obviously be quickly decomposed). (b) The Asp-194–Ile-16 salt bridge being destroyed, the thus relaxed active center conformation would allow the mixed anhydride to reside within the cleft where it would be shielded from the solvent. At pH >7, it would be better exposed and would suffer hydrolysis. One could also envisage more complex mechanisms where an acyl-His-57 may be formed either directly or by way of an Asp-194 mixed anhydride intermediate, but thus far all our data are consistent with the simpler (perhaps simplistic) Asp-194–mixed anhydride hypothesis. Since an acyl-Ser-195 intermediate can be clearly ruled out in the EEDQ inhibition reaction, it would seem logical to conclude that our results point to a heretofore unsuspected capacity of Asp-194 to participate directly in the active center chemistry of $\alpha$-CT.

**Acknowledgments.** We are grateful to the National Research Council of Canada for the financial support of this work. One of us (W. T. R.) was a recipient of a National Research Council of Canada Bursary and Scholarship. The skillful technical assistance of Mrs. M. DiTullio was highly appreciated.

**W. T. Robinson, B. Belleau***
*Department of Chemistry, McGill University*
*Montreal, Canada*
*Received March 7, 1972*

## Stereochemistry of the Photochemical Diels–Alder Reaction

*Sir:*

The well-known[1-3] "photochemical Diels–Alder reaction" can, in theory, be a concerted ($_{\pi}4_s + {}_{\pi}2_a$) or ($_{\pi}4_a + {}_{\pi}2_s$) cycloaddition.[4] In fact, there are many examples in which stereoselectivity is observed, but in no case has the reaction been shown to be completely under electronic symmetry control. There are three experimental reasons for this: (1) in some cases, it is not possible to determine which cis–trans isomer of the starting hexatriene actually cyclizes, since cis–trans isomerization is fast relative to cyclization (*e.g.*, eq 1); (2) in other examples, the steric restraints on the product bicyclohexene are so great that the reaction must find a route to only one bicyclohexene, whether it is the product desired by orbital symmetry control or not (*e.g.*, eq 2); or (3) the 1,3,5-hexatriene is insufficiently labeled to indicate whether the reaction is stereoselective or not (*e.g.*, eq 3).

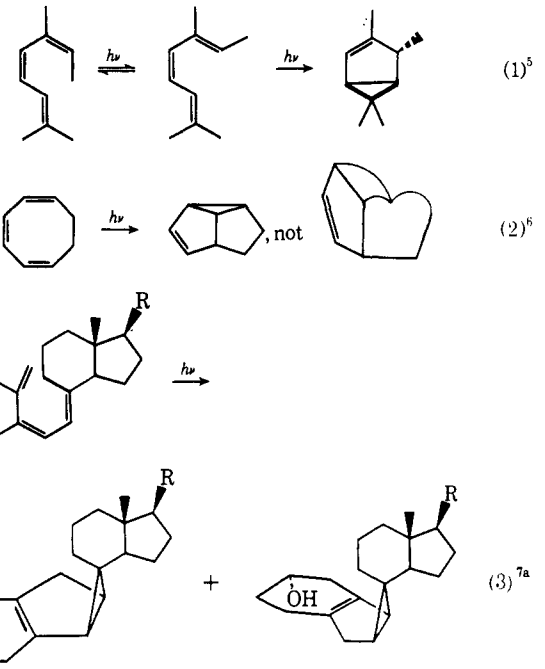
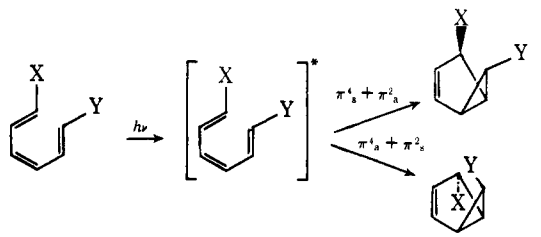



