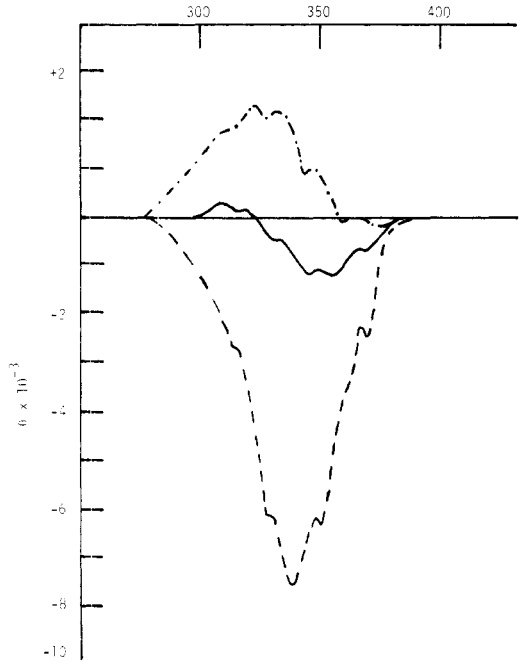

Figure 1. CD curves of dihydroepi-α-cyperone (**4**, —), dihydro-α-cyperone (**3**, - - -), and 11-methyl-10-epieudesm-4-en-3-one (**5**, - - -).

en-3-one, **15**) were prepared by straightforward modifications of the methods described for enones **3** and **4**, respectively (see Experimental Section).

Results and Discussion

The CD curves of enones **3** and **4** (Figure 1)[15] were compatible with the ORD data of Djerassi;[3] however, the CD curve of 7-*tert*-butyl enone **5** (Figure 1) was markedly different from either, with a strongly negative Cotton effect. The CD curves of the pair of 14-norenones **14** and **15**, analogous to the cyperones, were essentially identical with those of the parent compounds, indicating that the interaction of the vinyl methyl with the 6-methylene group did not appreciably distort the chromophore in enones **3** and **4**. The chiroptical properties of these compounds indicated not only that there were conformational differences between dihydro-α-cyperone (**3**) and its C-10 epimer (**4**) as suggested by Djerassi[3] but also that the *tert*-butyl enone **5**, in which ring B was assumed to be in a twist conformation, appeared to have adopted yet a third conformation. Although these data are indicative of conformational differences as a function of the nature of the C-7 substituent, they reveal little concerning the nature of these differences.

In an attempt to obtain evidence concerning the nature of these conformational differences, we undertook a lanthanide induced shift (LIS) study of the ^{1}H NMR spectra of these enones. In these studies, standard aliquots of a solution of Eu(fod)$_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octandionato)europium] were added to standard solutions of the ketonic substrate. Since it has been shown that the metal position in the reagent–substrate complex relative to the carbonyl oxygen is similar for structurally similar cyclohexanones,[16] the relative induced shifts of the various methyl groups in these enones should be indicative of the conformation of the molecule.

Table I. Lanthanide-Induced Shifts for Ketones Related to Epi-α-cyperone[a]

compd	H(4)	H(14)	H(15)	H(12)	H(13)	H-*t*-Bu
17	14.63		3.20			
16		9.33	3.03			
14	14.63		3.20	0.47	0.47	
3		10.00	3.19	1.14	1.14	
13	13.56		3.02	1.00	0.83	
4		10.40	3.39	1.68	1.14	
15	13.72		3.13			1.02
5		10.00	3.58			1.53

[a] Data are expressed in terms of the slope of the line obtained by plotting the change in Eu(fod)$_3$ concentration vs. change in chemical shift for a given proton (Δ[Eu]/$\Delta\delta$). The concentration of substrate ketones ranged from 0.445 to 0.582 M.

In addition to dihydro-α-cyperone (**3**), dihydroepi-α-cyperone (**4**), and *tert*-butyl enone **5**, the LIS studies were carried out on the 14-nor analogues (**13**, **14**, and **15**) and the simple model octalones **16** and **17**. The results of these studies are summarized in Table I.

The enones of the 10-epi-α-cyperone series (**4** and **15**) show a significant difference in the induced shifts of the protons of the individual isopropyl methyls (H-12 and H-13), particularly when compared to the equality in induced shifts for the same protons in dihydro-α-cyperone (**3**) and its 14-nor analogue (**14**). Examination of models of these enones indicates that in the most favorable twist conformations of enones **4** and **15** (isopropyl pseudoequatorial), there should be little difference in the magnitude of the induced shifts of the individual methyl groups. If enones **4** and **15** exist preferentially with ring B in a chair conformation in which the axial isopropyl group has as a preferred conformation that rotamer about the C(7)–C(11) bond in which the methine proton is directed intraannularly, then the LIS data are readily explained. Also, in this conformation H-12 and H-13 should be magnetically nonequivalent, as is observed, due to the anisotropy of the π system of the enone.

The LIS data for the *tert*-butyl enones **5** and **13** proved rather puzzling since inspection of models in which ring A was in the normal half-chair conformation and ring B in a twist conformation with a pseudoequatorial *tert*-butyl group indicated that the induced shift for *tert*-butyl protons should be essentially the same as that for the isopropyl protons in enones **3** and **14**. The induced shifts were, however, more similar to those of the most shifted protons of the apparently axial isopropyl group in enones **4** and **15**, suggesting that the conformations of enones **5** and **13** were probably similar.

In order to gain further insight into the conformations of these enones, we carried out a study of their ^{13}C NMR spectra, and a detailed analysis was made of the chemical shift differences as a function of stereochemistry.[17]

The ^{13}C NMR signals were assigned by using the standard methods of comparison with model compounds, deuterium substitution, off-resonance decoupling, and LIS studies using Yb(dpm)$_3$.[17] The ^{13}C spectra of enones **16**[18] and **17**[19] had been reported and were used as a foundation

(15) The CD curve of enone **3** depicted in Figure 1 is that of the enantiomer, obtained by reversing the sign of Θ for each point used in plotting the curve.

(16) Schneider, H. J.; Weigand, E. F. *Tetrahedron* **1975**, *31*, 2125.

(17) (a) Levy, G. C.; Nelson, G. L. "C-13 Nuclear Magnetic Resonance for Organic Chemists"; Academic Press: New York, 1972. (b) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972. (c) Wilson, N. K.; Stothers, J. B. *Top. Stereochem.* **1974**, *8*, 1. (d) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden and Son: New York, 1976.

(18) Buckwalter, B. L.; Burfitt, I. R.; Nagel, A. A.; Wenkert, E.; Naf F. *Helv. Chim. Acta* **1975**, *58*, 1567.

(19) Birnbaun, G. I.; Stoessel, A.; Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1974**, *52*, 993.

