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# Regio- and stereoselective ring-opening of epoxides using organic dithiophosphorus acids as nucleophiles

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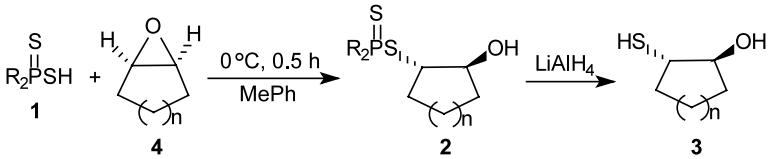
**Abstract**—A practical method for the synthesis of β-hydroxymercaptans has been successfully developed through the ring-opening of epoxides with organic dithiophosphorus acids **1**. Highly regio- and stereoselective products, β-hydroxyalkyl dithiophosphates, which were transformed to the corresponding synthetically valuable β-hydroxymercaptans by further reduction, were obtained under mild reaction conditions without any catalyst or promoter. Highly enantioselective ring-opening reaction of cyclohexene epoxide with **1** was realized in the presence of a chiral (salen)Ti(IV) complex. © 2002 Elsevier Science Ltd. All rights reserved.

The stereoselective ring-opening of *meso*-epoxides with various nucleophiles is an important transformation in organic synthesis because it is a powerful strategy for the formation 1,2-bifunctionalized systems, and at the same time establishes two contiguous stereogenic centers. A wide variety of nucleophiles are used in the aforementioned ring-opening reaction.[1] Among them, sulfur nucleophiles are important and lead to the formation of synthetically valuable β-hydroxymercaptans or β-hydroxysulfides. The typically used sulfur nucleophiles are alkane- and arene-thiols.[1–8] This ring-opening reaction is generally carried out in the presence of a catalyst or promoter such as Ti(OPr-*i*)$_4$,[2] metal(II) D-tartrates,[3] quaternary ammonium salts,[4] polyethylene glycol 4000,[5] Ga/Li bis(binaphthoxide) complex[6] and metal salen complexes,[7,8] etc. The resulting products, β-hydroxysulfides, can be obtained with high regio- and stereoselectivity. In addition, some other sulfur nucleophiles containing silicon have also been described. For example, the ring opening reaction with $Ph_3SiSH$, the mono protected form of $H_2S$, takes place with high regioselectivity in the presence of the $Et_3N$/MeOH system to give β-hydroxymercaptans in good yields.[9] Other silicon–sulfur reagents, such as *i*-$Pr_3SiSH$ in the presence of DBU,[10] $Me_3SiNCS$, $Me_3SiOCSMe$ and $Me_3SiSPh$ in the presence of $Bu_4NF$[11] are regioselective ring-opening nuleophiles which lead to the corresponding β-hydroxysulfides.

Early in 1965, Pudovik reported the reaction of dithiophosphorus acids with α-substituted epoxides.[12] However, there has been no any further investigation into this reaction during the past three decades. Recently, we discovered that when dithiophosphorus acids were used as the nucleophiles, this ring-opening reaction could occur not only regioselectively, but also enantioselectively. Additionally, the following features are also worth noting. (1) Mild reaction conditions without any catalyst or promoter. (2) The reagents are readily available. (3) The resulting products can be transformed further into synthetically valuable β-hydroxymercaptan intermediates **3** through reduction. Therefore, this work affords a convenient and practical method for the synthesis of β-hydroxymercaptans, especially the synthesis of optically active β-hydroxymercaptans (Scheme 1).




**Scheme 1.**

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Phosphorus–sulfur reagent **1** reacted with *meso*-epoxides **4** at 0°C for 0.5 h in toluene to form compounds **2** in excellent yields (Table 1) whose structures were confirmed by $^{31}$P NMR, $^{1}$H NMR and elemental analyses. The reaction was found to be completely stereoselective and the *trans* products were obtained. Compounds **2** were directly reduced with $LiAlH_4$ to give β-hydroxymercaptans **3** in 54–63% yields (Table 2).[13]

Similarly, the reactions of the phosphorus–sulfur reagent **1b** with mono-substituted epoxides **5** operated under the same conditions to form the ring-opened products **6**, highly regioselectively, in excellent yields (Table 3). Compounds **6** can also be transformed into the corresponding β-hydroxymercaptans through reduction (Table 2).[13] In each case, the nucleophilic ring-opening occurred on the less hindered carbon of the epoxides (Scheme 2). The structures of compounds **6** were confirmed by $^{31}$P NMR, $^{1}$H NMR and elemental analyses.

