Based on the above observations, we propose the following mechanism for the electrolytic reduction of these complexes:

$$[Ir(dppe)_2X_2]^+ \xrightarrow[A]{1\,e} \quad X_2 = O_2, S_2, Se_2$$

$$\begin{tikzcd}
{[Ir(dppe)_2X_2]^0} \arrow[d, "k_d"] & & \\
{[Ir(dppe)_2]^+ + X_2\cdot^-} \arrow[r, "1\,e", "B"'] & {[Ir(dppe)_2]^0} \arrow[d, "k_H"', "{0.8CH_3CN \; 0.2RH}"] & \\
 & {Ir(dppe)_2H + 0.8CH_2CN\cdot} \arrow[r, "0.8\,e", "B"'] & {CH_2CN\cdot^-} \\
 & {+\ 0.2R\cdot} &
\end{tikzcd}$$

That is, the first reduction wave (A) represents addition of one electron to an orbital which is highly antibonding between the metal and the $X_2$ group; the latter immediately and irreversibly dissociates off as the $X_2\cdot^-$ radical anion. We thus get back unadducted $Ir(dppe)_2^+$ which is further reduced at wave B by one electron to form a highly reactive Ir(0) $d^9$ complex; the latter then abstracts a hydrogen atom from the environment to form orange $Ir(dppe)_2H$ precipitate. Since approximately 80% of the hydride comes from $CH_3CN$ it is plausible to assume that the $CH_2CN\cdot$ radical formed can be further reduced to the corresponding anion at wave B, thus accounting for the coulometric $n = 1.7$-$1.8$ for that wave. It is, however, also possible that both the $CH_2CN\cdot$ and $R\cdot$ radicals are reduced at wave B, but that a competing coupling reaction decreases $n$ from 2 to ~1.8. The anomalous $n$ values obtained for the $S_2$ complex are presumably due to interference by $S_2\cdot^-$ or its reaction products.[10]

The two most important implications of this research are: (1) The lowest unoccupied molecular orbital, to which one electron is added at wave A, must be strongly antibonding between the metal and the $X_2$ group. In terms of the Dewar-Chatt model the orbital involved arises from interaction between a metal d orbital and the $\pi^*$ orbital of $X_2$ which lies in the $MX_2$ plane. (2) The progression of the first reduction wave (A) to more negative potential for $X_2 = Se_2 \rightarrow S_2 \rightarrow O_2$ is taken to indicate that this $\pi$-back-bonding interaction enhances in the same direction, thereby causing stepwise destabilization of the lowest unoccupied molecular orbital along this sequence. These two conclusions are supported by molecular orbital calculations on the model complexes $Rh(PH_3)_4X_2^+$ using Fenske's method.[12] Details will be presented elsewhere.

### References and Notes

(1) L. Vaska, and D. L. Catone, *J. Am. Chem. Soc.*, **88,** 5324 (1966).
(2) J. A. McGinnety, N. C. Payne, and J. A. Ibers, *J. Am. Chem. Soc.*, **91,** 6301 (1969).
(3) A. P. Ginsberg and W. E. Lindsell, *Chem. Commun.*, 232 (1971).
(4) W. D. Bonds and J. A. Ibers, *J. Am. Chem. Soc.*, **94,** 3413 (1971).
(5) (a) M. J. S. Dewar, *Bull. Soc. Chim. Fr.*, **18,** C79 (1951); (b) J. Chatt and L. A. Duncanson, *J. Chem. Soc.*, 2339 (1953).
(6) $Ir(dppe)_2H$: monoclinic $P2_1/n$; $a = 21.260$ (5), $b = 20.809$ (3), $c = 10.107$ (3) Å; $\beta = 91.44$ (2)°; $V = 4470$ (2) Å$^3$; and $Z = 4$. Anisotropic least-squares refinement gave $R_1 = 3.65\%$ and $R_2 = 4.15\%$ for 3452 independent reflections. The important bond lengths (Å) and angles (deg) are: Ir–$P_1$ 2.278 (2), Ir–$P_2$ 2.245 (2), Ir–$P_3$ 2.279 (2), Ir–$P_4$ 2.271 (2); $P_1$–Ir–$P_2$ 83.99 (9), $P_3$–Ir–$P_4$ 87.64 (9), $P_1$–Ir–$P_3$ 106.14 (9), $P_1$–Ir–$P_4$ 107.02 (9), $P_2$–Ir–$P_3$ 125.07 (9), $P_2$–Ir–$P_4$ 141.89 (9).
(7) This complex is identical with a known compound[8] in color, stoichiometry, and $\nu$(Ir–H) frequency, but the high-field proton NMR spectrum observed by us differs from the previously reported spectrum.
(8) R. A. Schunn, *Inorg. Chem.*, **9,** 2567 (1970).
(9) Moisture was proven not to be the hydride source since addition of a small amount of $D_2O$ in the electrolysis produced no observable Ir–D stretching band in the ir spectrum.
(10) In contrast to our proposal that the electrochemical reduction of $Ir(dppe)_2^+$ takes place by a one-electron transfer followed by hydrogen abstraction, a previous study of this compound[11] concluded that a two-electron transfer followed by proton abstraction is involved. This, however, is clearly inconsistent with the observed cathodic-anodic peak separation and scan rate dependence of the cyclic voltammograms, and also with the fact that deuteration occurs with $CD_3CN$ but not $D_2O$.
(11) G. Pilloni, E. Vecchi, and M. Martelli, *Electroanal. Chem. Interfacial Electrochem.*, **45,** 483 (1973).
(12) M. B. Hall and R. F. Fenske, *Inorg. Chem.*, **11,** 768 (1972).

