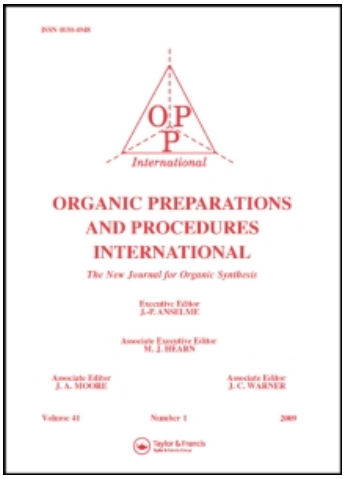

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A CHEMOENZYMATIC SYNTHESIS OF (R)-2-(1-HYDROXYETHYL)-1,3-DITHIANE

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3. D. F. DeTar and M. Carmack, *J. Am. Chem. Soc.*, **68**, 2025 (1946).

4. K. Kindler, *Ann.*, **431**, 187 (1923).

5. G. N. Mott, US Patent 5041657; *Chem Abstr.*, **115**: P 182861e (1991).

6. J. H. King and F. H. McMillan, *J. Am. Chem. Soc.*, **68**, 525 (1946).

7. K. D. Raner, C. R. Strauss, J. S. Thorn and R. W. Trainor, *J. Org. Chem.*, **60**, 2456 (1995).

8. A patent application has been filed.

9. E. R. Shepard, H. D. Porter, John F. Noth and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

10. E. Mosettig and J. van de Kamp, *J. Am. Chem. Soc.*, **55**, 3442 (1933).

11. C. H. Davis and M. Carmack, *J. Org. Chem.*, **12**, 76 (1947).

12. A. Burger and S. Avakian, *ibid.*, **5**, 606 (1940).

13. A. Werner, *Ann.*, **322**, 151 (1902).

14. A. C. Ott, L. A. Mattano and G. H. Coleman, *J. Am. Chem. Soc.*, **68**, 2633 (1946).

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A CHEMOENZYMATIC SYNTHESIS OF (R)-2-(1-HYDROXYETHYL)-1,3-DITHIANE

Submitted by (12/14/94)

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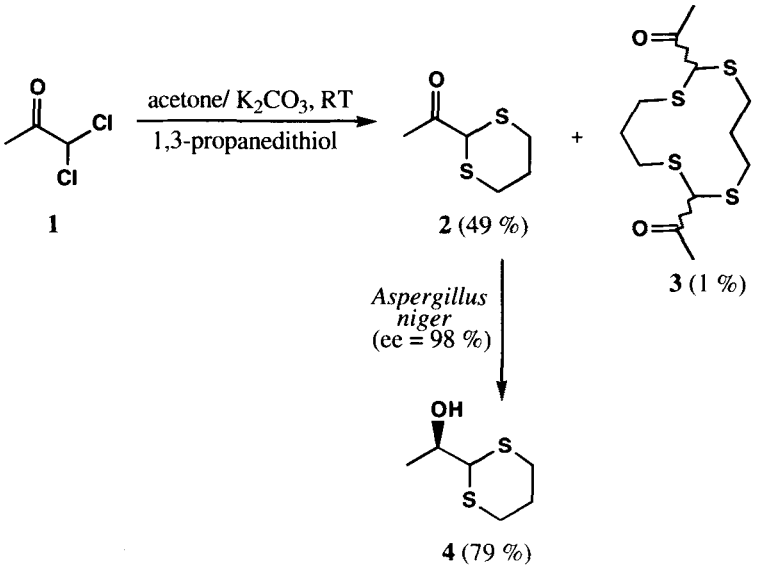
Enantiomerically pure hydroxyalkyl-1,3-dithianes are versatile bifunctional building blocks for the preparation of chiral natural products and drugs.[1-5] The hydroxyl group can be converted to other functional groups by activation and substitution, while the dithiane group can be deprotonated and then treated with electrophiles. Subsequent hydrolysis or reductive desulfurization offers an access to hydroxyketones and alcohols respectively. It is also possible to hydrolyze hydroxyalkyldithianes to yield hydroxyaldehydes.[6,7] This paper reports a new, inexpensive one-step preparation of 2-acetyl-1,3-dithiane (**2**) and the first microbiological preparation of (R)-2-(1-hydroxyethyl)-1,3-dithiane ((**R**)-**4**)[2,8] by reduction of ketone **2**.

