in their ^{13}C NMR spectra. In addition, irradiation of either H-3a or H-8a of isoptilocaulin simplifies H-8b to the downfield half of an AB quartet (J = 12 Hz) coupled to H-5a at 2.1 ppm, confirming the structures shown.[9b]

The stereochemistry of the fused ring system should be trans from the H-5a–H-8b coupling constant (10 Hz) in isoptilocaulin, while the coupling constants for H-8b with H-3a and H-8a in isoptilocaulin (J = 5 Hz each) argue from molecular models for cis H-8a, H-8b and H-3a, H-8a relationships in isoptilocaulin, as shown in **2**. Assuming the same relationships in ptilocaulin gives the H-3a, H-8b, and H-5a stereochemistry of **1**, while the coupling constants of H-7 with H-6 cis and H-6 trans (J = 12 and 6 Hz) argue from molecular models for a β-7-CH_3 stereochemistry, as shown in **1**. The absolute stereochemistry is not yet assigned.[11]

The structures of ptilocaulin and isoptilocaulin appear to be unique; though the biosynthetic pathway leading to them is obscure, they are most likely derived from addition of guanidine to a polyketonide chain. Like many sponge metabolites it cannot be excluded that they are produced by a symbiont rather than the sponge.

Acknowledgment. This work was supported by grants from the National Institute of Allergy and Infectious Diseases (AI 04769) and the National Science Foundation (PCM 77-12584). Mass spectra and NMR spectra were obtained on instruments supported, respectively, in part by grants from the National Institute of General Medical Sciences (GM 27029) and the National Science Foundation (CHE 79-16100). We thank the government of Honduras for permission to carry out scientific studies in its territorial waters.

(11) **Footnote Added in Proof**: The relative stereochemistry assigned C-3a, C-7, and C-8b has been confirmed by a recent X-ray study on ptilocaulin nitrate (Dr. S. R. Wilson, University of Illinois). However, H-5a is cis to H-8b rather than trans; their dihedral angle in the cis-fused system explains the large coupling constant (10 Hz).

Palladium(0) Catalyzed Reaction of 1,4-Epiperoxides. Conversion of a Prostaglandin Endoperoxide to Primary Prostaglandins

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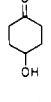
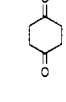
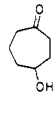
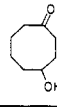
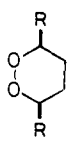
1,4-Epiperoxides (endoperoxides) serve as key substances in a variety of chemical[1] and biochemical transformations.[2] An extensive study of the catalytic decomposition of epiperoxides has been done only with metals such as Cu(I), Cu(II),[3] Fe(II),[2b,4] or Co(II)[5] which are capable of inducing reaction via a one-electron redox process. The study of catalysis with metals which cause the reaction to occur by a two-electron transfer seems to be quite limited.[6] We have chosen to concentrate on the catalytic reaction of cyclic peroxides with a zero-valent Pd complex which has a propensity to recycle the metal through a two-equivalent change.[7] Behavior of prostaglandin (PG) endoperoxides under the influence of such metals is of course of matter of wide interest.

Purified 1,4-epiperoxides [**1**, R–R = $(CH_2)_n$, n = 1–4] are stable in dichloromethane or benzene solution. However, when a catalytic amount of $Pd(PPh_3)_4$ (5 mol%) is added to the solution, the O–O bond is cleaved under mild conditions to give the 4-hydroxy ketone (**2**) and 1,4-diol (**3**) as the major products. The reactivity of the substrates are dependent on the ring systems. The results are shown in Table I.

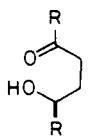
Table I. Palladium(0) Catalyzed Reaction of 1,4-Epiperoxides[a]

entry	epiperoxide[b]	conditions: temp, °C	conditions: time, h	product (% yield)
1		28	25	 (40)[c,d]
2		17[f]	3	 (25)[d,e]  (20)[d,e] (41)[d] (29)[d] (20)[d]
3		28[g]	25	(54)[d] (18)[d] (27)[d]
4		60	5	 (44)[h,i]  (4)[i,j]  (39)[i,k]
5		60[f]	5	(49)[f] (3)[f] (37)[f]
6		60	10	 (62)[i,m]  (13)[i,m]  (25)[i,n]
7		60[o]	10	(60)[f] (12)[f] (28)[f]
8		60[f]	11	(68)[f] (10)[f] (22)[f]
9		60[g]	10	(77)[f] (2)[f] (21)[f]
10		65[f]	15	 (73', 70[p])[q]  (23', 20[p])[r]

