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A practical synthesis of differentially-protected *cis*-1,2-cyclopentanedithiols and *cis*-3,4-pyrrolidinedithiols

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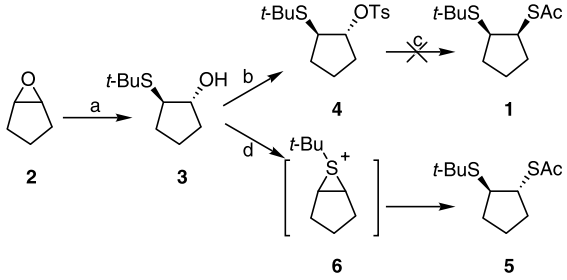
Abstract—A practical method for the synthesis of *cis*-1,2-cyclopentanedithiols and *cis*-3,4-pyrrolidinedithiols with differentially protected sulfurs, needed for the design of new metal-chelating ligands, has been developed. © 2002 Published by Elsevier Science Ltd.

The 1,2-dithio functionality as a metal-chelating ligand has found applications in coordination chemistry[1] and medicinal chemistry.[2,3] In connection with our ongoing efforts to design and synthesize selective matrix metalloproteinase enzyme inhibitors,[4,5] we have been especially interested in the synthesis of *cis*-1,2-cyclopentanedithiols having different protecting groups on sulfur that would allow further selective elaboration (e.g. **1**, Scheme 1). Stereospecific synthesis of the *cis*-stereoisomer of this type of compound is challenging due to the potent nucleophilic properties of sulfur. Photoaddition of a thiol to a vinylsulfide was the only reported method for the synthesis of several *cis*-1,2-dithiocycloalkanes.[6,7] However, this free-radical addition procedure was of very limited utility because of long reaction times, low yields and especially harsh reaction conditions for the synthesis of the vinylsulfide starting materials (pyrolysis). Obviously a more convenient and practical method was required.



Scheme 1. (a) *t*-BuSNa, EtOH, 0°C to rt, 93%. (b) TsCl, TEA, $Me_3N{\cdot}HCl$, CH_2Cl_2, 0°C, 95%. (c) AcSK, DMF, 40°C. (d) AcSH, PPh_3, DIAD, THF, 0°C to rt, 92%

We first examined the possibility of synthesizing *cis*-1-acetylthio-2-*tert*-butylthiocyclopentane (**1**) from readily available cyclopentene oxide (**2**). As shown in Scheme 1, epoxide ring opening with sodium *tert*-butylthiolate gave *trans*-2-*tert*-butylthiocyclopentanol (**3**) in high yield. The alcohol was converted to the tosylate **4**,[8] but subsequent reaction of **4** with potassium thiolacetate gave complex mixtures and failed to give the desired *cis*-dithiocyclopentane **1** in meaningful yield. We then applied the efficient method described by Volante for one-step conversion of alcohols to thiolacetates by a modified Mitsunobu procedure.[9] The substitution was successful under mild reaction conditions, but pure *trans*-dithiocyclopentane **5** was obtained in high yield. The net retention of configuration during thiolacetate formation was presumably due to nucleophilic attack by the vicinal sulfur, forming episulfonium intermediate **6**, prior to the attack of thiolacetate.[10,11] The nucleophilicity of the vicinal sulfide was apparently not suppressed enough by the bulky *tert*-butyl group to prevent episulfonium formation.

It was obvious that the first sulfur protecting group held the key to the successful synthesis of *cis*-1,2-dithiocyclopentanes. We therefore explored the use of an electron-withdrawing protecting group on sulfur by attempting the preparation of *cis*-1,2-diacetylthiocyclopentane (**7**) from *trans*-2-acetylthiocyclopentanol (**8**) (Scheme 2). To our delight, the alcohol was converted to the thiolacetate under Volante's conditions with

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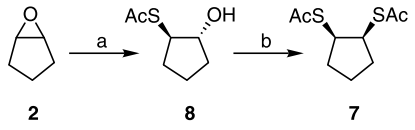
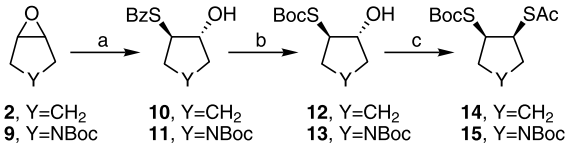