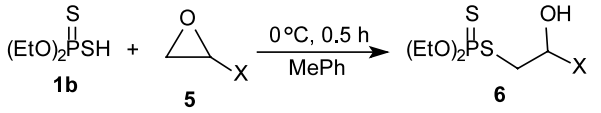
The reaction of **1b** with (+)-(*R*)-styrene oxide[14] was also studied. The reaction was found to be highly regioselective and stereospecific. The corresponding (+)-(*R*)-**7** was obtained in 91% yield and in 88% ee (Scheme 3).[15]

**Table 1.** Analytical data for compounds **2**

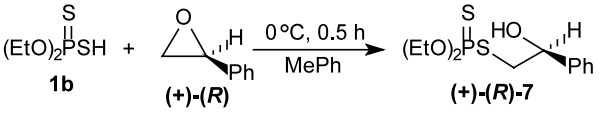
| 2 | R | *n* | $n_D^{20}$ | Yield (%) | $^{31}$P NMR ($\delta$, ppm) |
|---|---|---|---|---|---|
| **a** | MeO | 2 | 1.5432 | 90 | 99.24 |
| **b** | EtO | 2 | 1.5262 | 95 | 94.18 |
| **c** | PrO | 2 | 1.5164 | 93 | 94.60 |
| **d** | BuO | 2 | 1.5144 | 87 | 94.57 |
| **e** | Et | 2 | 1.5513 | 90 | 81.86 |
| **f** | Ph | 2 | Thick | 92 | 64.18 |
| **g** | EtO | 1 | 1.5268 | 93 | 93.70 |
| **h** | Ph | 1 | Thick | 95 | 62.87 |
| **i** | EtO | 4 | 1.5120 | 88 | 94.96 |
| **j** | Ph | 4 | Thick | 91 | 65.15 |

**Table 3.** Analytical data for compounds **6**

| 6 | X | $n_D^{20}$ | Yield (%) | $^{31}$P NMR ($\delta$, ppm) |
|---|---|---|---|---|
| **a** | H | 1.5244 | 92 | 95.14 |
| **b** | Me | 1.5204 | 88 | 95.60 |
| **c** | Et | 1.5138 | 95 | 96.48 |
| **d** | Ph | 1.5706 | 93 | 92.21 |
| **e** | $PhCH_2O$ | 1.5564 | 94 | 95.29 |




**Scheme 2.**

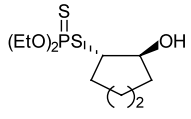
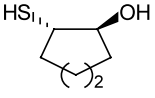
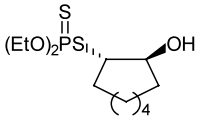
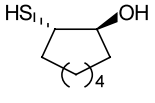
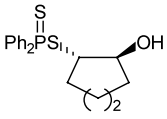
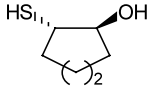
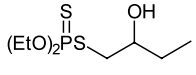
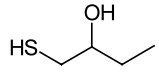


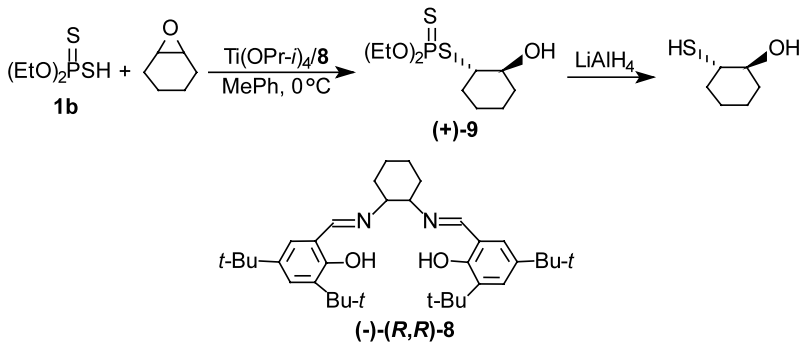

**Scheme 3.**

Tang[7] firstly reported the enantioselective ring-opening reaction of *meso*-epoxides with various thiols catalyzed by a chiral (salen)Ti(IV) complex formed in situ from salen **8** and Ti(OPr-*i*)$_4$. The highest ee value obtained was 63%. We applied this catalytic system to the ring-opening reaction of cyclohexene epoxide with **1b**. The corresponding ring-opened product **9** was obtained in 94% yield and in 73% ee (Scheme 4).[16] Thioester **9** was further reduced to give (+)-(*S*,*S*)-2-mercaptocyclohexanol in 57% yield and 74% ee, $[\alpha]_D$ +29.0 (*c* 2, $CHCl_3$).[17]

