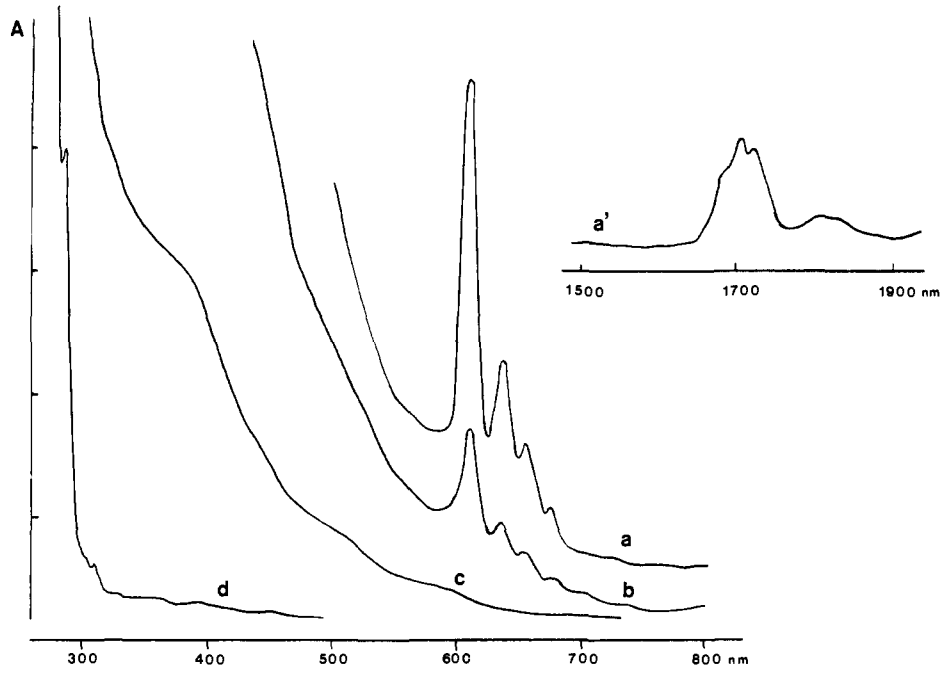

Figure 1. Spectrophotometrical study: (a) Absorption spectrum of the initial solution of $U^{IV}(COT)_2$ in THF ($\sim 10^{-3}$ M). (b) After addition of reducing agent ($Np^-/U^{IV} \sim 0.4$). (c) Absorption spectrum of the U(III) compound ($Np^-/U^{IV} \sim 1$) with its IR component (a'). (d) Absorption spectrum of naphthalene.

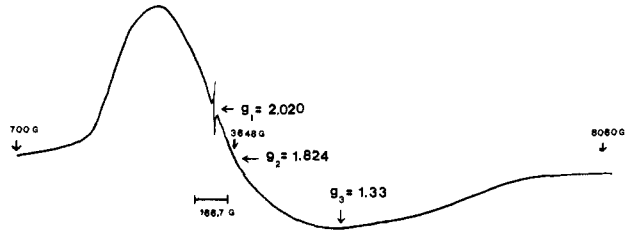

Figure 2. ESR spectrum of a frozen solution cooled to 6 K.

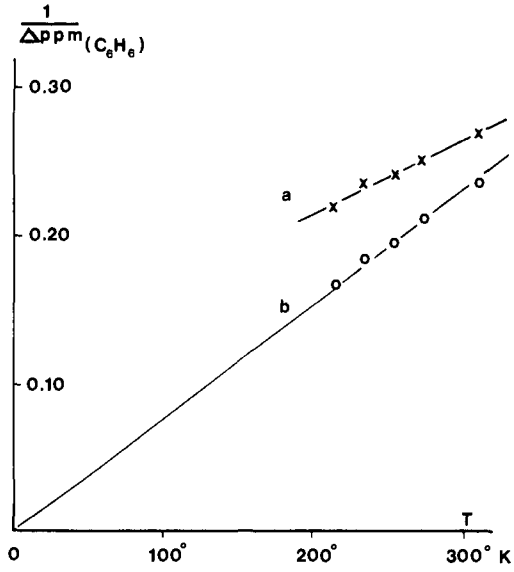

Figure 3. $1/\Delta_{C_6H_6}$ (Δ in ppm) vs. temperature (K). (O) values for U(IV);[8] (X) our values for U(III).

with its characteristic ESR signal possessing hfs due to ^{47}Ti ($I = 5/2$) and ^{49}Ti ($I = 7/2$) and a g value of 1.971.[9] In this reaction the uranium compound is oxidized to $U^{IV}(COT)_2$ as shown by the four absorption peaks.