Scheme 2. (a) AcSH, rt, 7 days, 65%. (b) AcSH, PPh_3, DIAD, THF, 0°C to rt, 92%

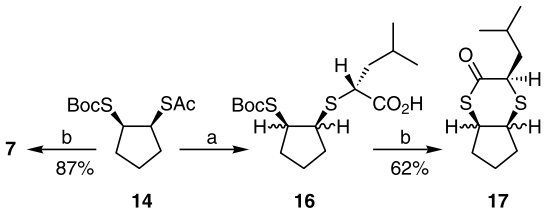
complete inversion of configuration, affording **7**[6] in high yield. This result was notable because earlier studies had shown that when the hydroxy group of **8** was activated by tosylation or mesylation, formation of the *S*-acetylepisulfonium intermediate still occurred.[11] The success with an electron-withdrawing blocking group on sulfur, combined with our ultimate need for differentially-protected *cis*-dithiols, led to our choice of *t*-Boc as the first sulfur protecting group in a new synthetic route to *cis*-1,2-dithiocyclopentane derivatives (Scheme 3).

As shown in Scheme 3, the first required step was ring-opening of an epoxide by a thiolacid. Epoxide ring-opening has been studied extensively,[12,13] but the reported procedures using sulfur nucleophiles are seldom efficient and often not practical.[14–16] Epoxide ring-openings with thiolacids are especially plagued by long reaction times and low yields.[17] We therefore explored the alumina-catalyzed epoxide ring-opening.[18,19] Although a variety of nucleophiles have been used with this procedure, there were no reports of the use of thiolacids. Reaction of epoxides **2** and **9**[20] with thiolbenzoic acid over alumina at room temperature was rapid and clean, affording the corresponding *trans*-β-benzoylthioalcohols **10** and **11** in almost quantitative yields.[21] Removal of the benzoyl groups from **10** and **11** and *t*-Boc protection of the resulting thiols was carried out in one pot, affording compounds **12** and **13** in good yields. Finally, application of the modified Mitsunobu reaction procedure gave the desired differentially-protected *cis*-dithio compounds **14** and **15** in high yields.

Examples of the selective deprotection of the thiols, and transformations allowing confirmation of the assigned stereochemistry of **14**, are outlined in Scheme 4. Selective cleavage of the Boc group, followed by acetylation, allowed correlation of **14** with the known[6] **7**. Treatment of **14** with methanolic methylamine selectively removed the acetyl protecting group, and subsequent addition of

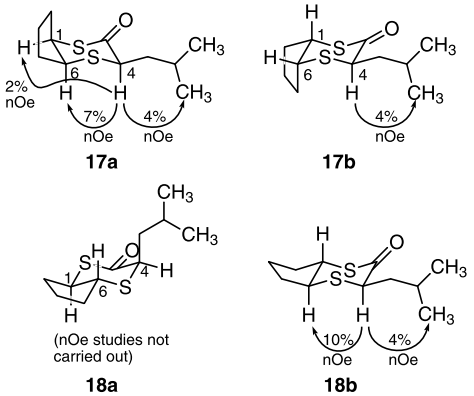


Scheme 3. (a) Alumina, PhCOSH, Et_2O, rt, 1 h, ~99%. (b) (i) EtONa, EtOH, 0°C, 10 min, (ii) Boc_2O, 0°C, ~85%. (c) CH_3COSH, PPh_3, DIAD, THF, 0°C to rt, ~90%.



Scheme 4. (a) (i) 40% $MeNH_2$, MeOH, 20 min; (ii) Br-Leu, K_2CO_3, DMF, 75%. (b) (i) 3N HCl in AcOH; (ii) AcCl, TEA, CH_2Cl_2.

