Transition-Metal-Centered Radicals in Organic Synthesis. Titanium(III)-Induced Cyclization of Epoxyolefins

William A. Nugent* and T. V. RajanBabu

Contribution No. 4818, Central Research and Development Department
E. I. du Pont de Nemours & Co., Inc.
Experimental Station, Wilmington, Delaware 19898

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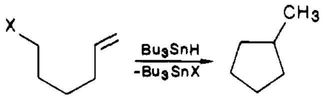
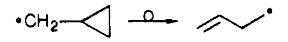
Hexenyl radical cyclizations are a powerful method for the synthesis of cyclopentane derivatives.[1] Nevertheless, one significant limitation in the usual synthetic procedure has been noted.[2,3] Treatment of an alkenyl halide with tributyltin hydride as exemplified by eq 1 necessarily results in a net loss of two functional groups.

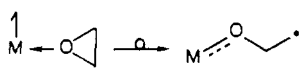


(1)

We wish to report a solution to this problem which allows the direct synthesis of functionalized cyclopentane derivatives. This new reaction is based on an analogy to the extremely facile rearrangement of cyclopropylmethyl radical to homoallyl radical (eq 2). A σ-complex of an epoxide with a paramagnetic transition metal[4] having a half-filled (π-symmetry) d orbital represents an electronic analogue of the cyclopropylmethyl moiety. By analogy to eq 2, release of ring strain might be expected to drive the homolytic C–O bond cleavage in eq 3.



(2)



(3)

To test this hypothesis, we added 2 molar equiv of bis(cyclopentadienyl)titanium(III) chloride[5] in THF dropwise[6] to a THF solution of 6,7-epoxy-1-heptene. The green color of the titanium(III) species instantly discharged to red upon exposure to the epoxide. Quenching the mixture with 10% D_2SO_4 in D_2O afforded 2-methylcyclopentanemethanol which was >85% monodeuteriated in the methyl group (ca. 70% yield by GLC[7]). As shown in Scheme I, this result suggests that after C–O bond cleavage, hexenyl radical cyclization indeed takes place. Moreover, the resultant primary radical is efficiently scavenged by a second equivalent of titanium(III) affording the indicated alkyltitanium(IV) species.

Scheme I

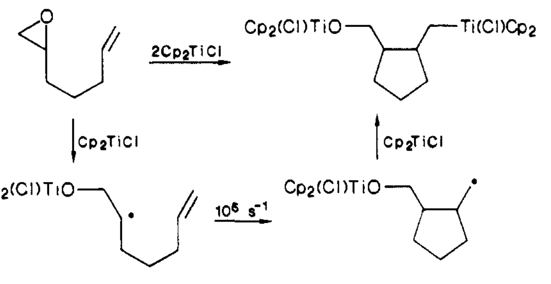
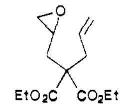
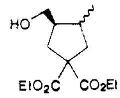
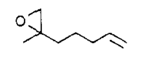
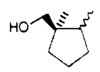
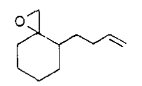
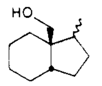
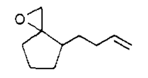
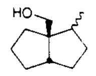
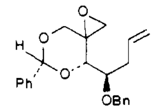
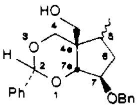
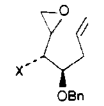
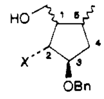


Table I. Isolated Yields of Cyclopentanemethanols by Epoxyolefin Cyclization

epoxyolefin[d]	product	no.	yield (%)	isomer ratio
		**1**	68 (76)[a]	85:15 (cis/trans)
		**2**	94	1:1
		**3**	82 (81)[a]	55:45 (endo/exo)
		**4**	88	90:10 (endo/exo)
		**5**	70	83:17 (endo/exo)
		**6**	74 (X = OAc) 44 (X = OBn)	*b* 45:30:15:10[c]

[a] Yields in parentheses using the in situ procedure on 5-mmol scale. [b] Mixture of four isomers of undetermined structures. [c] In order: 1,2-trans, 1,5-cis; 1,2-trans, 1,5-trans; 1,2-cis, 1,5-cis; 1,2-cis, 1,5-trans. See Supplementary Material for details of assignments. [d] See Supplementary Material for preparation; starting epoxy olefins 3 and 4 were mixtures of diastereomers.

