

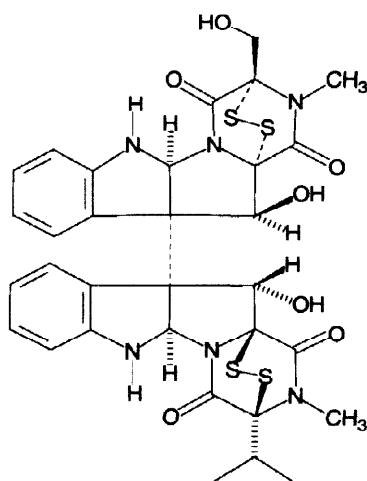
**REGIO- AND STEREOSPECIFIC SYNTHESIS OF (O-TIPS)-PROTECTED 2-HYDROXYALKYLMERCAPTANS FROM EPOXIDES AND TRIISOPROPYLSILANETHIOL**

Jorge C. Justo de Pomar<sup>1</sup> and John A. Soderquist\*  
Department of Chemistry, University of Puerto Rico  
Rio Piedras, PR 00931-3346

Received 1 December 1997; revised 9 April 1998; accepted 14 April 1998

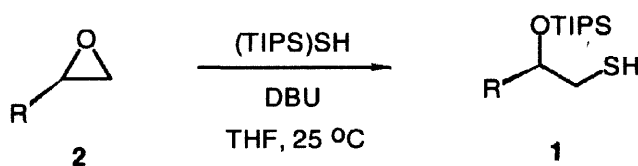
**Abstract:** The regioselective ring-opening of both mono- and disubstituted epoxides with triisopropylsilylanethiol/DBU has been developed to provide 2-triisopropylsilyloxyalkylthiols (**1**) in high yields. Non-racemic **1** is easily prepared from optically active epoxides. Moreover, the further elaboration of **1**, through the exposed mercapto functionality, provides controlled access to unsymmetrical mono-protected bis-(2-hydroxyalkyl) sulfides and functionalized thioesters.

© 1998 Elsevier Science Ltd. All rights reserved.




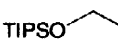

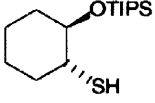

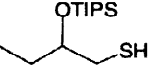
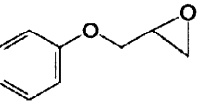
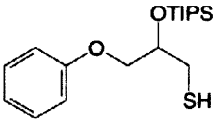

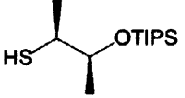
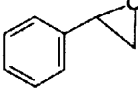
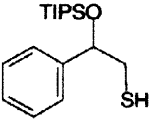

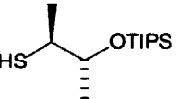
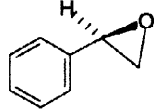
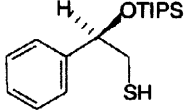

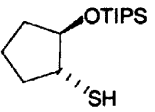
**Figure 1. Leptocin d.**

The  $\beta$ -hydroxyalkylpolysulfide functionality has been observed as an integral part of many bacterial metabolites with biological activity. The most notable of these are the leptosins (Fig. 1) which are extracted from marine bacteria,<sup>2</sup> and possess antitumor activity. Moreover, verticillins,<sup>3</sup> arugosin C,<sup>4</sup> and chetomins,<sup>5</sup> which are extracted from marine bacteria, exhibit antibiotic activity. While the exact mechanism of action is not known, each contains the vicinal arrangement between sulfur and the hydroxy functionality. Moreover, all have a *trans* relationship between these groups and for several, the sulfur is present as a di- or poly-sulfide. We felt that a new methodology based upon the regio- and stereospecific nucleophilic ring-opening of epoxides employing the anion derived from triisopropylsilylanethiol, ((TIPS)SH), would provide ready access to this functionality. As a bonus feature of this approach, the TIPS groups was found to spontaneously rearrange to oxygen, giving the free mercaptan (**1**) with the TIPS-protected alcohol in a single step.



