Selective Transformations of a Diprotected 2-Oxobutanedial

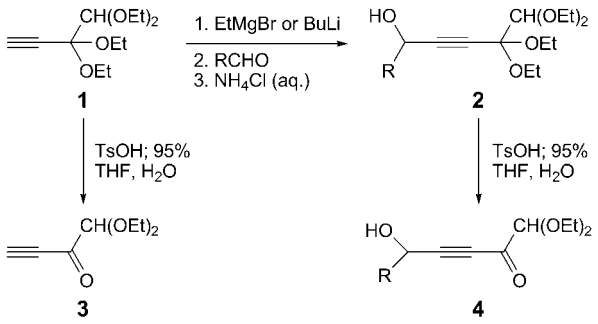
by **Marit K. Leiren**, **Stig Valdersnes**, and **Leiv K. Sydnes***

Department of Chemistry, University of Bergen, Allégt. 41, NO-5007 Bergen

The reactivity of 1,1-diethoxy-3-(1,3-dithian-2-yl)propan-2-one, a diacetal of oxobutanedial, and some of its derivatives toward selected reagents has been studied. As expected, hydride and *Grignard*-type additions take place at the oxo moiety only and give the corresponding alcohols in good-to-excellent yields. Standard reductive amination occurs at the oxo moiety as well, but the reaction was in most cases not selective and furnished the expected amine mixed with 3-(1,3-dithian-2-yl)-1,1-diethoxypropan-2-ol. The conversion of the diethyl acetal moiety to an aldehyde group is generally an efficient transformation, but some aldehydes are unstable, making the deprotection useless. If the acetal contains a tertiary alcohol or a benzyloxy moiety, however, stable products are formed in good yields. Attempts to convert the 1,3-dithiane substituent into an aldehyde group without concomitant decomposition of the product were totally unsuccessful. The chemical potential of this moiety, therefore, has to be utilized at an earlier stage and under different conditions.

Introduction. – We have reported a simple and efficient synthesis of 3,3,4,4-tetraethoxybut-1-yne (**1**) [1–4], which has been used to prepare a large variety of compounds with diverse structures [5–7]. The first and simplest conversion carried out was deketalization of **1** and a number of 4,4,5,5-tetraethoxypent-2-yn-1-ol derivatives, **2**, which afforded the corresponding α,β-unsaturated acetylenic ketones **3** and **4**, respectively, in good-to-very-good yields (*Scheme 1*). From **3** and **4**, a number of other compounds have been prepared, often in excellent yields, by treatment with nucleophiles prone to undergo *Michael* additions [7–10].

Scheme 1



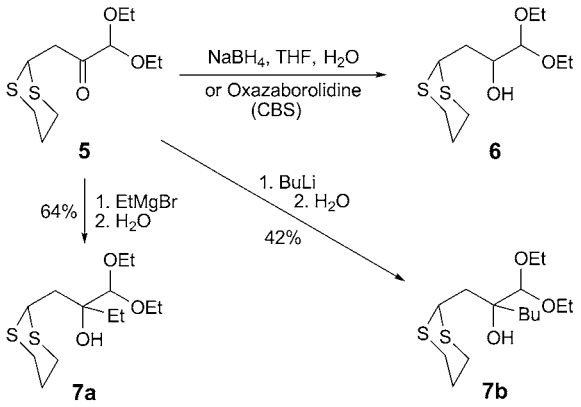
One interesting product obtained in this way was 3-(1,3-dithian-2-yl)-1,1-diethoxypropan-2-one (**5**), which can be acquired in up to 91% yield by subjecting **3** to a

reaction with propane-1,3-dithiol under basic conditions [9]. During this reaction, an internal redox reaction takes place, and a ketone with two protected aldehyde functions is obtained. Since one is an acetal moiety, whereas the other is a thioacetal, the four C-atoms in **5** (*cf. Scheme 2*) accommodate three C=O groups, which, in principle, can be utilized one after another in a variety of chemical transformations. This dithiane also appears to be thermally stable when kept at room temperature and below, and the compound has, therefore, a potential as an attractive starting material for the synthesis of multifunctionalized compounds. We are currently investigating the fundamental scope of this potential, and here we report some of the results obtained so far.

Results and Discussion. – For the sake of synthetic efficiency, transformations involving the ketone moiety should be performed first. Most of the relevant transformations take place under acidic or basic conditions, and since acetals are acid labile and 1,3-dithianes contain an acidic H-atom at C(2), the stability of the protecting groups in **5** under realistic reaction conditions will definitely be put to test when transformation of the keto function is addressed first. That appeared indeed to be the case.

Reactions Involving the Keto Function of **5**. Both protecting groups survived very well the reaction conditions prevailing, when ketone **5** was reacted under basic conditions. Hydride reduction with $NaBH_4$ as well as (*S*)-oxazaborolidine (*Corey-Bakshi-Shibata* (*CBS*) catalyst) gave 3-(1,3-dithian-2-yl)-1,1-diethoxypropan-2-ol (**6**) in 80 and 97% yield, respectively (*Scheme 2*). Since the latter reducing agent is chiral, alcohol **6** is expected to exhibit optical activity when this hydride is applied [11]. That was indeed the case, but the ee value was as low as 20% as determined by NMR spectroscopy of the benzyl-ether derivative of **6**, employing (−)-(*R*)-2-acetoxy-2-phenylacetic acid as solvating agent [12] (*vide infra*). Why the ee value is so low is not clear, but one explanation can be that the chiral reducing-agent complex is not sufficiently stable when exposed to **5**, and forms in part one or several achiral complexes through complexation with chalcogen atoms present in **5**, which is achiral.