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## A Remarkable Epoxide Opening. An Expeditious Synthesis of Vernolepin and Vernomenin

*Sir:*

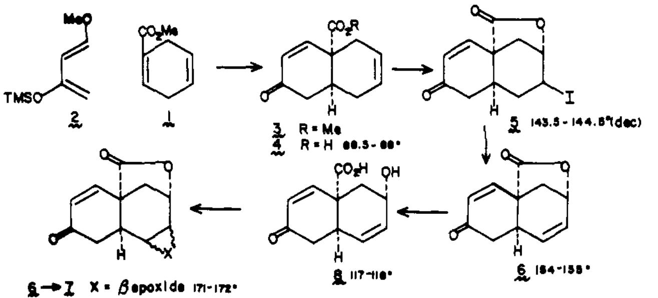
The novel structural and stereochemical features of the sesquiterpenes vernolepin (**19**) and vernomenin (**20**)[1,2] have stimulated a great deal of synthetic activity.[3,4] The tumor inhibitory properties which have been ascribed to these compounds[5] (albeit only in preliminary screening experiments which lack clear clinical implications) augment interest in their assemblage. Extensive studies have recently culminated in the first total synthesis of **21** and **22** by Grieco and co-workers.[6] As a consequence of the demonstration of the feasibility of bis $\alpha$-methylenation on synthetic precursors **17** and **18,** these "*bis-nor*" compounds may now be regarded as terminal objectives in a total synthesis exercise. Below we report a short stereospecific synthesis of **17** and **18.**

A Diels-Alder strategy was employed to ensure the required $5\alpha,10\alpha$ (steroid numbering) fusion (**1** + **2** → **3**). The angular function at position 10 induces the proper $\alpha$-oxygen asymmetry at $C_8$ (**4** → **5**). The $\alpha$-hydroxyl group at $C_8$ is used, in a Henbest fashion,[7] to introduce $6\alpha,7\alpha$-oxido stereochemistry (**8** → **9**). Eventually, this epoxide is opened by dilithioacetate to give the necessary $6\alpha,7\beta$ substituents. A key feature of the synthesis is the use of a spiro orthoester linkage which simultaneously protects the A ring lactone while exerting a strong orientational influence on the direction of epoxide opening (**15a** → **16a**). The synthesis is described below.