Table II. ^{13}C Chemical Shifts of α-Cyperone and Related Enones[a]

carbon	compd									
	16[b]	3	4	5	17[b]	14	15	13	1	2
1	37.8	37.5	37.4	36.4	38.1	37.9	38.1	36.2	37.5	37.7
2	33.9	33.8	34.0	34.1	34.1	34.0	34.1	34.2	33.8	34.0
3	198.8	199.0	198.7	198.6	199.6	199.7	199.3	199.2	199.0	198.7
4	128.4	128.6	130.2	130.0	124.3	124.5	125.9	126.3	128.9	129.3
5	162.9	163.2	162.7	165.9	170.6	171.0	169.9	173.9	162.1	162.0
6	27.8	31.5	30.6	27.9	32.8	36.5	35.7	31.9	33.0	31.2
7	27.0	45.2	42.5	44.0	27.3	45.5	42.4	45.1	46.0	41.1
8	21.6	24.6	23.8	21.2	21.8	25.0	23.9	21.4	27.0	23.2
9	42.2	42.2	37.1	37.7	41.6	41.5	36.5	37.6	42.0	36.0
10	36.2	36.1	36.1	35.9	36.0	35.8	35.8	36.0	35.9	36.0
11		33.0	27.9	33.7		32.8	26.7	34.2	149.1	147.6
12		19.8[c]	21.9			19.7[c]	20.9[c]		109.4	111.2
13		19.4[c]	20.5			19.5[c]	20.6[c]		20.6	22.6
14	10.8	10.8	11.2	11.3					10.9	11.0
15	22.5	22.5	23.2	25.1	22.1	22.2	22.8	24.7	22.5	23.2
t-Bu				27.5				27.5		

[a] In parts per million downfield from Me_4Si. [b] Chemical shifts from this work, assignments from ref 18 and 19. [c] Assignments in any vertical column may be interchanged.

for shift assignments in other compounds. Deuterium substitution was carried out at C-2 and C-6 and in the 14-nor series at C-4 by treatment with deuterium oxide and mild acid. A sample of enone **4**, partially deuterated at C-11, C-12, and C-13, was prepared by reduction of ketol **6** with deuterium and palladium, followed by dehydration. The chemical shift assignments for the enones are summarized in Table II.[20]

The interpretation of the ^{13}C chemical shifts for those enones (**3**, **4**, **14**, and **15**) with an isopropyl group at C-7 is quite straightforward. As expected on the reasonable assumption that an equatorial substituent at C-7 will not distort the A ring of these enones, the ^{13}C chemical shifts of those carbons associated with ring A of these compounds (C-1 to C-5, C-10, C-14, C-15) are essentially identical with those of the unsubstituted enones (**16** and **17**, respectively). In enones **3** and **14**, the carbons α and β to the isopropyl methine (C-6 to C-8) were significantly deshielded due to α and β effects with a magnitude appropriate for an equatorial alkyl substituent at C-7.[17b] Also, as expected for an undistorted conformation for ring B, the chemical shift of C-9 in these enones was the same as that in the corresponding enones unsubstituted at C-7.

The ^{13}C spectra of dihydroepi-α-cyperone (**4**) and its 14-nor analogue (**15**) were entirely consistent with a ring B chair conformation bearing an axial isopropyl group and were incompatible with a ring B twist conformation. In particular, in both these enones the isopropyl methine (C-11) and C-9 are shielded by 5.0–5.1 ppm relative to the same carbons in enones **3** and **14**, consistent with a γ-gauche effect caused by the interaction of an axial substituent at C-7 (C-11) with C-9.[17,21] Confirmatory evidence for this conformation is the observation that C-7 in enones **4** and **15** is shielded relative to C-7 in enones **3** and **14**.[17b,22] Also, the isopropyl methyl carbons in enones **4** and **15** are deshielded relative to those of enones **3** and **14**, again indicative of an axial isopropyl group.[23]

It has been noted that, in general, the ^{13}C chemical shifts of the carbon atoms in a twist conformation cyclohexane ring are quite shielded relative to those of a structurally similar chair conformation.[23,24] In particular, it has been found that a carbon located directly across a twist conformation cyclohexane ring from a substituted carbon atom is shielded by 1.5–4.3 ppm.[23] Quite significantly, the C-10 signal in enones **3**, **4**, **14**, and **15** all have virtually the same chemical shifts, as do the angular methyl carbons (C-15), indicating that ring B in these enones exists predominantly in the chair conformation.

The only significant and unpredicted difference in ^{13}C chemical shifts in enones **4** and **15** relative to those either unsubstituted at C-7 (**16**, **17**) or with an equatorial substituent at C-7 (**3** and **14**) is a downfield shift of 1.4–1.8 ppm for C-4. This deshielding may be due to distortion of ring A in the region of the enone system, which may also be responsible for the observed differences in the chiroptical properties of dihydro-α-dyperone and its C-10 epimer.

Comparison of the ^{13}C chemical shift data of α-cyperone (**1**) and epi-α-cyperone (**2**) (Table II)[25] with their dihydro analogues (**3** and **4**) indicates that with the exception of the obvious differences caused by replacing two sp^3 hybrid carbons with two sp^2 hybrid carbons the ^{13}C spectra of enones **1** and **3** were identical as were those of enones **2** and **4**.[26] All of the chemical shift differences between α-cyperone and epi-α-cyperone were the same as those between their dihydro analogues, and it may be concluded that both series of compounds have the same preferred conformations.

The interpretation of the ^{13}C spectra of the *tert*-butyl enones **5** and **13** were less straightforward than that of the 7-isopropyl compounds. Using dihydroepi-α-cyperone (**4**) and its 14-nor analogue (**15**) as models, one can see (Table II) that the chemical shifts of C-2, -3, -4, and -14 (enone

(20) A detailed description of the ^{13}C shift assignments is found in the Ph.D. dissertation of William E. Swain, Clemson University, 1979.

(21) (a) Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1974**, *52*, 870. (b) Grover, S. H.; Marr, D. H.; Stothers, J. B.; Tan, C. L. *Ibid.* **1975**, *53*, 1351.

(22) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1972**, *94*, 5318.

(23) Loomes, D. J.; Robinson, M. J. T. *Tetrahedron* **1977**, *33*, 1149.

(24) (a) Roberts, J. D.; Weigert, F. J.; Kroschwitz, J. I.; Reich, H. J. *J. Am. Chem. Soc.* **1970**, *92*, 1338. (b) van der Graaf, B.; von Bekkum, H.; von Konigsweld, H.; Sinnema, A.; van Been, A.; Wepster, B. M.; von Wijke, A. M. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 135. (c) Pelletier, S. W.; Djarmati, Z. *J. Am. Chem. Soc.* **1976**, *98*, 2626.

(25) The detailed ^{13}C analysis was performed initially on the dihydro compounds for several reasons. (1) The vast bulk of the empirical stereochemical ^{13}C NMR correlations have been carried out with sp^3-hybridized carbon atoms bonded to the cyclic systems.[17-19,21-23] (2) The *tert*-butyl enones must have an sp^3 carbon bonded to the cyclic system, and for comparison purposes it was deemed necessary to use compounds which also had an sp^3 carbon bonded to the ring. (3) Although no conformational free-energy data for the isopropenyl group are available, the presence of an sp^2-hybridized carbon bonded to the cyclohexane ring should lead to a smaller conformational free-energy difference for isopropenyl than for isopropyl.

(26) The differences in chemical shifts in the region of the isopropenyl group compared with those in the region of the isopropyl group are almost certainly due to changes in steric interactions caused by differing C-(11)–C(13) bond angles in the two series.

