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# Communications

## Simple Total Syntheses of Biologically Active Pentathiadecane Natural Products, 2,4,5,7,9-Pentathiadecane 2,2,9,9-Tetraoxide (Dysoxysulfone), from *Dysoxylum richii*, and 2,3,5,7,9-Pentathiadecane 9,9-Dioxide, the Misidentified Lenthionine Precursor SE-3 from Shiitake Mushroom (*Lentinus edodes*)[1]

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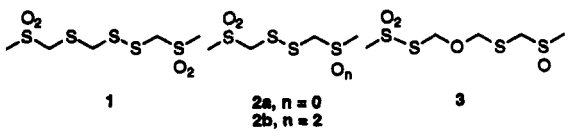
*Summary:* Brief total syntheses are reported for 2,4,5,7,9-pentathiadecane 2,2,9,9-tetraoxide (dysoxysulfone, 1), from the Fijian tree *Dysoxylum richii*, 2,3,5,7,9-pentathiadecane 9,9-dioxide (8), from shiitake mushroom (*Lentinus edodes*), and 2,4,5,7-tetrathiaoctane 2,2-dioxide (2a) from *Tulbaghia violacea*, starting from 1,2,4-trithiolane (4) for 1, 1,2,4,6-tetrathiepane (5) for 8, and 2,4,5,7-tetrathiaoctane (9) for 2a and employing regiospecific oxidation of intermediate penta- or tetrasulfides using $KMnO_4$ along with $Zn(OAc)_2$ or $FeCl_3$ to prevent product degradation by the base produced during oxidation.

Sulfur-rich, low molecular weight natural products are of interest because of their intriguing structures, pronounced flavors, and physiological activity, the latter often associated with usage of extracts of the plant in traditional medicine. In addition to the well-studied *Allium* spp. compounds,[2] notable examples include the following: dysoxysulfone (1, 2,4,5,7,9-pentathiadecane 2,2,9,9-tetraoxide), the active component of a tea made from the leaves of the tree *Dysoxylum richii* (Gray) C.D.C. (Meliaceae), used in traditional Fijian medicine;[3] 2,4,5,7-tetrathiaoctane 2,2-dioxide (2a) from *Tulbaghia violacea*, a plant commonly used in herbal remedies in South Africa;[4] 2,4,5,7-tetrathiaoctane 2,2,7,7-tetraoxide (2b), 2,3,7,9-tetrathia-5-oxadecane 2,2,9-trioxide (3; SE-3), and derived cyclic polysulfides 1,2,4-trithiolane (4), 1,2,4,6-tetrathiepane (5), 1,2,3,5,6-pentathiepane (6; lenthionine), and 1,2,3,4,5,6-hexathiepane (7), antibiotic flavorants from shiitake mushrooms (*Lentinus edodes*).[5] While symmetrical 2b[6] and 4–7 (eq 1)[5a] are readily prepared, syntheses of acyclic compounds 1, 2a, and 3 have not been reported. In planning syntheses of these compounds, we discovered that the structure proposed for shiitake mushroom compound SE-3 (3) is incorrect. We propose an alternative structure closely related to 1, namely 2,3,5,7,9-pentathiadecane 9,9-dioxide, 8. We herein report simple total syntheses of 1, 2a, and 8, starting from compounds 4 and 5 for synthesis of 1 and 8, respectively, along with biological



1 2a, n = 0; 2b, n = 2 3

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(1) Presented at the 19th IUPAC Symposium on the Chemistry of Natural Products, Karachi, Pakistan, Jan 16–20, 1994.

(2) Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135.

(3) (a) Jogia, M. K.; Andersen, R. J.; Mantus, E. K.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 4919. (b) The plant, when bruised, is reported to give off a strong odor of garlic or onion. The use of the plant is described thus by a wise old native: "The leaves must be chopped up very small, and then put into a *bulomakou* (bully-beef) tin—if no *bulomakou* tin, a salmon tin can be used ... add only a little water, put it on the fire and boil. Drink this, and all the pains in head, arms, legs or body, will go!"[3c] Dysoxysulfone is said to display antimicrobial activity but the limited amount of material available from natural sources prevented determination of the level of activity.[3a] (c) Parham, H. B. R. *Polynesian Soc. Mem.* **1943**, *16*, 1.

(4) Burton, S. G.; Kaye, P. T. *Planta Med.* **1992**, *58*, 295.