Previous syntheses[9-11] of **2** starting from lithiated 1,3-dithiane require anhydrous solvents and organometallic reagents and give only moderate yields. Therefore, we have worked out a more economic synthesis of **2**. Reaction of 1,1-dichloroacetone (**1**) with 1,3-propanedithiol and K_2CO_3 in acetone gave **2** in 49% yield; 2,8-bis-acetyl-1,3,7,9-tetrathiacyclododecane (**3**) (mixture of diastereomers) was isolated as a by-product in very low yield (1%). The integration of the singlets at δ 4.59 and 4.45 showed that *cis*- and *trans*-isomers were formed in approximately equal amounts. The reaction of geminal dihalides with 1,3-propanedithiol has previously been used only for the preparation of the parent 1,3-dithiane.[12,13]



Microbiological reduction of **2** with *Aspergillus niger* (DSM 821)[14] gave **(R)-4** (ee = 98%) in high yield. Within 18 hrs, the starting material was completely consumed and **(R)-4** was isolated as the sole product. Best optical yields were obtained by carrying the reduction under growth conditions in culture medium. Enantiomeric excess was determined by GLC-analysis after derivatization with (R)-MTPA chloride.[15,16]

In conclusion, the convenient synthesis of 2-acetyl-1,3-dithiane (**2**) followed by microbiological reduction with *Aspergillus niger* offers an efficient two-step approach to **(R)-4** in very high optical yield. Since reduction of **2** with *Saccharomyces cerevisiae* has been reported[9,17] to give **(S)-4**, this enantiomer also can be prepared more economically now.

EXPERIMENTAL SECTION

Melting points (uncorrected) were obtained on a Reichert Heiztischmikroskop. Elemental analyses were prepared on a Carlo Erba CHNO Elemental Analyzer 1106. Optical rotations were determined on a Perkin Elmer 241. GLC was performed on a Shimadzu GC-14A, column: AT-50 (30 m, 0.25 mm I.D., Alltech), isothermal: 215°, carrier: helium, v = 20 cm/sec., split 1:50, FID. IR spectra were obtained on a Philips PU 9800 FTIR-Spektrometer. NMR spectra were determined on a Bruker AM 400, TMS as

internal standard. Mass spectra were obtained on a Finnigan MAT 8430. Kieselgel 60 (230-400 mesh), Merck, was used for Flash Column Chromatography (FCC). *Aspergillus niger* (DSM 821) was purchased from Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig.

Reaction of 1 with 1,3-Propanedithiol.- A solution of 1,1-dichloroacetone (**1**) (4.76 g, 37.5 mmol) in acetone (25 mL) and a solution of 1,3-propanedithiol (3.24 g, 30.0 mmol) in acetone (25 mL) were added alternately in 5 mL portions to a stirred suspension of K_2CO_3 (9.12 g, 66.0 mmol) in acetone (20 mL). Stirring was continued for 1 hr, then water was added followed by extraction with ethyl acetate. The organic layer was dried (K_2CO_3) and concentrated *in vacuo*. The crude product was purified by FCC (pentane/ethyl acetate 10:1) to afford **2** (2.38 g, 49%), pale yellow liquid, and **3** (0.06 g, 1%), colorless needles, respectively.

2-Acetyl-1,3-dithiane (2), MS (EI, 70 eV): m/z (%) = 162 (M^+, 11) , 119 (100), 45 (11), 43 (16); IR (film, NaCl): ν = 2925, 1709, 1422, 1352, 1262, 1242, 1190, 1151, 911 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.28 (s, 1 H, CH), 3.17-3.24 (m, 2 H), 2.58-2.64 (m, 2 H), 2.36 (s, 3 H, CH_3), 1.97-2.13 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ = 200.44 (C=O), 48.11 (CH), 27.73 (CH_3), 26.38 (2 SCH_2), 25.23 (CH_2).