5) were virtually identical. C-1 is, however, shielded by 1.0–1.9 ppm, indicating some deformation of ring A, while the chemical shift of C-10 is essentially the same in the 7-*tert*-butyl enones and enones **4** and **15**. As noted above, a carbon in the 4-position relative to a substituent on a twist conformer is normally shielded relative to those of a chair cyclohexane[23] as are the remainder of the ring carbons.[23,24] The balance of the ring B carbons (C-5 to C-9) are not particularly shielded relative to the same carbons in enones **4** and **15**, which did not seem consistent with the expected twist conformation for enones **5** and **13**. In fact, C-5 in enones **5** and **13** is *deshielded* by 3.2 and 4.0 ppm, respectively, relative to the isopropyl compounds.

The best explanation for the observed ^{13}C chemical shifts in enones **5** and **13** appeared to be a chair conformation for ring B in which an axial *tert*-butyl group has a preferred conformation in which one of the *tert*-butyl methyl groups is eclipsed with C-5. The deshielding of C-5 would be due to a syn δ effect,[17c,d,21a] and the shielding of C-6 and C-8 relative to that in the isopropyl analogues (**4** and **15**) would be caused by an additional γ-gauche interaction with the remaining *tert*-butyl methyl groups. C-9 in enones **5** and **13** is slightly deshielded relative to C-9 in enones **4** and **13**, which could be attributed to a δ effect partially offsetting the γ-gauche effect caused by interaction with C-11. The conformation in which one *tert*-butyl methyl is eclipsed with the sp^2-hybridized C-5 minimizes the interactions of the internal methyl of the *tert*-butyl group with the axial hydrogens in the cyclohexane ring. Also, when the differences in ^{13}C chemical shifts between the *tert*-butyl-substituted enones (**5** and **13**) and their unsubstituted analogues (**16** and **17**) were compared with similar shift differences in rigid systems in which *tert*-butyl groups were constrained in an axial conformation,[23] these shift differences seemed entirely consistent with a chair conformation and an axial *tert*-butyl group in enones **5** and **13**.

The small differences in chemical shifts at C-1 and C-15 (angular methyl) in *tert*-butyl enones **5** and **13** when compared with those of their isopropyl analogues (**4** and **14**) were attributed to deformations in ring A. This deformation combined with the deformation responsible for the deshielding of C-4 would then be responsible for the observed differences in chiroptical properties as a function of the stereochemistry and nature of the substituent at C-7 in all those enones related to epi-α-cyperone.

The existence of a flexible, completely carbocyclic system bearing an axial *tert*-butyl group was unprecedented at the time this working hypothesis for the conformation of enones **5** and **13** was adopted, although axial *tert*-butyl groups in rigid[23,27] and heterocyclic[28] systems were known. However, very recently a decahydroquinoline derivative with an axial *tert*-butyl group on a nonrigid carbocyclic ring has been reported.[29] If allowances are made for differences in the preferred conformation about the C-7, C-15 bond in enones **5** and **13** suggested above and that found for the analogous bond in the decahydroquinoline derivative,[29] the ^{13}C data for enones **5** and **13** appear consistent with a preferred chair conformation bearing an axial *tert*-butyl group.

In order to obtain additional evidence concerning the conformations of both *tert*-butyl enone **5** and dihydroepi-α-cyperone (**4**), we examined their 200- and/or 220-MHz ^1H NMR spectra.[30] Although the C-2 and allylic protons at C-6 in these enones overlap to form an ill-defined, four-proton envelope at 60 MHz, they are cleanly resolved at 200 and 220 MHz. A first-order analysis of the 220-MHz spectrum of dihydroepi-α-cyperone (**4**) was entirely consistent with the chair conformation of ring B with an axial isopropyl group. The allylic protons at C-6 constitute the MX portion of an AMX spin system, with the equatorial proton appearing as a doublet of triplets centered at δ 2.79. In addition to a 15.0-Hz geminal coupling constant, this proton shows a 2.3-Hz coupling with the equatorial proton at C-7 and a 2.3-Hz W coupling with the equatorial proton at C-8. The equatorial proton at C-6 in dihydro-α-cyperone (**3**), the C-7 epimer of enone **4**, shows similar W coupling with the equatorial proton at C-8. The axial proton at C-6 in enone **4** appears as a doublet of doublets centered about δ 2.21 in which each peak is further split into a multiplet (J = 1.1 Hz) by homoallylic coupling with the vinyl methyl protons. Irradiation of the vinyl methyl signal collapsed this pattern to a clean doublet of doublets (J_{MX} = 15.0 Hz, J_{AM} = 5.1 Hz). The relatively small vicinal coupling constants for the protons at H-6 combined with the 2.3-Hz W coupling are consistent only with a chair conformation for ring B in enone **4** in which the isopropyl group is axial. The protons α to the carbonyl group at C-2 appeared as an 18-line pattern between δ 2.33 and 2.63, confirmed by selective deuteration at C-2 under basic conditions.[31]

The 220-MHz spectrum of 7-*tert*-butyl enone **5** could not be interpreted by a first-order analysis. The region downfield from the vinyl methyl signal (δ 1.78) showed a six-line pattern for one proton centered at δ 1.93 and a 19-line, four-proton pattern between δ 2.27 and 2.70. Selective deuteration at C-2[31] caused considerable perturbation of the six-line pattern at δ 1.78, and this signal is thus assigned to one of the protons at C-1, with the perturbations caused by vicinal H–D coupling to C-2. The lower field, four-proton pattern was now reduced to the XY portion of an AXY system, centered about δ 2.36. The X proton of this system showed a small (<1 Hz) coupling with the vinyl methyl, and the system as a whole had J_{XY} = 16.6 Hz, J_{AX} = 7.1 Hz, and J_{AY} = 6.5 Hz. Although vicinal equatorial–equatorial and/or equatorial–axial coupling constants as great as 7 Hz have been reported, these coupling constants are usually less than 5.5 Hz.[32] Also, the chemical shift difference between these protons (δ 2.32, 2.41; $\Delta\delta$ = 0.09) is less than normally found for equatorial and axial protons in a normal chair conformation. However, examination of models of enone **5** in which ring B is in that twist conformation with a pseudoequatorial *tert*-butyl group in which other steric interactions in ring B are minimized indicates that the dihedral angle between the pseudoaxial protons at C-6 and C-7 is approximately 170°. The pseudoequatorial–pseudoaxial dihedral angle about C-6 and C-7 is then approximately 50°. This would then lead to predicted coupling constants of approximately 15 and 4 Hz, respectively, assuming no unusual electronic affects.[32]

In order to resolve the apparent incompatibility of the ^{13}C and high-resolution ^1H NMR data, we carried out a

(27) Woodworth, C. W.; Buss, V.; Schleyer, P. v. R. *Chem. Commun.* **1968**, 569.
(28) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1966**, *88*, 5347.
(29) (a) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1979**, *44*, 1081. (b) Hargrave, K. D.; Eliel, E. L. *Tetrahedron Lett.* **1979**, 1987.

(30) The spectra determined at Rockefeller University were carried out at 220 MHz. Those determined at the University of South Carolina and Lousiana State University were carried out at 200 MHz.
(31) Lund, E.; Budzikiewicz, H.; Wilson, J. M.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 1528. The position of deuteration under these conditions in enones **4** and **5** was verified by ^{13}C NMR.
(32) Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden Day: San Francisco, 1964; pp 49–52, 104, 144–146.