(5) (a) Morita, K.; Kobayashi, S. *Chem. Pharm. Bull.* **1967**, *15*, 988. (b) Takazawa, H.; Tajima, F.; Miyashita, C. *Yakugaku Zasshi* **1982**, *102*, 489; *Chem. Abstr.* **1982**, *97*, 69141.

(6) Grossert, J. S.; Bharadwaj, M. M.; Faught, J. B.; Tersiz, A. *Can. J. Chem.* **1980**, *58*, 1106.

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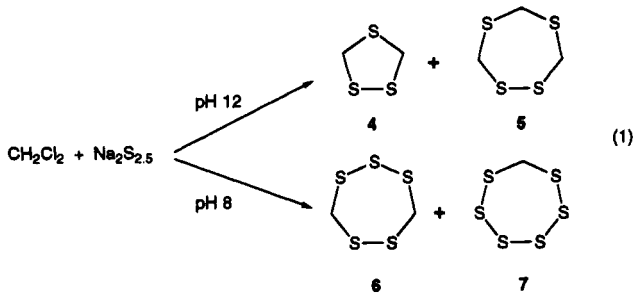
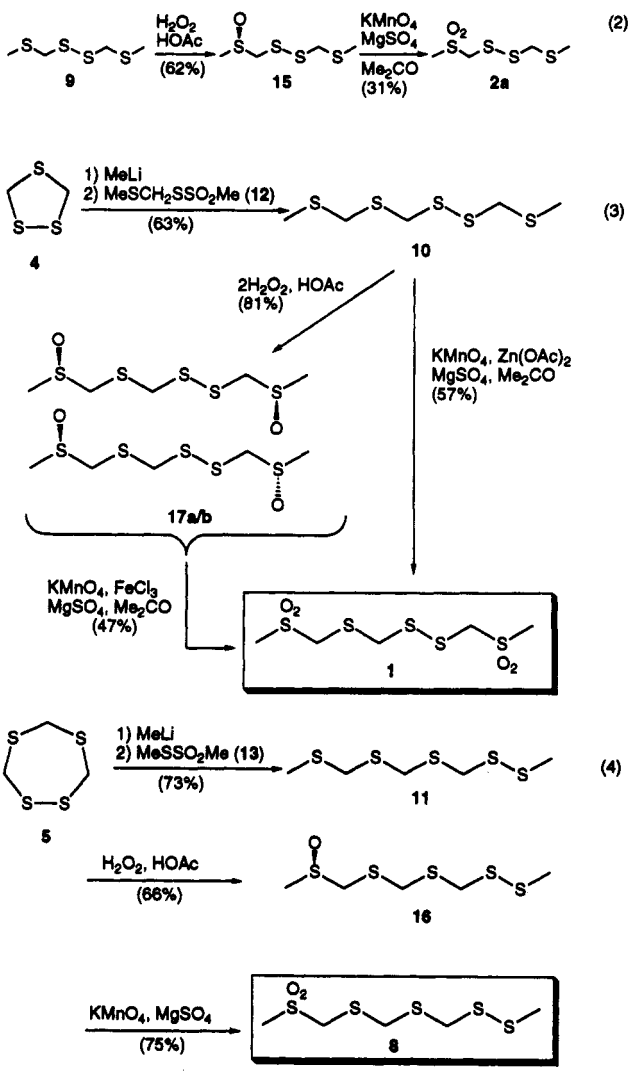



activity data for 1 and 8; our synthesis of 8 supports the revised structure of SE-3.

Compound SE-3 was originally identified as 2,3,7,9-tetrathia-5-oxadecane 2,2,9-trioxide (3).[5a] While the $C_5H_{12}S_4O_4$ formula is consistent with the low-resolution mass spectral *m/e* 264 parent ion (HRMS data are not given for the *m/e* 264 ion), the reported $^1$H NMR spectrum ($\delta$ 2.50 (3 H, s), 3.05 (3 H, s), 3.97 (2 H, s), 4.05 (2 H, s), and 4.19 (2 H, s) ppm) is incompatible with the proposed structure because the $\alpha$-, $\gamma$-, and $\epsilon$-sulfinyl $CH_2$ protons in 3 should be diastereotopic and because the chemical shift of 4.05 and 4.19 ppm for the $OCH_2S$ groups is at too high a field compared to chemical shifts for this position in 1,3-thioxane and related compounds (ca. 4.7–5.0 ppm).[7a] Furthermore, the infrared bands at 977, 962, and 953 cm$^{-1}$ ascribable to a sulfoxide are in fact far outside the known range of 1040–1065 cm$^{-1}$.[7b] Finally, many of the electron-impact mass spectral (EI-MS) fragmentation processes proposed for 3 seem improbable.[5a] The alternative structure for SE-3, 2,3,5,7,9-pentathiadecane 9,9-dioxide, 8 ($C_5H_{12}S_5O_2$), nicely fits all of the data, including the EI-MS base peak at *m/e* 185 ($C_4H_9S_3O_2$ by HRMS;[5a] $M^+$ – MeSS), which serves to distinguish 8 from isomers $MeSO_2CH_2SCH_2SSCH_2SMe$ and $MeSO_2CH_2SSCH_2SCH_2SMe$. We therefore sought to confirm this structure by synthesis.

