phenylphosphine (0.53 g, 2.02 mmol). After 0.5 h at 20 °C, excess glyoxal (10 mL, 40% solution in water) was added, followed by excess triethylamine (ca. 5 mL) and stirring was then continued at 20 °C for 3 h. The solvent was then removed in vacuo and the residue extracted into dichloromethane, which was then washed with water. The organic layer was dried ($MgSO_4$) and evaporated to yield a viscous oil which was purified by chromatography on a silica column (eluent initially hexane/dichloromethane, 1:1 v/v, followed by neat dichloromethane) to afford compound **17a** as a viscous yellow oil [0.47 g, 71%]. NMR: δ_H ($CDCl_3$) 9.27 (1 H, d, J = 1.8 Hz), 6.59 (1 H, d, J = 1.8 Hz), 2.44 (3 H, s), 2.38 (3 H, s). MS: m/e (EI) 332; (CI) 333 (M^+).

2-(Formylmethylene)-5,6-dihydro-1,3-dithiolo[4,5-*b*][1,4]diselenin (17b) was similarly prepared from compound **13b** (0.80 g) and isolated as a yellow solid (0.55 g, 78%), mp 102–104 °C. NMR: δ_H ($CDCl_3$) 9.36 (1 H, d, J = 1.5 Hz), 6.68 (1 H, d, J = 1.5 Hz), 3.40 (4 H, s). MS: m/e (EI) 330; (CI) 331 (M^+). Anal. Calcd for $C_7H_6OS_2Se_2$: C, 25.62, H, 1.84. Found: C, 25.47; H, 1.90.

2-(Dimethoxyphosphoryl)-4,5-bis(methylseleno)-1,3-dithiole (18a). A mixture of dithiolium salt **14a** (0.45 g, 1.20 mmol), trimethyl phosphite (0.15 g, 1.21 mmol), and sodium iodide (0.18 g, 1.2 mmol) in dry acetonitrile (50 mL) was stirred at 20 °C overnight under dry nitrogen. The solvent was evaporated and the residue extracted into dichloromethane, which was washed with water, the organic layer was then dried ($MgSO_4$), and the solvent was removed. The resulting oil was passed down a neutral alumina column, eluting with hexane/dichloromethane (1:1 v/v) to yield compound **18a** as a red oil (0.38 g, 80%). NMR δ_H ($CDCl_3$) 4.81 (1 H, d, J = 4.4 Hz), 3.88 (6 H, d, J = 11.0 Hz), 2.34 (6 H, s).

2-(Dimethoxyphosphoryl)-5,6-dihydro-1,3-dithiolo[4,5-*b*][1,4]diselenin (18b) was similarly prepared from salt **14b** (0.50 g) and isolated as a white solid, which rapidly turned black on exposure to air. Recrystallization from dichloromethane/hexane gave 0.31 g, 59%, mp 100–102 °C. NMR: δ_H ($CDCl_3$) 4.83 (1 H, d, J = 6.2 Hz), 3.86 (6 H, d, J = 10.6 Hz), 3.30 (4 H, m). MS: m/e (EI) 398; (CI) 399 (M^+). Anal. Calcd for $C_7H_{11}O_3PS_2Se_2$: C, 21.22; H, 2.80. Found: C, 21.79; H, 2.83.

Vinylogous TTF Derivatives 5, 6, and 8–10. General Procedure. A solution of phosphonate ester **18** (1.0 mmol) in dry tetrahydrofuran (THF) (30 mL) was cooled to −78 °C under nitrogen and treated with *n*-butyllithium (1.6 M, 1.1 mmol), causing an immediate color change from red to yellow. After 0.5 h, a solution of aldehyde **16** (0.9 mmol) in THF (10 mL) was added by syringe into the reaction mixture, which was allowed to warm to 20 °C over 16 h. The solvent was then evaporated, and the residue was dissolved in dichloromethane (50 mL), which was washed with water, dried ($MgSO_4$), and evaporated to yield the crude product, which was purified by elution through an alumina column (eluent hexane/dichloromethane ca. 2:1 v/v). The product was recrystallized from hexane/dichloromethane.

