J. Am. Chem. Soc. **1991**, *113*, 5449-5450

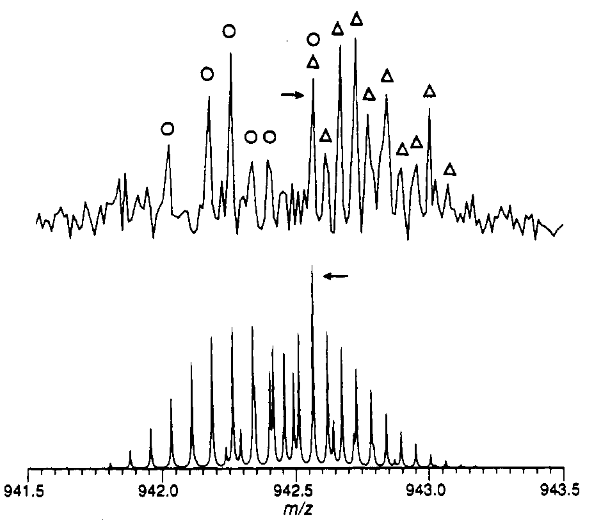

Figure 2. ESI/FT mass spectrum of a 1:1 mixture of (○) chicken cytochrome *c*, $(M + 13H)^{13+}$, and (Δ) equine myoglobin, $(M + 18H)^{18+}$. Top: measured spectrum, data in Table I. Bottom: calculated isotopic distribution. Arrow: m/z 942.564.

containing ~1:2 of the components) that still shows RP = 52K, a half-height width of $m = 0.33$ for $z = 18$; if this overlapping peak were shifted by 0.1 Da from the other, both peaks would have to be recorded at RP = 70K to produce the observed 52K. Note that this approaches the accuracy needed to distinguish between different elemental compositions; for example, replacing S by CH_6N changes the mass by 0.078 Da. The utility of this capability for unknown identification will be reported separately.

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Registry No. Cytochrome *c*, 9007-43-6.

Practical Asymmetric Synthesis of Both Erythro and Threo Aldols: Unusual Effect of Silyl Groups

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Despite innumerable investigations of asymmetric aldol methodologies in recent years,[1] little is known of the asymmetric synthesis of parent aldols, i.e., β-hydroxy aldehydes **1** (X = H) because of the great difficulty of generating chiral aldehyde enolates (or their equivalents) for aldol condensations and the instability of the resulting β-hydroxy aldehydes **1** (X = H).[2] The β-hydroxy aldehyde unit is undoubtedly a valuable synthetic intermediate for further carbon-chain elongation leading to 1,3-dihydroxy functionality, which is a fundamental structural unit

Scheme I

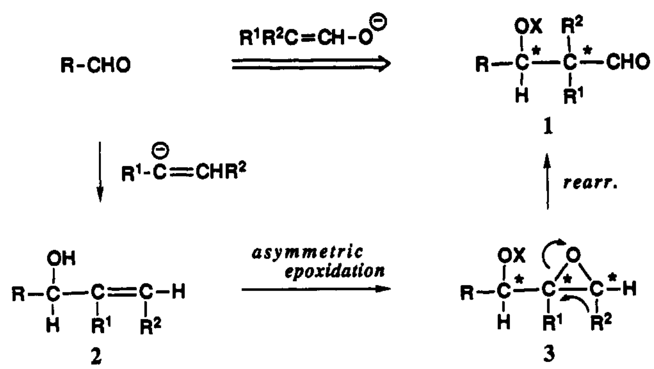

Table I. Effect of Silyl Groups on the Rearrangement of Erythro Epoxy Silyl Ether **4** with MABR[a]

entry	substrate **4**	yield,[b] % (ratio of **8**:**9**)[c]
1	R = *i*-Pr	78 (1:2.7)
2	R_3 = $PhMe_2$	65 (1.5:1)
3	R_3 = Ph_2Me	77 (6:1)
4	R_3 = *t*-$BuPh_2$	72 (10:1)
5	R = Ph	73 (40:1)