The cyclization/protonolysis sequence[8] was applied to a series of substituted epoxyolefins containing synthetically useful functionality; isolated yields are shown in Table I. Several observations are noteworthy. Successful synthesis of **1** indicates that the reaction conditions are compatible with the carbonyl functionality.[9] Products **2** through **5** stress that this procedure is especially well suited to the introduction of quaternary centers. The ring fusions in products **3** through **5** are cis. Preponderant formation of the endo isomer in each case is precedented.[10] The substrates for products **5** and **6** are derivatives of naturally occurring sugars, providing access to the enantiomerically pure carbocycles.[11]

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(1) Julia, M. *Pure Appl. Chem.* **1974**, *40*, 553-567. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073-3100. Burnett, D. A.; Choi, J.; Hart, D. J.; Tsai, Y. *J. Am. Chem. Soc.* **1984**, *106*, 8201-8209. Curran, D. P.; Kuo, S. *J. Am. Chem. Soc.* **1986**, *108*, 1106-1107. Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384-6385. RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522-4530.

(2) Curran, D. P.; Chen, M.-H; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489-2490.

(3) Begley, M. J.; Bhandal, H.; Hutchinson, J. H.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1317-1320. See, also: Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303-304.

(4) Reduction of epoxides to olefins by a variety of low-valent transition-metal species have been studied.[4a] Kochi[4b] was the first of several workers to propose that some of these reactions may proceed by discrete one-electron steps via the carbon-centered radical. (a) For a review, see: Wong, H. C.; Fok, C. C. M.; Wong, T. *Heterocycles* **1987**, *26*, 1345-1382. (b) Kochi, J. K.; Singleton, D. M.; Andrews, L. J. *Tetrahedron* **1968**, *24*, 3503-3515.

(5) Most of these studies were carried out with isolated $[Cp_2TiCl]_2$ prepared according to Manzer.[5a] However, it appears that material generated in situ from commercially available Cp_2TiCl_2 and granulated zinc[5b] (and containing an equivalent of $ZnCl_2$) gives comparable yields (Table I). (a) Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 84-86. (b) Green, M. L. H.; Lucas, C. R. *J. Chem. Soc., Dalton Trans.* **1972**, 1000-1003.

(6) "Inverse addition" of the titanium reagent to the epoxide is advantageous when a secondary radical is being generated since it minimizes any reduction of the radical prior to cyclization (i.e., it suppresses competitive formation of diene). For compound **7** "normal" addition of epoxide to the titanium reagent was used to optimize the efficiency of scavenging the cyclized radicals by titanium(III).

(7) The product is a 2:1 mixture of cis and trans isomers. In contrast to these results, cyclization of an epoxyacetylene (6,7-epoxy-1-heptyne) followed by deuteriolysis produced 2-methylenecyclopentanemethanol containing no deuterium in the methylene group.

(8) In a typical reaction, Cp_2TiCl (430 mg, 2.0 mg-atom) in THF (25 mL) was added dropwise to a solution of the epoxyolefin (1.0 mmol) in THF (25 mL) under N_2. After 10 min the reaction was quenched with 10% H_2SO_4 (50 mL), and the product was extracted with ether (3 × 50 mL), washed with saturated sodium bicarbonate then water (50 mL each), and dried ($MgSO_4$). After distillation of solvent, the products were purified by flash chromatography as described in the Supplementary Material. For products **7** and **8**, iodine (254 mg, 1.0 mmol) was added, and the mixture was stirred for 2 h and then hydrolyzed as above.