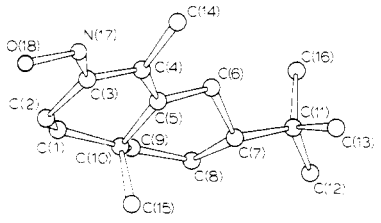

Figure 2. Atom numbering scheme and solid-state conformation of the oxime of enone **5**; the hydrogen atoms have been omitted for clarity.

Table III. Fractional Atomic Coordinates (×10⁴) for the Nonhydrogen Atoms with Estimated Standard Deviations in Parentheses

atom	x	y	z
C(1)	2707 (7)	2184 (4)	242 (4)
C(2)	5125 (6)	2626 (3)	545 (3)
C(3)	5998 (6)	3555 (3)	-425 (3)
C(4)	4787 (5)	3697 (3)	-1700 (3)
C(5)	3028 (5)	2940 (3)	-2062 (3)
C(6)	1707 (7)	3113 (3)	-3330 (4)
C(7)	284 (5)	2045 (3)	-3837 (3)
C(8)	-1163 (7)	1428 (5)	-2839 (4)
C(9)	-338 (6)	1643 (4)	-1438 (4)
C(10)	2167 (5)	1897 (3)	-1183 (3)
C(11)	-879 (6)	2239 (3)	-5209 (4)
C(12)	-2397 (9)	1138 (4)	-5600 (5)
C(13)	777 (9)	2492 (5)	-6213 (4)
C(14)	5667 (7)	4746 (3)	-2544 (4)
C(15)	3134 (7)	874 (3)	-1437 (4)
C(16)	-2126 (9)	3194 (4)	-5296 (5)
N(17)	7790 (5)	4250 (3)	-216 (3)
O(18)	8849 (4)	4044 (3)	1025 (2)

single-crystal, X-ray analysis of the oxime of racemic enone **5**. The ^{13}C NMR spectrum of the oxime indicated that the oxime and parent ketone had the same ring-B conformation as the parent ketone.

Crystal Structure and Solid-State Conformation of the Oxime of (+)-11-Methyl-10-epieudesm-4-en-3-one. The conformation of the oxime of racemic enone **5** in the solid state, as established by X-ray analysis, is shown in Figure 2. Positional parameters for the nonhydrogen atoms are given in Table III and bond lengths and bond and torsion angles (Table IV), anisotropic thermal parameters for the nonhydrogen atoms (Table V), and positional and thermal parameters for the hydrogen atoms (Table VI) are included in the supplementary material.[33]

Molecules of the oxime of enone **5** occur in the solid state as dimers associated by O–H···N (O···N 2.785 Å) hydrogen bonds around crystallographic centers of symmetry. All bond lengths and valency angles are close to accepted values.[34] Ring A, with endocyclic torsion angles[35] of $\omega_{1,2}$ = 49.9°, $\omega_{2,3}$ = -18.8°, $\omega_{3,4}$ = -6.9°, $\omega_{4,5}$ = 0.4°, $\omega_{5,10}$ = 30.2°, and $\omega_{10,1}$ = -54.8°, approximates an envelope form in which C(1) is the out-of-plane atom. The significant departure of the torsion angle about the C(3)–C(4) bond from an ideal envelope value of 0°, i.e., that which would maximize π overlap in the C=C—N=O moiety, may be ascribed principally to the twisting which occurs around this bond in order to relieve an unfavorably short O(18)···H(2β) steric interaction and results in nearly equal O(18)···H(2α) and O(18)···H(2β) distances.[36a] The endocyclic torsion angles in ring B ($\omega_{5,6}$ = -24.1°, $\omega_{6,7}$ = 53.7°, $\omega_{7,8}$ = -25.0°, $\omega_{8,9}$ = -30.5°, $\omega_{9,10}$ = 58.3°, $\omega_{10,5}$ = -29.6°) characterize a twist form with one approximate C_2 axis passing through C(6) and C(10) and the other bisecting the C(6)–C(7) and C(9)–C(10) bonds. The *tert*-butyl group is rotated about the C(7)–C(11) bond by a mean of 12° from a perfectly staggered conformation with respect to the C(6)–C(7) and C(7)–C(8) ring bonds. This orientation reflects the nonequivalent nature of H(6β) and H(8β) in the twist form, and the rotation serves to minimize nonbonding interactions between the C(6) and C(8) methylene hydrogens and those on the *tert*-butyl substituent.[36b]

Conclusions

All of the available NMR data, both ^1H and ^{13}C, indicate that epi-α-cyperone (**2**), its dihydro derivative, and the 14-normethyl analogue (**15**) all exist predominently in a ring-B chair conformation in which the substituent at C-7 is axial. The differences in chiroptical properties between epi-α-cyperone and its derivatives and α-cyperone and its derivatives are almost certainly due to small changes in the spatial relationship between the π electrons of the olefinic portion of the enone system and the carbonyl oxygen.[37] By use of Snatzke's empirical approach to the interpretation of CD curves of conjugated enones,[37] it is apparent that a slight flattening of ring A in the epi-α-cyperone series would result in the change in Cotton effect which is observed relative to dihydro-α-cyperone (Figure 1). This is also consistent with the slight changes in the ^{13}C NMR chemical shifts of C-4 in the 10-epi series, relative to the natural cyperones, which are discussed above.

The ^1H and ^{13}C NMR and crystal structure data for *tert*-butyl enone **5**, and by analogy normethyl enone **13**, appear to be mutually contradictory. The ^{13}C data appear to indicate a chair or distorted chair conformation for ring B while the crystal structure data show that ring B is in a twist conformation with a pseudoequatorial *tert*-butyl group. The ^1H NMR data are compatible with neither conformation; however, the observation that both H-6, H-7 vicinal coupling constants are greater than 5.5 Hz indicates that H-7 should be outside the geminal protons at C-6,[32] suggesting a twist conformation for ring B. The magnitude of these vicinal coupling constants is, however, not consistent with the conformation found by X-ray analysis. The most probable explanation for these apparently contradictory data is that enone **5** (and **13**) exists in solution as an equilibrium mixture of chair and twist conformers, the oxime of which crystallizes preferentially in the twist conformation. A crude approximation of the position of this equilibrium may be made if it is assumed that the vicinal H-6, H-7 coupling constants in the chair conformer of enone **5** are the same as those in enone **4** and that the coupling constants in the twist conformer are those predicted on the basis of the Karplus relationship.[32] Application of Eliel's equation for the determination of conformational equilibria from coupling constants,[38] given the above assumptions, indicates that in solution about 50–75% of enone **5** exists in the twist conformation and the balance in the chair conformation. This is not an unreasonable conclusion since it has been found that *trans*-3,5-di-*tert*-butylcyclohexanone contains a significant,

(33) See paragraph at end of paper regarding supplementary material.
(34) *Spec. Publ.-Chem. Soc.* **1958**, *No. 11*; **1965**, *No. 18*.
(35) These crystals contain both enantiomers. The discussion of torsion angles and α,β hydrogen atom designations refer to one enantiomer only, viz., that in which the methyl group at C(10) is defined as being on the α face of the molecule.
(36) (a) O(18)···H(2α) 2.80(4), O(18)···H(2β) 2.51(4) Å. (b) The shortest intramolecular H···H distances (Å) involving these groups are as follows: H(6α)···H(13C), 2.29 (7); H(6α)···H(16β), 2.66 (7); H(6β)···H(16B), 2.41 (8); H(6β)···H(16C), 2.67 (7); H(8β)···H(12B), 2.19 (8); H(8β)···H(14C), 2.40 (6).
(37) Snatzke, G. "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry"; G. Snatzke, Ed.; Heyden and Son: London, 1967; pp 203–223.
(38) Eliel, E. L. *Chem. Ind. (London)* **1959**, 568.

though unspecified, amount of the chair conformer.[23] The strongly negative CD curve of enone **5** is consistent with the planar enone structure determined by X-ray and shown in Figure 2.[33]

Finally, it should be noted that there are no data, either spectral or chiroptical, indicating that any of these enones adopt a nonsteroidal-type conformation,[9] nor are there any data indicating that allylic interactions between a vinyl methyl group at C-4 and the C-6 methylene caused any significant distortions of these molecules.