Among the reported routes to  $\beta$ -hydroxyalkyl mercaptans, the ring-opening of epoxides by sulfur nucleophiles is rarely an efficient process.<sup>6</sup> The use of  $\text{H}_2\text{S}$  and dithiourea is plagued by low

**Table 1.** 2-(Triisopropylsiloxy)alkylthiols (**1**) from the (TIPS)SH-mediated ring-opening of epoxides.

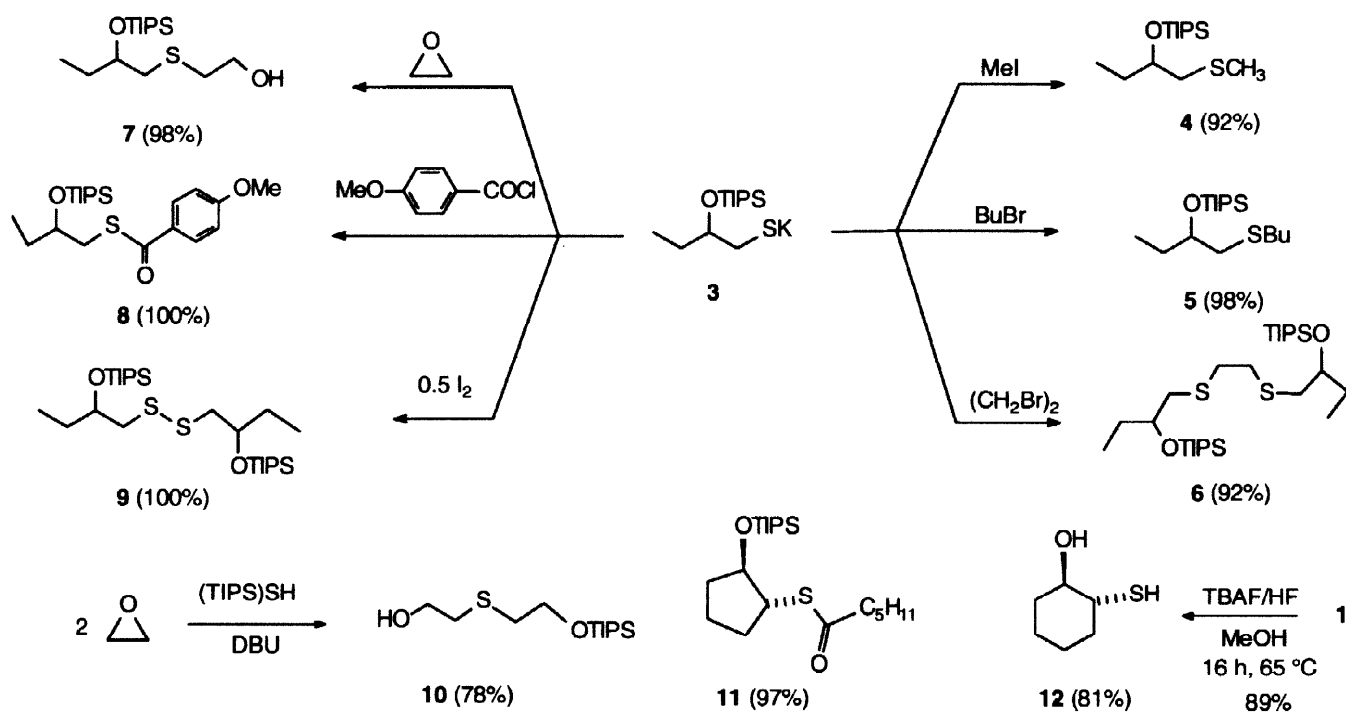
Entry	<b>2</b>	<b>1</b>	Yield <sup>a</sup>	Entry	<b>2</b>	<b>1</b>	Yield <sup>a</sup>
1			<b>a</b> 88	6			<b>f</b> 79 <sup>b</sup>
2			<b>b</b> 92	7			<b>g</b> 65
3			<b>c</b> 59 <sup>b</sup>	8			<b>h</b> 85
4			<b>d</b> 75 <sup>b</sup>	9			<b>i</b> 64 <sup>d</sup>
5			<b>e</b> 65 <sup>b,c</sup>				