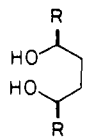
[a] The substrates are stable in the absence of Pd catalysts. Unless otherwise stated, the reaction was carried out with 5 mol % of $Pd(PPh_3)_4$ in dichloromethane under argon atmosphere. Known compounds were identified by comparison of the chromatographic and/or spectral properties with those of authentic samples. [b] Coughlin, D. J.; Brown, R. S.; Salomon, R. G. *J. Am. Chem. Soc.* 1979, *101*, 1533. [c] McIntosh, J. M.; Beaumier, P. *J. Org. Chem.* 1972, *37*, 2905. [d] Determined by ^1H NMR analysis. [e] Salomon, R. G.; Salomon, M. F. *J. Am. Chem. Soc.* 1977, *99*, 3501. [f] Benzene was used as solvent. [g] Ten equivalents of 2-propanol was added. [h] Haslanger, M.; Lawton, G. *Synth. Commun.* 1974, *4*, 155. [i] Determined by GLC analysis. [j] A commercially available compound. [k] Grob, C. A.; Baumann, W. *Helv. Chim. Acta* 1955, *38*, 594. [l] Reaction in the presence of 5 mol % of 2,4,6-tri-*tert*-butylphenol. [m] Doering, W. E.; Sayigh, A. A.-R. *J. Org. Chem.* 1961, *26*, 1365. [n] Kende, A. S.; Chu, J. Y.-C. *Tetrahedron Lett.* 1970, 4837. [o] Reaction in the presence of 5 mol % of *m*-dinitrobenzene. [p] Isolated yield after silica gel column chromatography. [q] Barrelle, M.; Apparu, M. *Bull. Soc. Chem. Fr.* 1972, 2016. [r] Cope, A. C.; Grisar, J. M.; Peterson, P. E. *J. Am. Chem. Soc.* 1959, *81*, 1640.



1



2



3

These observations can be interpreted as being due to competing one-and two-equivalent change pathways in spite of the use of a Pd(0) catalyst.[8] Participation of a Pd(II) species is not im-

(1) (a) Denny, R. W.; Nickon, A. *Org. React.* **1973**, *20*, 133. Nakanishi, K. In "Natural Products Chemistry"; Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds.; Academic Press: New York, 1975; Vol. 2. Chapter 12. (b) Wasserman, H. H.; Murray, R. W. "Singlet Oxygen"; Academic Press: New York, 1979. (c) Kondo, K.; Matsumoto, M. *Tetrahedron Lett.* **1976**, 4363 and references cited therein.

(2) For example, see: (a) van Dorp, D. A. In "Chemistry, Biochemistry and Pharmacological Activity of Prostanoids", Roberts, S. M., Scheinmann, F., Eds.; Pergamon: New York, 1979; pp 233–242. (b) Turner, J. A.; Herz, W. *Experientia* **1977**, *33*, 1133. (c) Adam, W.; Eggelte, H. J. *J. Org. Chem.* **1977**, *42*, 3987. (d) Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2501. (e) Porter, N. A. *Free Radicals Biol.* **1980**, *4*, 261.

(3) Porter, N. A.; Nixon, J. R.; Gilmore, D. W. *ACS Symp. Ser.* **1978**, *No. 69*, 89.

(4) Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 1895. See also ref 2a.

(5) Boyd, J. D.; Foote, C. S.; Imagawa, D. K. *J. Am. Chem. Soc.* **1980**, *102*, 3641.

(6) Recently $Rh_2(CO)_2Cl_2$ catalyzed reaction of an unsaturated 1,4-epiperoxide was briefly described. Hagenbuch, J.-P.; Vogel, P.; *J. Chem. Soc., Chem. Commun.* **1980**, 1062.

(7) For site-selective oxygenation of unsaturated carbon frameworks by Pd(0) catalyzed reaction of epoxides, see: (a) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623. (b) Suzuki, M.; Watanabe, A.; Noyori, R. *Ibid.* **1980**, *102*, 2095.