2,4,5,7-Tetrathiaoctane (9) (eq 2)[8] and 2,4,5,7,9- and 2,3,5,7,9-pentathiadecane (10 and 11, respectively) seemed logical target compounds in the synthesis of 2a, 1, and 8, respectively, assuming that selective oxidation can then be achieved. In forming the S–S bonds in 10 and 11, 4 could serve as the source of three of the sulfur and two of the carbon atoms in 10 (eq 3),[9] while 5 could serve as the source of four of the sulfur and three of the carbon atoms in 11 (eq 4). Specifically, we envisioned methyllithium-induced nucleophilic S–S cleavage followed by capture of the resultant thiolate ions by the sulfur electrophiles *S*-(methylthio)methyl methanesulfonothioate (12; $MeSCH_2SSO_2Me$) in the synthesis of 10 from 4 and methyl methanesulfonothioate (13; $MeSSO_2Me$) in the synthesis of 11 from 5. We further anticipated that 12 could be prepared from readily available chloromethyl methyl sulfide (14).




In the event, treatment of 14 with sodium methanethiosulfonate in acetonitrile (55 °C, 5.5 h) gave 12 in 59% yield.[10] Treatment of 1,2,4-trithiolane 4 with methyllithium at −78 °C followed by immediate addition of the resultant lithium compound to an excess of 12 and chromatography to remove unreacted 12 gave 2,4,5,7,9-pentathiadecane (10; 63% yield).[10] Similar treatment of 1,2,4,6-tetrathiepane (5), substituting 13 for 12, afforded 2,3,5,7,9-pentathiadecane (11; 73% yield).[10] Oxidation of

(7) (a) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G., Jr.; Mizsak, G. C.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524. (b) Conley, R. T. *Infrared Spectroscopy*; Allyn and Bacon: Boston, 1966; p 179. Rao, C. N. R. *Chemical Applications of Infrared Spectroscopy*; Academic Press: New York, 1963; p 304.

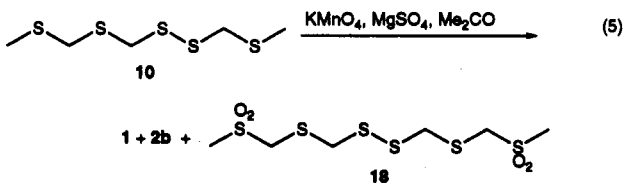
(8) (a) Altamura, M. R.; Hasselstrom, T.; Long, L., Jr. *J. Org. Chem.* **1963**, *28*, 2438. (b) Compound 9 is also present in extracts of *Tulbaghia violacea*, of the Bazilian medicinal plant *Gallesia integrifolia* ("pau d'alho"),[8c] and of the mushroom *Marasmius alliaceus*.[8d] (c) Akisue, M. K.; Wasicky, R.; Akisue,. G.; De Oliveira, F. *Rev. Farm. Bioquim. Univ. S. Paulo* **1984**, *20*, 145. (d) Gmelin, R.; Luxa, H. H.; Roth, K.; Höfle, G. *Phytochemistry* **1976**, *15*, 1717. (e) We prepared 9 via reaction of chloromethyl methyl sulfide with sodium thioacetate followed by sequential treatment with $K_2CO_3$ and $I_2$.

(9) For a related example of this reaction, see: Dubs, P.; Joho, M. *Helv. Chim. Acta* **1978**, *61*, 2809.