4,4′,5,5′-Tetrakis(methylseleno)-2,2′-ethanediylidenebis-(1,3-dithiole) (5) was obtained from ester **18a** and aldehyde **17a** and isolated as a orange solid in 58% yield, mp 132–134 °C. NMR: δ_H ($CDCl_3$) 5.78 (2 H, s), 2.32 (12 H, m). MS: m/e 605 (M^+). Anal. Calcd for $C_{12}H_{14}S_4Se_4$: C, 23.93; H, 2.34. Found: C, 23.82; H, 2.40.

4,5-Bis(methylseleno)-4′,5′-bis(methylthio)-2,2′-ethanediylidenebis(1,3-dithiole) (6) was obtained from ester **18d**[10] and aldehyde **17a** and isolated as large orange plates in 76% yield, mp 120–122 °C. NMR: δ_H ($CDCl_3$) 5.76 (2 H, s), 2.40 (3 H, s), 2.39 (3 H, s), 2.31 (3 H, s), 2.30 (3 H, s). MS: m/e 510 (M^+). Anal. Calcd for $C_{12}H_{14}S_6Se_2$: C, 28.34; H, 2.77. Found: C, 28.37; H, 2.78.

4,5:4′,5′-Bis(ethylenediseleno)-2,2′-ethanediylidenebis-(1,3-dithiole) (8) was obtained from ester **18b** and aldehyde **17b** and isolated as a yellow solid in 55% yield, mp > 340 °C after recrystallization from carbon disulfide/methanol. NMR: δ_H (CS_2) 5.71 (2 H, s) and 3.31 (8 H, s). Anal. Calcd for $C_{12}H_{10}S_4Se_4$: C, 24.09; H, 1.68; S, 21.43. Found: C, 23.85; H, 1.65; S, 21.34. The compound was too involatile to give a mass spectrum (EI, CI, or DCI modes).

4,5-(Ethylenediseleno)-4′,5′-dimethyl-2,2′-ethanediylidenebis(1,3-dithiole) (9) was obtained from ester **18c**[12] and aldehyde **17b** and isolated as a yellow solid in 62% yield, mp 198–200 °C. NMR: δ_H ($CDCl_3$) 5.80 (2 H, dd), 3.33 (4 H, s), 1.90 (3 H, s), 1.89 (3 H, s). MS: m/e (EI) 444; (CI) 445 (M^+). Anal. Calcd for $C_{12}H_{12}S_4Se_2$: C, 32.58; H, 2.73. Found: C, 32.78; H, 2.75.

4,5-(Ethylenediseleno)-4′,5′-bis(methylseleno)-2,2′-ethanediylidenebis(1,3-dithiole) (10) was obtained from ester **18a** and aldehyde **17b** and isolated as an orange solid in 65% yield, mp 123–125 °C. NMR: δ_H ($CDCl_3$) 5.81 (2 H, s), 3.33 (4 H, s), 2.31 (3 H, s), 2.30 (3 H, s). MS: m/e 604 (M^+). Anal. Calcd for $C_{12}H_{12}S_4Se_4$: C, 24.01; H, 2.01. Found: C, 23.81; H, 1.94.

Complexation of Donors with TCNQ. Equimolar amounts of donor **5**, **6**, and **8–10** and TCNQ were dissolved in boiling dichloromethane [for donors **5**, **6**, **9**, and **10**] or 1,1,2-trichloroethane [for donor **8**] and the dark solution stored at 20 °C for 24 h. The precipitated complex (30–50% yield) was removed by filtration. Data for the complexes are collated in Table I.

Acknowledgment. We thank S.E.R.C. for funding this work.

Registry No. **1**, 31366-25-3; **2**, 66946-48-3; **5**, 138518-80-6; **5**·TCNQ, 138518-81-7; **6**, 138518-82-8; **6**·TCNQ, 138518-83-9; **7**, 127661-08-9; **8**, 138518-84-0; **8**·TCNQ, 138518-85-1; **9**, 138518-86-2; **9**·TCNQ, 138518-87-3; **10**, 138518-88-4; **10**·2TCNQ, 138518-89-5; **11a**, 128346-96-3; **11b**, 118355-60-5; **12a**, 138518-91-9; **13a**, 138518-92-0; **13b**, 138518-93-1; **14a**, 138518-95-3; **14b**, 138518-97-5; **17a**, 138518-98-6; **17b**, 138518-99-7; **18a**, 138519-00-3; **18b**, 138519-01-4; **18c**, 69212-98-2; **18d**, 138519-02-5; 1,3-dithiole-2-thione, 930-35-8; glyoxal, 107-22-2.