Diels-Alder reaction of methyl 2,5-dihydrobenzoate (**1**)[8] with the diene, **2**[9] (4 equiv of **2**; mesitylene; reflux; 48 h), gives a 50% yield (39% efficiency)[10] of dienone **3.**[11] Although this yield is not impressive, it should be noted that cyclohexenecarboxylates are notoriously unreactive as dienophiles.[9b]

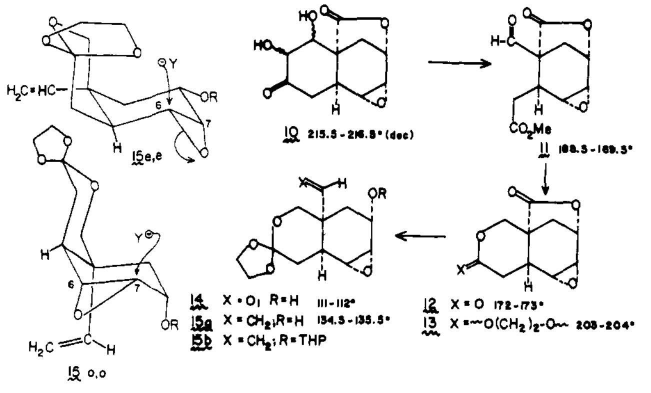
Ester **3** is saponified in quantitative yield to give acid **4.**[11] Iodolactonization of **4** ($NaHCO_3$-$KI_3$-$H_2O$; room temperature; 48 h) affords **5**[11] (88% yield). Reaction of **5** with diazabicycloundecene (DBU) provides dienonelactone **6** in 87% yield. This compound exhibited strong resistance to attack by peracids.[12] However, upon reaction with excess $p$-nitroperbenzoic acid for 10 days, a 33% yield of the undesired $6\beta,7\beta$-isomer, **7,**[11] was obtained. This reflects the deactivation of the $\alpha$-face of the molecule by the $\alpha$-lactone bridge.

The epoxide stereochemistry was controlled as follows. Reaction of lactone **6** with aqueous sodium hydroxide (THF, room temperature 5 h) gave a quantitative yield of hydroxy acid **8.**[11] In sharp contrast to the case of **6**, **8** reacts with 1.1 equiv of $m$-chloroperbenzoic acid (MCPBA; room temperature; 10 h) to give an epoxy acid, mp 117–118°, which, upon treatment with sodium acetate-acetic anhydride (80°; 3 h) gives **9**[11] (85% from **6**). The stereochemical and rate differences suggest that epoxidation of hydroxy acid **8** occurs under strong acceleration by the neighboring hydroxyl group.[7,13]



Hydroxylation of **9** was achieved (93%) by osmylation (0.6 equiv of $O_sO_4$; 1.6 equiv of $Ba(ClO_3)_2$; aqueous THF; 45°; 3 days). The highly insoluble diol, **10**,[11] suffered smooth degradation[14] with lead tetraacetate (5.7 equiv of $Pb(OAc)_4$; 1:1 benzene-methanol; room temperature; 6 h) to afford the aldehydo methyl ester, **11**,[11] in 86% yield. Reduction of the latter with lithium tri-*tert*-butoxyaluminum hydride (1.1 equiv; THF; −10°; 30 min) followed by heating the resultant hydroxyester with Amberlite IR-120 (benzene; reflux; 4 h) gave the unstable dilactone, **12.**[11] The A ring lactone of **12** undergoes rapid and selective orthoesterification by reaction with ethylene glycol in the presence of TsOH and magnesium sulfate (benzene; reflux 4-8 h).[15,16] The yield of the highly crystalline orthoester **13**[11] from aldehyde ester **11**, without purification of intermediates, is 60%. Treatment of **13** with 3 equiv of diisobutylaluminum hydride (toluene-DME) at −76° gives a near quantitative yield of hydroxyaldehyde **14.**[11,17] The setting for epoxide opening was now completed by the reaction of **14** with triphenylmethylenephosphorane (2.5 equiv of triphenylmethylphosphonium bromide; 2.5 equiv *n*-BuLi; hexane-DME) to give **15a**[11] in 79% yield.

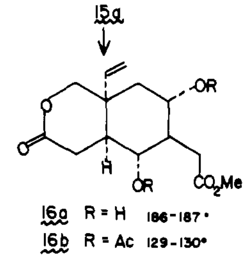
The low energy chair conformer of the cis-fused system would be expected to be **15e,e** in which the substituents on the B-ring are equatorial.[18] It is seen that trans-diaxial opening in this conformer by nucleophile Y would result in attack at position 6. The chair conformer, **15a,a**, required for such attack at position 7, should be disfavored on the grounds of a multiple axial repulsions. On the other hand, the path for diaxial attack in conformer **15e,e** is encumbered by the axial oxygen of the ethylene orthoester linkage. Accordingly, product formation might occur via the disfavored[18] conformer, **15a,a.** Such an occurrence would fall within the scope of the well-known Curtin–Hammett principle.[19]