Scheme 2



Regiospecific transformations were also observed, when **5** was treated with EtMgBr and BuLi, but the expected products, 2-(1,3-dithian-2-ylmethyl)-1,1-diethoxybutan-2-ol (**7a**) and 2-(1,3-dithian-2-ylmethyl)-1,1-diethoxyhexan-2-ol (**7b**), were obtained in rather moderate yields (*Scheme 2*). The reason for this could be that the strongly basic organometallic reagents are partly consumed by reactions with the acidic 1,3-dithiane CH H-atom, but if that is the only explanation, it is somewhat surprising that compounds **7** were not formed in higher yield when 2 equiv. of the reagents were applied.

Both protecting groups also survived a number of attempts to achieve reductive amination of **5** under various acidic to basic reaction conditions. As the results in the *Table* indicate, catalytic hydrogenation in the presence of Et_2NH failed completely, probably due to the presence of S-atoms, and **5** was recovered in essentially quantitative yield. Switching to borane and applying $LiClO_4$ as catalyst for imine formation, as reported by *Tavakol* and *Zakery* [13], gave no amine either, but a significant fraction of the ketone was converted to the corresponding alcohol **6**. However, when $NaBH(OAc)_3$ was used as reducing agent [14], amine formation did indeed occur and gave a mixture of two products, *N*-[3-(1,3-dithian-2-yl)-1,1-diethoxypropan-2-yl]propan-1-amine (**8**) and alcohol **6**, provided THF and not EtOH was used as solvent (*Scheme 3*). As expected, the best results were obtained under acidic conditions, but the highest yield of **8** did never exceed 57%, even when the reaction time was extended to 27 h (*Table*). Also in this case, a significant amount of alcohol **6** was obtained, which clearly indicates that the reaction conditions have to be optimized so that the iminium formation becomes more efficient and reduce the amount of ketone that will be available for borohydride reduction to **6**.

Scheme 3

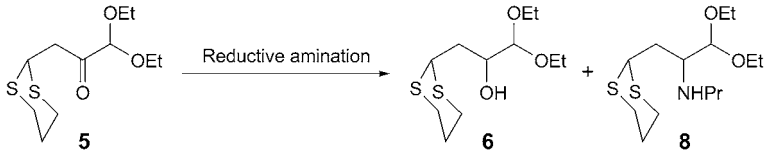


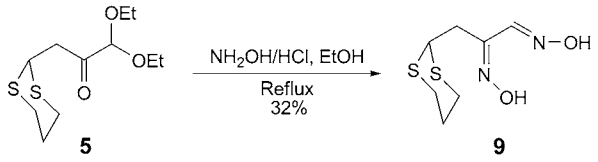
Table. *Results of Reductive Amination of Ketone* **5** *under Various Conditions*

Amine	Reaction conditions	Reaction time [h]	Yield of isolated products [%]	
			6	**8**
Et_2NH	H_2, Pd/C (5%), dry MeOH	6	0	0
Et_2NH	Diborane, dry THF, $LiClO_4$	17	41	0
$PrNH_2$	$NaBH(OAc)_3$, EtOH, NH_4OAc	25	5	0
$PrNH_2$	$NaBH(OAc)_3$, dry THF	27	47	23
$PrNH_2$	$NaBH(OAc)_3$, dry THF, AcOH	27	16	57

The final transformation involving **5** was treatment with NH_2OH under acidic conditions. When reacted with a 20% excess of amine at 30–35°, a number of products were formed in low yields. Unfortunately, the chromatographic properties of several of the products were quite similar under a variety of conditions, so no compound could be isolated with decent purity, and this prevented reliable structure elucidation. The

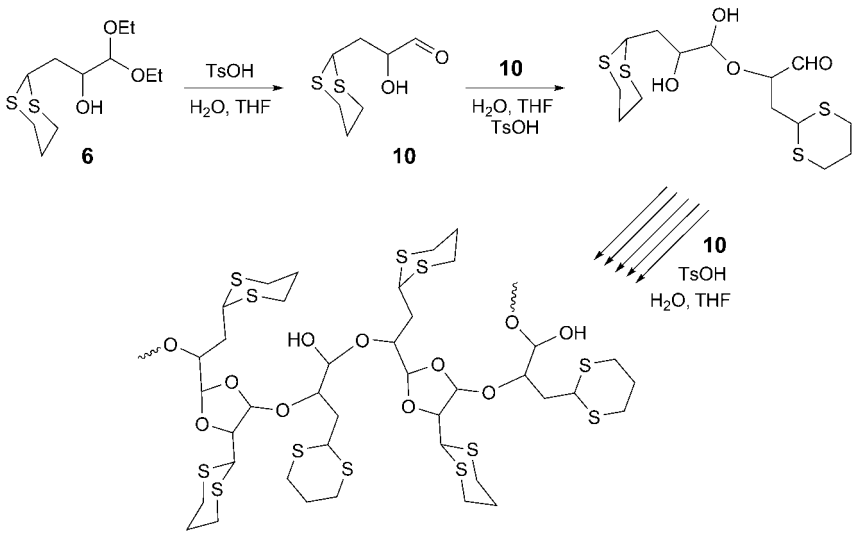
reaction was, therefore, repeated with 3 mol-equiv. of NH_2OH at 65°, and this reduced the number of products and led to formation of one main product, (1*E*,2*Z*)-3-(1,3-dithian-2-yl)-*N*,*N*′-dihydroxypropane-1,2-diimine (**9**), which was isolated in 32% yield (*Scheme 4*). The minor products were not isolated in pure form and have, therefore, not been identified. Formation of **9** is probably triggered by the reaction of **5** with NH_2OH, which gives the corresponding ketoxime and H_2O upon condensation. The H_2O then facilitates acetal deprotection and aldehyde generation under the slightly acidic conditions prevailing during the reaction, and aldoxime formation subsequently occurs and furnishes dioxime **9** as an orange solid.