(9) The ketone and nitrile functionality are similarly unaffected by Cp_2TiCl. Preliminary experiments suggest that the reaction is incompatible with the aldehyde functionality and gives reduced yields in the presence of an allyl ether.

(10) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. *Tetrahedron Lett.* **1981**, *22*, 2811-2814.

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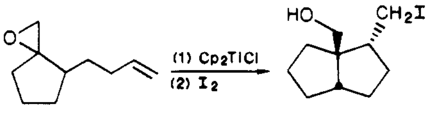
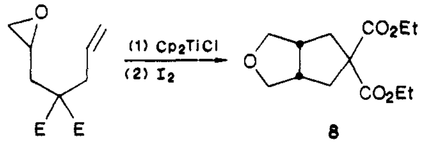
Treatment of the nucleophilic organotitanium derivative in Scheme I with electrophiles other than the proton should provide a route to bifunctional cyclopentane derivatives. To demonstrate this approach we treated two of the product mixtures with iodine. The iodoalcohol **7** was isolated in isomerically pure form (as the *tert*-butyldimethylsilyl ether) in 63% yield. In contrast, the *cis*-organotitanium intermediate in eq 5 cyclized to tetrahydrofuran **8** in 52% isolated yield. In both cases other isomeric products were presumably formed but were not isolated.



7 (4)



8 (5)

We acticipate that this reaction, while quite useful in its own right, may also be the prototype for other novel transformations based on transition-metal-centered radicals.[12] As a first step in this direction we plan to explore *intermolecular* additions of epoxides to activated olefins.

Supplementary Material Available: Details of isolation and characterization (^{13}C NMR, ^{1}H NMR, HRMS, elemental analysis) of products **1–8** (4 pages). Ordering information is given on any current masthead page.

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(11) Other radical routes from carbohydrates to chiral cyclopentanes: Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102–3104. RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609–611.

(12) Roskamp and Pedersen have reported that another d^1 complex, $NbCl_4(THF)_2$, promotes an unprecedented dimerization of silylimines and nitriles to vicinal diamines. However, they note that 5-hexenenitrile is not cyclized suggesting that there is no long-lived carbon radical associated with the system: Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152–3154.

Electrosynthesis of Porphyrins from *a*,*c*-Biladienes

D. Jeyakumar, Kevin M. Snow, and Kevin M. Smith*

Department of Chemistry, University of California
Davis, California 95616

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One of the most successful syntheses of porphyrins from open-chain tetrapyrroles involves the copper(II)-catalyzed cyclization of 1′,8′-dimethyl-*a*,*c*-biladiene salts **1** to give copper(II) porphyrins **2**. This procedure was discovered in 1961 by Johnson and Kay[1] and has been generalized[2–5] for preparation of completely unsymmetrical porphyrins by way of tripyrrenes and 1′,8′-dimethyl-*a*,*c*-biladienes. The approach does suffer some disadvantages, the most notable being the vigorous conditions required in the final cyclization step [Cu(II) in dimethyl formamide at 140–150 °C], the erratic yields of porphyrin (varying between 20 and 75%), and the fact that the product is a copper(II) porphyrin **2** which must subsequently be demetalated with concentrated sulfuric and trifluoroacetic acids. A room temperature copper(II)-promoted cyclization procedure and other metal salt oxidants have been described[6] but do not offer substantial improvements.