(9) Saito, E.; Billiau, F., to be published.

In the same way, instead of a Ti^{IV} compound, we can use $U^{IV}(C_5H_5)_3Cl$ which is reduced to $U^{III}(C_5H_5)_3$ while the $U^{III}COT$ compound is oxidized to $U^{IV}(COT)_2$. The $U(C_5H_5)_3$ is identified by its chemical shift of 20 ppm.[8] This shows that the U^{III} has more reducing power when ligated to COT than to C_5H_5.

This study has shown that it is possible to reduce $U^{IV}(COT)_2$ to a cyclooctatetraenyluranium(III) compound in a THF solution by using a stoichiometric amount of a strong reducing agent. The U^{III} compound, whose structure has still to be determined with certitude, is very soluble in THF and has reducing properties toward $Ti(OR)_4$ and $U(C_5H_5)_3Cl$.

Ptilocaulin and Isoptilocaulin, Antimicrobial and Cytotoxic Cyclic Guanidines from the Caribbean Sponge *Ptilocaulis* aff. *P. spiculifer* (Lamarck, 1814)[1]

Gary C. Harbour, Adrienne A. Tymiak, and Kenneth L. Rinehart, Jr.*

Department of Chemistry, Roger Adams Laboratory
University of Illinois at Urbana-Champaign
Urbana, Illinois 61801

Paul D. Shaw

Department of Plant Pathology
University of Illinois at Urbana-Champaign
Urbana, Illinois 61801

Robert G. Hughes, Jr.

Department of Cell and Tumor Biology
Roswell Park Memorial Institute
Buffalo, New York 14263

Stephen A. Mizsak, John H. Coats, Gary E. Zurenko, Li H. Li, and Sandra L. Kuentzel

The Upjohn Company
Kalamazoo, Michigan 49001
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In our recent report[2] on the most bioactive extracts obtained during the *Alpha Helix* Caribbean expedition 1978, we noted that

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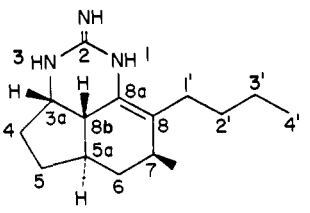
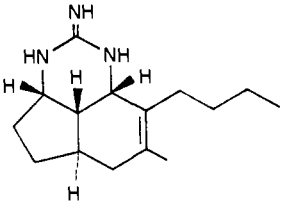
at least three sponge species[3] were identified as having very similar antimicrobial spectra and apparently containing the same antimicrobial compounds.[4a] One of these, the rope-like orange sponge *Ptilocaulis* aff. *P. spiculifer* (Lamarck, 1814) (AHCE 21-III-78-1-7, #650),[3] collected in March 1978 by scuba at Burn Cay, Honduras (latitude 15°10'N, longitude 82°35'W, depth 10–14 m), appeared on our "most active" lists against gram-positive and gram-negative bacteria, yeasts and filamentous fungi, as well as on that for cytotoxicity.[4b] We now assign the novel structures **1** and **2** to the major antibacterial compounds present in *Ptilocaulis* aff. *P. spiculifer*, which we have named ptilocaulin and isoptilocaulin, respectively.