Anal. Calcd. for $C_6H_{10}OS_2$: C, 44.41; H, 6.22. Found: C, 44.25; H, 7.01

2,8-*bis*-Acetyl-1,3,7,9-tetrathiacyclododecane (3) (Mixture of Diastereomers), mp. 163° (pentane/ethyl acetate); MS (EI, 70 eV): m/z (%) = 324 (M^+, 8) , 218 (33), 175 (84), 133 (33), 119 (100), 106 (36), 101 (17), 87 (17), 73 (14), 45 (26), 43 (73); IR (KBr): ν = 2923, 1701, 1356, 1266, 1255, 1240, 1146, 574 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.59 (s, 1 H, CH), 4.45 (s, 1 H, CH), 2.93-3.06 (m, 4 H), 2.70-2.85 (m, 4 H), 2.37 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 1.91-2.00 (m, 4 H); ^{13}C NMR ($CDCl_3$): δ = 199.65 (C=O), 199.50 (C=O), 60.47 (CH), 58.63 (CH), 27.74 (2 CH_2), 27.04 (2 CH_2), 25.28 (CH_2), 24.70 (CH_2), 27.24 (CH_3), 26.34 (CH_3).

Anal. Calcd. for $C_{12}H_{20}O_2S_4$: C, 44.41; H, 6.22. Found: C, 44.26; H, 6.00

(R)-2-(1-Hydroxyethyl)-1,3-dithiane ((R)-4).- Culture medium (*ad* 1 L): glucose monohydrate, 22 g; yeast extract (Sigma), 5 g; soy bean flour (Difco), 5 g; NaCl, 5 g; K_2HPO_4, 5 g; pH was adjusted to 6.5 with HCl.

Culture medium (100 mL) in a 500 mL conical flask was inoculated with spores of *Aspergillus niger* (DSM 821). The solution was cultivated at 27° and 120 rpm for 1 d. 10 mL of this culture medium were transferred into a conical flask containing culture medium (100 mL) and cultivated under the conditions described above. Then the solution was decanted and wet mycelium was obtained. Wet mycelium (5 g) was incubated in culture medium (100 mL) under the same conditions for 2 hrs. 2-Acetyl-1,3-dithiane (**2**) (50 mg, 0.31 mmol) was added to the suspension and stirring was continued for 18 hrs. Then the mixture was extracted with ethyl acetate and the organic layer was dried over K_2CO_3. The volatile compounds were evaporated *in vacuo* and the crude product was purified by FCC (pentane/ethyl acetate 5:1) to yield (R)-2-(1-hydroxyethyl)-1,3-dithiane (**(R)-4**) (40 mg, 79%) as a colorless liquid; $[\alpha]_D^{20}$ = + 5.6° (c 2.2, methanol), $[\alpha]_D^{20}$ = + 5.8° (c 1.2, methanol);[2] ee 98%, determined by GLC after derivatization with (R)-MTPA chloride,[15,16] derivative of **(R)-4**: t_R = 26.5 min, derivative of **(S)-4**: t_R = 26.9 min (racemate[18]); MS (EI, 70 eV): m/z (%): 164 (M^+, 18), 119 (100), 46

(14); IR (film, NaCl): ν 3434, 2973, 2930, 2899, 1422, 1389, 1374, 1277, 1248, 1127, 1078, 1055, 789 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.08 (dq, J = 6.8 Hz, J = 6.2 Hz, 1 H, C*H*OH), 3.79 (d, J = 6.8 Hz, 1 H, CH), 2.92-2.99 (m, 2 H), 2.70-2.78 (m, 2 H), 2.55 (br. s, 1 H, OH), 1.94-2.13 (m, 2 H), 1.40 (d, J = 6.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): δ 68.19 (CHOH), 53.21 (CH), 27.91 (CH_2), 27.53 (CH_2), 25.29 (CH_2), 20.33 (CH_3).

