Communications to the Editor

Total Synthesis of Verrucarol

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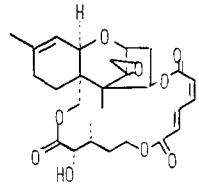
The trichothecanes are a group of sesquiterpenoid mycotoxins that exhibit a wide array of biological activity, including significant cytotoxicity.[1] The more potent of this class are the macrocyclic di- and trilactones of verrucarol (**2**) such as the roridins, baccharins, and verrucarins. Because of our interest in the synthesis of verrucarin A (**1**),[2] as well as our desire to showcase an alternative approach to the trichothecane ring system, we now report the total synthesis of (±)-verrucarol (**2**).



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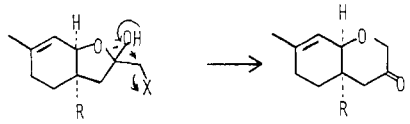
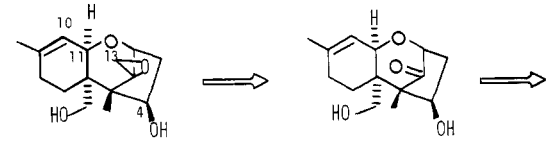
A variety of approaches to the trichothecanes[3] have appeared in the literature, culminating in the syntheses of trichodermol[4a,b] and, most recently, verrucarol[4c] and calonectrin.[4d] To resolve the stereochemistry of the tetrahydrochromanone, a ring enlargement of a 6,5-ring system, which would thermodynamically prefer a cis ring juncture, to the 6,6-ring system, as shown in eq 1, was



(1)

envisioned and realized in our initial work.[3b] Application of this concept[5] reduces the problem to a synthesis of **3** which, upon dissection via the indicated cleavage, simplifies to a Diels-Alder reaction[3d,4,6] of the diene **4** and dienophile **5**. This approach creates



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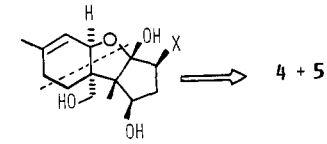

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the chirality of verrucarol in the Diels-Alder reaction—a reaction known to respond well to asymmetric induction.[7] The prochiral dione **5** contains all the functionality necessary for the five-membered ring of verrucarol, with only differentiation of the enantiotopic carbonyl groups of **5**, which become diastereotopic after cycloaddition, required.

The dienophile was available in four steps from the familiar 2-methyl-1,3-cyclopentanedione.[8] Condensation of the dione with allyl alcohol[9] **6** (Scheme I) initially forms an enol ether, which suffers a Claisen rearrangement[10] to yield **7**. Oxidative cleavage of the terminal olefin[11] gave a labile acid, which was immediately esterified with diazomethane and then treated with DBU to give the desired dienophile **5** (mp 30-32 °C). Although **5** was unreactive toward the acetoxydiene **4a**,[6a,e,12] the siloxydiene[13] **4b** reacted at 128 °C to yield the expected adduct **8** as the only isolated product. However, upon warming this adduct above 135 °C, an intramolecular ene reaction ensued to yield the highly crystalline tricycle **9** (mp 147-148.5 °C)[24] in an overall yield of 63%[14] from **5**. Analysis of the conformation for the surprisingly mild ene reaction[15] reveals that only one of the two diastereotopic

(1) Reviews: Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. Bamberg, J. R.; Strong, F. M. In "Microbiol Toxins"; Kadis, S., Ed.; Academic Press: New York, 1973; Vol. 3, pp 207-292. Doyle, T. W.; Bradner, W. T. In "Anticancer Agents Based on Natural Product Models"; Cassidy, J. M., Douros, J., Eds.; Academic Press: New York, 1980; Chapter 2.

(2) Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242.

(3) For some recent approaches see: (a) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 658. (b) Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1978**, *43*, 2938. (c) Roush, W. R.; D'Ambra, T. E. *Ibid.* **1980**, *45*, 3927. (d) White, J. D.; Matsui, T.; Thomas, J. A. *Ibid.* **1981**, *46*, 3376. (e) Pearson, A. J.; Ong, C. W. *J. Am. Chem. Soc.* **1981**, *103*, 6686 and references cited therein.