Scheme 4



Deacetalization. The formation of dioxime **9** from **5** indicates that the acetal group is fairly sensitive to aqueous acidic conditions, and this turned indeed out to be the case. When **5** was mixed with acidic aqueous THF, a complex mixture was formed, from which 3-(1,3-dithian-2-yl)-2-oxopropanal, the expected product from deacetalization, could not be isolated and not any other well-defined product for that matter. Treatment of alcohol **6** under similar conditions was more successful in the sense that the compound reacted relatively quickly and afforded 3-(1,3-dithian-2-yl)-2-hydroxypropanal (**10**), the expected aldehyde, but isolation of **10** was a major problem due to polymerization (*Scheme 5*). Only a small amount of an impure sample of **10** was

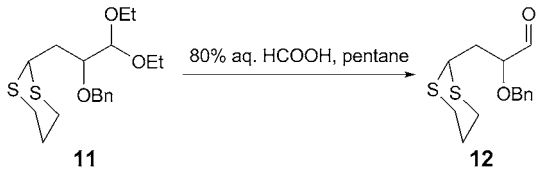
Scheme 5



isolated, and this sample did not survive because polymerization occurred quickly and gave a white solid, which was lacking aldehyde groups (the NMR signals at 9.72 and 205.7 ppm due to the CHO group in **10** disappeared) and contained mainly ether and thioether moieties, as well as OH groups according to spectroscopic data. A transformation in accordance with these observations is outlined in *Scheme 5*.

The lack of CHO groups, and the presence of ether moieties and OH groups in the polymeric material formed during the decomposition of **10** indicate that hemiacetal formation is a key step in this transformation. To avoid this destructive reaction, the OH group in **10** was protected before deacetalization was carried out. This was accomplished by benzylation under phase-transfer conditions [15], which furnished 2-(benzyloxy)-3-(1,3-dithian-2-yl)propanal diethyl acetal (**11**) in 74% yield. And indeed, when **11** was reacted with aqueous HCOOH at room temperature, the corresponding aldehyde, 2-(benzyloxy)-3-(1,3-dithian-2-yl)propanal (**12**), was formed and isolated in 94% yield (*Scheme 6*). This opens the way for chain elongation from C(1) and such transformations are currently being explored.

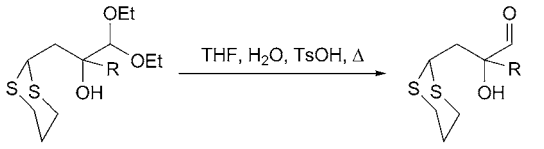
Scheme 6



11 **12**

The OH group in aldehyde **10** is secondary and should, therefore, form hemiacetals significantly more easily than tertiary alcohol moieties. It was, therefore, regarded as possible that alcohols **7a** and **7b** could remain deprotected and furnish 2-hydroxyalkanals that would be considerably more stable than **10**. To our satisfaction, this prediction turned out to be correct: when the two tertiary alcohols were reacted with H_2O in THF under acidic conditions just like **6**, the corresponding aldehydes, 2-(1,3-dithian-2-ylmethyl)-2-hydroxybutanal (**13a**) and 2-(1,3-dithian-2-ylmethyl)-2-hydroxyhexanal (**13b**), were formed in quite satisfactory yields (*Scheme 7*).

Scheme 7



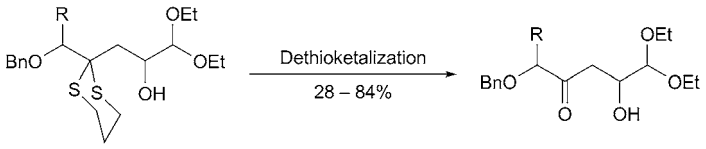
7a R = Et
7b R = Bu

13a R = Et, 66%
13b R = Bu, 99%

Dethioacetalization. Attempts were then made to regenerate the aldehyde group protected as a 1,3-dithiane. Several methods are available for this purpose, from classical heavy metal-based procedures to milder, more contemporary methods under aqueous conditions [16]. We have successfully applied methods based on MeI [17] and I_2 [18] in basic aqueous MeCN to regenerate C=O groups in high yields from

derivatives of **6** (*Scheme 8*) [9], but, when the same reagents were used to perform dethioketalization of **5** and **6**, however, the results were very disappointing: extensive decomposition took place, and some white polymeric material remained stuck to the glass wall at the top of the column when the product mixture was worked up by flash chromatography. Only small amounts of viscous organic material could be eluted, and no pure compound, only mixtures of products, were isolated. Since spectroscopic evidence established that the thioacetal group had disappeared, dethioacetalization had apparently taken place, but the resulting product, assumed to be an aldehyde, had not survived the reaction conditions. This indicates that the problems experienced are associated with the presence of an CHO group, implying that C(2) in the 1,3-dithiane motif in **5** and **6** should be disubstituted before other transformations are carried out. Investigations along this line of thinking are currently in progress.

