Synthetic Approaches towards the Novel 1,3-Dioxo-1,2-dithiolane Moiety in the Antitumour Antibiotic Substance Leinamycin

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A number of complementary synthetic approaches to the β-thiolactone intermediate **9** for elaboration to the novel 1,3-dioxo-1,2-dithiolane moiety **6** found in the antitumour antibiotic substance leinamycin **1** are described.

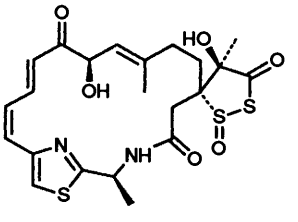
Thus, deprotection of the benzylthio ether produced from 3-methylbut-2-enoic acid and toluene-α-thiol, leads to the mercapto acid **12** which on cyclisation produces the thiolactone **13**. α-Methylation of the thiolactone **13**, followed by α-oxygenation then gives rise to the substituted β-thiolactone **9**. The β-thiolactone **9** is also produced when: (i) the sodium glycidate **17** is stirred with sodium sulfide leading to **18**, followed by thiolactonisation; (ii) thioacetone is treated with the ketene derived from 2-acetoxypropanoyl chloride; and (iii) by irradiation of 3-methyl-2-trimethylsilyloxybut-2-ene **22** with thiophosgene leading to **23**, followed by hydrolysis.

The β-thiolactone **9** is then converted in three steps into the 1,3-dioxo-1,2-dithiolane **6** by: (i) ring opening to the thioic acid **15**, using hydrogen sulfide–triethylamine; (ii) ring closure of **15** to **8** in the presence of aqueous ferric chloride; and finally (iii) oxidation using dimethyldioxirane.

Treatment of the ethyl glycidate **19** with disodium disulfide in hot ethanol for 3 days provides the 1,2-dithiolane **8** directly, but in low yields (11–15%).

When the aforementioned reaction sequences are translated to the glycidate **24**, derived from 4-methylcyclohex-3-enone and α-chloropropanoic acid, the syntheses of the key intermediates **25**, **27** and **26** *en route* to the spiro-fused 1,3-dioxo-1,2-dithiolane **7** and leinamycin **1** (see Scheme 1) were secured.

Leinamycin **1** is a new and potent antitumour antibiotic which has been isolated recently from *Streptomyces sp.*[1] The compound shows a structure based on a novel and unusual 1,3-dioxo-1,2-dithiolane ring which is spiro-fused to a thiazole containing 18-ring lactam. Although 1,2-dithiolanes, like α-lipoic acid **2**[2] and guinesine **3**,[3] and their *S*-oxides, *e.g.* asparagusic acid *S*-oxide **4**[4] and brugierol **5**[5] are not uncommon in Nature, the 1,3-dioxo-1,2-dithiolane residue **6** is unique to leinamycin. Synthetic work amongst members of this interconnected group of secondary metabolites, *i.e.* 1,2-dithiolanes and their oxides, has been limited,[6] in spite of their obvious and diverse biological potencies. As part of a program towards a total synthesis of leinamycin **1** we have examined a number of complementary routes to the 1,3-dioxo-1,2-dithiolane residue **6** embedded in this unusual structure, and also to the spiro-fused compound **7**, a key intermediate *en route* to leinamycin (see Scheme 1). The outcome of our studies in this area are summarised in this paper.[7]



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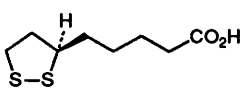

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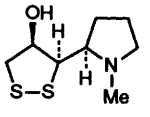

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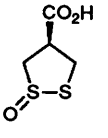

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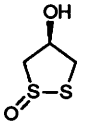

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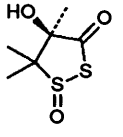
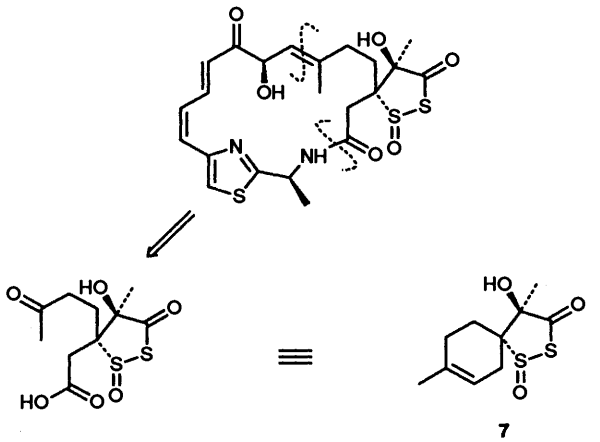


6

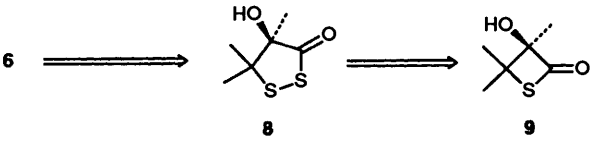
The general strategy we have followed in our synthesis of the 1,3-dioxo-1,2-dithiolane **6** relied on access to the central β-thiolactone intermediate **9**, which we planned to open and close to the 1,2-dithiolane **8** using sulfide ion followed by oxidative cyclisation (Scheme 2). A number of synthetic routes to the thiolactone **9** were therefore developed, and these will be described in turn.