(4) (a) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989. (b) Still, W. C.; Tsai, M.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. (c) Schlessinger, R. H.; Nugent, R. A. *Ibid.* **1982**, *104*, 1116. (d) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *Ibid.* **1982**, *104*, 1114.

(5) The 1-oxa[3.2.1]bicyclooctane skeleton has been formed by such a rearrangement. However, the migrating oxygen in both cases was a phenol and not a simple alcohol. Anderson, W. K.; Lee, G. E. *J. Org. Chem.* **1980**, *45*, 501. Goldsmith, D. J.; John, T. K.; Kwong, C. D.; Painter, G. R.; III *Ibid.* **1980**, *45*, 3989.

(6) The Diels-Alder has become a popular entry to the A ring of the trichothecanes; see: (a) Snider, B. B.; Amin, S. G. *Synth. Commun.* **1978**, *8*, 117. (b) Nakahara, Y.; Tatsuno, T. *Chem. Pharm. Bull.* **1980**, *28*, 1981. (c) Kraus, G. A.; Frazier, K. J. *J. Org. Chem.* **1980**, *45*, 4820. (d) Kraus, G. A.; Roth, B. J. *Ibid.* **1980**, *45*, 4825. (e) Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, P.; Weakly, T. J. R.; Ullah, Z. *J. Chem. Soc., Perkin Trans, 1* **1981**, 1096.

(7) For use of chiral dienes see: Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595. David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 299. David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. David, S.; Eustache, J.; Lubineau, A. *Ibid.* **1979**, 1795. Korolev, A.; Mur, V. *Dokl. Akad. Nauk. SSSR* **1948**, *59*, 251; *Chem. Abstr.* **1949**, *42*, 6676. Most work involves chiral dienophiles. See: Boeckmann, R. K., Jr.; Naegeby, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 754. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. Jurczak, J.; Tracy, M. *J. Org. Chem.* **1979**, *44*, 3347. Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Chem. Commun.* **1979**, 437; Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, *31*, 6359. Wallborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333.

(8) Historically this dione gained fame as a synthon for the steroidal D ring. Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412 and references cited therein. More recently, it has been used for condensed cyclopentanoids such as the coriolins; see: Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380. It is also the starting material of the only other reported synthesis of verrucarol (ref 4c).

(9) Colonge, J.; Poilane, G. *Bull. Soc. Chim. Fr.* **1955**, 953.

(10) For Claisen rearrangements on cyclohexadiones see: Tamura, Y.; Kita, Y.; Shimagaki, M.; Terashima, M. *Chem. Pharm. Bull.* **1971**, 571.

(11) Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. *J. Org. Chem.* **1977**, *42*, 3749. Lee, D. G.; Chang, V. S. *Ibid.* **1978**, *43*, 1532.

(12) Cookson, R. C.; Cramp, M. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1980**, 197.

(13) Rosner, A.; Tolkiehn, K.; Krohn, K. *J. Chem. Res. Miniprint*, **1978**, 3831. We have found that the siloxydiene **5b** is most easily obtained by treating the acetoxydiene **4a** with 2.1 equiv of *n*-BuLi at −78 °C and quenching the yellow solution with trimethylsilyl chloride at 0 °C.

(14) The compounds **9** and **10** are in equilibrium with each other. The ratio, though usually 2 or 3 to 1, varies due to selective destruction of one or the other product under the reaction conditions. In practice **9** is separated by chromatography and reequilibrated in refluxing mesitylene to give **10** in the reported yield.