(*S*)-2-bromo-4-methylpentanoic acid[22] and K_2CO_3 in DMF gave the *S*-alkylated intermediate **16** as a mixture of two diastereomers. For confirmation of stereochemistry, the *t*-Boc protecting group was removed by brief treatment with 3N HCl in AcOH and the resulting mercaptoacids were cyclized to give the bicyclic thioesters **17** as a mixture of two diastereomers. The diastereomers were separated by column chromatography and ^1H NMR studies on the resulting **17a** and **17b** confirmed the assignment of *cis*-stereochemistry to **14**. As summarized in Fig. 1, **17b** showed no nOe between H4 and either H1 or H6, while in **17a** there were significant nOes between H4 and both H1 and H6. For comparison purposes, *trans*-1-acetylthio-2-*tert*-butylthiocyclopentane (**5**) was similarly transformed into the bicyclic thioester diastereomers **18a** and **18b**. The coupling constants and nOe data confirmed the *trans* ring fusion in these compounds (Fig. 1).



Cpd	H1	H4	H6
17a	3.80, dt, J = 9, 7 Hz.	3.52, dd, J = 5, 9 Hz.	4.02, dt, J = 3, 7 Hz.
17b*	3.61, q, J = 8 Hz.	3.33, dd, J = 6, 9 Hz.	3.98, q, J = 8 Hz.
18a*	3.64, dt, J = 7, 11 Hz.	3.67, dd, J = 6, 9 Hz.	3.09, dt, J = 7, 11 Hz.
18b	3.12, dt, J = 7, 11 Hz.	3.82, dd, J = 6, 7.5 Hz.	3.55, dt, J = 7, 11 Hz.

* The H1 and H6 assignments may be interchanged.

Figure 1. Stereochemistry assignments based on ^1H NMR at 500 MHz.

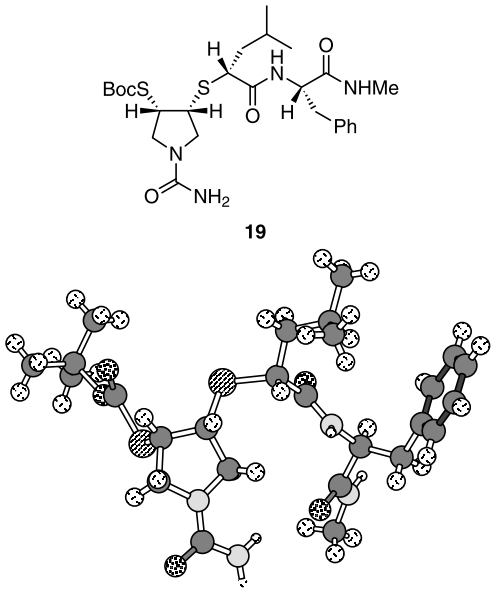


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Figure 2. X-Ray crystal structure of *cis*-3,4-pyrrolidinedithiol derivative **19**.

Selective cleavage of each of the *t*-Boc protecting groups in the *cis*-3,4-pyrrolidinedithiol derivative **15** was possible.[23] Treatment of **15** with dry 2N HCl in EtOAc at room temperature selectively removed the *N*-*t*-Boc group, while selective cleavage of the *S*-*t*-Boc group in **15** was achieved in 2N NaOH in aqueous MeOH. Both the *N*- and *S*-*t*-Boc groups could be removed simultaneously with 3N HCl in AcOH. By application of these procedures, **15** was transformed into the matrix metalloproteinase inhibitor precursor **19**, the structure and stereochemistry of which was confirmed by X-ray crystallography (Fig. 2).

General procedure for alumina-mediated epoxide ring-opening with thiolacids. To a stirred slurry of 36 g of alumina in 30 mL of dry ether was added the thiolacid (25 mmol). After 10 min the epoxide (5 mmol) was added and stirring was continued at rt for 2 h. The mixture was filtered and the alumina was washed several times with ether until nothing else was eluted (TLC analysis). The combined filtrate was extracted with saturated aqueous $NaHCO_3$, then was dried over Na_2SO_4 and evaporated to give the *trans*-β-hydroxythioesters which were used without further purification.

Acknowledgements

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