Experimental Section

Microanalyses were performed by Galbraith Laboratories or Atlantic Microlab. Infrared spectra, reported in reciprocal centimeters, were routinely measured, unless otherwise noted, as liquid films between sodium chloride plates on a Perkin-Elmer Model 137 spectrophotometer. Routine ^{1}H NMR spectra were recorded at 60-MHz by using either a Varian A-60A or Hitachi Perkin-Elmer R-24 spectrometer; signals are reported in parts per million (δ) relative to tetramethylsilane. All NMR spectra were carried out in deuteriochloroform solution. Ultraviolet spectra were obtained in 95% ethanol solution on a Cary-14 ultraviolet–visible spectrophotometer; optical rotatory dispersion and circular dichroism measurements were obtained in dioxane solution by using a JASCO ORD/UV-5 spectropolarimeter. Gas chromatographic analyses were performed on a F&M Model 810 instrument utilizing hydrogen flame detection. Unless otherwise noted, 2 m × 3.3 mm columns were employed with 80–100-mesh Chromosorb W as the support and SE-30 as the stationary phase. Melting points were obtained by using a Mel-Temp apparatus or a Kofler hot-stage apparatus and are uncorrected.

^{13}C NMR spectra were recorded on a Bruker HX-90 spectrometer operating at 22.6 MHz in the Fourier transform mode. Compounds were studied as 0.10–0.20 M solutions in deuteriochloroform, unless otherwise noted, with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million relative to Me_4Si unless otherwise stated.

10-Epieudesm-11-ene-3β,5α-diol (8). The reduction of ketol **6** with lithium aluminum hydride in tetrahydrofuran was carried out in the usual manner. From 5.0 g (0.021 mol) of ketol there was obtained after recrystallization from hexanes 2.9 g (58%) of off-white needles, mp 94–96 °C. The analytical sample (mp 96–97 °C) was crystallized from the same solvent: ^{1}H NMR δ 0.95 (s, 3 H, CH_3), 1.02 (d, J = 6 Hz, CH_3CH), 1.68 (d, J = 1 Hz, vinyl CH_3), 3.84 (m, 1 H, CHOH), 4.61 (br s, 2 H, CH_2=C).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92. Found: C, 75.67; H, 10.76.

10-Epieudesm-11-ene-3α,5α-diol (9). A solution of 15.0 g (0.064 mol) of ketol **6** in 65 mL of anhydrous ether and 65 mL of *tert*-butyl alcohol was added to 200 mL of liquid ammonia. Lithium wire was added to the reaction mixture in small pieces with vigorous stirring until a permanent blue color was obtained. After being stirred for 0.5 h, the reaction was quenched with methanol and the ammonia allowed to evaporate. The resulting slurry was poured into 200 mL of brine and the mixture extracted with three portions of ether. The ethereal extracts were combined, washed with dilute hydrochloric acid, water, and brine, and dried, and the solvent was removed to give a white solid. Recrystallization from cyclohexane afforded 11.3 g (74%) of white crystals, mp 125–127 °C. The analytical sample (mp 127–128 °C) was prepared from the same solvent: ^{1}H NMR δ 0.98 (s, 3 H, CH_3), 1.03 (d, J = 6 Hz, CH_3CH), 1.68 (s, 3 H vinyl methyl), 3.22 (m, 1 H, CHOH), 4.58 (br s, 2 H, CH_2=CH).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92. Found: C, 75.63; H, 11.00.

The 3-acetate of diol **9** (**10**) was prepared in the usual manner with acetic anhydride–pyridine. From 12.7 g (0.053 mol) of diol there was obtained 13.6 g (92%) of material (mp 92–95 °C) after one recrystallization from hexanes. The analytical sample (mp 95–96 °C) was crystallized from the same solvent: IR 3700, 1730; ^{1}H NMR δ 0.92 (d, J = 7 Hz, 3 H, CH_3CH), 1.03 (s, 3 H, CH_3), 1.73 (s, 3 H, vinyl CH_3), 2.05 (s, 3 H, CH_3CO), 4.70 (br s, 2 H, CH_2=C).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.86; H, 10.00. Found: C, 72.86; H, 10.09.

11-Cyclopropyl-10-epieudesma-3α,5α-diol (11). To 75 mL of anhydrous ether were added 15.8 g (0.24 mol) of zinc dust and 2.4 g (0.024 mol) of cuprous chloride, and the mixture was heated at reflux with stirring under nitrogen for 30 min. To this mixture were added 13.4 g (0.048 mol) of acetate **10** and 9.7 mL (0.12 mol) of freshly distilled methylene iodide, and the solution was heated at reflux 24 h. An additional 15.7 g of zinc dust and 2.4 g of cuprous chloride were added followed by 9.7 mL of methylene iodide, and reflux was continued for an additional 24 h. The resulting mixture was filtered through Celite and poured into 100 mL of saturated ammonium chloride. The layers were separated, and the aqueous layer was extracted twice with ether. The combined ethereal solutions were washed thoroughly with saturated sodium bicarbonate, water, and brine and dried, and the solvent was removed to afford 16.8 g of crude product as a waxy solid. All attempts to crystallize the product were unsuccessful; however, the spectral properties were consistent with the structure: IR 3700, 1730 (C=O); ^{1}H NMR δ 0.19 (s, 4 H, cyclopropyl CH_2), 0.89 (d, J = 7 Hz, CH_3CH), 0.89 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.97 (s, 3 H, CH_3CO), 4.43 (m, 1 H, CHOAc).

A solution of 16.8 g (0.057 mol) of crude acetate in 75 mL of dry tetrahydrofuran was added dropwise to a slurry of 3.3 g of lithium aluminum hydride in 300 mL of tetrahydrofuran and the mixture heated at reflux for 1.5 h. The product was isolated in the usual manner, and the resulting yellow oil was chromatographed on 280 g of silica gel. Elution with 30% ethyl acetate in benzene afforded 13.9 g of solid material which on crystallization from hexanes afforded 7.0 g of white needles, mp 132–134 °C. Three additional recrystallizations provided the analytical sample: mp 134–135 °C; ^{1}H NMR δ 0.21 (s, 4 H cyclopropyl CH_2), 0.90 s, 3 H CH_3), 0.97 (s, 3 H, CH_3), 1.02 (d, J = 6 Hz, CH_3CH), 3.22 (m, 1 H, CHOH).

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.19; H, 11.11. Found: C, 76.16; H, 11.18.

