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Synthesis and biological activity of *S*-oxo-[(methylthio)-methyl]cysteinols

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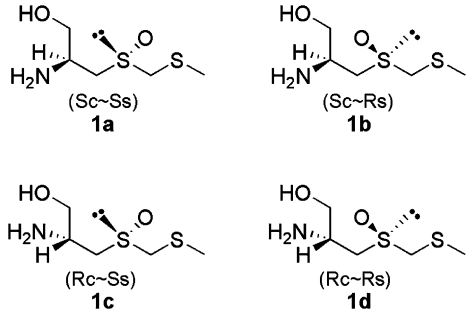
Abstract—A convenient route was developed to synthesize *S*-oxo-[(methylthio)-methyl]cysteinols on a large scale from cheap L-serine as the starting material. The structures of diastereoisomers were determined by NMR, CD spectra, and X-ray diffraction analysis. All four diastereoisomers were examined for their ability to inhibit certain bacteria from growing.

S-Oxo-[(methylthio)-methyl]cysteinol played an important role in chemical structure and biological activity of natural products as amine moiety, such as in sparsomycin.[1] Its derivatives also showed a wide variety of biological properties. Some of them were the aroma and flavor components of vegetables of the genus *Brassica*[2] (cabbage, cauliflower, broccoli, etc.) and *Allium*[3] (garlic, onion, leek, society garlic, etc.). *S*-Oxo-*S*-methyl cysteine possesses the ability to lower serum cholesterol level by inhibition of cholesterol synthesis and as an inhibitor of platelet aggregation.[4] Additionally, *S*-oxo-[(methylthio)-methyl]-cysteine undergoes α,β-elimination catalyzed by cysteine sulfoxide (C-S) lyases, generating reactive sulfenic acid intermediates, which are responsible for the characteristic rotting vegetable smells.[5]

S-Oxo-[(methylthio)-methyl]cysteinol (**1c**,**d**) had been synthesized from L-cysteine by several research groups.[6] However, the compounds (**1a**,**b**) could be only obtained in small quantity because of the expensive starting material D-cysteine[6a,b,d] or low yield with difficult separation.[6c] Large quantity of cysteinols (**1a**–**d**, Scheme 1) is needed in our research. Here, we report a convenient route to prepare two diastereoisomers (**1a**,**b**) of *S*-oxo-[(methylthio)-methyl]cysteinol on a large scale from the cheap L-serine as the starting material. All compounds have been fully characterized by NMR, CD spectra, and X-ray diffraction analysis. The antibacterial activities of all the four diastereoisomers (**1a**–**d**) against certain bacteria were also evaluated.



Scheme 1.

We synthesized amine alcohols (**1a**,**b**) from L-serine based on Ottenheijm's method[6b] according to the route shown in Scheme 2. Esterification of L-serine and subsequent refluxing with 1 equiv triphosgene gave (*S*)-2-oxo-oxazolidine-4-carboxylic acid methyl ester **2** in 86% yield.[7] The ester group was converted into tosylate **3** by a two-step sequence in 66% yield, involving sodium borohydride reduction and tosylate formation.[8] Boc protection and subsequent iodine replacement gave compound **4**. Treatment of **4** with cesium carbonate[9] in MeOH led to the cleavage of the oxazolidine ring. D-Cystinol was prepared by treatment of **5** with NaSH in MeOH solution and subsequent I_2 oxidation in good yield. Treatment with 3 equiv of NCS and AcOH afforded sultines **7a** in 43% yield and **7b** in 38% yield, respectively. Reaction of **7a** and **7b** at −78 °C with 3 equiv of

