is not perturbed by the enzymatic cyclization, the enzymatically generated product is shown to be (1*S*,5*S*,7*R*)-β-*trans*-bergamotene.[15]

Acknowledgment. This work was supported by a grant from the National Institutes of Health, GM30301, and by an N.I.H. Fogarty Center Senior International Fellowship to D.E.C.

(15) For a related example of the assignment of the absolute configuration of a natural product by ^2H NMR analysis of the diterpene pleuromutilin derived from a chirally deuterated precursor see: Hasler, H.; Dissertation; ETH Zurich, 1979; No. 6359.

Chemoselective Reduction of Oxiranes by Methylmetals in the Presence of the Copper(I)–Phosphine Complex

Michiharu Mitani,* Hiroyuki Matsumoto, Naruko Gouda, and Kikuhiko Koyama

Department of Synthetic Chemistry
Faculty of Engineering, Shinshu University
Wakasato, Nagano 380, Japan

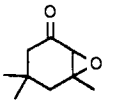
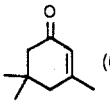
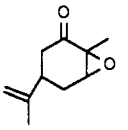
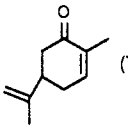
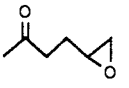
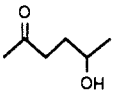
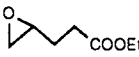
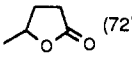
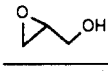
Received August 14, 1989

The organocopper "ate" complexes such as homocuprates[1] and mixed cuprates[2] have been known to perform the alkylative ring opening of oxiranes, whereas such competing pathways as rearrangement and halohydrin formation occur during the reaction of oxiranes with other organometallic compounds, particularly Grignard reagents.[3] In this investigation, we have found that methylmetal compounds react with oxiranes in the presence of the copper(I)–phosphine complex to afford the reductive ring opening. The reduction of oxiranes to alcohols has been known to be attained by a variety of reducing agents including metal hydrides. However, the preferential reduction of the epoxide over such readily reducible functionalities as a carbonyl group has, up to now, been difficult.[4]

Our results are indicated in Table I. Cyclohexene oxide in ether was added dropwise to an equimolar amount of methylmagnesium iodide in an ether solution containing 10 mol % of $CuBr(PBu_3)_2$ at 0 °C under nitrogen. The reaction was stopped after 2 h by the addition of aqueous NH_4Cl to give cyclohexanol in 73% yield. The reaction of 1,2-epoxybutane with methylmagnesium iodide led to halohydrin formation as the main pathway (67%), and butanols were obtained only as minor products (2-butanol, 14%; 1-butanol, 4%). The addition of an equimolar amount of $CuBr(PBu_3)_2$ enhanced the reduction reaction (2-butanol, 16%; 1-butanol, 8%). However, the use of methyllithium instead of the Grignard reagent afforded 2-butanol as the sole volatile product in 86% yield. Carbonyl, carbalkoxy, and cyano functionalities were compatible with these reaction conditions, i.e., acetophone, cyclohexanone, 4-heptanone, ethyl benzoate, methyl propionate, and benzonitrile were recovered intact after treatment with methylmagnesium iodide or methyllithium in the presence of $CuBr(PBu_3)_2$. Thus, when oxiranes containing a carbonyl or carbalkoxy functionality elsewhere in the molecule, such as isophorone oxide, carvone oxide, 5,6-epoxy-2-hexanone, and ethyl 4,5-epoxypentanoate, were subjected to the reaction with methyllithium in the presence of $CuBr(PBu_3)_2$, the products based on the chemoselective reduction of the epoxy ring were obtained. While the reaction of styrene oxide with methylmagnesium iodide in the presence of $CuBr(PBu_3)_2$ gave preferentially the methyl addition products (**7**, 42%; **8**, 30%) and styrene (which was probably formed by the dehydration of 1- and/or 2-phenylethyl alcohol, the primary reduction product) as the minor product (14%), the use of $CuBrPBu_3$ instead of $CuBr(PBu_3)_2$ resulted in the preferential formation of the reduction products (styrene, 25%; 2-phenylethyl alcohol, 48%). The methylmetal seems to be more effective for the reduction of oxiranes than other alkylmetals as revealed by the observation that, in the reaction with 1,2-epoxybutane in the presence of 10 mol % of $CuBr(PBu_3)_2$, the methyl, *n*-butyl, and *tert*-butyl Grignard reagents gave 18, 8,[5] and 0% of butanols, respectively.