11-Cyclopropyl-5α-hydroxy-10-epieudesman-3-one (7). A. The reaction of ketol **6** with methylene iodide and the zinc–copper couple was carried out as described above. From 8.0 g (0.032 mol) of **6** there was obtained 7.4 g of a mixture of two compounds (TLC). The crude product was dissolved in benzene–ethyl acetate (9:1) and chromatographed on 200 g of Woelm silica gel. The first fractions eluted with this solvent contained an oily α,β-unsaturated ketone (IR) which was not characterized further. Later fractions eluted with the same solvent pair afforded ketol **7** as a white solid. Recrystallization from hexanes afforded 1.03 g (12%) of white needles, mp 94–98 °C. The analytical sample (mp 99–100 °C) was crystallized from the same solvent: IR 3660, 1720; ^{1}H NMR δ 0.20 (cyclopropyl CH_2), 0.90 (s, 3 H, CH_3), 1.08 (d, J = 6 Hz, CH_3CH), 1.27 (s, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.80; H, 10.40. Found: C, 76.90; H, 10.56.

B. Diol **11** was oxidized with Jones reagent in the usual manner. From 5.0 g (0.020 mol) of diol there was obtained 4.5 g (91%) of ketol **7** (mp 99–100 °C) identical in all respects with that described in A above.

11-Methyl-5α-hydroxy-10-epieudesman-3-one (12). To a solution of 1.5 g (0.006 mol) of ketol **7** in 50 mL of glacial acetic acid was added 0.75 g of Adams catalyst, and the mixture was shaken with hydrogen at 40 psi for 12 h. An additional 0.75 g of catalyst was added and the hydrogenation continued for an additional 12 h. After removal of the catalyst, the resulting viscous oil was treated with Jones reagent in the usual manner. The product crystallized from hexanes to give 1.3 g (87%) of white needles, mp 105–108 °C. The analytical sample (mp 109–110 °C) was prepared by crystallization from the same solvent: IR 3705, 1710; ^{1}H NMR δ 0.81 (s, 9 H, $(CH_3)_3C$), 1.02 (d, J = 7 Hz, CH_3CH), 1.21 (s, 3 H, CH_3).

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.19; H, 11.11. Found: C, 76.12; H, 11.21.

(±)-11-Methyl-5α-hydroxy-10-epieudesman-3-one (12). To 5.0 g (0.030 mol) of 5-*tert*-butyl-2-methylcyclohexanone[11] was added 0.8 mL of 3 N sodium ethoxide under nitrogen, and the mixture was cooled to −10 °C. To this cooled solution was added dropwise 2.6 g (0.031 mol) of ethyl vinyl ketone followed by the addition of another 0.8 mL of base and 2.6 g of ethyl vinyl ketone. The mixture was maintained at −15 °C for 3 days and then poured into saturated ammonium chloride and extracted with three

portions of ether. The ethereal extracts were washed with brine and dried, and the solvent was removed to give a brown oil. Distillation afforded 3.9 g of a viscous oil [bp 120–145 °C (0.03 mm)] which on trituration with hexanes afforded 0.660 g of white crystals, mp 92–102 °C. The mother liquors were dissolved in benzene–ethyl acetate (9:1) and chromatographed on 70 g of Woelm silica gel. Elution with these solvents gave an additional 2.0 g of solid material. Recrystallization of the crystalline material from hexanes gave 2.07 g (27%) of white prisms, mp 106–109 °C. The solution infrared spectrum (CCl_4) of this racemic product was identical with that of the enantiomer described above.

11-Methyl-10-epieudesm-4-en-3-one (5). To a solution of 0.40 g (0.0016 mol) of ketol **12** in 25 mL of toluene was added a few crystals of toluenesulfonic acid, and the mixture was heated at reflux for 72 h in a Soxhlet extraction apparatus packed with 3A molecular sieves, with additional *p*-toluenesulfonic acid added at 12-h intervals. The reaction mixture was cooled, washed with saturated aqueous sodium bicarbonate, and dried, and the solvent was removed at reduced pressure. This oil was a mixture of three materials (TLC) and was dissolved in benzene and chromatographed on 15 g of Woelm silica gel. Elution with benzene afforded the desired enone, which was further purified by distillation (air bath) [bp 105–106 °C (0.025 mm)] to give 0.299 g (80%) of a clear, off-white oil which was homogeneous by TLC and GLC: IR 1655, 1610; UV λ_{max} 253 nm (ϵ 15 500); ^{1}H NMR δ 0.89 (s, 9 H, $(CH_3)_3C$), 1.21 (s, 3 H, CH_3), 1.78 (s, 3 H, vinyl CH_3); CD (*c* 0.006 33, 25 °C) $[\Theta]_{390}$ 0, $[\Theta]_{380}$ −209, $[\Theta]_{368}$ −2451, $[\Theta]_{366}$ −2191, $[\Theta]_{349}$ −6258, $[\Theta]_{345}$ −6154, $[\Theta]_{337}$ −7510, $[\Theta]_{329}$ −6049, $[\Theta]_{326}$ −6049, $[\Theta]_{316}$ −3651, $[\Theta]_{314}$ −3651, $[\Theta]_{300}$ −1252, $[\Theta]_{290}$ −417.

Anal. Calcd for $C_{16}H_{26}O$: C, 82.05; H, 11.11. Found: C, 81.85; H, 11.18.

The 2,4-dinitrophenylhydrazone formed red needles (mp 204–205 °C) from ethanol.

Anal. Calcd for $C_{22}H_{30}N_4O_4$: C, 63.77; H, 7.25; N, 13.53. Found: C, 63.77; H, 7.29; N, 13.51.

(±)-11-Methyl-10-epieudesm-4-en-3-one (5). To a solution of 0.250 g (0.001 mol) of racemic ketol **12** in 24 mL of methanol was added a solution of 0.397 g of sodium hydroxide in 4 mL of water. The reaction mixture was heated at reflux under nitrogen for 19 h, cooled, diluted with brine, and concentrated to a small volume. The residue was taken up in ether, washed with brine, and dried, and the solvent was removed to give 0.237 g of yellow oil, the IR of which indicated that it contained some residual starting material. Purification as described above for the optically active material afforded 0.206 g (89%) of racemic enone **5**, the spectral properties of which were identical with those of the optically active material.

The oxime formed needles (mp 160–161 °C) from aqueous methanol.

Anal. Calcd for $C_{16}H_{27}NO$: C, 77.11; H, 10.84; N, 5.62. Found: C, 77.06; H, 10.92; N, 5.59.

10-Epieudesm-4-en-3-one (Dihydroepi-α-cyperone, 4). This compound was prepared from 5α-hydroxy-10-epieudesm-11-en-3-one[2b,10] by a modification of the method of Hikino.[12] The IR and ^{1}H NMR agreed with those reported:[12] UV λ_{max} 251 nm (ϵ 14 500); CD (*c* 0.015, 25 °C) $[\Theta]_{390}$ 0, $[\Theta]_{380}$ −86, $[\Theta]_{369}$ −644, $[\Theta]_{364}$ −644, $[\Theta]_{354}$ −1223, $[\Theta]_{349}$ −1051, $[\Theta]_{342}$ −1158, $[\Theta]_{333}$ −408, $[\Theta]_{329}$ −472, $[\Theta]_{323}$ 0, $[\Theta]_{319}$ +193, $[\Theta]_{315}$ +129, $[\Theta]_{308}$ +300.