[a] Epoxide rearrangement was effected in CH_2Cl_2 with 2 equiv of MABR at −78 to −20 °C. [b] Isolated yield. [c] The threo:erythro ratios were determined by 200-MHz ^1H NMR or HPLC analysis.

embedded in numerous natural products of acetate and propionate origin.[3] In this context, we have studied a new, asymmetric synthesis of erythro and threo aldols based on the Lewis acid promoted rearrangement of optically active epoxy silyl ethers **3** (X = SiR_3),[4-6] which is readily derivable by Sharpless asymmetric epoxidation[7] of allylic alcohols **2** followed by simple silylation as illustrated in Scheme I. Since both erythro and threo epoxy silyl ethers are easily accessible in optically active forms,[8,9] the only remaining problem is the stereoselectivity of the epoxide rearrangement. Reported herein are our results, which successfully permit the practical asymmetric synthesis of both erythro and threo β-hydroxy aldehyde derivatives.

Rearrangement of erythro epoxy silyl ether **4** (R_3 = *t*-$BuMe_2$; >98% ee, $[\alpha]^{22}_D$ −6.80° (*c* 1.00, $CHCl_3$))[8] with exceptionally bulky, oxygenophilic methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR), which has been recently developed in our laboratory as a highly effective epoxide-rearrangement agent,[4] yielded a mixture of threo and erythro β-siloxy aldehydes **8** and **9** (R_3 = *t*-$BuMe_2$) in 75% yield, though the observed threo/erythro selectivity was quite disappointing (ratio, ~1:1.4). Even bulky triisopropylsilyl ether **4** (R = *i*-Pr) showed poor selectivity (**8**:**9** (R = *i*-Pr) = 1:2.7). In marked contrast, however, erythro epoxy triphenylsilyl ether **4** (R = Ph; >98% ee, $[\alpha]^{23}_D$ +10.0° (*c* 1.02,

(1) Reviews: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Mukaiyama, T. *Org. React.* (*N.Y.*) **1982**, *28*, 203. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984, Vol. 3B, Chapter 2. (d) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Vol. 5B, p 177.

(2) For example, see: (a) Bianchi, D.; Cesti, P.; Golini, P. *Tetrahedron* **1989**, *45*, 869. (b) Ghiringhelli, D. *Tetrahedron Lett.* **1983**, *24*, 287. (c) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1903.

(3) (a) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (c) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59. See also ref 2b.

(4) For another type of epoxy silyl ether rearrangement, see: Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431.

(5) Certain erythro and threo epoxy alcohols are reported to rearrange stereospecifically with $BF_3{\cdot}OEt_2$ or alumina catalyst: Cheer, C. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1968**, *90*, 178.

(6) Epoxy alcohol rearrangement with Ti(O-*i*-Pr)$_4$: Morgans, D. J.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462.

(7) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Hill, J. G.; Sharpless, K. B. *Org. Synth.* **1984**, *63*, 66. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(8) The optically active erythro epoxy alcohols are derived by Sharpless asymmetric epoxidation of allylic alcohols with Ti(O-*i*-Pr)$_4$/(+)-DIPT and *t*-BuOOH according to ref 7.

(9) The optically active threo epoxy alcohols can be prepared by the Mitsunobu inversion of the hydroxy group of optically active erythro isomers: Mitsunobu, O. *Synthesis* **1981**, 1.