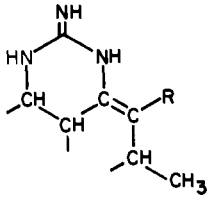
1



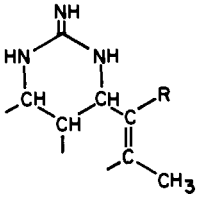
2

Ptilocaulin nitrate, isolated as colorless crystals (mp 183–185 °C, $C_{15}H_{26}N_3^+NO_3^-$[5a] and isoptilocaulin nitrate, isolated as a yellow oil containing ca. 10% of ptilocaulin nitrate (estimated from the ^{1}H NMR spectrum), were obtained by extraction of sponge samples with methanol–toluene (3:1), partitioning with 1 N sodium nitrate, chloroform extraction of the aqueous layer, subsequent silica gel chromatography of the chloroform layer eluting with a continuous gradient of methanol (0–15%) in chloroform, and size exclusion chromatography on Sephadex LH-20 eluting with methanol. Ptilocaulin is the more bioactive; it has ID_{50} 0.39 μg/mL (concentration required for 50% inhibition of cell growth in culture) against L1210 leukemia cells and the following antimicrobial minimum inhibitory concentrations (MIC's) (μg/mL): *Streptococcus pyogenes*, 3.9; *S. pneumoniae*, 15.6; *S. faecalis*, *Staphylococcus aureus*, *Escherichia coli*, all 62.5. Isoptilocaulin has ID_{50} 1.4 μg/mL vs. L1210 leukemia cells and the following antimicrobial MIC's (μg/mL): *S. pyogenes*, 25; *S. pneumoniae* and *S. aureus*, 100; *S. faecalis* and *E. coli*, >100.

The two compounds are isomers, giving molecular ions with the formula $C_{15}H_{25}N_3$,[5b] which indicates five degrees of unsaturation. Differences between the two isomers can be explained by the presence of the unit a in ptilocaulin and the unit a′ in isoptilocaulin.

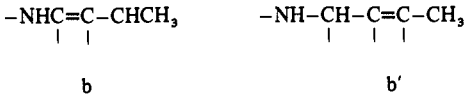


a



a′

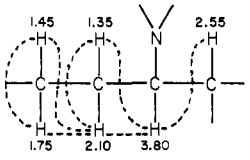
The three nitrogens in both ptilocaulin and isoptilocaulin are present in guanidine groups, identified by the ^{13}C NMR resonances[6,7] for their nitrates at 153.2 (CD_3OD) for **1** and 156.4 ppm (CD_3CN) for **2**. Both ptilocaulin and isoptilocaulin nitrates show clear N,N′-disubstituted guanidine patterns in their ^{1}H NMR spectra,[8] with signals at 8.90 ppm (1 H, s, NH), 8.36 (1 H, d, NH, J = 4.0 Hz), and 7.44 (2 H, s, NH_2) for ptilocaulin ($CDCl_3$) and at 7.71 ppm (1 H, s, NH), 7.33 (1 H, s, NH), and 6.97 (2 H, s, NH_2) for isoptilocaulin ($CDCl_3$). Isoptilocaulin gives two ^{13}C NMR signals for >CH–N<, at 54.2 and 50.2 ppm (off-resonance doublets, CD_3CN), and ptilocaulin only one, at 51.6 ppm (CD_3OD). The protons of the two >CH–N< units of isoptilocaulin are found at 3.85 (1 H, m) and 3.96 ppm (1 H, d, J = 5.5 Hz) and both are coupled to a third proton at 2.37 ppm (1 H, m), indicating a six-membered ring as in unit a′. Ptilocaulin's one >CH–N< proton is at 3.78 ppm, coupled to a proton at 2.55 ppm, as in a, and its UV_{max} at 225 nm (ε 10000), lacking in isoptilocaulin, is appropriate for an enamine. Also in agreement with a and a′, both ptilocaulin and isoptilocaulin have two disubstituted alkene carbons, at 128.1 and 122.8 ppm for ptilocaulin and at 135.9 and 132.4 ppm for isoptilocaulin. A methyl doublet in ptilocaulin, $CH_3CH<$, at 1.03 ppm (J = 6.9 Hz), is replaced by an allylic methyl singlet, $—C(CH_3)=$, at 1.73 ppm in isoptilocaulin, arguing the unit b in the former and unit b′ in the latter. The cyclic guanidine group and the alkene account for three units of unsaturation, leaving two rings.



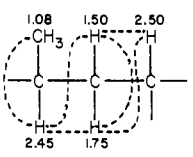
b b′

An *n*-butyl group is identified as the group R in a and a′ of ptilocaulin and isoptilocaulin by the facile loss (allylic cleavage) of C_3H_7[5b] from the molecular ions of both **1** and **2** to give the base peak m/z 204, by the ^{1}H NMR spectrum (–CH_2–CH_2–CH_2–CH_3 protons at 2.2 m, 1.4 m, 1.35 m, and 0.90 t, respectively, for **1**),[9a] by the ^{13}C NMR spectrum, with signals at 31.6, 31.4, 23.3, and 14.3 for **2** vs. 30.5, 29.0, 22.8, and 14.1 for the *n*-butyl carbons of 2-ethyl-1-hexene,[10] and by the ozonolysis of isoptilocaulin to give a single diketone, $C_{15}H_{25}N_3O_2$,[5b] whose mass spectrum shows losses of C_5H_9O (base peak)[5b] as well as C_2H_3O.[5b]