Thus, in one approach to the β-thiolactone **9** we first added the elements of toluene-α-thiol to 3-methylbut-2-enoic acid **10**, producing the benzyl thioether **11**,[8] which on deprotection and cyclisation of the resulting mercapto acid **12** in the presence of isobutyl chloroformate and triethylamine[9] gave rise to the thiolactone **13** (Scheme 3). α-Methylation of the thiolactone **13**, to **14**, followed by α-oxygenation using a modified Vedejs reagent (MoO_5·py·DMPU†)[10] then provided the required substituted β-thiolactone **9**. When a solution of **9** in carbon tetrachloride saturated with hydrogen sulfide at −78 °C was treated dropwise with triethylamine[11] it was ring-opened to the corresponding mercapto thioic acid **15** which then underwent smooth oxidative cyclisation to the 1,2-dithiolane **8** on exposure to aqueous ferric chloride.[12] The synthesis of the 1,3-dioxo-1,2-dithiolane residue **6**, present in leinamycin **1**, was then completed by oxidation of the 1,2-dithiolane **8** using dimethyldioxirane.[13] Compound **6** displayed spectroscopic features which were in close agreement with those reported for

† py = pyridine; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one.

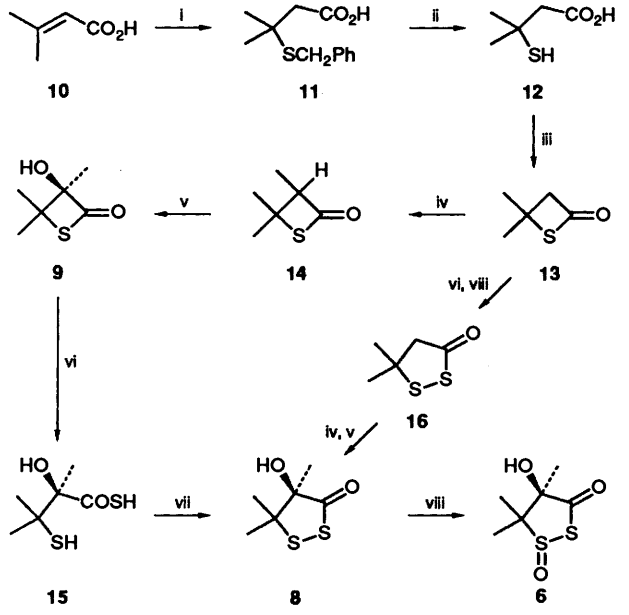


Scheme 1



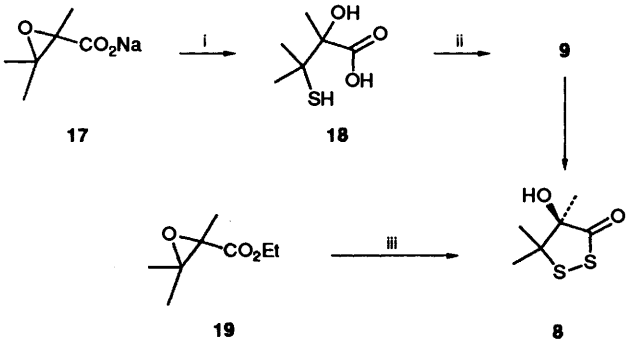
Scheme 2

the same dioxodithiolane residue in naturally derived leinamycin.* In a modification of this general approach, we found that the 1,2-dithiolane intermediate **8** could also be synthesised from the β-thiolactone **13** following conversion into **16** (using H_2S–Et_3N, then $FeCl_3$) and α-methylation/α-oxidation, as before.