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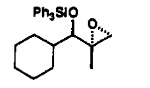
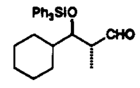
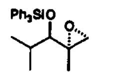
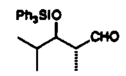
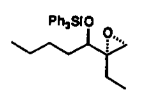
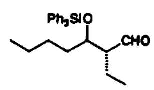
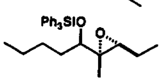
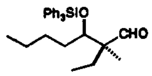
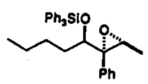
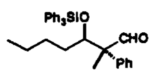
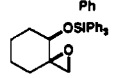
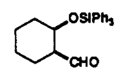
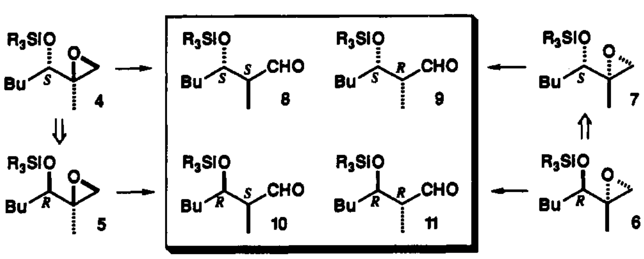
Table II. Stereoselective Rearrangement of Epoxy Silyl Ethers with MABR[a]

entry	substrate	conditions (°C, h)	major isomer of siloxy aldehyde	yield, %[b] (erythro/threo)[c]
1		-78, 1; -40, 1.5		92 (1 : 6)
2		-78, 1; -40, 2[d]		88 (1 : 100)
3		-78, 1; -40, 0.5		86 (1 : 6)
4		-78, 2; -40, 2[d]		82 (1 : 30)
5		-40, 2; -20, 0.5		67 (1 : 100)
6		-40, 2; -20, 2		47 (4 : 1)
7		-40, 2; -20, 2[d]		64 (200 : 1)
8		-78, 0.5		83 (0 : 1)
9		-40, 2; -20, 2[d]		85 (1 : 0)

[a] Unless otherwise stated, the rearrangement was carried out in CH_2Cl_2 with 2 equiv of MABR under the indicated conditions. [b] Isolated yield. [c] Determined by 200-MHz ^1H NMR or HPLC analysis. [d] Use of toluene as solvent.

$CHCl_3$)) on treatment with MABR gave threo β-siloxy aldehydes **8** (R = Ph; >98% ee, $[\alpha]^{22}_D$ +38.5° (*c* 1.00, $CHCl_3$)) almost exclusively (**8**:**9** (R = Ph) = 40:1). It should be noted that reaction of erythro epoxy silyl ether **4** (R = Ph) with conventional Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ gave none of the desired β-siloxy aldehydes.[10]



Selected results of the rearrangement of erythro epoxy silyl ethers **4** with MABR to β-siloxy aldehydes **8** and **9** are summarized in Table I and show the following characteristic features. Apparently, the observed stereoselectivity reflects the marked electronic effect of silyl substituents rather than their steric effect (entries 1–5), and the more electron withdrawing triphenylsilyl group exhibited better selectivity than the more sterically hindered *tert*-butyldiphenylsilyl group (entry 5 vs 4).[11] The even more hindered triisopropylsilyl group did not significantly alter the selectivity (entry 1). The stereoselectivity of the phenylsilyl series (i.e., $PhMe_2Si$, Ph_2MeSi, and Ph_3Si groups) increases with increasing electronegativity of the silyl groups (entries 2, 3, and 5). Furthermore, rearrangement of a dimethylphenylsilyl system bearing an electron-withdrawing fluoro group at the para position exhibited higher selectivity [R_3 = (p-FC_6H_4)Me_2, 75% (**8**:**9** = 2:1)] relative to the unsubstituted system (entry 2). This rearrangement proceeded with anti migration of the hydride to the epoxide moiety. Use of nonpolar toluene showed higher selectivity than use of CH_2Cl_2 [R_3 = $PhMe_2$, 60% (**8**:**9** = 3.5:1) in toluene]. Notably, the stereoselectivity was markedly decreased with less bulky dimethylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide or methylaluminum bis(4-bromo-2,6-diisopropylphenoxide). The similar electronic effect of silyl groups was observed in the rearrangement of optically active threo epoxy silyl ether **5** to erythro β-siloxy aldehyde **10** [R_3 = *t*-$BuMe_2$, 68% (**10**:**11** = 2.2:1); R_3 = $PhMe_2$, 42% (2.6:1), R = Ph, 81% (12:1)].[9]