With respect to the mechanism for this reduction reaction of oxiranes, a pathway via the intermediary generation of the methylcopper–phosphine complex may be first envisaged since it has been well-known that the reaction of alkylmetals with cuprous halides generates the alkylcopper species. However, the me-

Table I. Reactions of Epoxides with $(RM)CuBr(PBu_3)_n$ Complexes

epoxide	RM	RM/CuBr/PBu_3 molar ratio	temp, °C	product (yield,[a] %)
	MeMgI	1/0.1/0.2	0	c-$C_6H_{11}OH$ (73)
 1	MeMgI	1/0.1/0.2	0	2-BuOH (2) (14), 1-BuOH (3) (4), $EtCH(OH)CH_2I$ (4) (67)
1	MeMgI	1/1/2	0	**2** (16), **3** (8), **4** (60)
1	*n*-BuMgI	1/0.1/0.2	0	**3** (8), 3-octanol (30), $EtCH(OH)CH_2Br$ (22)
1	*t*-BuMgCl	1/0.1/0.2	0	-
1	MeLi	1/1/2	-50	**2** (86)
	MeLi	1/1/2	-50	 (65)
	MeLi	1/1/2	-50	 (73)
	MeLi	1/1/2	-50	 (70[b])
	MeLi	1/1/2	-50	 (72[b])
 5	MeMgI	1/1/2	0	$PhCH{=}CH_2$ (**6**) (14), PhCH(OH)Et (**7**) (42), $PhCH_2CH(OH)$-Me (**8**) (30)
5	MeMgI	1/1/1	0	**6** (25), $PhCH_2CH_2OH$ (48), **8** (8)
	MeLi[c]	1/1/1	-50	$MeCH(OH)CH_2OH$ (85)

[a] Determined by VPC analysis unless stated otherwise. [b] Yield after isolation by silica gel column chromatography. [c] Two equivalents of methyllithium was used.

(1) (a) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813. (b) Johnson, C. R.; Herr, R. W.; Wieland, D. M. *J. Org. Chem.* **1973**, *38*, 4263. (c) Hartman, B. C.; Livinghouse, T.; Rickborn, B. *J. Org. Chem.* **1973**, *38*, 4346.

(2) (a) Acker, R. D. *Tetrahedron Lett.* **1977**, 3407. (b) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305. (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.

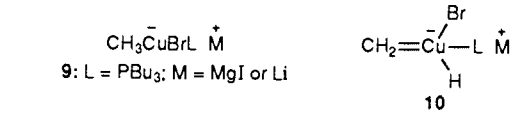
(3) Herr, R. W.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 4979.

(4) A chemoselective reduction of epoxides in the presence of such modestly reducible groups as carbamoyl and carboxyl has been performed with $NaBH_4$ in a mixed solvent containing MeOH. Ookawa, A.; Hiratsuka, H.; Soai, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1813.

(5) It is interesting that the *n*-butyl Grignard reagent gave only 1-BuOH as the reduction product, whereas the methyl Grignard reagent afforded a mixture of 2- and 1-butanols, the former being major and the latter being minor.