Supplementary Material Available: Crystal structure determination (3 pages). This material is contained in many 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.

Piperidinium Tetrathiotungstate as Sulfur Transfer Reagent: Synthesis of Cyclic Disulfides

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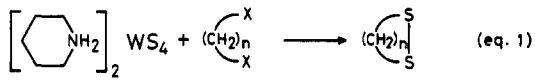
Piperidinium tetrathiotungstate has been found to react with a number of 1,*n*-dihalo compounds to afford the corresponding cyclic disulfides in good yields, under mild reaction conditions. This new methodology has been used as a key step in the synthesis of (±)-lipoic acid (**35**) and asparagusic acid (**37**).

There are a number of methods available in the literature for preparing cyclic disulfides. The preferred method varies with ring size. The common procedures involve either conversion of a dihalide or a ditosylate to a disulfide by displacement with disulfide anion (prepared in situ from sodium sulfide and sulfur)[1] or the oxidation of a

0022-3263/92/1957-1699$03.00/0

dithiol by various oxidizing agents.[2] Cyclic disulfides have also been obtained by the steam distillation of an appropriate Bunte salt.[3] The reaction of 1,3-dielectrophiles with S_4^{2-} followed by desulfurization with copper is known to produce 1,2-dithiolanes usually in moderate yields.[4] Harpp et al. have reported the high-yield preparation of cyclic disulfides by oxidation of alkyltin thiolates using iodine or bromine without the need of high dilution.[5]

We have recently shown the efficacy of tetrathiometalates (MS_4^{2-}) of molybdenum and tungsten in bringing about the formation of disulfides from alkyl halides in intermolecular reactions.[6] It was of interest to find out whether cyclic disulfides can be formed efficiently from 1,*n*-dihalo compounds via intramolecular pathways. Our interest in the chemistry of cyclic disulfides, in general, and the synthesis of some naturally occuring 1,2-dithiolanes, in particular, arose from the fact that our methodology of novel alkylation with tetrathiometalates could be extended to intramolecular reactions as well (eq 1).



(eq. 1)

1

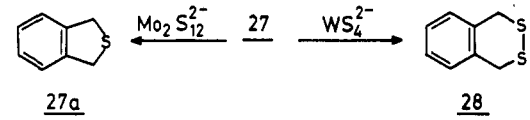
X = -Cl, -Br, -I, -OTs, -OMs.

The reaction of tetrathiotungstate 1 with 1,3-dibromopropane took place readily at room temperature (28° C, 2 h). However, attempts to isolate the pure 1,2-dithiolane system always led to polymerized material 3.[7] This is in accordance with the earlier observation[2,5] that unsubstituted dithiolane systems are prone to polymerization. Treatment of 1,3-dibromobutane 4 with 1 at room temperature (28 °C) initially posed a few problems. We obtained the dimer 5 instead of the desired 3-methyl-1,2-dithiolane system 6. This probably results from a higher order of reactivity of primary bromide, compared to the secondary bromide. This problem, however, was overcome by carrying out the reaction in the dark at a higher temperature (60 °C, 4 h) in a more dilute solution. In this case 1,2-dithiolane 6[8] was obtained in 61% yield.

2,4-Dibromopentane (7) on treatment with 1 gave the corresponding 1,2-dithiolane (8)[7,9] in 64% yield. Compound 8 was also obtained as the only product by reaction of ditosylate 9[10] with 1 (Table I). 2,2-Dimethyl-1,3-dibromopropane (10) on reaction with 1 for 6 h gave the corresponding 4,4-dimethyl-1,2-dithiolane (11).[9] Similarly, when the ditosylate 12 was treated with 1 equiv of 1, the corresponding 1,2-dithiolane system 13 was obtained in 54% yield.