Scheme 8



Financial support from the *Research Council of Norway*, the University of Bergen, and the *Munin Foundation* is gratefully acknowledged. Thanks are also due to Dr. *Bjarte Holmelid* for recording mass spectra, and Prof. *Victor S. Martin* for excellent working conditions during a sabbatical stay at Universidad de La Laguna, Tenerife, Spain in 2013.

Experimental Part

1. *General*. See [19]. FC, Flash chromatography; DART-MS, Direct analysis in real-time mass spectrometry.

2. *Starting Materials. 3,3,4,4-Tetraethoxybut-1-yne* (TEB; **1**) was prepared from ethyl vinyl ether in a four-step synthesis in 50% total yield according to published procedures [2][3]. Treatment of TEB with *Dowex 50W* in moist acetone gave *1,1-diethoxybut-3-yn-2-one* (**3**), which showed spectroscopic data in accordance with the literature [3]. 1,3-Dithiane **5** was prepared from *Michael* acceptor **3**, propane-1,3-dithiol, and MeONa as described in [9].

3. *3-(1,3-Dithian-2-yl)-1,1-diethoxypropan-2-ol* (**6**). *$NaBH_4$ Reduction of* **5**. Ketone **5** (1.84 g, 6.98 mmol), $NaBH_4$ (0.150 g, 3.76 mmol), THF (27 ml), and H_2O (1.0 ml) were stirred for 45 min at 0°. H_2O (9 ml) was added before most of the THF was evaporated under reduced pressure. Additional H_2O (7 ml) and CH_2Cl_2 (15 ml) were then added, and the org. phase was collected. The aq. phase was extracted with CH_2Cl_2 (3×18 ml), and the combined org. extract were dried ($MgSO_4$), filtered, and concentrated. FC (hexanes/AcOEt 4:1) afforded 1.01 g (80%) of **6** as a slightly yellow oil.

*(*S*)-Oxazaborolidine Reduction of* **5**. (*S*)-Oxazaborolidine (1.0 mmol) was dissolved in a 1.0M soln. of BH_3 in THF (6.0 ml, 6.0 mmol). The mixture was stirred, and a THF (40 ml) soln. of **5** (18 g, 68 mmol) and a 1.0M soln. of BH_3 in THF (30 ml, 30 mmol) were added simultaneously at r.t. over 50 min. Additional BH_3 soln. (20 ml, 20 mmol) was added after 2 h, and the mixture was stirred for another 2 h, before it was cooled (ice/H_2O), and the reaction was quenched with MeOH (15 ml). H_2O was added, and the hydrolyzate was extracted with CH_2Cl_2. The combined extract was dried ($MgSO_4$) and filtered. Removal of the solvent gave 17.71 g (97%) of essentially pure *3-(1,3-dithian-2-yl)-1,1-diethoxypropan-2-ol* (**6**). Colorless liquid. $[\alpha]_D^{20} = -7$ ($c = 0.01$, $CHCl_3$). IR (film): 3462*m*, 2973*s*, 2914*s*, 1424*m*, 1376*m*, 1341*m*, 1278*m*, 1132*s*, 1063*s*, 910*s*, 771*w*, 729*m*, 649*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.30 (*m*, 2 H); 3.96–

3.87 (*m*, 1 H); 3.81–3.50 (*m*, 4 H); 3.01–2.78 (*m*, 4 H); 2.49 (br. *s*, 1 H); 2.20–1.78 (*m*, 4 H); 1.23 (*t*, *J* = 7.0, 3 H); 1.22 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 104.2 (CH); 68.0 (CH); 63.2 (CH_2); 62.9 (CH_2); 43.4 (CH); 37.2 (CH_2); 30.0 (CH_2); 29.5 (CH_2); 25.8 (CH_2); 15.1 (2 Me). EI-MS: 266 (9, M^+), 220 (16), 161 (8), 133 (100), 119 (87), 103 (92), 88 (19), 75 (67), 59 (14), 47 (68). HR-MS: 266.1011 (M^+, $C_{11}H_{22}O_3S_2^+$; calc. 266.1010).