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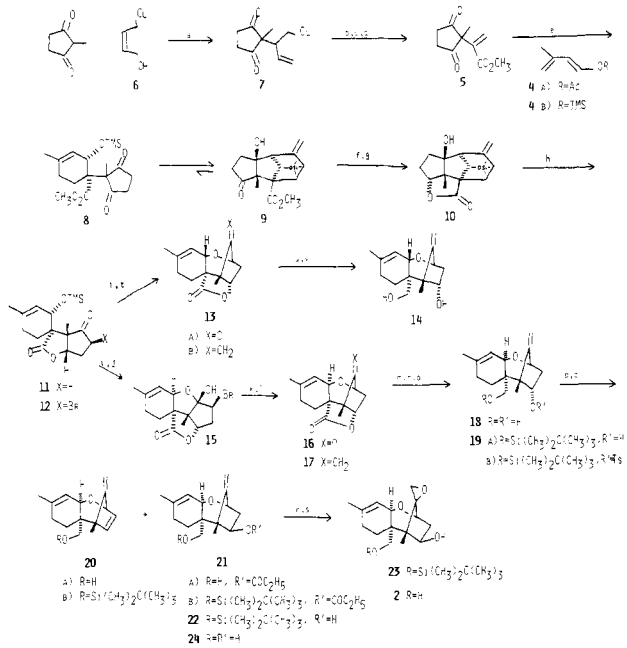
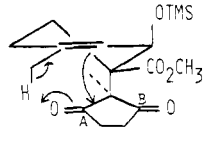
Scheme I



[a] pTSA, toluene, $-H_2O$; followed by mesitylene, reflux, 9 h (93%).[25] [b] $KMnO_4$ (4.0×), H_2O, HOAc, CH_2Cl_2, $R_4{}^+NBr^-$, 0 °C to room temperature, 2 h. [c] CH_2N_2. [d] DBU, benzene–ether (48% from 7). [e] **4b** (1.9×), mesitylene, 1.0 M, 155 °C for 9 h, (63%).[14] [f] $NaBH_4$ (1.9×), MeOH, room temperature, 20 min. [g] $CrO_3 \cdot 2pyr$ (3×), CH_2Cl_2, room temperature, 35 min (92% from 9).[26] [h] hot tube, 16 cm, 470 °C, 1.2–1.5 mm (89%).[16] [i] Lithium tetramethylpiperidide (1.4×), THF, −20 to 0 °C, 1.5 h; then TMSCl, 0 °C to room temperature, 10 min; then Br_2·dioxane, CH_2Cl_2, pyridine, −78 °C, 8 min, all in one pot. [j] 10% CF_3CO_2H (13×) in ethylene dichloride, H_2O (2.7×), 32 °C for 14 h, 45 °C for 1 h, 55 °C for 15 min. [k] n-$Bu_4N^+F^-$ (3×), THF (70% from **11**). [l] $Ph_3P{=}CH_2$, LiBr (1.3×), THF, 60 °C, 6 min (95%). [m] DibalH (8×), toluene, room temperature, 6.5 h (95%). [n] *tert*-Butyldimethylsilyl chloride (1.5×), DMAP (2.0×), CH_2Cl_2, 4.5 h, 0 °C; worked up with hexane and cold $NaHSO_4$ (82%).[24] [o] TsCl (8×), pyridine (1.3 M in TsCl), 34 °C, 60 h (79%).[25] [p] $CsO_2CCH_2CH_3$ (20×), 1,3-dimethyl-2-imidazolidinone, (0.1 M in **19b**), 150 °C, 7 h; then after workup, *tert*-butyldimethylsilyl chloride (10×), imidazole (20×), DMF, 42 °C, 12 h. [q] K_2CO_3 (10×), 15% aqueous MeOH, 20 h, room temperature (31% for **22**, 39% for **20b** both from **19b**). [r] $Mo(CO)_6$ (0.33×), *tert*-butyl hydroperoxide (3.45×), benzene (0.068 M in **22**), 63 °C, 1.5 h (85%). [s] n-$Bu_4N^+F^-$ (7.4×), THF, room temperature, 4.5 h (91%). [t] n-$Bu_4N^+F^-$ (2.5×), THF, room temperature, 1.5 h (62% based on **11**). [u] $Ph_3P{=}CH_2$, LiBr (1.2×), THF, 52 °C, 10 min (71%). [v] DibalH (6×), hexane (0.33 M in **13b**), room temperature, 35 h (78%).

carbonyl groups could align itself in the proper orientation to undergo an ene reaction. Since pyrolysis of the ene product regenerates the simple adduct, this ene–retroene sequence represents a diastereotopic differentiation and a method of protection.