(−)-2-Carone. (−)-2-Carone was prepared by a modification of the procedure described by Dauben et al.[13b] To a solution of 25.0 g (0.16 mol) of (+)-dihydrocarvone in 150 mL of chloroform was added a trace of anhydrous aluminum chloride. Dry hydrogen chloride was bubbled through the solution until the vinyl peak was no longer present in the IR (5 h). The solution was filtered and concentrated to give 31.3 g of crude chloro ketone. Without characterization, this material was cooled in an ice bath, and 14.0 g (0.24 mol) of potassium hydroxide in 70 mL of methanol was added in portions. The mixture was stirred for 16 h as the temperature gradually increased to ambient temperature as the ice melted. The solution was filtered, diluted with 100 mL of ether, washed with brine (3 × 50 mL), dried, and concentrated to a pale yellow oil. Distillation afforded 20.8 g (83%) of colorless liquid [bp 80–94 °C (7.2 mm)], the spectral properties of which were consistent with those reported.[13b]

Eudesma-4,11-dien-3-one (α-Cyperone, 1). This material was prepared from (−)-2-carone by the procedure of Caine and Gupton.[13a] The spectral properties agreed with those reported.[13a] Attempted isolation of this compound from the mother liquors of the preparation of ketol **6** by the method of Howe and McQuillen[2b] led to material contaminated with ca. 25% of enone **2**.

Eudesm-4-en-3-one (Dihydro-α-cyperone, 3). To a solution of 0.304 g (1.4 mmol) of α-cyperone (**1**) in 30 mL of dry benzene was added 0.157 g (0.17 mmol) of tris(triphenylphosphine)rhodium chloride. After the flask was flushed with hydrogen, the mixture was sealed and stirred for 9 h. The dark solution was filtered through 20 g of Merck neutral alumina, activity II, with benzene as the eluent. After removal of the solvent, distillation afforded 0.292 g (95%) of very faint yellow oil [bp 109–112 °C (0.02 mm, air bath)], homogeneous by TLC and GLC. The IR and NMR spectra agree with those reported by Hikino:[12] CD (*c* 0.0132, 25 °C), $[\Theta]_{390}$ 0, $[\Theta]_{382}$ +100, $[\Theta]_{380}$ +50, $[\Theta]_{372}$ −200, $[\Theta]_{362}$ 0, $[\Theta]_{358}$ +50, $[\Theta]_{356}$ 0, $[\Theta]_{346}$ −1050, $[\Theta]_{342}$ −900, $[\Theta]_{333}$ −2200, $[\Theta]_{327}$ −1900, $[\Theta]_{322}$ −2350, $[\Theta]_{312}$ −1750, $[\Theta]_{308}$ −1750, $[\Theta]_{296}$ −750.

14-Noreudesma-4,11-dien-3-one. This enone was prepared from 2-carvone by following the general method of Caine and Gupton[13a] but by substituting methyl vinyl ketone for ethyl vinyl ketone.[39] The initial alkylation product, **3-(3-oxobutyl)-2-carone** was obtained as a colorless oil: bp 96–115 °C (0.05 mm); IR 1729, 1685; ^{1}H NMR δ 0.90, 1.05, 1.09 (s, 3 H each, CH_3), 2.09 (s, 3 H, CH_3CO).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.68; H, 9.91. Found: C, 75.68; H, 9.96.

Treatment of this compound with ethanolic hydrogen chloride afforded 11-chloro-14-noreudesm-4-en-3-one as off-white crystals from hexane: mp 107–108 °C; IR 1650, 1610; ^{1}H NMR δ 1.22 (s, 3 H, CH_3), 1.58 (s, 6 H, $(CH_3)_2CCl$), 6.67 (s, 1 H, C=CH).

Anal. Calcd for $C_{14}H_{21}ClO$: C, 69.85; H, 8.73. Found: C, 69.82; H, 8.81.

Dehydrohalogenation produced the title enone as an off-white liquid, bp 108–110 °C (0.05 mm), the spectral properties of which were in agreement with those reported by Humber and Pinder.[40]

14-Noreudesm-4-enone (14). The above enone was reduced with tris(triphenylphosphine)rhodium chloride as catalyst by the previously described procedure. After chromatography on Woelm silica gel and distillation there was obtained 0.126 g (78%) of an oil [bp 109–111 °C (0.04 mm)], the spectral properties of which agreed with those reported by Marshall:[41] CD (*c* 0.0177, 25 °C) $[\Theta]_{390}$ 0, $[\Theta]_{380}$ +37, $[\Theta]_{371}$ +224, $[\Theta]_{366}$ 0, $[\Theta]_{360}$ −187, $[\Theta]_{356}$ −112, $[\Theta]_{346}$ −1306, $[\Theta]_{341}$ −1082, $[\Theta]_{332}$ −2126, $[\Theta]_{326}$ −1567, $[\Theta]_{320}$ −1865, $[\Theta]_{310}$ −1231, $[\Theta]_{308}$ −1231, $[\Theta]_{280}$ 0. The 2,4-dinitrophenylhydrazone formed red needles from ethanol: mp 154–155 °C (lit.[41] mp 155–156 °C).

14-Nor-10-epieudesm-4-en-3-one (15). This enone was prepared by the dehydration of 14-nor-5α-hydroxy-10-epieudesman-3-one, which was in turn obtained by catalytic reduction of 14-nor-5α-hydroxy-10-epieudem-11-en-3-one.[42] The spectral properties agreed with those reported for the enantiomer:[42] CD (*c* 0.0169, 25 °C) $[\Theta]_{390}$ 0, $[\Theta]_{380}$ −39, $[\Theta]_{367}$ −626, $[\Theta]_{360}$ −450, $[\Theta]_{353}$ −938, $[\Theta]_{344}$ −156, $[\Theta]_{339}$ −430, $[\Theta]_{334}$ 0, $[\Theta]_{330}$ +508, $[\Theta]_{325}$ +196, $[\Theta]_{318}$ +743, $[\Theta]_{311}$ +430, $[\Theta]_{307}$ +567, $[\Theta]_{302}$ +312.

Deuterium-Labeling Procedures. A. As required for ^{13}C experiments, a solution of 0.500 g of the appropriate enone in 10 mL of diglyme was added to 5 mL of 2 N deuterium chloride in deuterium oxide. The reaction mixture was heated on a steam bath for 15 h, poured into water, cooled, and extracted with two portions of ether. The combined ethereal extracts were washed with saturated aqueous sodium bicarbonate, water, and brine and dried, and the solvent was removed at reduced pressure. The resulting product was distilled at reduced pressure (air bath). NMR analysis of these products indicated essentially complete deuteration at C-2, C-6, and, where possible, C-4.

B. To 10 mL of a solution of sodium deuterioxide prepared by adding 0.350 g of sodium to 20 mL of a 1:1 mixture of dry

(39) Following the completion of our preparation of this compound, the reaction of 2-carone with methyl vinyl ketone was reported by: Caine, D.; Deutsch, H.; Gupton, J. T. *J. Org. Chem.* **1978**, *43*, 343.

(40) Humber, D. C.; Pinder, A. R. *J. Org. Chem.* **1966**, *31*, 4188.