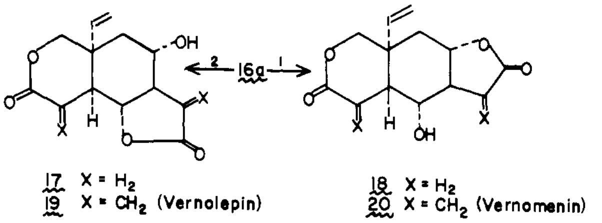


In the event, reaction of **15a** with dilithioacetate[20] (25 equiv of dianion; 60°; 22 h) followed by acid workup and esterification with diazomethane gave a 57% yield of the dihydroxymethyl ester, **16a.** Rigorous confirmation of the structure of **16a** was realized via its derived diacetate, **16b**, mp 129-130°, whose richly detailed 250-MHz NMR spectrum ($CCl_4$) is identical with that of the same compound emanating from the Grieco synthesis.[6] We are unable to find any evidence for the formation of products derived from attack at $C_6$.

It is interesting to note that the tetrahydropyranyl ether **15b** (**15a** + excess dihydropyran-TsOH; PhH; room temperature; 30 min) does not appear to react with dilithioacetate under the forcing conditions described above. Starting **16b** was recovered to the extent of 80% from the neutral portion. While this negative result is unfortunate from the standpoint of positional control over the formation of **17** and **18**, it may be of relevance to defining the nature of the successful conversion of **15a** → **16a.** If epoxide opening in the case of **15a** occurs in a trans-diequatorial sense on conformer **15e,e** or in a trans-diaxial sense on a twist-boat version of **15**, the presence of the THP ether would not be expected to complicate the reaction. However, the bulky group could well further destabilize conformer **15a,a.** If this is, in fact, the required conformer, the lack of reaction may be rationalized.[21]

Reaction of **16a** with TsOH/PhH under reflux for 90 min gave a 90% yield, of a 2:1 mixture of **17** ($R_f$ silica gel[22]-EtOAc = 0.23) and **18** ($R_f$ = 0.36). These compounds were readily separated by silica gel chromatography to give homogeneous **17**, mp 179-180°, and **18** (amorphous solid). These compounds have been converted to vernolepin and vernomenin by Grieco and co-workers.[6]





Experiments to modify our synthesis so as to allow for regiochemical control over the formation of lactones **17** and **18** are in progress. These, as well as further experiments designed to clarify the factors governing the highly specific (and useful) opening of epoxide **15a**[21] will be described in due course.

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## References and Notes

(1) S. M. Kupchan, R. Hemingway, D. Werner, and A. Karim, *J. Am. Chem. Soc.*, **90**, 2596 (1968).

(2) S. M. Kupchan, R. Hemingway, D. Werner, A. Karim, A. McPhail, and G. A. Sim, *J. Org. Chem.*, **34**, 3903 (1969).

(3) (a) B. M. Trost and C. H. Miller, *J. Am. Chem. Soc.*, **97**, 7182 (1975); (b) P. A. Grieco, J. A. Noguez, and Y. Masaki, *Tetrahedron Lett.*, 4213 (1975); (c) P. A. Grieco, J. J. Reap, and J. A. Noguez, *Synth. Commun.*, **5**, 155 (1975); (d) P. A. Grieco, K. Hiroi, J. J. Reap, and J. A. Noguez, *J. Org. Chem.*, **40**, 1450 (1975); (e) C. G. Chavdarian and C. H. Heathcock, *ibid.*, **40**, 2970 (1975); (f) J. A. Marshall and D. E. Seitz, *ibid.*, **40**, 534 (1975); (g) R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 1713 (1974); (h) S. Danishefsky, P. F. Schuda, and K. Kato, *J. Org. Chem.*, **41**, 1081 (1976); (i) H. Marshall, F. Vogel, and P. Weyerstahl, *Chem. Ber.*, **107**, 2852 (1974); (j) J. V. Frosch,

I. T. Harrison, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc., Perkin. Trans. 1*, 2005 (1974); (k) A. Tanaka, T. Nakata, and K. Yamashita, *Agr. Biol. Chem.*, **37,** 3465 (1973).