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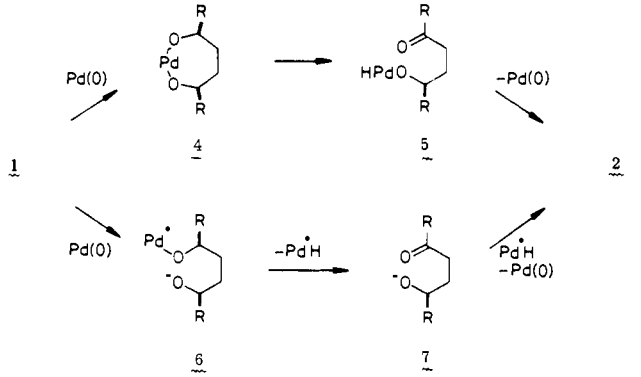
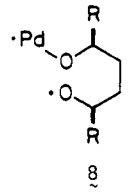
portant, because these epiperoxide substrates are inert to $PdCl_2(PPh_3)_2$. The catalytic conversion **1** → **2**[9] is best accounted for by the well-known Pd(0)/Pd(II) redox mechanism. The



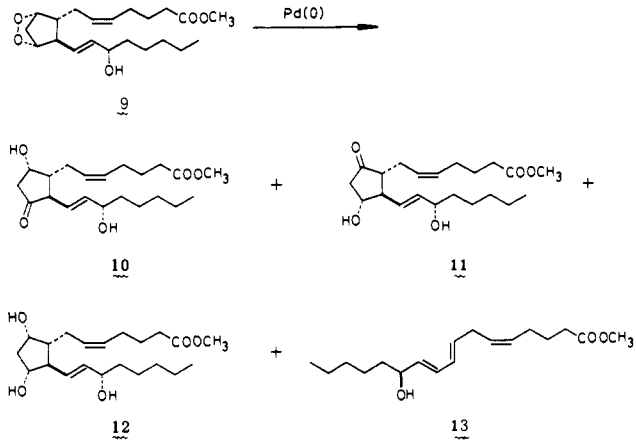
reaction would involve the front-side insertion of Pd(0) into the O–O linkage of **1**,[10] giving the seven-membered structure **4**, or a back-side S_N2 displacement by Pd(0)[11] to generate the zwitterion **6**. Subsequent hydrogen reorganization, leading to **2**, occurs via a palladium hydride species formed by β elimination. The efficiency of the catalytic process is ascribed to the eminent nucleophilicity of Pd(0) and hydrogen-carrying ability of Pd(II).[7,12] The formation of levulinaldehyde as a byproduct from 1,3-epiperoxycyclopentane (Table I, entry 1 and 2) is considered as a result of intramolecular retro aldol reaction of the intermediate **5** or **7** (R–R = CH_2). This leakage was suppressed to some extent by the addition of an alcoholic substance to the reaction system (cf. entry 3). Both this aldehyde and 3-hydroxycyclopentanone are stable under this neutral reaction condition.

Apparently the *catalytic* diol formation, **1** → **3**, involves radical intermediates. However, the radical species differ distinctly from free radicals formed by thermolysis or photolysis of epiperoxides.[13] A simple explanation for this can be made on the basis of a Pd(0)/Pd(I) one-equivalent redox mechanism.[4,5,14] It is conceivable that reaction of Pd(0) species and an epiperoxide **1**, a strong oxidizing substrate, produces an inner-sphere radical, depicted as **8**,[15] which abstracts hydrogen atoms from donors present



nearby to give the corresponding 1,4-diol **3**. Secondary alcohols serve as an efficient hydrogen donor for **8**. Thus the reaction of 1,4-epiperoxycycloheptane [**1**, R–R = $(CH_2)_3$] in the presence of 10 equiv of 2-propanol (entry 9) produced acetone in 19% yield at the expense of the 1,4-diketone formation.[16] It is apparent that the initially formed hydroxylic products are partly dehydrogenated under the reaction conditions. Since addition of 2,4,6-tri-*tert*-butylphenol (0.5–5 mol %), an oxygen radical terminating agent, did not affect the reaction to any great extent (entry 5 and 8),[8c] chain mechanism is unlikely to be operative in the radical reaction.[17]

The catalytic production of the hydroxy ketones and diols is formally related to the biogenetic conversion of PG endoperoxides (PGGs and PGHs) to primary PG derivatives.[2] Therefore, we have examined the behavior of a PG endoperoxide in the presence of Pd(0) catalyst. Consistent with the result obtained with the model systems, when PGH_2 methyl ester (**9**)[18] was exposed to 10 mol % of $Pd(PPh_3)_4$ (CH_2Cl_2, 19 °C, 3 h), a mixture of methyl esters of PGD_2 (**10**) (17%), PGE_2 (**11**) (11%), $PGF_{2\alpha}$ (**12**) (41%), and (5*Z*,8*E*,10*E*,12*S*)-12-hydroxy-5,8,10-heptadecatrienoic acid (HHT, **13**) (4%) was produced.[19] The fragmentation giving **13** seems to proceed via a radical intermediate analogous to **8**.