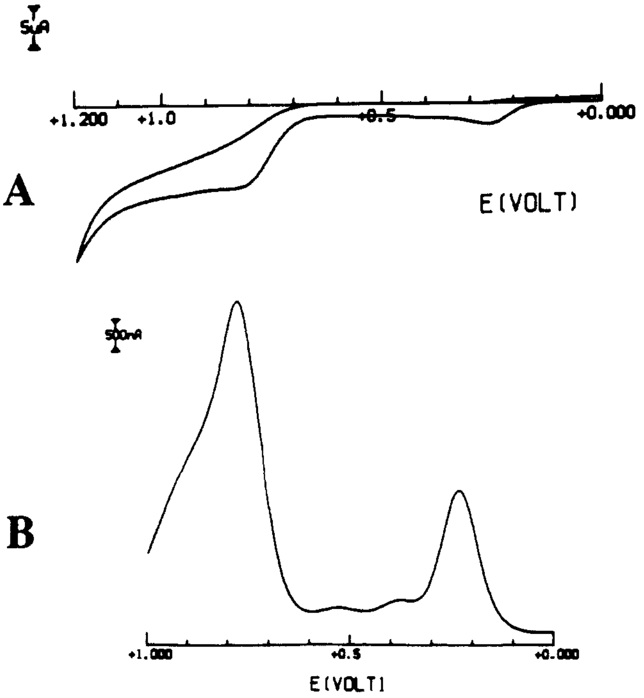
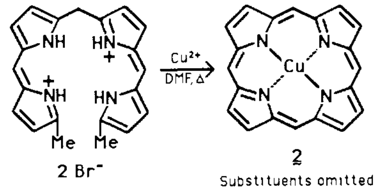


Figure 1. Cyclic voltammogram[11] (A) and square wave voltammogram (B) of chloroethyl-*a*,*c*-biladiene **3**.

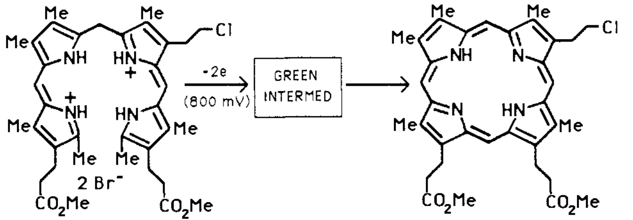


2 Br⁻

1

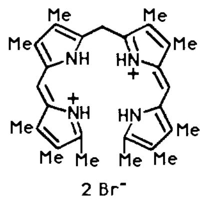
2

Substituents omitted for clarity



3

4



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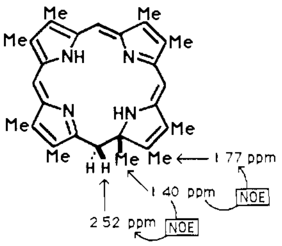

6

Using carbon-13 labeling, the mechanism of the *a*,*c*-biladiene cyclization was investigated,[7,8] these studies establishing both the origin of the new meso carbon atom as well as a plausible pathway from 1′,8′-dimethyl-*a*,*c*-biladiene to copper(II) porphyrin.[8,9] No

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(1) Johnson, A. W.; Kay, I. T. *J. Chem. Soc.* **1961**, 2418–2423.

(2) de Almeida, J. A. P. B.; Kenner, G. W.; Rimmer, J.; Smith, K. M. *Tetrahedron* **1976**, *32*, 1793–1799.

(3) Smith, K. M.; Craig, G. W. *J. Org. Chem.* **1983**, *48*, 4302–4306.

(4) Engel, J.; Gossauer, A. *Liebigs Ann. Chem.* **1976**, 1637–1658.

(5) Mironov, A. F.; Rumyantseva, V. D.; Rozynov, B. V.; Evstigneeva, R. P. *Zh. Org. Khim.* **1979**, *7*, 165–168. Mironov, A. F.; Kulish, M. A.; Kobak, V. V.; Rozynov, B. V.; Evstigneeva, R. P. *Zh. Obshch. Khim.* **1974**, *44*, 1407–1410. Kulish, M. A.; Kozhich, D. T.; Mironov, A. F.; Evstigneeva, R. P. *Bioorg. Khim.* **1978**, *4*, 1237–1243.

(6) Smith, K. M.; Minnetian, O. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 277–280.

(7) Smith, K. M.; Kehres, L. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2329–2335.

(8) Smith, K. M.; Minnetian, O. M. *J. Org. Chem.* **1985**, *50*, 2073–2080.

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