Reduction of the remaining ketone produced the lactone **10** which upon thermolysis, underwent the retroene reaction to give **11**[16,24] in 89% yield. Now all that is required to ripen the molecule for formation of the trichothecane ring system is the introduction of a leaving group α to the carbonyl group and inversion of configuration at C-11. The initial problem was solved by quenching the ketone enolate with trimethylsilyl chloride and, in the same pot, introducing 1 equiv of bromine as its dioxane complex.[17] The resulting bromo ketone **12** was exposed to trifluoroacetic acid at 0 °C and then tetra-*n*-butylammonium fluoride. Neither the product **13a**[24] nor its further transformation product diol **14** showed any observable coupling between the vinyl hydrogen and the methine proton next to oxygen, suggesting cyclization to the 11-epitrichothecane skeleton as depicted. This same product was obtained by direct treatment of **12** with fluoride ion. X-ray analysis of **13a** confirmed this result.[18] The ease of cyclization is noteworthy considering the strain of the boat conformation required for the tetrahydropyran-3-one ring. Treatment of the bromo ketone with trifluoroacetic acid under thermodynamically controlled conditions (35–50 °C) produces the hemiketal **15**.[19] While exposure of the latter to DBU proved unrewarding, fluoride-initiated rearrangement proceeded smoothly to the desired ring system **16**[24] in a 70% yield from ketone **11**. Hence the trichothecane framework and its C-11 epimer are readily available in 11 and 10 steps, respectively, from the commerically available dione in an overall yield of 16%.

The final stage of our synthesis began with a methylene Wittig reaction to introduce the final carbon at C-13. Exposure of the resulting diene **17** to excess diisobutylaluminum hydride furnished the diol **18**, which for the first time showed the characteristic 5.5-Hz coupling between the hydrogens at C-10 and C-11. With the next obstacle being the inversion of stereochemistry at C-4, the primary alcohol was selectively protected[20] as its *tert*-butyldimethylsilyl ether **19a**[24] followed by tosylation of the secondary alcohol. Treatment of the tosylate **19b** with cesium propionate[21] at 150 °C yielded a mixture of olefins **20a** and **20b**, as well as the inverted esters **21a** and **21b**. This mixture was resilylated and the propionate ester hydrolyzed to give the alcohol **22** and the olefin **20b** in 31% and 39% yields, respectively, from the tosylate **19b**.

The final hurdle was formation of the 12,13-epoxide, a problem whose only resolution to date involves protection of the trisubstituted olefin as its bromo ether.[4c,d] Wanting to avoid such a protection–deprotection sequence, we studied the oxidation of **22** in detail[27] and found that the molybdenum-catalyzed *tert*-butyl hydroperoxide epoxidation[22] gives, in 85% yield, silyl verrucarol (**23**)[24] which was identical with the same compound obtained from

(15) For a recent review of intramolecular ene reactions see: Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *7*, 476. Intramolecular ene reactions where a ketone serves as the enophile are rare. For some see: Niva, M.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3148. Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

(16) Pyrolysis gives a preponderance of **12** (4:1). The equilibrium mixture favors **12** even more, but the length and temperature of the hot tube must be kept to a minimum in order to avoid undesired side reactions such as the retro Diels–Alder. One recycle of recovered **11** gives **12** in the reported yield.

(17) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785. Quenching the enolate directly with various brominating agents always gave significant amounts of recovered starting material.

(18) The X-ray structure was performed by Dr. Ken Haller, University of Wisconsin–Madison.

(19) The inversion of stereochemistry presumably arises from trapping of the allylic carbonium ion by the hydrated form of the ketone. The initial products of this reaction are a mixture of dienes, coming from elimination of the allylic carbonium, which are slowly converted to the hemiketal **14**.

(20) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

(21) Kruizinga, W. H.; Strytveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321. Note should be taken of the use of 1,3-dimethyl-2-imidazolidinone as the solvent, which proved superior to DMF at the temperatures needed for the displacement.

(22) For a review of metal-catalyzed oxidations see: Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(23) This compound was made from natural verrucarol; see: Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.* **1980**, *21*, 4549.