Acknowledgment. We thank Professors H. Sakurai and L. S. Hegedus for helpful discussion about the reaction mechanism. We are also indebted to Drs. K. Kondo and M. Matsumoto of Sagami Chemical Research Center for their kind suggestions for the preparation of the epiperoxide substrates.

(8) For the multiplicity of reaction pathways in oxidative addition on Pd(0), see: (a) Kochi, J. K. "Organometallic Mechanisms and Catalysis"; Academic Press: New York, 1978; pp 161–168. (b) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7145, 7832. (c) Klabunde, K. J.; Roberts, J. S. *J. Organomet. Chem.* **1977**, *137*, 113.

(9) For the base-induced reactions, see: Gollnick, K.; Schenck, G. O. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967; p 255.

(10) Schott, H.; Wilke, G. *Angew. Chem.* **1969**, *81*, 896.

(11) Pierson, G. O.; Runquist, O. A. *J. Org. Chem.* **1969**, *34*, 3654. Herz, W.; Ligon, R. C.; Kanno, H.; Schuller, W. H.; Lawrence, R. V. *Ibid.* **1970**, *35*, 3338 and references cited therein. Denney, D. B.; Goodyear, W. F.; Goldstein, B. *J. Am. Chem. Soc.* **1960**, *82*, 1393. For the theoretical treatment, see: Yonezawa, T.; Yamamoto, O.; Kato, H.; Fukui, K. *Nippon Kagaku Zasshi* **1966**, *87*, 26. Yonezawa, T.; Kato, H.; Yamamoto, O. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 307. Ohkubo K.; Kitagawa, F. *Nippon Kagaku Kaishi* **1973**, 2147. Kikuchi, O.; Suzuki, K.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1086.

(12) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.

(13) Thermolysis of 1,3-epiperoxycyclopentane in benzene at 73 °C gives 4,5-epoxypentanal as the major (86%) product (cf. Table I, entry 2). See: Salomon, R. G.; Salomon, M. F.; Coughlin, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 660.

(14) $Pd(PPh_3)_4$ dissociates into PPh_3 and $Pd(PPh_3)_n$ (n = 3 or 2) in solution. Triphenylphosphine does reduce cyclic peroxides to the diols (stoichiometric reaction). However, many lines of evidence indicate that under the present catalytic conditions participation of the dissociated phosphine ligand is unimportant: (1) Throughout the reaction neither palladium mirror nor black precipatates formed; the yellow to yellowish brown, homogeneous system remained unchanged. (2) Catalyst concentration does not affect the product ratio and yield to any great extent. For example, the catalysis of **1** [R–R = $(CH_2)_3$] with 2.5 to 20 mol % of $Pd(PPh_3)_4$ under the standard conditions gave the 1,4-diol in 25–30% yield. The yield, 29%, obtained by using 2.5 mol % of the catalyst is much higher than that expected from the stoichiometric reaction of triphenylphosphine. (3) Reaction of triphenylphosphine and the 1,4-epiperoxide derived from 1,3-cycloheptadiene, an unsaturated analogue of **1** [R–R = $(CH_2)_3$], gave 1,2-epoxy-3-cycloheptene quantitatively (CH_2Cl_2, 60 °C). However, the $Pd(PPh_3)_4$-catalyzed reaction of the unsaturated epiperoxide produced the corresponding 1,4-diol in ca. 20% yield, together with other disproportionation products; no or very little epoxycycloheptene (<3%, if any) was obtained.

(15) Sosnovsky, G.; Rawlinson, D. J. In "Organic Peroxides"; Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 1, Chapter 9. Wilt, J. W. In "Free Radicals"; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. 1, Chapter 3. Dixon, B. G.; Schuster, G. B. *J. Am. Chem. Soc.* **1979**, *101*, 3116 and references cited therein. See also Chapter 4 in ref 8a.

(16) In the reaction of dichloromethane, a trace amount of 1,1,2,2-tetrachloroethane was detected. Chloroform was not formed.

(17) Five mole percent of *m*-dinitrobenzene, an efficient anion radical quencher, neither inhibited the catalysis nor affected the product ratio (entry 7). This suggests that both one- and two-equivalent change reactions proceed via direct atom-transfer process and not by one-electron transfer mechanism. See: Hegedus, L. S.; Miller, L. L. *J. Am. Chem. Soc.* **1975**, *97*, 459.

(18) Porter, N. A.; Byers, J. D.; Holden, K. M.; Menzel, D. B. *J. Am. Chem. Soc.* **1979**, *101*, 4319.

(19) The reaction was monitored by a high-speed TLC scanner (Shimadzu CS-920 model).