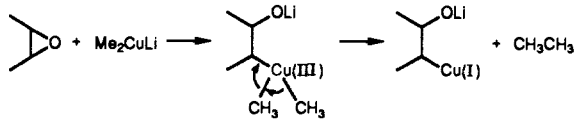
0002-7863/90/1512-1286$02.50/0

thylcopper-phosphine complex has been reported not to react with oxiranes,[1a,b] and in fact, the reaction of methyllithium with 1,2-epoxybutane in the presence of cuprous iodide instead of cuprous bromide in our reaction system did not give any product including butanol, which probably would be attributed to the intervention of the methylcopper-phosphine complex. Thus, a pathway through an intemediary methylcopper-phosphine complex might be less possible. Although a dimethylcopper(I) complex might be next postulated as the working species in our reactions, its possibility might be also less likely[6] since the treatment of an alkyllithium such as methyllithium or *n*-butyllithium with the CuI-phosphine complex has been reported to afford not the dialkylcopper(I) complex but the alkylcopper-phosphine complex,[7] and the dimethylcopper complex, even if generated, would afford the methyl addition products with oxiranes.[1] Thus, although the mechanism cannot be clearly defined at this stage, we supposed that the "ate" complex **9** holding a bromine atom might have a definite lifetime under our reaction conditions because of the poorer leaving ability of bromine compared to iodine and be a key species for the reduction of oxiranes. For the reduction of oxiranes by **9**, in turn, three pathways might be assumed as possible candidates. They are (1) electron transfer from **9** to the epoxy ring followed by a hydrogen abstraction,[8] (2) generation of the methylenecopper hydride-phosphine complex **10** by α-elimination from **9**,[9,10] and (3) hydrogen transfer from **9** to the epoxy ring. The possibility of pathway 1 would be diminished[11] because the more negative



reduction potential of the oxirane compared to the ketone[12] is inconsistent with the explanation by the electron transfer pathway of this reaction to bring about the preferential reduction of the epoxy ring over the carbonyl functionality, and one-electron transfer from the low-valent transition-metal compounds to oxiranes cleaves the ring bond between the oxygen and the more substituted carbon[13] while the products due to the cleavage of the ring bond between the oxygen and the less substituted carbon are obtained in our reaction system. When electron-rich olefins such as *n*-butyl vinyl ether and 1-phenyl-1-(trimethylsiloxy)ethylene were subjected to the reaction with methylmagnesium iodide in the presence of $CuBr(PBu_3)_2$, the corresponding cyclopropane derivatives, were formed, although in minor amounts, suggesting the intervention of **10**. Detailed mechanistic investigations are in progress.

(6) This possibility, however, might not be entirely excluded because a pathway via a metalated intermediate of Cu(I) arising from a Cu(III) precursor as shown below has been suggested by a referee; cf.: Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2391.



(7) (a) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128. (b) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; Filippo, J. S., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

(8) In the addition reaction of the cuprates to allylic epoxides or α,β-unsaturated carbonyl compounds, the electron-transfer pathways has been postulated. See ref 7a. Also see: (a) Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 3047. (b) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141.

(9) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978; pp 285-288.

(10) For a recent investigation on the copper hydride-phosphine complex, see: Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

(11) In the case of α-epoxy ketones such as isophorone oxide and carvone oxide, however, the possibility that α,β-unsaturated ketones as the reduction products were formed through the electron-transfer pathway may not be excluded because lithium dimethylcuprate has been reported to perform the reduction of the epoxy group of steroidal α-epoxy ketones via electron transfer to the carbonyl group, giving β-hydroxy ketones along with α,β-unsaturated ketones and β-methyl ketones as consecutive derivatives; cf.: Bull, J. R.; Lachmann, H. H. *Tetrahedron Lett.* **1973**, 3055.

(12) Willits, C. O.; Ricciuti, C.; Knight, H. B.; Swern, D. *Anal. Chem.* **1952**, *24*, 785.

(13) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561.