**Table I**

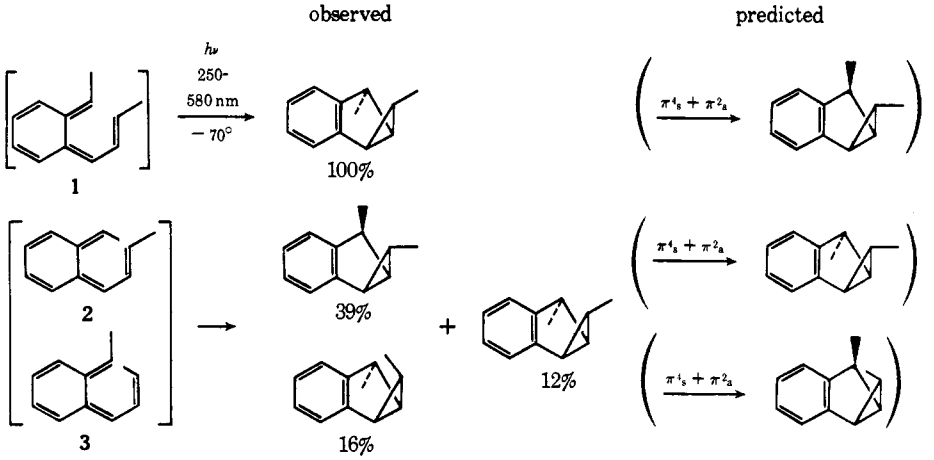
| Reactant | Ref | Temp, ~°C | % products[a] 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | Unknown compounds |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5** | 11b | 20 | 16 | 50 | 3 | 5 | 0 | 20 | 1 | 4 | 0 | 0 | 0 |
| **5** | 11b | −70 | 0 | 50 | 0 | 0 | 0 | 50 | 0 | 0 | 0 | 0 | 0 |
| **5** | 11a | 20 | 25 | 50 | 6 | 11 | 0 | 0 | 4 | 2 | 0 | 0 | 2 |
| **4** + 3% **5** | 11b | 20 | 50 | 0 | 11 | 20 | 0 | 2 | 3 | 13 | 0 | 0 | 1 |
| **4** | 11b | −70 | 50 | 0 | 0 | 0 | 14 | 6 | 0 | 0 | 8 | 20 | 2 |
| **4** + 5% **5** | 11a | 20 | 50 | 3 | 12 | 21 | 0 | 0 | 5 | 8 | 0 | 0 | 1 |

[a] All new compounds (**6**, **7**, **8**, **10**, and **11**) were identified and characterized by means of their nmr, uv, and low- and high-resolution mass spectra. The ir spectrum of **8** is characteristic of an allene (1950 $cm^{-1}$).



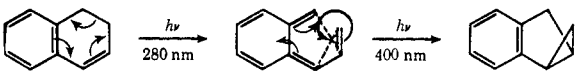

We report here the photoinduced Diels–Alder-like cyclization of 1,3,5-hexatrienes[7b] which cis–trans isomerize immeasurably slowly relative to their rate of cyclization, which have no strong steric restraints on closure to bicyclohexenes, and which are adequately labeled to indicate any stereoselectivity. The benzo-

(1) A. Padwa and S. Clough, *J. Amer. Chem. Soc.*, **92**, 5803 (1970), and references cited within.
(2) (a) L. Ulrich, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **53**, 1323 (1970); (b) J. Meinwald and D. A. Seeley, *Tetrahedron Lett.*, 3739, 3743 (1970).
(3) (a) H. Kleinhuis, R. L. C. Wijting, and E. Havinga, *ibid.*, 255 (1971); (b) K. Salisbury, *ibid.*, 737 (1971).
(4) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 814 (1969).
(5) K. J. Crowley, *J. Org. Chem.*, **33**, 3679 (1968).
(6) W. R. Roth and B. Peltzer, *Angew. Chem.*, **76**, 378 (1964); *Justus Liebigs Ann. Chem.*, **685**, 56 (1965); J. Zirner and S. Winstein, *Proc. Chem. Soc.*, 235 (1964); O. L. Chapman, G. W. Borden, R. W. King, and B. Winkler, *J. Amer. Chem. Soc.*, **86**, 2660 (1964).
(7) (a) Reference 4 and references cited therein; (b) actually pentaenes which have orbital symmetries exactly analogous to 1,3,5-hexatrienes; see A. Streitwieser, Jr., and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Vol. 1, Pergamon Press, New York, N. Y., 1965, p 71.




hexatrienes **1–3** cyclize to bicyclohexenes with stereoselectivity which reflects control by steric hindrance of the termini and sluggishness of terminal rotation relative to the rate of cyclization, rather than orbital symmetry control, indicating a nonconcerted, but fast, cyclization.