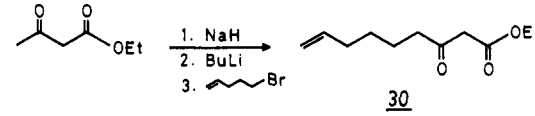
In order to find out whether the present methodology could be effectively extended to synthesize higher cyclic dithia analogues, we treated 1,4-dibromobutane (14), 1,5-dibromopentane (16), and 1,6-dibromohexane (18), with

Scheme I

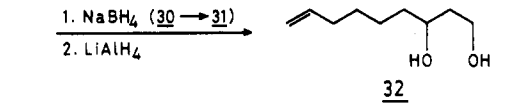


27a 28

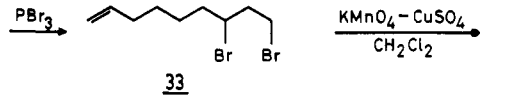
Scheme II



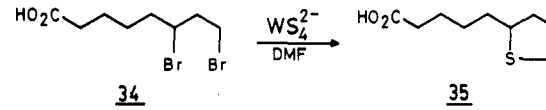
30



32



33



34 35

1 and obtained the corresponding dithiane 15,[8,11] dithiepane 17,[11] and dithiaoctane 19[11] in 74%, 50%, and 46% yield, respectively. At this point, it was decided to gauge the scope of this novel reaction to the formation of disulfide which is part of a spiro cyclic system. Accordingly, the tetrabromo compound 20[12] was allowed to react with 2 equiv of 1 to obtain compound 22[13,14] (55%) and dibromodithiolane 21 (13%). The spiro compound 22 has been used by Fujihara[13] for the synthesis of macrocyclic poly(thioethers), and compound 22 has recently been synthesized by Christophersen[14] from 20 in two steps in an overall yield of 18%.

In order to test the efficacy of the present methodology for construction of systems related to the dithia analogue of prostaglandin,[15] it was decided to look at the synthesis of the model system, dithianorbornene (24). 3,5-Dibromocyclopentene (23)[16] when treated with 1 at 0 °C for 12 h gave the bicyclic compound 24 in 20% yield.[17] The low yield of 24 in this reaction can be attributed to the unstable nature of the starting material and highly volatile nature of the product. Another allylic cyclic disulfide 26[17] could be prepared (43%) by the reaction of 1 with ditosylate 25, (18 h). Harpp and Macdonald[18] have recently shown that α,α'-dibromo-*o*-xylene (27)[19] on treatment with the persulfido complex, $Mo_2S_{12}^{2-}$, in a sealed tube at 90 °C for 20 h gave 1,3-dihydroisothianaphthalene (27a) as

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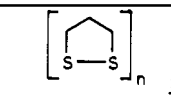
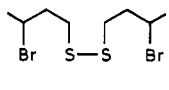
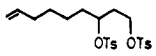
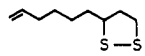
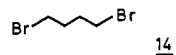
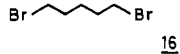
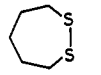
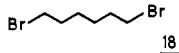
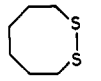
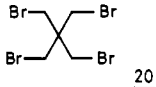
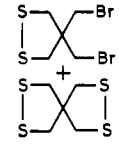
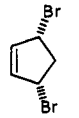
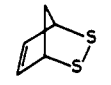
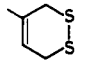
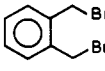
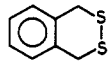
Table I

	substrate	temp (°C)	time (h)	product	yield (%)
1	 2	28	2	 3	67
2	 4	28	4	 5	54
3	4	60	4	 6	61
4	 7	28	5	 8	64
5	 9	28	12	8	54
6	 10	28	6	 11	68
7	 12	28	12	 13	54
8	 14	28	3	 15	74
9	 16	28	5	 17	50
10	 18	28	8	 19	46
11	 20	28	12	 21 + 22	12 + 55
12	 23	0	12	 24	20
13	 25	28	18	 26	43
14	 27	28	4	 28	94

the only product in 67% yield (Scheme I). Interestingly, reaction of **1** with **27** afforded the cyclic disulfide **28**[20] as the only product in excellent yield (Scheme I). The present methodology is more effective for the direct conversion of dihalo compounds to cyclic disulfides (46–94%) than the procedures reported (4–60%) thus far.[1,3,4]

Having demonstrated the usefulness of piperidinium tetrathiotungstate **1** in the formation of cyclic disulfides from the corresponding dihalo compounds or ditosylates, it was decided to apply this methodology to the synthesis of (±)-α-lipoic acid (**35**) and asparagusic acid (**37**). Several

(20) Luttringhaus, A.; Hagele, K. *Angew. Chem.* **1955**, *67*, 304.