Synthesis of a Membrane-Insertable, Sodium Cation Conducting Channel: Kinetic Analysis by Dynamic ^{23}Na NMR

Akio Nakano,† Qingshan Xie, Jesus V. Mallen, Luis Echegoyen,* and George W. Gokel*

Department of Chemistry, University of Miami Coral Gables, Florida 33124

Received October 16, 1989

We report herein the synthesis and characterization of a rationally designed, completely synthetic compound that inserts in phosphatidylcholine (pc) vesicles. Using the dynamic (equilibrium) NMR method presented initially by Riddell and Hayer,[1] recently extended by Hinton et al.,[2] we demonstrate that this molecule significantly enhances the rate at which Na^+ is transported compared to a closely related carrier model. We believe this enhanced rate to be due to formation of a channel-like structure.

Cation transport in nature generally occurs by either the carrier or channel mechanism. The former has been studied extensively while few attempts of the latter approach have been reported.[3-8] In recognition of nature's ability to set the structural stage using covalent bonds and then to permit flexible systems to adapt to the functional requirements, we prepared (see below) a tris(macrocyclic) system. It was thought that the three macrorings would provide donor relays at the two membrane surfaces and a third, internal relay point. The macrorings would be held together by two spacers, and the channel would be completed by two side arms. Spacer and side-arm length was estimated from distances known for gramicidin channels.[9-11] Relay distances in gramicidin channels are obviously much closer than in the present case but represent only one of many possibilities.

Two compounds were prepared for the present study. We have previously reported[12] *N,N'*-didodecyl-4,13-diaza-18-crown-6 (**1**), which was chosen as the carrier. The tris(macrocyclic) system *N,N'*-bis{12-[*N*-(*N'*-dodecyl-4,13-diaza-18-crown-6)]dodecyl}-4,13-diaza-18-crown-6 (**2**), the synthesis of which is shown in Scheme I, has three diaza-18-crown-6 residues linked and terminated by dodecyl chains. It was anticipated that the inner

* Address correspondence concerning design and synthesis to G.W.G. and concerning NMR and kinetics to L.E.

† On leave from Toa University, Shimonoseki, Japan.

(1) Riddell, F. G.; Hayer, M. K. *Biochem. Biophys. Acta* **1985**, *817*, 313-317.

(2) Buster, D. C.; Hinton, J. F.; Millett, F. S.; Shungu, D. C. *Biophys. J.* **1988**, *53*, 145-152.

(3) (a) Behr, J. P.; Lehn, J. M.; Dock, A. C.; Moras, D. *Nature* **1982**, 295. (b) Julien, L.; Lehn, J.-M. *Tetrahedron Lett.* **1988**, 3803-3806.

(4) Tabushi, I.; Kuroda, Y.; Yokoto, K. *Tetrahedron Lett.* **1982**, 4601-4604.

(5) (a) Neevel, J. G.; Nolte, R. J. M. *Tetrahedron Lett.* **1984**, 2263-2266. (b) Kragton, U. F.; Roks, M. F. M.; Nolte, R. J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1275-1276.

(6) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960-961.

(7) Führhop, J.-H.; Liman, U.; David, H. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 339-340.

(8) Carmichael, V. E.; Dutton, P. J.; Fyles, T. M.; James, T. D.; Swan, J. A.; Zojaji, M. *J. Am. Chem. Soc.* **1989**, *111*, 767-769.

(9) See: Urry, D. W.; Trapane, T. L.; Venkatachalam, C. M. *J. Membr. Biol.* **1986**, *89*, 107 and references therein.

(10) Wallace, B. A.; Ravikumar, K. *Science* **1989**, *241*, 182.

(11) Langs, D. A. *Science* **1989**, *241*, 188.

(12) Gatto, V. J.; Arnold, K. A.; Viscariello, A. M.; Miller, S. R.; Morgan, C. R.; Gokel, G. W. *J. Org. Chem.* **1986**, *51*, 5373-5384.

0002-7863/90/1512-1287$02.50/0