Extensive spin decoupling of the ^{1}H NMR spectrum of ptilocaulin establishes the units c and d, with those protons decoupled joined by dotted lines. Although the decouplings shown were



c



d

observed, there is obvious ambiguity in the overlap of the protons at 1.45–1.50 and 1.75. However, the right-hand terminal proton of d at 2.50 *is not* coupled to those at 1.35 and 2.10 and must be separated from them by a methylene carbon bearing the protons at 1.45 and 1.75. Combination of groups c and d with a and a′ can give only structures **1** and **2** for ptilocaulin and isoptilocaulin, respectively, which agree with the numbers and types of methyl (2), methylene (6), methine (4), and quaternary (3 >C=) carbons

(1) Presented in part at the Marine Chemistry Symposium, Chemical Institute of Canada, Halifax, Nova Scotia, June 4, 1981.

(2) Rinehart, K. L., Jr.; Shaw, P. D.; Shield, L. S.; Gloer, J. B.; Harbour, G. C.; Koker, M. E. S.; Samain, D.; Schwartz, R. E.; Tymiak, A. A.; Weller, D. L.; Carter, G. T.; Munro, M. H. G.; Hughes, R. G., Jr., Renis, H. E.; Swynenberg, E. B.; Stringfellow, D. A.; Vavra, J. J.; Coats, J. H.; Zurenko, G. E.; Kuentzel, S. L.; Li, L. H.; Bakus, G. J.; Brusca, R. C.; Craft, L. L.; Young, D. N.; Connor, J. L. *Pure Appl. Chem.* **1981**, *53*, 795–817.

(3) Identified by Dr. G. J. Bakus, Curator of Invertebrates, Allan Hancock Foundation, University of Southern California, Los Angeles, CA 90007.

(4) (a) See Table 17 of ref 2. (b) See Tables 9–13 of ref 2.

(5) (a) Microanalyses (C, H, N) or (b) HREIMS data agree with the formula shown.

(6) Carter, G. T.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4302–4304.

(7) Cheng, M. T.; Rinehart, Jr., K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7409–7411.

(8) Corral, R. A.; Orazi, O. O.; Gonzalez, M. E. *Rev. Latinoam. Quim.* **1978**, *9*, 184–189.

(9) (a) The 1′, 2′, 3′, and 4′ protons of isoptilocaulin are found at 2.2, 1.3, 1.3, and 0.91 ppm, respectively. (b) Remaining protons of isoptilocaulin are assigned tentatively as follows: H-4, 1.35, 2.00; H-5, 1.35; H-5a, 2.00; H-6, 2.10.

(10) "Carbon-13 NMR"; Sadtler Research Laboratories, Inc.: Philadelphia, 1976; Spectrum No. 1102C.

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

M. Suzuki and R. Noyori*

Department of Chemistry, Nagoya University Chikusa, Nagoya 464, Japan

N. Hamanaka

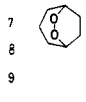
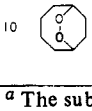
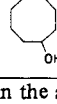
Research Institute, Ono Pharmaceutical Co. Shimamoto, Osaka 618, Japan

Received April 30, 1981.

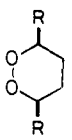
1,4-Epiperoxides (endoperoxides) serve as key substances in a variety of chemical[1] and biochemical transformations.[2] An extensive study of the catalytic decomposition of epiperoxides has been done only with metals such as Cu(I), Cu(II),[3] Fe(II),[2b,4] or Co(II)[5] which are capable of inducing 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.

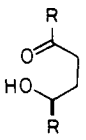
Table I. Palladium(0) Catalyzed Reaction of 1,4-Epiperoxides[a]

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

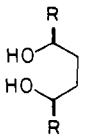
[a] The substrates are stable in the absence of Pd catalysts. Unless otherwise stated, the reaction was carried out with 5 mol % of $Pd(PPh_3)_4$ in dichloromethane under argon atmosphere. Known compounds were identified by comparison of the chromatographic and/or spectral properties with those of authentic 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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