(4) For reviews of $\alpha$-methylenelactone syntheses see (a) P. A. Grieco, *Synthesis*, 67 (1975); (b) R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, **5,** 245, (1975).

(5) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14,** 1147 (1971).

(6) P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98,** 1612 (1976).

(7) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(8) A. A. Petrov and K. B. Rall, *Zh. Obskck. Khim.*, **26,** 1588 (1956).

(9) (a) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96,** 7807 (1974); (b) *J. Org. Chem.*, **40,** 538 (1975).

(10) In this thus far unoptimized reaction, ca. 20–40% of recovered 1 is obtained contaminated with varying degrees of methyl benzoate. Resubmission of accumulated low boiling fractions to the cycloaddition provides more of compound **3.**

(11) The structure and homogeneity of this product is supported by its infrared, NMR, and mass spectra.

(12) Cf. R. B. Woodward, F. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 1 (1958).

(13) It is possible that the neighboring carboxyl also functions as a directing group (cf. S. A. Cerefice and E. K. Fields, *J. Org. Chem.*, **41,** 355 (1976)). However, this would probably only be possible in a high energy conformer in which the carboxy and hydroxy groups are 1,3-diaxial to the B-ring.

(14) R. Hirschmann, N. G. Steinberg, and R. Walker, *J. Am. Chem. Soc.*, **84,** 1270 (1962).

(15) R. A. Le Mahieu and R. W. Kierstead, *Tetrahedron Lett.*, 5111 (1970).

(16) While the formation of orthoesters from lactones with ethylene glycol has precedent,[15] the rapidity of the reaction in the case of **12** is unusual. In the absence of magnesium sulfate, disappearance of **12** is complete after 30 min. However, under these conditions, **13** is only obtained in ca. 20% yield. The preponderance of material is converted into water soluble products which have not been identified. The utilization of excess magnesium sulfates slows down the conversion of **12** → **13** but leads to a much higher yield of the latter. The nature of the role of the magnesium sulfate remains to be determined.

(17) The NMR spectrum of **14** suggests the presence of 10–20% of hemiacetal valence isomer.

(18) While the likely preferred conformation of **15** R = OH and R = OTHP can only be surmised on the basis of general considerations of conformational analysis, the fully resolved 250-MHz spectrum ($CDCl_3$) of its derived acetate, **15** (R = OAc), leaves little doubt that its preferred conformation is, in fact, **15e,e.** The crucial features are: (i) AcO–CH, $\delta$ 5.29 ppm, coupled to the adjacent AB system at $C_9$ by $J = 9.6$ and 7.5 Hz and (ii) a pronounced W coupling, $J = 1.4$ Hz, between the junction hydrogen ($\delta$ 2.28 ppm) at $C_5$ and the equatorial proton ($\delta$ 3.57 ppm) of the isolated AB methylene at $C_1$.

(19) For an excellent discussion of this principle see E. Eliel, "The Stereochemistry of Carbon Compounds", McGraw-Hill, New York, London, 1962.

(20) P. L. Creger, *J. Org. Chem.*, **37,** 1907 (1972).

(21) Under the strongly basic conditions, **15a** is certainly deprotonated. Conceivably trans-diaxial attack at position 7 of conformer **15a,a** (R = lithium counterion) is assisted by a Lewis acid effect of the proximate axial lithium counterion on the emerging alkoxide at position 6. Such an effect might account for the nonreactivity of the THP derivative of compound **15.** Clearly investigations of ring openings on a series of structurally varied epoxycyclohexanols is necessary before this reaction is understood.

(22) Merck F-254 precoated silica gel plates; 0.25 mm thickness.

