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BENZYLOXYMETHYL GROUP AS A CONVERTIBLE INTERNAL LIGAND FOR La(OTf)$_3$-CATALYZED 7-*endo* RING-OPENING OF HYDROXY EPOXIDE†

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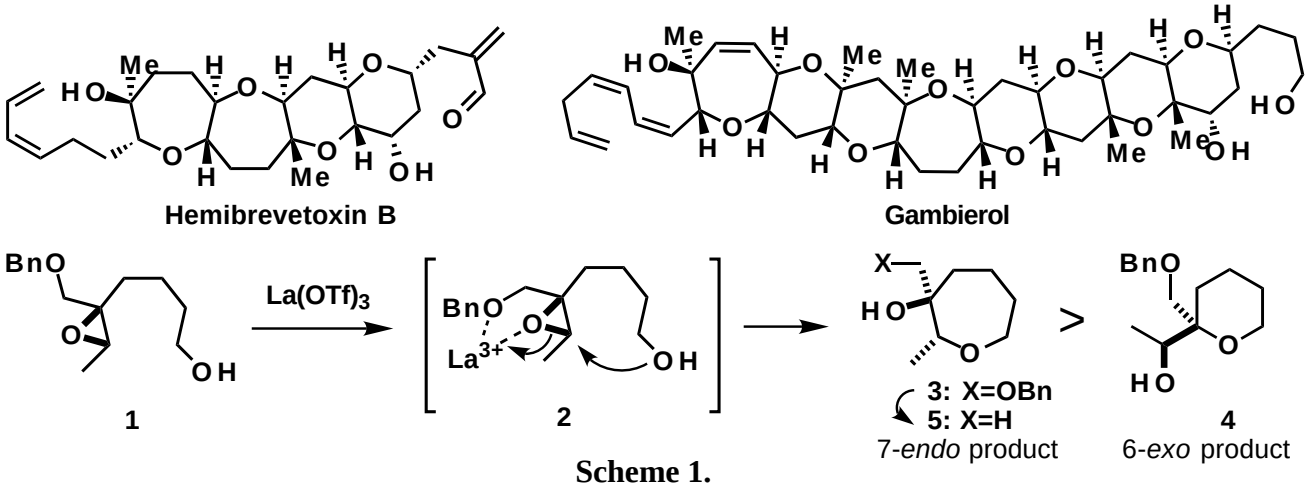
† Dedicated to Professor Shô Itô on the occasion of his 77th birthday.

Abstract- The benzyloxymethyl group at C5 of *cis*-5,6-epoxyheptanol promoted 7-*endo* selective ring-opening of the hydroxy epoxide under La(OTf)$_3$-catalyzed conditions to give *r*-2-methyl-*c*-3-benzyloxymethyl-*t*-3-hydroxyoxepane, whose benzyloxymetyl group was transformable to a methyl group.

Marine polyether compounds, represented by hemibrevetoxin B[1] and gambierol,[2] often have an *r*-2-alkyl-*t*-3-hydroxy-*c*-3-methyloxepane unit at one end of the fused polyether system. To date, many synthetic studies on these polyethers have been reported, while construction of the C3 stereocenter of the unit has been achieved mostly by nucleophilic methylation of the corresponding oxepan-3-one structure.[3] Recently, we have developed La(OTf)$_3$-catalyzed 7-*endo* selective cyclization of the hydroxy epoxide having a methoxymethyl group as an internal ligand, which could be potentially applicable to the synthesis of the above oxepane unit.[4] Here, we report the availability of a benzyloxymethyl group as a transformable internal ligand in the La(OTf)$_3$-catalyzed 7-*endo* selective cyclization for a new entry to the *r*-2-alkyl-*t*-3-hydroxy-*c*-3-methyloxepane unit (Scheme 1).

Cyclization reactions of *cis*-5-benzyloxymethyl-5,6-epoxyheptanol (**1**) under several conditions are shown in Table 1. As in the previous results,[4a,b] the *endo*/*exo* selectivity of the cyclization was strongly influenced by the type of Lewis acid. Lewis acids having less nucleophilic ligands, BF_3•OEt_2, Sn(OTf)$_2$, and Zn(OTf)$_2$, as well as Brönsted acid, CSA, gave 6-*exo* product (**4**)[5] selectively in 33-89 yields (Entries 1-4). In the case of La(OTf)$_3$ including La_2O_3,[4b] 7-*endo* product (**3**)[5] was mainly produced in good



Scheme 1.

Table 1. Cyclization reactions of **1**.