(24) All new compounds reported except for **12**, **15**, and **20a**, **21a**, and **21b** have been fully characterized by IR, ^1H NMR (270 MHz), and high-resolution mass spectroscopy and/or combustion analysis. Full spectral data for compounds **9**, **11**, **13a**, **16**, **19a**, and **23** can be found in the supplementary material.

(25) Yields based on recovered starting material.

(26) During the sodium borohydride reaction some overreduction occurred, giving lactol. Therefore the oxidation step was necessary to get a homogeneous sample of lactone **10**.

natural sources[23] except for optical activity and melting point. Simple treatment of **23** with fluoride ion yielded (±)-verrucarol [mp 165.5–167 °C (ether–chloroform)],[28] again identical with the natural material except for optical activity and melting point.[29]

Presently work is underway to synthesize 11-epiverrucarol from the diol **14**. We are also hoping to convert the triene **20b** to some of the C-3,C-4 diols such as anguidine. This highly efficient synthesis of the trichothecane skeleton and its C-11 epimer should provide some intriguing analogues, not readily available from natural sources, in quantities suitable for biological testing.

Acknowledgment. We express our warm appreciation to the National Cancer Institute for their generous support. We are grateful to Dr. Ken Haller for collaborating in the X-ray determination of a critical intermediate and Professor Christoph Tamm for providing a generous authentic sample of the natural products.

Registry No. (±)-**2**, 80514-49-4; **4b**, 58274-64-9; **5**, 82891-01-8; **6**, 7523-44-6; (±)-**7**, 82891-02-9; (±)-**8**, 82902-13-4; (±)-**9**, 82891-03-0; (±)-**10**, 82891-04-1; (±)-**11**, 82891-05-2; (±)-**12**, 82891-06-3; (±)-**13a**, 82891-07-4; (±)-**14**, 82916-70-9; (±)-**15**, 82891-08-5; (±)-**16**, 82916-71-0; (±)-**17**, 82891-09-6; (±)-**18**, 82891-10-9; (±)-**19a**, 82891-11-0; (±)-**19b**, 82891-12-1; (±)-**20a**, 82891-13-2; (±)-**20b**, 82891-14-3; (±)-**21a**, 82891-15-4; (±)-**21b**, 82891-16-5; (±)-**22**, 82891-17-6; (±)-**23**, 82891-18-7; 2-methyl-1,3-cyclopentanedione, 765-69-5; cesium propionate, 38869-24-8.

Supplementary Material Available: Full spectral data for compounds **9**, **11**, **13a**, **16**, **19a**, and **23** (2 pages). Ordering information is given on any current masthead page.

(27) Peracid oxidation (mCPBA, −26 °C) exhibited moderate chemoselectivity (66% at 60% conversion). Both the undesired 9,10-monoepoxide and the 9,10,12,13-diepoxide could be detected in the ^{1}H NMR (270 MHz) spectrum. When $VO(acac)_2$ was used as the metal catalyst, decomposition as well as the desired oxidation accompanied the disappearance of starting material.

(28) Our melting point for racemic verrucarol is some 6 °C higher than that reported by Schlessinger and Nugent (ref 4c). Since these authors were the first to prepare the racemate, we are somewhat puzzled by the literature citation given by these authors for racemic verrucarol. To our knowledge all literature melting points are for the optically pure compound (mp 155–156 °C, ref 29).

(29) Gutzwiller, J.; Mauli, R.; Sigg, H. P.; Tamm, Ch. *Helv. Chim. Acta* **1964**, *47*, 2234.

Macrocyclization via an Isomerization Reaction at High Concentrations Promoted by Palladium Templates

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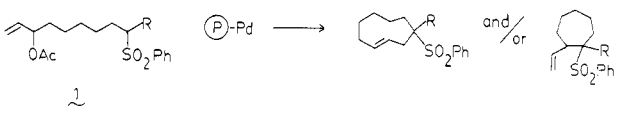
The ability to form medium and macrocyclic rings has normally relied upon high dilution to ensure intramolecular vs. intermolecular reactions.[1] The inefficiency associated with large volumes of solvent, which can be somewhat ameliorated by the use of slow addition techniques, encourages exploration of methodology that avoids high dilution. The principle of "pseudodilution" within cross-linked polymers,[2] which has been so successfully employed in peptide synthesis, had not been successfully applied to macrocyclization (except for cyclic peptides[3]) at the time we initiated our work.[4] Most recently, the use of this approach for macrolactonization has been reported; however, substrate concentrations were still <0.003 M.[5] We report an approach to forming medium and large rings via C–C bond formation that permits utilization of 0.1–0.5 M concentrations of substrates in simple bulk solution.