4. *Treatment of* **5** *with Organometallic Reagents. 2-(1,3-Dithian-2-ylmethyl)-1,1-diethoxybutan-2-ol* (**7a**). To ketone **5** (0.262 g, 0.991 mmol) in dry THF (2 ml), stirred under N_2, was added a 3.0M soln. of EtMgBr in Et_2O (0.74 ml, 2.2 mmol) over 5 min at r.t. The progress of the reaction was monitored by TLC. After 1.5 h at reflux, all starting material had been consumed, and the mixture had turned dark yellow. H_2O (7 ml) and CH_2Cl_2 (20 ml) were added, and the org. phase was collected. The aq. phase was then extracted with CH_2Cl_2 (3 × 10 ml), and the combined org. extract was dried ($MgSO_4$), filtered, and concentrated under vacuum. FC (hexanes/AcOEt 9:1) of the residue gave 0.189 g (64%) of **7a**. Colorless liquid. IR (ATR): 3600–3400, 2973, 2931, 2896, 2860, 1661, 1422, 1275, 1240, 1110, 1058, 909, 866, 804, 663, 646. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.36–4.33 (*m*, 2 H); 3.90–3.80 (*m*, 2 H); 3.67–3.53 (*m*, 2 H); 2.94–2.82 (*m*, 4 H); 2.76 (*s*, 1 H); 2.10–1.85 (*m*, 4 H); 1.70–1.59 (*m*, 2 H); 1.26–1.20 (*m*, 6 H); 0.94 (*t*, *J* = 8.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 107.2 (CH); 76.2 (C); 66.5 (CH_2); 66.0 (CH_2); 42.2 (CH); 39.9 (CH_2); 30.3 (CH_2); 28.8 (CH_2); 25.7(2 CH_2); 15.7 (2 Me); 14.4 (Me); 8.2 (Me). DART-MS: 265 (100, $[M + H - Et]^+$), 249 (84, $[M + H - EtO]^+$). HR-MS: 249.0990 ($[M + H - EtO]^+$, $C_{11}H_{21}O_2S_2^+$; calc. 249.0983).

2-(1,3-Dithian-2-ylmethyl)-1,1-diethoxyhexan-2-ol (**7b**). Ketone **5** (0.279 g, 1.06 mmol) and dry THF (2 ml) were charged in a dry two-necked flask kept under N_2 and cooled (−78°). BuLi (1.6M in THF, 1.55 ml, 2.42 mmol) was added dropwise over 5 min. The mixture was stirred (1.3 h), and the progress was monitored by TLC. Then, the temp. was raised to 0°, before H_2O (7 ml) and CH_2Cl_2 (15 ml) were added, and the org. phase was collected. The aq. phase was extracted with CH_2Cl_2 (3 × 10 ml), and the combined org. phases were dried ($MgSO_4$), filtered, and concentrated. FC (hexanes/AcOEt 9:1) afforded 0.144 g (42%) of **7b**. Bright-yellow oil. IR (ATR): 3600–3350, 2971, 2930, 2898, 2872, 1444, 1242, 1160, 1112, 1058, 908, 868, 814, 730, 947, 606. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.36–4.33 (*m*, 2 H); 3.91–3.78 (*m*, 2 H); 3.74–3.56 (*m*, 2 H); 2.9–2.82 (*m*, 4 H); 2.77 (*s*, 1 H); 2.09–1.84 (*m*, 4 H); 1.60–1.55 (*m*, 2 H); 1.43–1.30 (*m*, 4 H); 1.25–1.23 (*m*, 6 H); 0.92 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 107.4 (CH); 76.2 (C); 66.6 (CH_2); 66.0 (CH_2); 42.2 (CH); 40.3 (CH_2); 36.1 (CH_2); 30.2 (CH_2); 30.0 (CH_2); 25.7 (CH_2); 25.4 (CH_2); 23.5 (CH_2); 15.71 (Me); 15.65 (Me); 14.3 (Me). DART-MS: 293 (100), 277 (84), 257 (27). HR-MS: 277.1297 ($[M + H - EtO]^+$, $C_{13}O_1S_2H_{25}^+$; calc. 277.1296).

5. *Reductive Amination of* **5**. To a mixture of **5** (0.529 g, 2.00 mmol), freshly distilled THF (8.0 ml), and $PrNH_2$ (0.30 ml, 2.22 g, 3.70 mmol), stirred under N_2 at r.t., was added a soln. of $NaBH(OAc)_3$ (0.635 g, 3.00 mmol) in glacial AcOH (0.11 ml, 2.0 mmol) over 4 min. The reaction was monitored by TLC, which indicated that alcohol **6** was formed along with an additional product. More $PrNH_2$ (0.05 ml, 0.35 g, 0.60 mmol) was, therefore, added after 0.5 h, and the mixture was then stirred at r.t. for 26.5 h, before H_2O (5 ml) was added. The aq. phase was extracted with CH_2Cl_2 (3 × 15 ml), and the combined org. phases were dried ($MgSO_4$), filtered, and concentrated. FC (hexanes/AcOEt 4:1) afforded 0.347 g (57%) of N-*[3-(1,3-dithian-2-yl)-1,1-diethoxypropan-2-yl]propan-1-amine* (**8**). Bright-yellow oil. IR (ATR): 3335–3325, 2971, 2928, 2896, 1461, 1422, 1372, 1340, 1275, 1242, 1116, 1057, 908, 774, 687, 666, 579. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.42 (*d*, *J* = 5.0, 1 H); 4.29 (*t*, *J* = 6.4, 1 H); 3.80–3.65 (*m*, 2 H); 3.58–3.50 (*m*, 2 H); 2.96–2.91 (*m*, 1 H); 2.88–2.83 (*m*, 4 H); 2.67–2.58 (*m*, 2 H); 2.14–2.08 (*m*, 1 H); 2.03–1.95 (*m*, 1 H); 1.90–1.83 (*m*, 1 H); 1.83–1.73 (*m*, 1 H); 1.53 (*q*, *J* = 7.3, 2 H); 1.22 (*t*, *J* = 7.1, 6 H); 0.92 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 104.6 (CH); 63.9 (CH_2); 63.4 (CH_2); 56.6 (CH); 49.4 (CH_2); 44.6 (CH); 35.9 (CH_2); 30.3 (CH_2); 30.1 (CH_2); 26.3 (CH_2); 23.7 (CH_2); 15.6 (Me); 15.5 (Me); 11.9 (Me). DART-MS: 308 (100, $[M + H]^+$), 262 (29). HR-MS: 308.1747 ($[M + H]^+$, $C_{14}H_{30}NO_2S_2^+$; calc. 308.1718).