<sup>a</sup>All yields are for analytically pure products. <sup>b</sup> Racemic. <sup>c</sup> Reaction was performed at reflux temperature (12 h). <sup>d</sup> Starting **2i** (95% ee) gave **1i** (95% ee by chiral GC).

regioselectivities and reaction yields. These factors, combined with the inherent inconvenience of working with H<sub>2</sub>S led to the development of procedures based upon triphenylsilanethiol/NEt<sub>3</sub>.<sup>7</sup> Although this approach avoids the stench of H<sub>2</sub>S, the opening of styrene oxide proved to be non-regiospecific, the product distribution exhibiting a striking dependence on the amine stoichiometry. We had encountered several cases where the highly hindered triisopropylsilylthiolates are clearly superior to their triphenylsilyl counterparts.<sup>8</sup> This suggested that the TIPS reagent may well provide, for the first time, regiochemical control and synthetically useful procedures for even the styrene systems. We chose to submit this hypothesis to test.

The cleavage of representative mono- and disubstituted epoxides with (TIPS)SH<sup>8</sup> was observed to proceed in a completely regiospecific manner (Table 1). In each case, the nucleophilic ring-opening occurs from the less hindered side of the epoxide. The reaction is operationally simple, being accomplished by the addition of the epoxide to a THF solution of TIPSSH and DBU (1:1:1) at room temperature. As expected, the reaction times vary with the epoxide substitution (*e.g.* **2a** (1 h), **2c** (72 h)) and the cyclopentene oxide reaction required reflux temperature (12 h). Comparative studies employing various thiolate sources clearly revealed that DBU is superior to NEt<sub>3</sub> as well as

Scheme 1



to KSTIPS and LiSTIPS for the preparation of **1**. Isolated product yields are range between 55-92% after a distillative work-up.<sup>9</sup> Even styrene oxide (**2h**) underwent exclusive ring-opening from the external position, a clear indication of the sterically governed process. This excellent selectivity, along with the availability of non-racemic epoxides, expands the scope of this reaction for the construction of chiral synthons. This is illustrated by the opening of (*R*)-styrene oxide (**2i**), which gives **11** regioselectively with no loss of stereochemistry by chiral GC analysis.

Accompanying the ring-opening, the TIPS group undergoes a facile 1,3-migration giving the (*O*-TIPS)-protected  $\beta$ -hydroxyalkyl mercaptan exclusively. Such 1,3-silyl rearrangements are well-documented,<sup>10</sup> although the related process with triphenylsilylanethiolate is very inefficient.<sup>7</sup> The *S*-*O* rearrangement is evidently irreversible since the generation of **3** (**1b**, KH, THF, 0 °C) gives only products of *S*-alkylation (**4-6**) in a very efficient process (Scheme 1). Even the disubstitution of 1,2-dibromoethane is easily achieved (*i.e.* **6**, 92% as a 1:1 *meso/dl* mixture).

Taking advantage of the stability of the TIPS-protected alcohol functionality, **3** was allowed to react with ethylene oxide (**2a**) producing the unsymmetrical sulfide **7** in which the 2-hydroxyethyl group contains only the unprotected alcohol functionality. This process can also be used to introduce two hydroxyethyl groups with one TIPS-protected, and the other free, in a one-pot reaction using 2.0 equiv of the epoxide (**10**). The *S*-acylation of **1** is also an efficient process through the addition of the acid chloride to the potassium thiolates (*e.g.* **3**) at room temperature. Both **8** and **11**

were isolated in excellent yields from this procedure.<sup>11</sup> Relevant to the above-mentioned metabolites, we also demonstrated that **1b** could easily be converted through **3** in THF to the corresponding disulfide (**9**) with 0.5 equivalent of iodine. Finally, we effected the deprotection of **1f** with TBAF/HF/THF at reflux temperature which provides **12** cleanly.<sup>12</sup>

**Acknowledgment.** The support of the DOE-EPSCoR (DE-FC02-91ER75674) program is gratefully acknowledged. We also thank Professor Kent Gates (U of Missouri) for supplying us with leading references to the verticillins, arugosin C, and the chetomins.