Anal. Calcd. for $C_6H_{12}OS_2$: C, 43.86; H, 7.38. Found: C, 43.74; H, 7.58

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REFERENCES

1. T. Sato and T. Fujisawa, *Biocatalysis*, **3**, 1 (1990).
2. H. Redlich and B. Schneider, *Ann.*, 412 (**1983**).
3. E. J. Corey, L. O. Weigel, D. Floyd and M. G. Bock, *J. Am. Chem. Soc.*, **100**, 2916 (1978).
4. M. Singer, C. Siegel, P. M. Gordon, A. K. Dutta and R. K. Razdan, *Synthesis*, 486 (**1994**).
5. J. Mulzer, *J. prakt. Chem.*, **336**, 287 (1994).
6. B.-T. Gröbel and D. Seebach, *Synthesis*, 357 (**1977**).
7. P. C. B. Page, M. B. van Niel and J. C. Prodger, *Tetrahedron*, **45**, 7643 (1989).
8. D. Bianchi, P. Cesti and P. Golini, *ibid.*, **45**, 869 (1989).
9. G. Guanti, L. Banfi and E. Narisano, *Tetrahedron Lett.*, **27**, 3547 (1986).
10. L. Colombo, C. Gennari, C. Scolastico and M. G. Beretta, *J. Chem. Soc., Perkin Trans. 1*, 1036 (**1978**).
11. P. C. B. Page, M. B. van Niel and D. Westwood, *ibid.*, 269 (**1988**).
12. J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **56**, 2177 (1934).
13. P. C. B. Page, S. S. Klair, M. P. Brown, M. M. Harding, C. S. Smith, S. J. Maginn and S. Mulley, *Tetrahedron Lett.*, **29**, 4477 (1988).
14. A. Belan, J. Bolte, A. Fauve, J. G. Gourcy and H. Veschambre, *J. Org. Chem.*, **52**, 256 (1987).
15. J. A. Dale, D. L. Dull and H. S. Mosher, *ibid.*, **34**, 2543 (1969).

16. J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

17. T. Fujisawa, E. Kojima, T. Itoh and T. Sato, *Chemistry Lett.*, 1751 (**1985**).

18. B. C. Newman and E. L. Eliel, *J. Org. Chem.*, **35**, 3641 (1970).

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CHALCONES BY THE WITTIG REACTION OF A STABLE YLIDE WITH ALDEHYDES UNDER MICROWAVE IRRADIATION

Submitted by (12/05/94)

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Microwave heating had been used for a variety of purposes such as moisture analysis,[1] the wet ashing of biological samples and dissolution of geological materials,[2] the regeneration of activated carbon,[3] the preparation of activated carbon from carbonaceous materials,[4] and treatment of sewage and sewage sludge.[5] It was, however, the pioneering papers of Gedye[6] and of Majetich[7] and their co-workers in 1986 that stimulated the interest of synthetic organic chemists in this new technique.

$$\mathbf{ArCHO} + \mathbf{Ph_3P{=}CHCOPh} \xrightarrow[\text{Silica gel, 5-6 min.}]{\text{microwave}} \mathbf{ArCH{=}CHCOPh}$$

Our interest in the development of thermal reactions using microwave heating led us to reinvestigate the Wittig reaction of the stable ylide, triphenylbenzoylmethylene phosphorane with aldehydes under microwave irradiation. This important reaction,[8] however, proceeds at a slow rate for example, between triphenylbenzoylmethylene phosphorane and benzaldehyde, requiring 3 days of reflux in benzene or 30 hours in THF (70% yield).[9-11] We now report that microwave irradiation for 5-6 min. effects this transformation in 82-96% yields. Remarkable rate enhancements and dramatic reductions of reaction times have been achieved and the yields have been improved.

EXPERIMENTAL SECTION

Melting points are uncorrected. The apparatus used in the experiment was a National NN-5252 domestic microwave oven.