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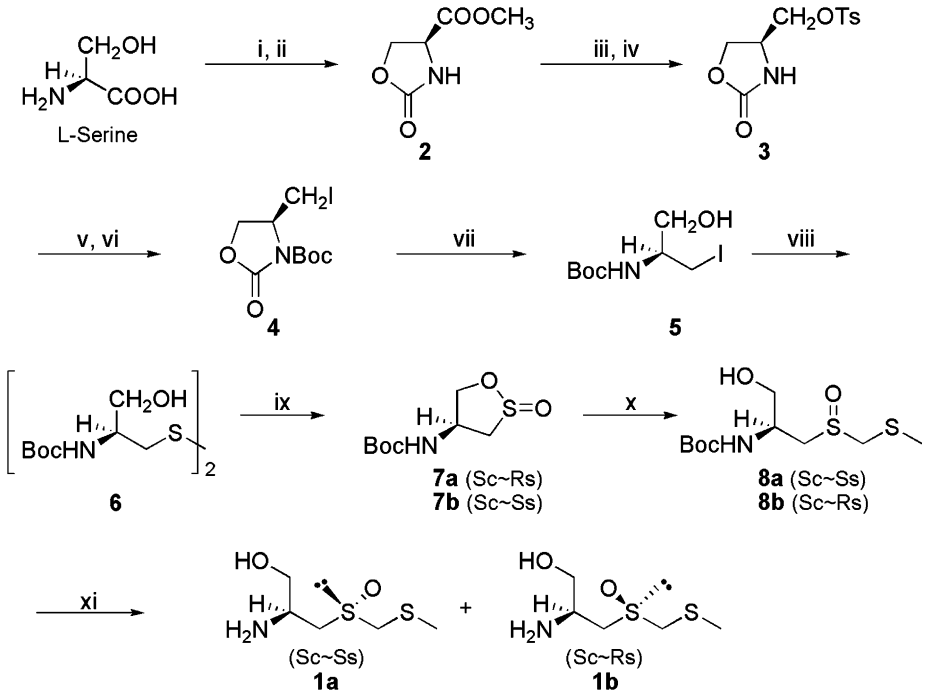

Scheme 2. Reagents and conditions: (i) CH_3OH, $SOCl_2$, reflux, 90%; (ii) triphosgene, THF, reflux, 86%; (iii) $NaBH_4$, EtOH, 0 °C, 86%; (iv) TsCl/Py, rt, 87%; (v) $(Boc)_2O$, DMAP, Et_3N, rt, 91%; (vi) NaI, acetone, reflux, 100%; (vii) Cs_2CO_3, CH_3OH, rt, 100%; (viii) NaHS, EtOH, overnight then I_2, 88%; (ix) NCS, AcOH, rt, 43% for **7a** and 38% for **7b**; (x) *n*-BuLi, TMEDA, CH_3SCH_3, THF, −78 °C, 73%; (xi) TFA, 0 °C, 99%.

(methylthio)-methyllithium gave the desired dithioacetal monoxides **8a** and **8b**. Finally, the amine alcohols **1a** and **1b** were obtained quantitatively by removal of Boc protecting group with CF_3COOH at 0 °C and subsequent deprotonation with an ion-exchange resin and freeze-drying.

Structures of the diastereoisomers have been determined by NMR and ESI-MS. ESI-MS analysis shows that $[MH^+]$ of four compounds (**1a**–**d**) are 184.06, 184.05, 184.11, and 184.13, revealing that these four compounds are in sulfoxide form. The position of the sulfoxide group was determined based on NMR spectroscopic data. Since the ^1H and ^{13}C chemical shifts of the terminal methyl group (2.33 and 17.05–17.51 ppm, respectively) correspond to a CH_3S– group rather than a $CH_3S(O)$– group, so the structure of the amino acid is determined as *S*-(methylthio-methyl)cysteinol-4-oxide. Ottenheijm's group had determined the absolute configuration of compound **1c** by total synthesis of sparsomycin with (*S*)-configuration of the sulfoxide sulfur atom.[6a] By comparing the ^1H NMR data of all the four compounds, it is found that compounds **1a** and **1d** have the same spectrum, and the signal pattern as $S(O)CH_2CH(NH_2)$ methylene protons displays a characteristic AB part of ABX spectrum with the coupling constants of $J_{AB} = 13.3$ Hz, $J_{AX} = 6.4$ Hz, $J_{BX} = 4.9$ Hz, and $J_{AB} = 13.3$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 4.8$ Hz, respectively. Compounds **1b** and **1c** have the other same spectrum with multiplets at 2.91 ppm because of overlapping. Additionally, **1a** and **1d** have nearly opposite specific rotation of +14° and −15.5°, respectively. The same is observed for **1b** (+63°) and **1c** (−66°). These data suggest that **1a** and **1d** can comprise a pair of enantiomers and have opposite configuration, the same is true for the pair of **1b** and **1c**. So it is concluded that the absolute configuration of the sulfoxide sulfur atom in **1b** and **1d** is determined as (*R*), and in **1a** and **1c** as (*S*).