(41) Marshall, J. A.; Roebke, H. *J. Org. Chem.* **1968**, *33*, 840.

(42) Marshall, J. A.; Fanta, W. I.; Roebke, H. *J. Org. Chem.* **1966**, *31*, 1016.

dioxane and deuterium oxide was added 0.100 g of the appropriate enone (4 or 5). The reaction mixture was heated at 65 °C, under nitrogen, for 0.25 h. The product was isolated from the cooled reaction mixture by extraction with ether and the product enone purified by distillation at reduced pressure (air bath). ^{13}C NMR indicated that complete and exclusive deuteration at C-12 had taken place.

C. 11,12-Dideuterio-10-epieudesm-4-en-3-one was prepared by catalytic reduction of ketol 6 with deuterium at a pressure of 14 psig. Dehydration afforded the deuterated enone.

Lanthanide Induced Shift Studies. Proton shift studies were performed by adding known volumes of standard deuteriochloroform solutions of $Eu(fod)_3$ to standard solutions of ketone in deuteriochloroform with tetramethylsilane as an internal reference. The appropriate NMR signal was measured after each increment of shift reagent, and the increase in the chemical shift ($\Delta\delta$) was obtained as: $\Delta\delta = \delta_{Eu} - \delta_0$ where δ_0 is the chemical shift with no shift reagent present and δ_{Eu} is the chemical shift with shift reagent added. Plots were then made of the lanthanide-induced shifts as a function of the molar ratio of shift reagent to substrate. The slope of each line was taken to be the relative induced shift for that signal. The spectra were recorded on a Varian A-60A (60 MHz) spectrometer, and the shift reagent was used as obtained from Aldrich Chemical Co. without further purification.

Crystal Structure of the Oxime of Enone 5. Crystal data: $C_{16}H_{27}NO$, mol wt 249.00; triclinic; a = 6.290 (3) Å, b = 12.010 (5) Å, c = 10.341 (5) Å, α = 85.20 (2)°, β = 95.56 (2)°, γ = 101.09 (2)°; U = 761.3 Å^3; Z = 2, d_{calcd} = 1.088 g cm^{-3}; $F(000)$ = 276; Cu Kα radiation, λ = 1.5418 Å; absorption coefficient for Cu Kα radiation, μ = 5.2 cm^{-1}; space group $P\bar{1}$ (C_i^1) or $P1$ (C_1^1), shown to be the former by structure analysis and refinement.

Crystallographic Measurements. Preliminary unit cell dimensions and space group information were obtained from oscillation and Weissenberg photographs taken with Cu Kα radiation and precession photographs taken with Mo Kα (λ = 0.7107 Å) radiation. A crystal of dimensions ca. 0.16 × 0.24 × 0.50 mm was cut from a larger crystal and oriented on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu Kα radiation). Refined unit cell parameters were derived from least-squares treatment of the diffractometer setting angles for 40 high-order reflections widely separated in reciprocal space. Intensities for all accessible reflections with $\theta \leq 67°$ were recorded by means of the θ–2θ scanning procedure as described previously.[43] From a total of 2755 independent measurements, only those 1609 for which $I \geq 2.0\sigma(I)$, where $\sigma^2(I)$ is the scan count plus the total background count, were corrected for the usual Lorentz and polarization effects prior to their use in the structure analysis. Absorption corrections, derived from the ϕ dependence of the intensity of the 040 reflection measured at χ = 90°, were also applied to these data.

Structure Analysis. The structure was solved by direct methods. At the outset, the correct choice of space group was assumed to be $P\bar{1}$, and the highest 250 $|E|$ values were input to the MULTAN[44] suite of programs. Examination of several E maps derived by use of those phase constants which produced the highest combined figures of merit yielded a set of approximate coordinates for all the nonhydrogen atoms. However, this model failed to refine when subjected to least-squares iterations, owing to the fact that the two molecules in the unit cell were misplaced with respect to the true crystallographic center of symmetry. This difficulty was circumvented, and the correct relative positions of the molecules were derived by reducing the symmetry to that of space group $P1$, employing coordinates appropriate to only one molecule, and reevaluating an electron-density distribution with weighted coefficients. The resulting distribution revealed the location of the second molecule in the unit cell and confirmed that the two molecules were indeed related by a center of symmetry. The coordinates of both molecules were then transformed so that they were related by a crystallographic center of symmetry at the origin of the unit cell, and all further calculations were performed with equivalent positions appropriate to space group $P\bar{1}$. Full-matrix, least-squares refinement of atomic positional and isotropic thermal parameters of the nonhydrogen atoms were followed by the evaluation of a difference Fourier synthesis which confirmed that all hydrogen atoms, save that on the hydroxy group, coincided with regions of significant positive electron density; this map was otherwise quite featureless. Continuation of the refinement, during which positional and thermal (anisotropic C, N, O; isotropic H) parameters were varied, led to convergence at R = 0.068.[45] Final atomic positional parameters for the nonhydrogen atoms are in Table III. Anisotropic thermal parameters (Table V), positional and isotropic thermal parameters for the hydrogen atoms (Table VI), and a listing of observed and calculated structure factors (Table VII) are available as supplementary material.[33]

Atomic scattering factors employed in all structure-factor calculations were those for C, N, and O from ref 46 and for H from ref 47. In the least-squares iterations, $\sum w\Delta^2$ ($\Delta = ||F_o| - |F_c||$) was minimized with weights, w, assigned according to the scheme $w^{1/2} = 1$ when $|F_o| \leq 12.0$ and $w^{1/2} = 12.0/|R_o|$ when $|F_o| > 12.0$.

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Registry No. 1, 473-08-5; 2, 2303-31-3; 3, 18663-53-1; 4, 22555-76-6; 5, 73839-07-3; 5 2,4-diphenylhydrazone, 73839-08-4; (±)-5, 73890-10-5; (±)-5 oxime, 73839-09-5; 6, 21683-08-9; 7, 73839-10-8; 8, 73839-11-9; 9, 73839-12-0; 10, 73839-13-1; 11, 73839-14-2; 11 acetate, 73839-15-3; 12, 73839-16-4; (±)-12, 73890-11-6; 13, 73890-12-7; 14, 66428-80-6; 14 2,4-dinitrophenylhydrazone, 23665-84-1; 15, 16735-08-3; 16, 878-55-7; 17, 826-56-2; 5-*tert*-butyl-2-methylcyclohexanone, 56569-76-7; ethyl vinyl ketone, 1629-58-9; 3-(3-oxobutyl)-2-carone, 73839-17-5; (−)-2-carone, 18541-52-1; (+)-dihydrocarvone, 5524-05-0; 14-noreudesma-4,11-dien-one, 13918-47-3; 11-chloro-14-noreudesm-4-en-3-one, 73890-13-8; methyl vinyl ketone, 78-94-4.

Supplementary Material Available: Tables of bond lengths and valency and torsion angles (Table IV), anisotropic thermal parameters (Table V), and hydrogen atom parameters (Table VI) (5 pages). Ordering information is given on any current masthead page.

(43) Miller, R. W.; McPhail, A. T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1527.
(44) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.
(45) $R = \sum||F_o| - |F_c||/\sum|F_o|$.
(46) Cromer, D. T.; Waber, J. T. *Acta Crystallogr.* **1965**, *18*, 104.
(47) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.