Scheme III

36 **37**

syntheses of lipoic acid have been reported in the recent past.[21] We have utilized our novel alkylation using metal–sulfur derivatives as the key step in the formation of the crucial carbon–sulfur bond. Following the strategy depicted in Scheme II, (±)-α-lipoic acid (**35**)[21] was synthesized in an overall yield of 12%, starting from ethylacetoacetate.

Although synthetic procedures for asparagusic acid **37** are available,[14,22] they suffer from the instability of the precursors and/or formation of product mixtures which are difficult to separate. Christophersen[14] reported a modified procedure for the synthesis of 4-substituted 1,2-dithiolanes which allows a better controlled preparation. Unfortunately, the yield obtained by this method is very low (33%).

A short approach to the synthesis of asparagusic acid (**37**) is depicted in Scheme III. Thus, by utilizing **1** for the crucial sulfur transfer reaction, diethyl malonate has been converted to asparagusic acid (**37**) in 40% overall yield.

Thus, this methodology provides a simple, versatile, and general route to the construction of a wide variety of medium-sized cyclic disulfides.

Experimental Section

All the reactions with 1 were performed in the dark. Dimethylformamide (DMF) was initially purified by azeotropic distillation with benzene, and the residual solvent was shaken with calcium oxide, filtered, and distilled at reduced pressure. The fraction having bp 76 °C (39 mmHg) was collected. All melting points and boiling points are uncorrected. Infrared (IR) spectra were recorded on Perkin-Elmer Model 1320 and 580 spectrophotometers and are reported in wavenumbers (cm^{-1}). Proton magnetic resonance (^1H NMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on a Bruker WP-80 instrument, and at 90 MHz on a JEOL FX-90Q instrument. Chemical shifts are reported in parts per million downfield from internal reference tetramethylsilane (TMS) (δ). Mass spectra (MS) were recorded on a JEOL JMS D-300 mass spectrometer. 1,3-Dibromopropane, 1,4-dibromobutane, 1,5-dibromopentane, and 1,6-dibromohexane were obtained from Fluka Co. and were used as received.

Preparation of Piperidinium Tetrathiotungstate 1.[23] Tungstic acid (5.0 g) was refluxed in a mixture of water (10 mL) and piperidine (15 mL) for 1 h. The resulting solution was filtered, and H_2S (**Caution: Toxic**)[24] was bubbled rapidly at 60 °C for 8 h. The reaction mixture was cooled, and the yellow crystals of **1** formed were filtered, washed with 2-propanol (50 mL) and ether (20 mL), and dried in vacuo (7.5 g, 78%). IR (KBr): 3020, 2990, 2950, 1620, 1600, 1540, 1470, 1440, 1390, 1300, 1030, 1020, 990, 910, 655, 455 cm^{-1}. $\lambda_{max}(CH_3OH)$: 396 (11968). Anal. Calcd for $C_{10}H_{24}N_2S_4W$: C, 24.79; H, 4.45; N, 5.78. Found: C, 24.58; H, 4.78; N, 5.72.

Synthesis of 3-Methyl-1,2-dithiolane (6). Treatment of **1** (1.936 g, 4 mmol) in DMF (25 mL) with 1,3-dibromobutane (**4**, 0.664 g, 4 mmol) in DMF (10 mL) at 60 °C for 4 h gave the crude product which was purified by flash chromatography on silica gel (1:5 ether/petroleum ether, 40–60 °C) to yield 3-methyl-1,2-dithiolane (**6**)[6] (0.301 g, 61%) as a pale yellow oil. IR (thin film):

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(22) Schotte, L.; Strom, H. *Acta Chem. Scand.* **1956**, *10*, 687.
(23) McDonald, J.; Friesen, G. D.; Rosenhein, L. D.; Newton, W. E. *Inorg. Chim. Acta* **1983**, *72*, 205.
(24) This very poisonous gas should only be prepared and used in an efficient fume cupboard.