(10) All yields are after chromatography. Partial spectroscopic data follows: 1: $^1$H NMR ($CDCl_3$) $\delta$ 4.39 (s, 2 H), 4.16 (s, 2 H), 4.03 (s, 2 H), 3.04 (s, 3 H), 3.02 (s, 3 H); $^{13}$C NMR ($CDCl_3$), $\delta$ 61.24, 51.57, 41.85, 39.32, 38.66. Anal. Calcd for $C_5H_{12}O_4S_5$: C, 20.26; H, 4.08. Found: C, 20.01; H, 4.28. 2a: $^1$H NMR ($CDCl_3$) $\delta$ 4.17 (s, 2 H), 4.04 (s, 2 H), 3.01 (s, 3 H), 2.22 (s, 3 H); $^{13}$C NMR ($CDCl_3$), $\delta$ 62.03, 45.19, 39.18, 15.38. 8: $^1$H NMR ($CDCl_3$), $\delta$ 4.17 (s, 2 H), 4.03 (s, 2 H), 3.94 (s, 2 H), 3.04 (s, 3 H), 2.49 (s, 3 H); $^{13}$C NMR ($CDCl_3$), $\delta$ 51.11 ($CH_2$), 40.07 ($CH_2$), 38.54 ($CH_3$), 34.71 ($CH_2$), 23.44 ($CH_3$); IR (KBr) 1296 (s), 1102 (m), 979 (m), 952 (m), 785 (m) cm$^{-1}$; HRMS calcd and found for $C_5H_{12}O_2S_5$ 263.9441. Anal. Calcd for $C_5H_{12}O_2S_5$: C, 22.71; H, 4.57. Found: C, 22.90; H, 4.60. 10: $^1$H NMR ($CDCl_3$), $\delta$ 4.07 (s, 2 H), 3.91 (s, 2 H), 3.79 (s, 2 H), 2.21 (s, 3 H), 2.13 (s, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 45.09, 40.48, 36.82, 15.26, 14.59. Anal. Calcd for $C_5H_{12}S_5$: C, 25.83; H, 5.21. Found: C, 26.04; H, 5.38. 11: $^1$H NMR ($CDCl_3$) $\delta$ 3.95 (s, 2 H), 3.92 (s, 2 H), 3.72 (s, 2 H), 2.45 (s, 3 H), 2.12 (s, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 39.98 ($CH_2$), 36.23 ($CH_2$), 32.65 ($CH_2$), 23.38 ($CH_3$), 14.55 ($CH_3$); HRMS calcd for $C_5H_{12}S_5$ 231.9543, found 231.9544. 15: $^1$H NMR ($CDCl_3$) $\delta$ 4.00 (q, $J$ = 13 Hz, 2 H), 3.94 (s, 2 H), 2.66 (s, 3 H), 2.20 (s, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 62.50, 45.81, 37.57, 15.38. 16: $^1$H NMR ($CDCl_3$) $\delta$ 4.05–3.77 (m, 6 H), 2.67 (s, 3 H), 2.48 (s, 3 H); $^{13}$C NMR ($CDCl_3$), $\delta$ 51.89 ($CH_2$), 39.93 ($CH_2$), 37.96 ($CH_3$), 35.55 ($CH_2$), 23.51 ($CH_3$); HRMS calcd for $C_5H_{12}OS_5$ 247.9492, found 247.9501. 17a/b: $^1$H NMR ($CDCl_3$) $\delta$ 4.23 (m, 2 H), 4.02 (m, 2 H), 3.84 (m, 2 H), 2.66 (s, 3 H), 2.64 (s, 3 H); $^{13}$C NMR ($CDCl_3$), $\delta$ 62.24, 62.20, 52.50, 52.40, 43.70 (double intensity), 37.6 (double intensity), 37.30, 37.20. All new compounds were also characterized by low-resolution mass spectrometric methods.

9 and 11 with 30% hydrogen peroxide in acetic acid gave 2,4,5,7-tetrathiaoctane 2-oxide (15; 62% yield) and 2,3,5,7,9-pentathiadecane 9-oxide (16; 66% yield), respectively.[10] Treatment of 10 with 2 equiv of 30% hydrogen peroxide in acetic acid gave two diastereomers of 2,4,5,7,9-pentathiadecane 2,9-dioxide (17a/b) in 81% yield.[10] The regioselectivity seen in the oxidation of 10 and 11 merits comment. While preferential oxidation of sulfide sulfur over disulfide sulfur is known,[11] selective oxidation of terminal methylthio sulfur in preference to internal sulfide sulfur is novel; it may be due to the diminished nucleophilicity of the latter sulfurs due to the dual, flanking, electron-withdrawing $RSCH_2$ groups.