6. *Oxime Formation from* **5**. A mixture of **5** (0.528 g, 2.00 mmol), EtOH (7 ml), and $NH_2OH \cdot HCl$ (0.414 g, 5.96 mmol) was left stirring under reflux for 50 min. The reaction was monitored by TLC, which showed that the color changes observed were accompanied by formation of several by-products. When all the starting material had reacted (50 min), H_2O (5 ml) and CH_2Cl_2 (20 ml) were added, and the org. phase was collected. The H_2O phase was extracted with CH_2Cl_2 (3 × 10 ml), and the combined org.

extract was dried ($MgSO_4$), filtered, and concentrated. FC (hexanes/AcOEt 4:1) afforded 0.142 g (32%) of *(1E,2Z)-3-(1,3-dithian-2-yl)*-N,N'*-dihydroxypropane-1,2-diimine* (**9**), an yellow-orange solid which was recrystallized from EtOH. M.p. 175–177°. IR (ATR): 3309–3214, 3006, 2961, 2925, 2892, 2820, 1612, 1481, 1396, 1185, 1151, 1116, 1011, 959, 940, 904, 886, 866, 822, 777, 727, 703, 684, 658, 648, 625, 585. ^{1}H-NMR (200 MHz, (D_6)DMSO): 11.84 (*s*, 1 H); 11.54 (*s*, 1 H); 7.63 (*s*, 1 H); 4.43 (*t*, *J* = 7.9, 1 H); 2.97 (*d*, *J* = 7.9, 1 H); 2.87–2.75 (*m*, 4 H); 2.01–1.96 (*m*, 1 H); 1.73–1.70 (*m*, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 151.4 (C); 146.9 (CH); 42.4 (CH); 29.1 (CH_2); 28.5 (2 CH_2); 25.3 (CH_2). DART-MS: 221 (100, $[M + H]^+$). HR-MS: 221.04293 ($[M + H]^+$, $C_7H_{13}N_2O_2S_2^+$; calc. 221.04184).

7. *Benzylation of* **6**: *Formation of 2-[2-(Benzyloxy)-3,3-diethoxypropyl]-1,3-dithiane* (**11**). Alcohol **6** (16.47 g, 61.9 mmol) was mixed with CH_2Cl_2 (50 ml), BnCl (10.1 g, 80.2 mmol), and (Bu_4N)HSO_4 (1.0 g, 2.9 mmol), and 50% (*w*/*w*) aq. NaOH (30.5 g) was added, and the mixture was refluxed. Additional BnCl (5.4 g, 42.8 mmol) was added after 4 h. After a total of 23 h, the mixture was allowed to cool to r.t., and H_2O was added. Extraction was carried out with CH_2Cl_2, and the combined org. extract was dried ($MgSO_4$) and filtered. Evaporation of the solvent gave 35.42 g of a yellow liquid. The crude product was purified by FC (hexanes/AcOEt 4:1) to give 16.67 g (74%) of **11**. Slightly yellow liquid. $[\alpha]_D^{20} = -7$ (*c* = 0.033; $CHCl_3$). IR (film): 2973*s*, 2895*s*, 1449*m*, 1424*m*, 1376*m*, 1312*m*, 1278*m*, 1244*m*, 1107*s*, 1063*m*, 910*m*, 820*m*, 739*m*, 702*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36 (*m*, 5 H); 4.72 (*m*, 2 H); 4.39 (*d*, *J* = 5.7, 1 H); 4.12 (*dd*, *J* = 4.7, 5.4, 1 H); 3.82–3.48 (*m*, 5 H); 2.84–2.62 (*m*, 4 H); 2.16–1.77 (*m*, 4 H); 1.23 (*t*, *J* = 7.0, 3 H); 1.21 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 138.6 (C); 128.2 (2 CH); 128.0 (2 CH); 127.4 (CH); 104.6 (CH); 76.6 (CH); 73.6 (CH_2); 64.0 (CH_2); 63.0 (CH_2); 43.6 (CH); 36.3 (CH_2); 30.0 (CH_2); 29.5 (CH_2); 25.9 (CH_2); 15.3 (Me); 15.2 (Me). EI-MS: 356 (10, M^+); 311 (37); 256 (23); 243 (11); 219 (7); 204 (18); 178 (54); 149 (19); 119 (15); 103 (100); 91 (93); 75 (46); 65 (7). HR-MS: 356.1483 (M^+, $C_{18}H_{28}O_3S_2^+$; calc. 356.1480).