2951, 2871, 1465, 1380, 970, 895 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.4 (d, 3 H); 1.9–2.3 (m, 2 H); 3.0–3.4 (m, 3 H). MS (m/e): 120 (M^+), 88, 56.

General Procedure for the Preparation of Cyclic Disulfides. Synthesis of 3,5-Dimethyl-1,2-dithiolane (8).[7,9] Reaction of 1 (1.936 g, 4 mmol) in DMF (5 mL) at 28 °C for 6 h yielded the product which after chromatographic purification using 5% ether/petroleum ether (40–60 °C) as eluent gave a yellow oil. IR (thin film): 2967, 2870, 1466, 1380, 1000–960, 890 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.12–1.22 (d, 6 H); 1.25–1.47 (m, 2 H); 3.06–3.47 (m, 2 H). MS (m/e): 134 (M^+), 90.

4,4-Dimethyl-1,2-dithiolane (11).[9] IR (thin film): 2950, 2870, 1385, 1365, 970, 895 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 6 H); 2.78 (s, 4 H). MS (m/e): 134 (M^+), 119, 70.

1,2-Dithiane (15).[8,11] MP: 28–30 °C (lit.[11] mp 32–33 °C). IR ($CHCl_3$): 2910, 1450, 1280, 745 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.95 (s, 4 H); 2.8 (s, 4 H). MS (m/e): 120 (M^+), 88.

1,2-Dithiepane (17).[11] Bp: 55–60 °C (4 mm) (lit.[11] bp 41 °C (2 mm)). IR ($CHCl_3$): 2910, 1450, 1280, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.73–2.06 (m, 6 H); 2.8 (t, 4 H). MS (m/e): 134 (M^+), 102, 70.

1,2-Dithiacyclooctane (19).[11] BP: 61–63 °C (2 mm) (lit.[11] bp 65.5 °C (2 mm)). IR ($CHCl_3$): 2910, 1450, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.53–1.88 (m, 8 H); 2.56 (t, 4 H). MS (m/e): 148 (M^+), 147, 115, 83.

Compound 21. IR (thin film): 2955, 2920, 2875, 2854, 970, 890 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 4 H); 3.53 (s, 4 H). Anal. Calcd for $C_5H_8Br_2S_2$: C, 20.55; H, 2.74. Found: C, 20.61; H, 2.85.

Compound 22.[13,14] MP: 69–70 °C (lit.[14] mp 70 °C). IR ($CHCl_3$): 2955, 2875, 960, 880 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 8 H). MS (m/e): 196 (M^+), 164, 132, 117, 99, 85.

1,2-Dithianorbornene (24). IR ($CHCl_3$): 3010, 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 1 H); 2.81 (s, 1 H); 4.17–4.3 (br s, 2 H); 5.68 (s, 2 H). MS (m/e): 130 (M^+).

4-Methyl-3,6-dihydro-1,2-dithiin (26).[17a] IR ($CHCl_3$): 3010, 2970, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 3 H); 3.10–3.14 (m, 4 H); 5.06–5.31 (t, 1 H). MS (m/e): 132 (M^+).

Compound 28.[20] Mp: 78–79 °C (lit.[20] mp 80 °C). IR (KBr): 3060, 2960, 1600 cm^{-1}. ^{1}H NMR (CCl_4): δ 4.03 (s, 4 H); 7.08 (br s, 4 H). MS (m/e): 168 (M^+), 136, 104.

Reaction of Ditosylate 12 with 1. Treatment of 1 (0.242 g, 0.5 mmol) in DMF (10 mL) with compound 12 (0.233 g, 0.5 mmol) in DMF (2 mL) at 28 °C for 12 h gave the crude product which on chromatographic purification using 15% ether/petroleum ether (40–60 °C) as eluent gave the dithiolane 13 (0.051 g, 54%) as a pale yellow oil. IR (thin film): 3080, 1640, 1500, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.04–1.30 (m, 8 H); 1.68–1.96 (m, 2 H); 2.72–2.88 (m, 2 H); 3.0–3.36 (m, 1 H); 4.32–4.64 (m, 2 H); 5.0–5.44 (m, 1 H). MS (m/e): 188 (M^+), 124. Anal. Calcd for $C_9H_{16}S_2$: C, 57.45; H, 8.50. Found: C, 57.81; H, 8.24.