Since enantiomeric erythro epoxy silyl ether **6** and its threo isomer **7** are readily accessible by the Sharpless asymmetric epoxidation using (−)-DIPT as a chiral auxiliary,[7,9] this method allows the practical asymmetric synthesis of four possible aldol isomers **8–11**. Other examples with triphenylsilyl substituents are illustrated in Table II. β-Siloxy aldehydes possessing an asymmetric quaternary α-carbon, hitherto not obtainable by ordinary asymmetric aldol reactions, can be readily synthesized with virtually complete stereoselectivity (entries 7 and 8).

(10) For example, $TiCl_4$ showed totally different behavior for the substrate **4** (R = Ph) resulting in formation of 2-methyl-2-[(triphenylsiloxy)methyl]hexanal and 2-methyl-1-(triphenylsiloxy)-3-heptanone in 68% yield.

(11) For the steric and electronic nature of Si–O interactions, see: (a) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgenson, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. (b) Stern, A. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 2953. See also: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130.

Design and Characterization of a Ligand-Binding Metallopeptide

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The design of peptides that mimic the structural and/or functional features of naturally occurring proteins or that have novel properties is an area of much current interest.[1] The incorporation of metal binding sites into designed peptides presents an opportunity to use the structural, spectroscopic, and chemical properties of metal ions to advantage. Initial results with designed metallopeptides have been reported[2,3] although the ability of such peptides to bind or activate ligands has not been demonstrated. We report here a strategy to convert a peptide with a structural site in which all of the ligands are provided by the peptide to one that has an open coordination position for substrate binding and potential activation. Our approach involves truncation of a metal-binding peptide to remove one of the ligands with the hope that such a truncated peptide will still bind metal ions.

Our initial studies have used a prototypical zinc finger peptide, CP1, which has the sequence ProTyrLys*Cys*ProGlu*Cys*GlyLysSerPheSerGlnLysSerAspLeuValLys*His*GlnArgThr*His*ThrGly.[4] CP1 binds Co^{2+} with a dissociation constant of 50 nM[4] and also binds a variety of other metal ions.[5] An attempt to create a peptide with a Cys-His-His coordination site by truncation of the first five amino acids proved unsuccessful; treatment of this amino terminal truncated peptide with Co^{2+} yielded no spectral indications of tetrahedral metal coordination even when a 10-fold excess of Co^{2+} had been added. In contrast to these results, truncation of the last four amino acids produced a peptide, termed CP1-C4, that binds Co^{2+} in a tetrahedral site with high affinity. The absorption spectrum of the complex formed between this peptide and Co^{2+} is shown in Figure 1. This is similar to but distinct from spectra of Co^{2+} complexes of zinc finger peptides that have two cysteinate and two histidine coordination sites. The intensity of the d–d bands in the visible region (ϵ > 500 $M^{-1}\,cm^{-1}$) strongly suggests tetrahedral coordination. Metal ion titration data[6] could be fit with a dissociation constant for the 1:1 CP1-

(1) DeGrado, W. F. *Adv. Protein Chem.* **1988**, *39*, 51.
(2) Handel, T.; DeGrado, W. F. *J. Am. Chem. Soc.* **1990**, *112*, 6710.
(3) Regan, L.; Clarke, N. D. *Biochemistry* **1990**, *29*, 10878.
(4) Krizek, B. A.; Amann, B. T.; Kilfoil, V. J.; Merkle, D. L.; Berg, J. M. *J. Am. Chem. Soc.*, in press.
(5) Krizek, B. A.; Berg, J. M., submitted for publication.