The benzohexatrienes are generated by photolysis

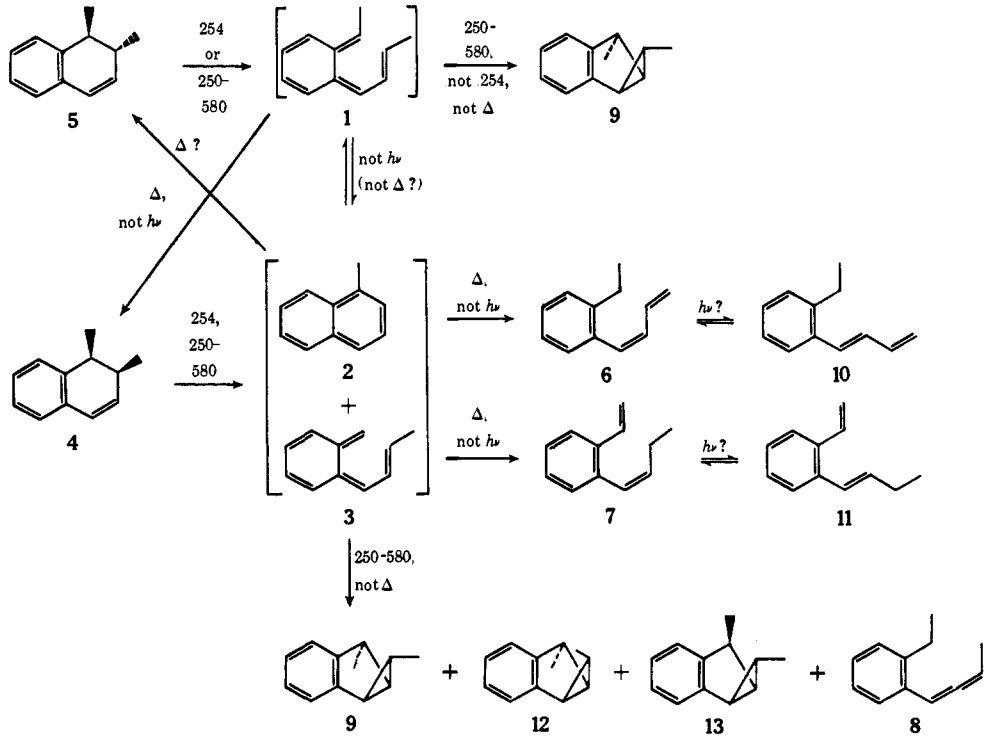



of 1,2-dihydronaphthalenes, a reaction discovered by Cookson[8] and further studied by several other groups.[2a,3] Evidence for the intermediacy of the formally nonaromatic benzohexatriene is both spectroscopic and chemical, and we incidently report here two new reactions which most logically proceed from these intermediates.

Deaerated ether solutions, *ca.* $10^{-2}$ *M* in *cis*- or *trans*-1,2-dihydro-1,2-dimethylnaphthalene (**4** or **5**),[9] were irradiated at *ca.* room temperature[10a] or *ca.* −70°[10b] with sources rich either in 254-[11a] or 250–580-nm[11b] uv light. The reactions were followed by glc analysis[12] through several half-lives of the reactant. Analyses after 50% consumption of reactant are given in Table I.