8. *Synthesis of Aldehydes* **10**, **12**, *and* **13** *by Decetalization of* **6**, **11**, *and* **7**, *Respectively. 3-(1,3-Dithian-2-yl)-2-hydroxypropanal* (**10**). To a soln. of **6** (0.538 g, 2.02 mmol) in THF (10.5 ml) and H_2O (4.5 ml) were added a few grains of TsOH (0.110 g, 0.578 mmol). The mixture was refluxed for 55 min, CH_2Cl_2 (7.5 ml) and brine (7.5 ml, 5.0 g NaCl) were added, and phase separation was followed by extraction of the aq. phase with CH_2Cl_2 (3 × 7.5 ml). The resulting combined org. extract was washed with a sat. aq. soln. of $NaHCO_3$ (15 ml), dried ($MgSO_4$), filtered, and concentrated. When the residue was mixed with a little eluent (hexanes/AcOEt 4:1) in preparation for workup by FC, a greasy polymeric material adhered to the glass wall. The viscous contents of the flask was worked up by FC (hexanes/AcOEt 4:1) and furnished 0.20 g (5.2%) of **10**. The compound polymerized before any mass spectrum could be recorded. IR (ATR): 3600–3100*s*, 2900–2800*s*, 1716*s*, 1421*s*, 1338*m*, 1275*m*, 1246*m*, 1174*m*, 1117*m*, 1070*s*, 1020*s*, 988*m*, 908*m*, 866*m*, 809*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.72 (*s*, 1 H); 4.51 (*d*, 1 H); 4.30 (*d*, 1 H); 2.99–2.82 (*m*, 6 H); 2.14–1.86 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 205.7 (CHO); 69.3 (CH); 44.0 (CH); 41.1 (CH_2); 30.2 (CH_2); 25.2 (CH_2).

2-(Benzyloxy)-3-(1,3-dithian-2-yl)propanal (**12**). To a soln. of **11** (5.3 g, 18.8 mmol) in pentane (50 ml) was added 80% aq. HCOOH (15 drops) at r.t. The mixture was stirred overnight before adding more 80% aq. HCOOH (2 ml). After a total of 6 d, the reaction was completed as judged by TLC. H_2O was added, and the mixture was extracted three times with CH_2Cl_2. Evaporation of the solvent gave 4.63 g of crude product as a yellow liquid. The crude product was purified by FC (hexanes/AcOEt 9:1) to give 3.97 g (94%) of **12**. Yellow liquid. IR (film): 3062*m*, 3030*m*, 2933*s*, 2865*s*, 2936*s*, 2717*w*, 1731*s*, 1496*m*, 1454*m*, 1422*m*, 1371*m*, 1316*w*, 1276*w*, 1242*m*, 1207*w*, 1183*w*, 1105*s*, 1052*m*, 1027*m*, 1002*m*, 909*m*, 892*w*, 869*w*, 817*w*, 774*w*, 739*s*, 699*s*, 663*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.69 (*s*, 1 H); 7.37–7.28 (*m*, 5 H); 4.72–4.55 (*m*, 2 H); 4.14–4.01 (*m*, 2 H); 2.89–2.62 (*m*, 4 H); 2.22–2.15 (*m*, 2 H); 2.12–1.78 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 202.2 (CH); 136.9 (C); 128.2 (2 CH); 127.8 (3 CH); 80.3 (CH); 72.6 (CH_2); 41.2 (CH); 35.9 (CH_2); 28.4 (CH_2); 28.2 (CH_2); 25.3 (CH_2). EI-MS: 282 (43, M^+), 253 (35), 197 (30), 191 (75), 173 (60), 163 (62), 150 (25), 145 (40), 137 (40), 132 (90), 121 (56), 117 (68), 103 (75), 92 (88), 89 (100). HR-MS: 282.0751 (M^+, $C_{14}H_{18}O_2S_2^+$; calc. 282.0748).

2-(1,3-Dithian-2-ylmethyl)-2-hydroxybutanal (**13a**). Hydroxy acetal **7a** (0.213 g, 0.723 mmol), THF (7 ml), and H_2O (3 ml) were stirred, before TsOH (0.029 g, 0.15 mmol) was added. The mixture was left under reflux for 2 h, monitoring the progress by TLC every 30 min. Brine soln. (6 ml, 2.2 g of NaCl) and CH_2Cl_2 (6 ml) were added, and the org. phase was collected. The aq. phase was extracted with additional

CH_2Cl_2 (3 × 6 ml), and the combined org. extract was treated with sat. aq. $NaHCO_3$ (10 ml). The org. phases were combined, dried ($MgSO_4$), filtered, and concentrated. FC (hexanes/AcOEt 4:1) gave 0.106 g (66%) of **13a** as a slightly yellow oil. The product crystallized after a few min. M.p. 56–58°. IR(ATR): 3580–3260 (br.), 2966*m,* 2902*s*, 2854*m*, 2835*m*, 1717*s*, 1460*m*, 1421*s*, 1352*m*, 1275*m*, 1242*w*, 1187*m*, 1123*m*, 1059*m*, 1031*s*, 982*m*, 906*s*, 863*m*, 807*s*, 730*m*, 646*m*, 627*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.60 (*s*, 1 H); 4.10–4.05 (*dd*, *J* = 4.0, 9.0, 1 H); 3.52 (*s*, 1 H); 2.89–2.86 (*m*, 2 H); 2.79–2.77 (*m*, 2 H); 2.37–2.31 (*dd*, *J* = 9.0, *J* = 16.4, 1 H); 2.20–2.15 (*dd*, *J* = 4.0, *J* = 16.4, 1 H); 2.11–2.03 (*m*, 1 H); 1.91–1.81 (*m*, 1 H); 1.71–1.65 (*q*, *J* = 7.5, 2 H); 0.87–0.79 (*t*, *J* = 7.5, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 202.8 (CHO); 80.0 (C); 42.7 (CH); 41.2 (CH_2); 30.2 (2 CH_2); 29.8 (CH_2); 25.3 (CH_2); 7.1 (Me). DART-MS: 221 (100, $[M - EtO]^+$). HR-MS: 221.0703 ($[M - EtO]^+$, $C_9H_{15}O_2S_2^+$; calc. 221.0670).