In conclusion, we have succeeded in developing a highly regio- and stereoselective ring-opening reaction of epoxides with the phosphorus–sulfur reagents **1**. Furthermore, an enantioselective ring-opening reaction was accomplished with an ee value of 73% in the presence

**Table 2.** Reduction of different thiophosphorus esters **2** and **6**

| Substrate | Product | Yield/% | $n_D^{20}$ |
|---|---|---|---|
|  |  | 55 | 1.5208 |
|  |  | 54 | 1.5258 |
|  |  | 65 | 1.5208 |
|  |  | 52 | 1.5104 |




**Scheme 4.**

of a chiral (salen)Ti(IV) complex. Reduction of the ring-opened product gave the corresponding β-hydroxymercaptan in good yield. Therefore, this method is very useful in organic synthesis, especially in multifunctional natural product synthesis.

## Acknowledgements

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13. For 2-mercaptocyclohexanol: pale yellow liquid (stench), $^1$H NMR ($CDCl_3$, $\delta$): 3.10 (m, 1H, CHOH), 3.05 (s, 1H, OH), 2.46 (m, 1H, CHSH), 1.99 (m, 2H, $CH_2$), 1.69 (m, 2H, $CH_2$), 1.49 (d, 1H, $J=8.5$ Hz, SH), 1.29 (m, 4H, $CH_2$). $M^+$: 132 (see Ref. 17). For 2-mercaptocyclooctanol: pale yellow liquid (stench), $^1$H NMR ($CDCl_3$, $\delta$): 3.44 (m, 1H, CHOH), 2.91 (s, 1H, OH), 2.85 (m, 1H, CHSH), 1.59 (d, 1H, $J=8.6$ Hz, SH), 1.29 (m, 12H, $CH_2$). Elemental analysis: Found: C, 59.80; H, 10.05. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06. For 1-mercapto-2-butanol: pale yellow liquid (stench), $^1$H NMR ($CDCl_3$, $\delta$): 3.60 (br, 1H, OH), 2.45 (m, 1H, CHOH), 2.38 (m, 2H, $CH_2$SH), 1.52 (m, 2H, $CH_2$), 1.34 (t, 1H, SH), 0.95 (t, 3H, $J=4.5$ Hz, $CH_3$).
14. This reagent was purchased from Acros Organics, the optical purity is 99%.
15. For **7**: Enantiomeric excess (88%) determined by HPLC with a chiral column (chiralcel OD). $[\alpha]_D$ +164.0 (*c* 2, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$, $\delta$): 1.23 (dt, 6H, $J=7.1$ Hz, $J_{PH}=16.9$ Hz, $CH_3$), 2.20 (s, 1H, OH), 3.91–4.10 (m, 6H, $CH_2$), 4.50 (m, 1H, CH), 7.31 (m, 5H, Ar-H). $^{31}$P NMR ($CDCl_3$, $\delta$): 92.21.
16. For **9**: Enantiomeric excess (73%) determined by HPLC with a chiral column (chiralcel OD). $[\alpha]_D$ +22.5 (*c* 2, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$, $\delta$): 1.30 (t, 6H, $J=7.0$ Hz, $CH_3$), 1.24–1.64 (m, 4H, $CH_2$), 1.69 (m, 2H, $CH_2$), 2.10 (m, 2H, $CH_2$), 2.61 (s, 1H, OH), 3.10 (m, 1H, CH), 3.36 (m, 1H, CH), 4.16 (m, 4H, $CH_2$). $^{31}$P NMR ($CDCl_3$, $\delta$): 94.18.
17. The absolute configuration was determined according to the following literature: Adams, H.; Bell, R.; Cheung, Y. Y. *Tetrahedron: Asymmetry* **1999**, *10*, 4129.