Polymer-supported transition-metal-mediated macrocyclization[6] offers a simplistic solution to this problem at first glance. With the catalyst anchored on an insoluble support,[7] a pseudodilution effect arises from the low concentration of the "active sites" in a phase apart from that containing the substrate. Thus, the substrate must diffuse to the catalytic site before it becomes activated for cyclization. The combinatorial effect of having relatively few catalytic sites and even fewer occupied at the same time should ensure an intramolecular reaction. Use of the sodium salt of **1**, R = CO_2CH_3 or $PhSO_2$ with a polystyrene polymeric



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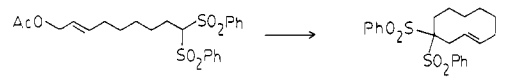
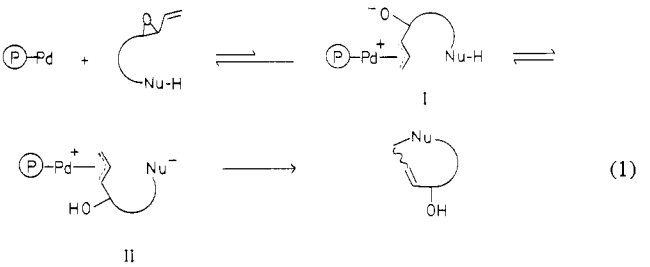
catalyst that bore both benzo-12-crown-4[8] and phosphine ligands binding palladium(0) as well as simple macroreticular polystyrene polymeric supports bearing palladium(0) ligated with phosphines led to both seven- and nine-membered ring products in low yields with varying amounts of starting material and/or elimination product.[9] The best result obtained involved the cyclization of **2**, which gave only 4,4-bis(benzenesulfonyl)-*E*-cyclononene in



2 3

20% yield with 76% recovery of starting material (83% yield based upon recovered starting material).

Perceiving that problem as related to the use of salts whose diffusion to the catalytically active sites on these lipophilic polymers was unfavorable, we sought a neutral cyclization precursor that upon binding to the active site generates both the nucleophilic and electrophilic partners required in the cyclization. Vinyl epoxides[10,11] as represented by **4** and **5** (Scheme I) represent ideal choices. The chemoselectivity in the final step of their synthesis, i.e., the alkylation of the bromo vinyl epoxides, should be noted. Thus, the vinyl epoxide is not a reactive electrophile in aprotic solvents in the absence of palladium catalysts. Equation 1 rep-



(1) For a recent critical evaluation of macrolactonization methods see: Galli, C.; Mandolini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 251. For reviews on macrolides see: Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Back, T. G. *Tetrahedron* **1977**, *33*, 3041. Newkome, G. R.; Sauer, J. D.; Roper, J. M.; Hager, D. C. *Chem. Rev.* **1977**, *77*, 513.

(2) Mazur, S.; Jayalekshmy, P. *J. Am. Chem. Soc.* **1979**, *101*, 677. Rebek, J., Jr., Trend, J. E. *Ibid.* **1979**, *101*, 737. Chang, Y. H.; Ford, W. T. *J. Org. Chem.* **1981**, *46*, 5364 and references therein.

(3) Fridkin, M.; Patchornik, A.; Katchalski, E. *Isr. J. Chem.* **1965**, *3*, 69; *J. Am. Chem. Soc.* **1965**, *87*, 4646.

(4) Crowley, J. I.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 3215; *Acc. Chem. Res.* **1976**, *9*, 135.

(5) Regen, S. L.; Kumura, Y. *J. Am. Chem. Soc.* **1982**, *104*, 2064.

(6) For palladium-catalyzed macrocyclization see: Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743 and earlier references therein. Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *Ibid.* **1977**, *99*, 3864.

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