2-(1,3-Dithian-2-ylmethyl)-2-hydroxyhexanal (**13b**). Hydroxy acetal **7b** (0.266 g, 0.825 mmol), THF (9 ml), H_2O (2.7 ml), and TsOH (0.070 g, 0.37 mmol) were stirred under reflux for 1.5 h, and the reaction progress was monitored on TLC every 20 min. Brine (10 ml, 3.0 g NaCl) was added, and CH_2Cl_2 (3 × 10 ml) was used to extract the aq. phase. The combined org. phases were collected, treated with a sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), filtered, and concentrated. The crude product showed that all starting material was consumed, and an aldehyde signal was present, but since the starting material was contaminated with compound **6**, it was necessary to perform FC (hexanes/AcOEt 4:1) to afford 0.202 g (99%) of **11b**. Bright-yellow oil. IR (ATR): 3560–3280 (br.), 2954*s*, 2931*s*, 2860*s*, 2824*s*, 2727*w*, 1720*s*, 1629*w*, 1466*m*, 1422*m*, 1372*m*, 1351*m*, 1275*m*, 1241*s*, 1185*m*, 1126*m*, 1070*m*, 1044*s*, 907*s*, 863*m*, 811*s*, 729*m*, 636*m*, 607*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.60 (*s*, 1 H); 4.09–4.06 (*dd*, *J* = 4.0, 8.0, 1 H); 3.54 (*s*, 1 H); 2.89–2.86 (*m*, 2 H); 2.79–2.76 (*m*, 2 H); 2.33–2.30 (*dd*, *J* = 8.0, 16.0, 1 H); 2.20–2.16 (*dd*, *J* = 4.0, 16.0, 1 H); 2.11–2.03 (*m*, 1 H); 1.91–1.80 (*m*, 1 H); 1.65–1.59 (*dd*, *J* = 8.0, 2 H); 1.39–1.22 (*m*, 4 H); 0.90–0.86 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 203.3 (CH); 80.4 (C); 43.5 (CH_2); 41.7 (CH_2); 37.7 (CH); 30.7 (CH_2); 30.3 (CH_2); 25.8 (CH_2); 25.4 (CH_2); 23.6 (CH_2); 14.5 (Me). DART-MS: 249 (100, $[M + H]^+$). HR-MS: 249.10026 ($[M + H]^+$, $C_{11}H_{21}O_2S_2^+$; calc. 249.09830).

REFERENCES

[1] L. K. Sydnes, *Eur. J. Org. Chem*. **2000**, 3511.
[2] O. H. Kvernenes, L. K. Sydnes, *Org. Synth.* **2005**, *83*, 184.
[3] L. K. Sydnes, B. Holmelid, O. H. Kvernenes, M. Sandberg, M. Hodne, E. Bakstad, *Tetrahedron* **2007**, *63*, 4144.
[4] B. Holmelid, O. H. Kvernenes, M. Hodne, L. K. Sydnes, *Arkivoc* **2008**, *(vi)*, *26*.
[5] L. K. Sydnes, S. Valdersnes, *Pure Appl. Chem.* **2007**, *79*, 2137.
[6] L. K. Sydnes, B. Holmelid, O. H. Kvernenes, S. Valdersnes, M. Hodne, K. Boman, *Arkivoc* **2008**, *(xiv)*, 242.
[7] L. K. Sydnes, B. Holmelid, M. Sengee, M. Hanstein, *J. Org. Chem*. **2009**, *74*, 3430.
[8] M. Sengee, L. K. Sydnes, *Synthesis* **2011**, 3899.
[9] S. Valdersnes, I. Apeland, G. Flemmen, L. K. Sydnes, *Helv. Chim. Acta* **2012**, *95*, 2099.
[10] L. K. Sydnes, R. Isanov, M. Sengee, F. Livi, *Synth. Commun.* **2013**, *43*, 2898.
[11] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc*. **1987**, *109*, 5551.
[12] D. Parker, *Chem. Rev.* **1991**, *91*, 1441.
[13] H. Tavakol, S. Zakery, *Chem. Papers* **2006**, *60*, 315.
[14] A. F. Abdel-Magid, K. G. Carlson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem*. **1996**, *61*, 3849; E. M. Dangerfield, C. H. Plunkett, A. L. Win-Mason, B. L. Stocker, M. S. M. Timmer, *J. Org. Chem*. **2010**, *75*, 5470.
[15] A. I. Vogel, B. S. Furniss, 'Vogel's Textbook of Practical Organic Chemistry', 5th edn., Longman, Harlow, 1989.
[16] T. W. Greene, P. G. M. Wuts, 'Protective Groups in Organic Synthesis', 2nd edn., John Wiley & Sons, New York, 1991.
[17] A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer Jr., J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1997**, *119*, 947; A. F. Petri, S. M. Kühnert, F. Scheufler, M. E. Maier, *Synthesis* **2003**, 940.

[18] M. J. Gaunt, A. S. Jessiman, P. Orsini, H. R. Tanner, D. F. Hook, S. V. Ley, *Org. Lett.* **2003**, *5*, 4819.
[19] S. Valdersnes, L. K. Sydnes, *Eur. J. Org. Chem.* **2009**, 5816.

Received February 23, 2013