### REFERENCES AND NOTES

1. Graduate student supported by DOE-EPSCoR (DE-FC02-91ER75674).
2. Takahashi, C.; Numata, A.; Yoshinori, I.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc. Perkin I* **1994**, 1859.
3. Minato, H.; Matsumoto, M.; Katayama, T. *J. Chem. Soc. Perkin I* **1973**, 1819.
4. Ballantine, J. A.; Ferrito, V.; Hassai, C. H.; Jenkins, M. L. *J. Chem. Soc. Perkin I* **1973**, 1825.
5. Safe, S.; Taylor, A. *J. Chem. Soc. Perkin I* **1972**, 472.
6. Rosowsky, A. in *Heterocyclic Compounds, Part 1*, Weissberger, A. Ed.; John Wiley and Sons, Inc.; New York, 1964, p 330.
7. Brittain, J.; Gareau, Y. *Tetrahedron Lett.* **1993**, *34*, 3363.
8. Miranda, E. I.; Diaz, M. J.; Rosado, I.; Soderquist, J. A. *Tetrahedron Lett.* **1994**, *35*, 3221.
9. A representative procedure for **1**: To (TIPS)SH (1.90 g, 10.0 mmol) and DBU (1.52 g, 10.0 mmol) in anhydrous THF (10 mL) at 25 °C under a N<sub>2</sub> atmosphere, was added **2h** (1.21 g, 10.0 mmol) dropwise. The mixture was stirred for 12 h and pentane (10 mL) was added. The solution was washed with NH<sub>4</sub>Cl (sat) solution (7 x 25 mL) and the extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and distilled to give 2.65 g (85%) of **1h** (bp 162-167 °C at 1 Torr). This and all products were fully characterized by <sup>1</sup>H and <sup>13</sup>C NMR, IR, MS and gave satisfactory elemental analyses or HRMS.
10. Colvin, E. *Silicon in Organic Synthesis*, Butterworths: London, 1981.
11. Representative procedure for the *S*-acylation: Under a nitrogen atmosphere, KH (0.434 g of 35% in oil) was purified by washing with pentane (4 X 10 mL), and removing the supernatant each time after centrifugation. To the THF (12 mL) dispersion at 0 °C, **1b** (0.906 g, 3.5 mmol) was added dropwise. After 30 min, *p*-anisoyl chloride (0.597 g, 3.5 mmol) was added dropwise. After 2 h, the reaction volume was doubled with pentane and the organic layer was washed with NH<sub>4</sub>Cl (sat) solution (7 X 25 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and distilled to give 1.367 g (100%) of **8** (181-4 °C at 3 Torr). For all of the products in Scheme 1, related procedures were followed with the exceptions of **6** and **9** which were isolated by flash chromatography (*e.g.* for **6**: SiO<sub>2</sub> (70-230 mesh) eluting first with hexanes (200 mL) followed by ethyl acetate/hexane (200 mL of a 1:4 mixture)).
12. Representative procedure for the TIPS deprotection: To **1f** (0.50 g, 2.0 mmol) was added TBAF (10.0 mL of 1.0 M.) and HF (2.0 mL of 50%) and the mixture was heated at reflux temperature for 16 h. Saturated brine solution (10 mL) was added and the mixture was extracted with ether (5 X 10 mL), the combined ether extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was recrystallized (*i*-PrOH/HxH (1:5) to give 0.21 g (81%) of **12** whose properties were identical to the commercial material.