Oxidation ($KMnO_4/MgSO_4$) of 15 gave 2,4,5,7-tetrathiaoctane 2,2-dioxide (2a; 31% yield),[10] spectroscopically identical to natural 2a.[4] Similar oxidation of 16 gave 2,3,5,7,9-pentathiadecane 9,9-dioxide (8; 75% yield), a colorless crystalline solid, mp 79–80.5 °C (lit.[5a] for 3, mp 80–82 °C), spectroscopically identical to SE-3.[5a,10,12] Oxidation of 17a/b to 1 proved more challenging than anticipated. Attempted $KMnO_4$–$MgSO_4$ oxidation led to a difficultly separable mixture of 1, 2b, and 2,4,6,7,9,11-hexathiadodecane 2,2,11,11-tetraoxide (18) (eq 5).[10] Pre-




(5)

sumably, base generated from the $KMnO_4$ triggers $\alpha,\beta$-elimination in 1 forming $MeSO_2CH{=}S$ and $MeSO_2CH_2SCH_2S^-$, the latter attacking S-5 of 1 giving 18 and $MeSO_2CH_2S^-$; attack on S-4 of 1 by $MeSO_2CH_2S^-$ would give 2b. While $Zn(MnO_4)_2$[13] is appealing as a permanganate oxidant likely to pose fewer problems associated with base formation than $KMnO_4$, its unavailability and pyrophoric character limit its usefulness. Fortunately, oxidation of 17a/b with a mixture of $KMnO_4$, $MgSO_4$, and 5 equiv of $FeCl_3$ in acetone leads cleanly to dysoxysulfone (1) in 47% yield with no detectable contamination from 2b or 18. Furthermore, 9 can be *directly oxidized to 1* in 57% yield using $KMnO_4$, $MgSO_4$, and 2 equiv of $Zn(OAc)_2$. Synthetic dysoxysulfone 1 (mp 107–108 °C; lit.[2a] mp 97–99 °C) is spectroscopically identical to the natural product.[3] The use of the mild Lewis acids $FeCl_3$ or $Zn(OAc)_2$ to prevent degradation by base in $KMnO_4$ oxidations or to directly catalyze $KMnO_4$ oxidation of sufides to sulfones merits further study.[14]

Minimum inhibitory concentrations (MIC) of 1 toward *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans* are 100, 20, and 10 μg/disk, respectively; analogous values reported[5b] for 2b are 12.5, 6.25, and 25 μg/disk, respectively. The MIC of 8 toward *Candida albicans* is 100 μg/disk. Against a human ovarian carcinoma cell line, 1, 2b, and 18 displayed $IC_{50}$ values of 5.0, 4.3, and 4.4 μg/mL, respectively; against a P388 murine luekemia cell line, 1, 8, and 18 displayed $IC_{50}$ in vitro cytotoxicity values of 0.49, 0.62, and 0.58 μg/mL, respectively; against human colon adenocarcinoma cell lines 1 displayed an $IC_{50}$ value of 7.4 μg/mL.

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**Supplementary Material Available:** Experimental procedures and spectral data for 1, 2a, 8–12, and 15–17 (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) E.g., see: Block, E.; Zhao, S.-H. *J. Org. Chem.* **1992**, *57*, 5815.
(12) The major peak found on reversed-phase HPLC analysis of a chloroform extract of homogenized shiitake mushrooms corresponded in retention time to synthetic 8.
(13) Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1983**, *105*, 7755.
(14) (a) In a similar manner, thioanisole was converted into thioanisole *S,S*-dioxide in 100% yield after 0.5 h at −25 °C using $KMnO_4/FeCl_3$/acetone; if the $FeCl_3$ is omitted only a trace of sulfone is isolated under these reaction conditions. (b) For $KMnO_4/MgSO_4$ oxidation of sulfoxides to sulfones, see: Block, E.; Corey, E. R.; Penn, R. E.; Renken, T. L.; Sherwin, P. F.; Bock, H.; Hirabayshi, T.; Mohmand, S.; Solouki, B. *J. Am. Chem. Soc.* **1982**, *104*, 3119 and references cited therein. (c) We were unable to prepare 1 from 17a/b or directly from 10 using heterogeneous $Cu(MnO_4)_2$[14d] or catalytic $OsO_4$.[14e] (d) Noureldin, N. A.; McConnell, W. B.; Lee, D. G. *Can. J. Chem.* **1984**, *62*, 2113. (e) Kaldor, S. W.; Hammond, M. *Tetrahedron Lett.* **1991**, *32*, 5043.