The CD spectra of compounds **1a**–**d** are shown in Figure 1. According to Mislow's rules,[10] methyl alkyl sulfoxides, which do not contain other strongly perturbing groups, have negative Cotton effects centered at the strong absorption band near 200 nm (acetonitrile) and have (*R*)-configuration. For sulfoxide **1a**–**d**, the contribution

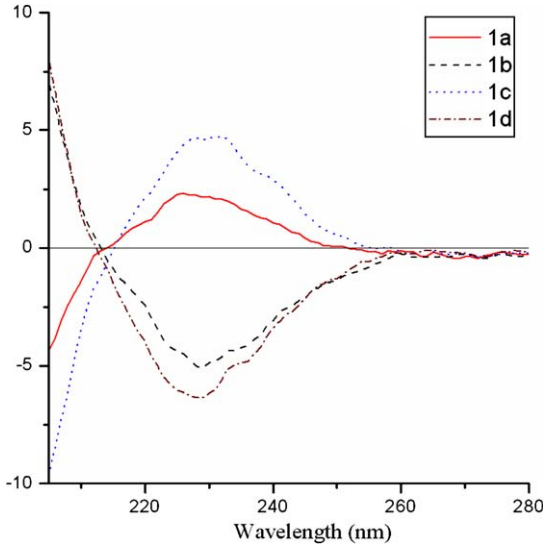

Figure 1. CD spectra of compounds **1a**–**d**.

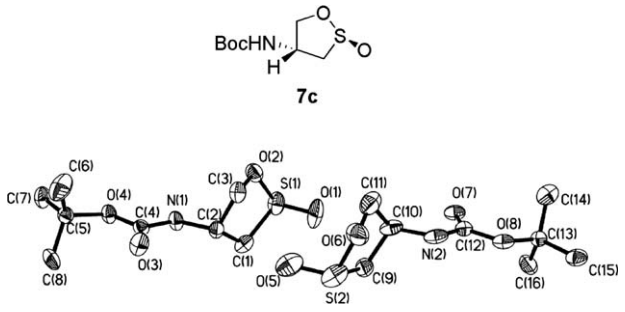

Figure 2. X-ray analysis of **7c** showing the *Rc* ~ *Ss* configuration.

of the chiral carbon is small, so the CD spectra of the diastereoisomers are nearly mirror images. The CD spectra show that compounds **1b** and **1d** have a negative sign of the Cotton effect at 220–240 nm, it correlates with (*R*)-configuration, while compounds **1a** and **1c** showing a positive sign have (*S*)-configuration. The assignment is also in accordance with the conclusion obtained by analysis of single-crystal X-ray diffraction of compound **7c** (Fig. 2).[11]

All the four diastereoisomers of *S*-oxo-[(methylthio)-methyl]cysteinol were tested against six bacteria including *Fusarium oxysporum* f. sp. *cucumerinum* Owen, and *Botrytis cinerea*, *Fulvia fulva*, *Sclerotinia sclerotiorum* de Bary, *Phytophthora capsici*, *Botryosphaeria berengeriama*. All the four compounds show low to moderate biological activities against certain bacteria at a concentration of 25 ppm.

In summary, we have reported herein a convenient route to prepare two diastereoisomers (**1a**, **1b**) of *S*-oxo-[(methylthio)-methyl]cysteinol on a large scale from the cheap L-serine as the starting material, with acceptable overall yield. All the four diastereoisomers (**1a**–**d**) can now be obtained conveniently in large quantity. All the four compounds were tested against certain bacteria. Further study of the derivatives of these compounds and their biological activities will be reported in due course.

Acknowledgements

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Supplementary data

Supplementary data contains experimental details of the syntheses, crystal structural data, biological data and NMR spectra of all the four diastereoisomers. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.089.

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11. CCDC No. 298255 contains the supplementary crystallographic data for compound **7c**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.