These results are consistent with Scheme I. The reactions **2**, **3** → **5** and **1** → **4** are analogous to observations of Schmid, *et al.*,[13] and are predicted on orbital symmetry grounds. The [1,7] hydrogen transfer reactions **2** → **6** and **3** → **7** should proceed most easily antarafacially,[14] *i.e.*, thermally allowed processes as observed, in contrast to the observation of Havinga,

**Scheme I**




(8) R. C. Cookson, S. M. de B. Costa, and J. Hudec, *Chem. Commun.*, 1272 (1969).

(9) Synthesis adapted from: L. M. Jackman and J. W. Lown, *J. Chem. Soc.*, 3776 (1962).

(10) (a) Ice–water or air baths; (b) 95% ethanol-Dry Ice bath.

(11) (a) Rayonet Photochemical Reactor; (b) 450-W medium-pressure Hg arc Hanovia lamp filtered through Corex.

(12) Most analytical and preparative separations were carried out on a 10 ft × 0.25 in. 17% TCEP column at *ca.* 175°.

(13) H. Heimgartner, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **53**, 173 (1970).

(14) See ref 4, p 828.

*et al.*, on a related system.[3a] The [1,5] hydrogen transfer reaction **3** → **8** should proceed most easily suprafacially,[14] *i.e.*, a thermal process if concerted, but is observed to be unquenched by cooling.

All of the observed hydrogen transfer reactions are reasonable pathways by which the benzohexatrienes may recover aromaticity, as are the observed photochemical Diels–Alder reactions. In contrast, the cis–trans isomerization reactions **1** ⇄ **2**, **3**, which do not have the thermodynamic incentive of recovery of aromaticity, are not observed at low temperature, as shown by the nearly mutually exclusive product mixtures in the low-temperature experiments. The thermal analog, which apparently does not occur either, is unreasonable and unprecedented.

In this example, the photochemical Diels–Alder reaction has been given a fair chance to demonstrate concertedness, which it failed to do. In light of this result and the very different photochemical Diels–Alder reaction of Padwa and Clough,[1] in which at least partial electronic control was demonstrated, it is clear that one must not depend on orbital symmetry control of stereoselectivity in exploiting this reaction.

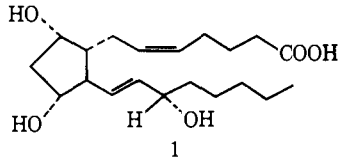
**Acknowledgment.** The author thanks the 3M Co. for partial support of this work and Miss Linda Chudnovsky for synthesis of some 1,2-dihydro-1,2-dimethylnaphthalene precursors.

**Douglas A. Seeley**
*Department of Chemistry, The Pennsylvania State University*
*University Park, Pennsylvania 16802*
*Received December 2, 1971*

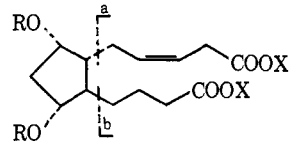
## Structure of a Deoxyprostaglandin in Man

*Sir:*

Prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$) (**1**) has been shown to have



**1**



**2**, X = H; R = H
**3**, X = $CH_3$; R = H
**4**, X = $CH_2CH_3$; R = H
**5**, X = $CH_3$; R = $(CH_3)_3Si$
**6**, X = $CH_3$; R = $CH_3CO$
**7**, X = $CH_2CH_3$; R = $(CH_3)_3Si$
**8**, X = $CH_2CH_3$; R = $CH_3CO$
**9**, X = $CH_3$; R = $(C^2H_3)_3Si$

many biological effects of which the actions on the uterus and corpus luteum have been studied extensively.[1] The structures of several metabolites of $PGF_{2\alpha}$ in humans and experimental animals were recently determined.[2a,b] The metabolites consisted of $C_{18}$, $C_{16}$, and $C_{14}$ derivatives formed by the action of 15-hydroxyprostanoate dehydrogenase, $\Delta^{13}$-reductase, and $\beta$ and $\omega$ oxidation systems. We now wish to report the isolation and structure of metabolite **2** formed by the reactions mentioned above and, in addition, elimination of the oxygen function originally at C-15.