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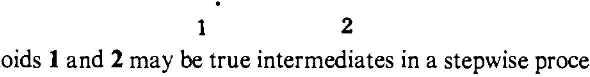
## The "Methane Carbon" Stereochemistry of the Acyclic Oxadi-$\pi$-methane Photorearrangement[1]

*Sir:*

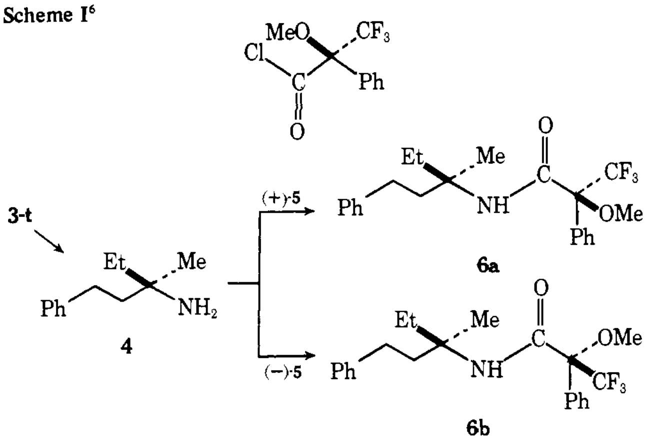
During the last 5 years, the oxadi-$\pi$-methane photorearrangement of $\beta,\gamma$-unsaturated ketones has been extensively investigated.[2] The possible mechanism of the reaction is pictured in qualitative valence bond terms in eq 1.[3] The diradicaloids **1** and **2** may be true intermediates in a stepwise process or may merely represent points on the energy hypersurface of a concerted $[_{\pi}2 + _{\sigma}2 + _{\pi}2]$ or $[_{\pi}2 + _{\sigma}2]$ cycloaddition. To gain more insight into the mechanistic details, the reaction stereochemistries of many $\beta,\gamma$-unsaturated ketones have been investigated,[4] and it has been found that a high degree of asymmetry is preserved at the "methane carbon". Both retention and inversion of this carbon have been reported, and this dichotomy has been attributed to steric factors.[4] It has been concluded, however, that the results favored a concerted $[_{\pi}2 + _{\sigma}2]$ pathway.[4g]



(1)

**1** **2**

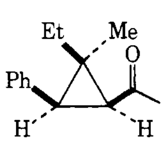
Scheme I[6]



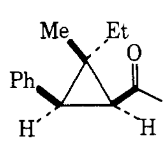
We have investigated the "methane carbon" stereochemistry of the oxadi-$\pi$-methane reaction of optically active *trans*-3-ethyl-3-methyl-5-phenyl-4-penten-2-one (**3-t**)[5] which, being acyclic, is free from all possible steric and conformational prejudices which were present in all previously studied compounds.

The degree of optical purity of the starting material **3-t** was established by the degradation of the ketone to the optically active amine **4** (hydrogenation, haloform reaction, Curtius degradation, and hydrolysis) followed by treatment with the optically active acid chlorides **5**[7] to yield the amides (Scheme I). The resulting diasteromeric amides **6a** and **6b** were found to be greater than 90% isomerically pure (NMR analysis), a result which indicates that the optical purity of **3-t** was at least 90%.

A benzene solution which was 0.01 M in optically active **3-t** and 0.01 M in chrysene[8] ($E_t$ = 57 kcal/mol) was irradiated through a Nonex filter (10% T at 314 nm) with a 450-W medium-pressure Hanovia lamp for 48 h. The sensitizer chrysene absorbed greater than 99% of the light under these conditions. The major products (Scheme II), isolated by silica gel chromatography, were the oxadi-$\pi$-methane products **7-t,t** and **7-t,c,** the 1,3-acyl shift product **8**, and the cis isomer (**3-c**) of the starting material as well as a small amount of the starting material. Neither of the other two possible oxadi-$\pi$-methane products, **7-c,c** and **7-c,t,** was detected (<1%).



7-c,c



7-c,t

The cyclopropyl ketone isomers **7-t,t** and **7-t,c** were separated by high-pressure liquid chromatography ($\mu$-porasil, 1% EtOAc–hexane) and were found to have small specific rotations, namely $[\alpha]^{25}{}_{405}$ −12° for **7-t,t** (99% purity by hplc, constant rotation) and $[\alpha]^{25}{}_{405}$ +10° for **7-t,c** (95% purity by HPLC). Independent synthesis of optically active **7-t,t**[9] ($[\alpha]^{25}{}_{405}$ −125 ± 3° (*c* 1.0, hexane)) indicated that the compound generated photochemically was *no more than 10% optically pure.*

Possible processes which could intervene in the production of largely racemized photoproducts **7-t,t** and **7-t,c** are: (a) photoracemization of starting enones; (b) formation and