Synthesis of (±)-α-Lipoic Acid (35). To a solution of 1 (0.484 g, 1 mmol) in DMF (10 mL) was added dropwise a solution of the dibromo acid 34 (0.302, 1 mmol) in DMF at 50 °C for 4 h. After the usual workup, the crude product after chromatographic purification on silica gel (25% ethyl acetate–petroleum ether, 60–80 °C) gave α-lipoic acid (35)[21] (0.132 g, 65%) as a solid. Mp: 45–47 °C (lit.[21] m.p. 46–48.5 °C). IR ($CHCl_3$): 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.60 (br s, 8 H); 2.13–2.37 (m, 2 H) 3.08 (t, 2 H); 3.50 (m, 1 H); 10.06 (s, 1 H). MS (m/e): 206 (M^+).

Synthesis of Asparagusic Acid (37). A solution of 1 (0.968 g, 2 mmol) in DMF (10 mL) was allowed to react with a solution of dibromo acid 36[25] (0.492 g, 2 mmol) in DMF (10 mL) at 28 °C for 5 h. It was worked up as described earlier to yield asparagusic acid (37)[14,22] (0.182 g, 77%), after chromatographic purification on silica gel (20% ethyl acetate–petroleum ether 60–80 °C), mp 74–76 °C (lit.[14] mp 75.5–76.5 °C). IR ($CHCl_3$): 3500, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.95–3.08 (m, 1 H); 3.22–3.29 (d, 4 H); 10.43 (s, 1 H). MS (m/e): 150 (M^+).

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Registry No. 1, 56181-21-6; 2, 109-64-8; 3, 33087-69-3; 4, 107-80-2; 5, 138152-58-6; 6, 55487-20-2; 7, 19398-53-9; 8, 55487-21-3; 9, 35196-66-8; 10, 5434-27-5; 11, 58375-01-2; 12, 115948-55-5; 13, 138152-59-7; 14, 110-52-1; 15, 505-20-4; 16, 111-24-0; 17, 6008-51-1; 18, 629-03-8; 19, 6008-69-1; 20, 3229-00-3; 21, 138152-60-0; 22, 176-02-3; 23, 17040-70-9; 24, 115018-95-6; 25, 138152-61-1; 26, 18655-86-2; 27, 91-13-4; 28, 3886-39-3; 30, 59697-70-0; 32, 138283-89-3; 33, 138152-62-2; 34, 138152-63-3; 35, 1077-28-7; 36, 41459-42-1; 37, 2224-02-4; $CH_3COCH_2CO_2Et$, 141-97-9; $H_2C{=}CH(CH_2)_3Br$, 1119-51-3; tungstic acid, 7783-03-1; piperidine, 110-89-4; H_2S, 7783-06-4.

Supplementary Material Available: Experimental details and spectral data for compounds 3, 5, 12, and 30–34 (5 pages). Ordering information is given on any masthead pages.

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Mechanism of Hydrolysis of Benzamidomethyl Derivatives of Phenols and Its Implications for Prodrug Design

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A series of *O*-benzamidomethyl derivatives of phenols was synthesized, and their rates of hydrolysis were investigated. The hydrolyses of the compounds follow pseudo-first-order kinetics resulting in quantitative and rapid regeneration of the phenol. The rates of hydrolysis were shown to be dependent on phenol nucleofugicity as well as the pK_a of the amide. The mechanism of hydrolysis apparently involves an elimination of the phenol anion from the conjugate base of the amide (E1cB-like).

Introduction

The most convenient, safest, and least expensive method of drug delivery is through oral ingestion. However, many drugs cannot be administered orally due to rapid metabolism by enzymes in the intestinal tract and liver.[1] The prodrug approach can be successful in improving the oral bioavailability of a drug by chemically modifying a functional group on the drug molecule that is particularly

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