[9$\beta$-$^3$H]$PGF_{2\alpha}$ (35 $\mu$g, specific activity 0.6 $\mu$Ci/$\mu$g) was administered intravenously to female subjects. The radioactive urine was added to urine containing unlabeled metabolites from administration of 20 mg of $PGF_{2\alpha}$ and the metabolites were isolated and separated as described in detail recently.[2a] Material in peak II (compound II) (see ref 2a) containing about 20% of administered radioactivity was treated with diazomethane and chromatographed with solvent system F-50, where 90% of the applied radioactivity appeared with 250–330 ml of effluent (18-g column). This material was further purified by thin-layer chromatography and silicic acid chromatography. Material in peak II was also treated with diazoethane to give the ethyl ester.[3]

The methyl (**3**) and ethyl (**4**) esters were converted into trimethylsilyl ether derivatives and acetates and analyzed by radio glc. The difference in retention time (1.2 C) between **5** and **7** and between **6** and **8** indicated that compound II was a dicarboxylic acid and the difference (1.1 C) between **5** and **6** and between **7** and **8** indicated the presence of two hydroxyl groups.[3]

In the mass spectrum of **5** (Figure 1) the ion with the highest *m/e* value appeared at *m/e* 458. The presence of two hydroxyl groups in compound II was supported by prominent ions at *m/e* 368 (M − 90) and 278 (M − (2 × 90)). Ions at *m/e* 267 and 255 were interpreted to be formed by loss of trimethylsilanol and the side chains attached to C-6 (a) and C-10 (b), respectively. An ion at *m/e* 217, $[TMSiO{=}CHCH{=}CHOTMSi]^+$, indicated that the cyclopentanediol part of the molecule was retained. An ion (*m/e* 227) with important structural implications was interpreted to be due to $[TMSiO{=}CHCH{=}CHCH{=}CHCH_2COOCH_3]^+$ and to be formed by cleavages between C-7 and C-8 and between C-6 and C-10. The mass spectrometric interpretations were supported by high-resolution mass spectrometry,[4] deuterium labeling of the trimethylsilyl groups (**9**), and the use of [3,4,6,9,10,12-$D_6$] compound II obtained by administering [5,6,11,12,14,15-$D_7$]$PGF_{2\alpha}$.[5] Additional support for the proposed structure and for the interpretations described above was obtained by mass spectrometric analysis of **6**, **7**, and **8**.

Compound II did not react either with borohydride or with methoxyamine which indicated the absence of a keto group. The presence of a double bond was established by catalytic hydrogenation of **6** and mass

(1) For references see "Prostaglandins," *Ann. N.Y. Acad. Sci.*, 180 (1971).
(2) (a) E. Granström and B. Samuelsson, *J. Biol. Chem.*, **246**, 5254 (1971); *ibid.*, **246**, 7470 (1971); E. Granström, *Eur. J. Biochem.*, **25**, 581 (1972); (b) E. Granström and B. Samuelsson, *ibid.*, 10, 411 (1969); K. Gréen, *Biochim. Biophys. Acta*, 231, 419 (1971).
(3) Methods for chromatographic separations and characterization of functional groups by glc are described in detail in ref 2a.
(4) The following ions were analyzed: *m/e* 368 (calcd for $C_{19}H_{32}SiO_5$, 368.2018; found, 368.2004 (−3.8 ppm)), 278 (calcd for $C_{16}H_{22}O_4$, 278.1518; found, 278.1518 (±0 ppm)), 267 (calcd for $C_{14}H_{23}SiO_3$, 267.1416; found, 267.1425 (+3.3 ppm)), 225 (calcd for $C_{13}H_{23}SiO_3$, 255.1416; found, 255.1409 (−2.7 ppm)), and 227 (calcd for $C_{11}H_{19}SiO_3$, 227.1102; found, 227.1113 (+4.8 ppm)). The equipment used was an Atlas SM 1 high-resolution mass spectrometer and a Gaertner spectrum plate comparator. We are indebted to Dr. R. Ryhage and Mr. R. Hjälm for the analyses.
(5) In agreement with previous results (M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **246**, 1073 (1971)) the deuterium atom originally at C-15 was lost by oxidation occurring in connection with reduction of the $\Delta^{13}$ double bond.