Entry	Conditions					Cyclic ethers		Recovery of **1**/%
	Lewis acid (eq)	Solvent	H_2O/eq	Temp./°C	Time	Yield/%	**3** : **4**[a)]	
1	CSA (0.1)	CH_2Cl_2	0	20	3 h	88	9 : 91	0
2	BF_3•OEt_2 (1.1)	CH_2Cl_2	0	-78 → 20	1 h	89	5 : 95	0
3	$Sn(OTf)_2$ (1.1)	CH_2Cl_2	0	20	1 h	87	9 : 91	0
4	$Zn(OTf)_2$ (1.1)	CH_2Cl_2	0	20	2 h	33	16 : 84	0
5	$La(OTf)_3$[b)] (1.1)	$ClCH_2CH_2Cl$	0	20	3 days	9	67 : 33	88
6	$La(OTf)_3$[b)] (1.1)	$ClCH_2CH_2Cl$	1.1	20	2 weeks	28	74 : 26	70
7	$La(OTf)_3$[b)] (1.1)	$ClCH_2CH_2Cl$	3.3	20	2 weeks	30	75 : 25	70
8	$La(OTf)_3$[b)] (1.1)	$ClCH_2CH_2Cl$	0	reflux	4 h	92	56 : 44	0
9	$La(OTf)_3$[b)] (1.1)	$ClCH_2CH_2Cl$	1.1	reflux	4 h	84	53 : 47	5

a) determined by GLC. b) La_2O_3 [20mol% to $La(OTf)_3$] was contained.

conversion yield in dichloroethane at 20 °C, although the reaction rate was very slow (Entry 5). The presence of 1.1 or 3.3 eq. of H_2O increased the ratio of **3**/**4**, while the reaction rate was slower than that in Entry 5 (Entries 6 and 7). Elevating the reaction temperature accelerated the reaction rate, though the ratio of **3**/**4** decreased even in the presence of 1.1 eq. of H_2O (Entries 8 and 9).

Next, transformation of the benzyloxymethyl group of **3** into the corresponding methyl group was demonstrated. Three-step conversion of **3** [(i) H_2, 5% Pd/C, MeOH; (ii) MsCl, Et_3N, CH_2Cl_2; (iii) K_2CO_3, MeOH] provided 4-methyl-1,5-dioxaspiro[2.6]nonane, which was reduced by $LiAlH_4$ to give **5** in a 58 % total yield.

Thus, the benzyloxymethyl group at C5 of *cis*-5,6-epoxyheptanol promoted 7-*endo* selective ring-opening of the hydroxy epoxide under $La(OTf)_3$-catalyzed conditions to afford *r*-2-methyl-*c*-3-benzyloxymethyl-*t*-3-hydroxyoxepane (**3**), whose benzyloxymethyl group was transformed into the methyl group. Application of this method to the syntheses of natural products and further search for the more reactive and selective Lewis acids are currently under way in our laboratory.

REFERENCES AND NOTES

1. A. V. K. Prasad and Y. Shimizu, *J. Am. Chem. Soc.*, 1989, **111**, 6476.
2. A. Morohashi, M. Satake, and T. Yasumoto, *Tetrahedron Lett.*, 1999, **40**, 97.
3. For example, most total syntheses of hemibrevetoxin B, except Nakata's synthesis, adopted nucleophilic methylation at the terminal oxepane unit, see; K. C. Nicolaou, K. R. Reddy, G. Skokotas, F. Sato, X.-Y. Xiao, and C.-K. Hwang, *J. Am. Chem. Soc.*, 1993, **115**, 3558; I. Kadota, P. Jung-Youl, N. Koumura, G. Pollaud, Y. Matsukawa, and Y. Yamamoto, *Tetrahedron Lett.*, 1995, **36**, 5777; M. Morimoto, H. Matsukura, and T. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6365; Y. Mori, K. Yaegashi, and H. Furukawa, *J. Am. Chem. Soc.*, 1997, **119**, 4557. See also, F. Fei and A. Murai, *Synlett*, 1995, 863.
4. (a) K. Fujiwara, T. Tokiwano, and A. Murai, *Tetrahedron Lett.*, 1995, **36**, 8063; (b) K. Fujiwara, H. Mishima, A. Amano, T. Tokiwano, and A. Murai, *Tetrahedron Lett.*, 1998, **39**, 393; (c) T. Tokiwano, K. Fujiwara, and A. Murai, *Chem. Lett.*, 2000, 272; (d) T. Tokiwano, K. Fujiwara, and A. Murai, *Synlett*, 2000, 335.
5. K. Fujiwara, A. Amano, T. Tokiwano, and A. Murai**,** *Tetrahedron***,** 2000, **56**, 1065.