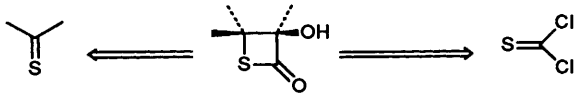
Scheme 3 *Reagents*: i, $PhCH_2SH$, piperidine; ii, Na–NH_3; iii, Bu^i-COCl, Et_3N; iv, NaH–MeI; v, KH–MoO_5·py·DMPU; vi, H_2S–Et_3N; vii, $FeCl_3$; viii, dimethyldioxirane, acetone

In a second and perhaps more direct approach to the 1,2-dithiolane **8** we found that, when the sodium glycidate **17**, derived in two steps from acetone and ethyl α-chloropropanoate, was stirred with sodium sulfide in methanol[14] at room temp. for 4 h, it underwent smooth epoxide ring-opening leading to the mercapto thioic acid **18** in 67% yield (Scheme 4). Following thiolactone **9** formation, the 1,2-dithiolane **8** was then secured from **17** in 50% overall yield. Interestingly, the same 1,2-dithiolane **8** could also be produced from the ethyl glycidate **19** in low yield (11–15%) in a 'one-pot' procedure by heating a solution of the compound in ethanol with disodium disulfide for 3 days.



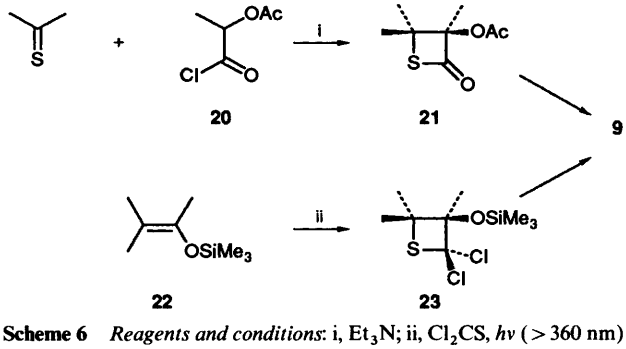
Scheme 4 *Reagents*: i, Na_2S, MeOH; ii, $NCP(O)(OEt)_2$, Et_3N; iii, Na_2S_2, heat

In a third and conceptually distinct stratagem, we have examined a route to the key β-thiolactone intermediate **9** towards **6**, based on [2 + 2]cycloadditions with both thioacetone and thiophosgene (Scheme 5).



Scheme 5

Thus, in the first of these [2 + 2]cycloaddition designs, triethylamine was introduced to a solution of thioacetone and 2-acetoxypropanoyl chloride **20** in dry dichloromethane, and the mixture was sealed and heated at 80 °C for 24 h.[15] Work-up and chromatography then gave the β-thiolactone **21**, precursor to **9**, in a modest 25% yield. In a second (photochemical) [2 + 2]cycloaddition approach[16] to **9** a solution of the trimethylsilyl enol ether **22** derived from 3-methylbutan-2-one in toluene was first irradiated at >380 nm in the presence of thiophosgene using light from a 450 W medium-pressure lamp filtered through basic 0.5 mol dm^{-3} aqueous sodium dichromate. The resulting crude, foul-smelling oil containing the α,α-dichlorothietane **23** was then treated with acid-washed silica whereupon it underwent facile hydrolysis to the β-thiolactone **9** in approximately 15% overall yield (Scheme 6).

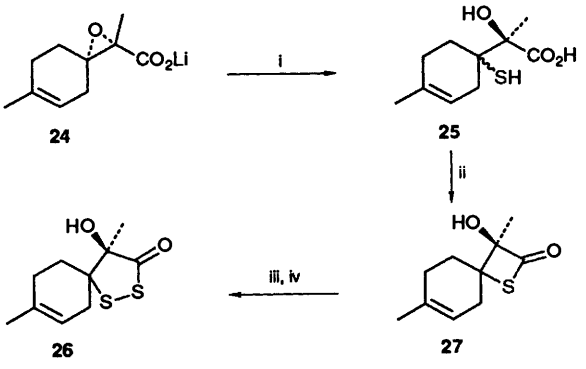


Scheme 6 *Reagents and conditions*: i, Et_3N; ii, Cl_2CS, *hν* (>360 nm)

Having evaluated the aforementioned routes to the 1,3-dioxo-1,2-dithiolane residue **6** present in leinamycin **1**, we came to the conclusion that the most practical approach to the key

* The full stereochemical detail of leinamycin has not been published. The relative stereochemistry given to the asymmetric centres, shown in **1**, is a working hypothesis, deduced from knowledge of the chirality of natural alanine in combination with energy minimisation calculations (unpublished work).

spiro-fused dithiolane compound **7**, *en route* to the natural product, was *via* the lithium glycidate **24** derived from 4-methylcyclohex-3-enone and α-chloropropanoic acid in the presence of lithium diisopropylamide. Thus, treatment of a mixture of diastereoisomers of the lithium glycidate **24** with hydrogen sulfide in the presence of titanium tetraisopropoxide first produced a 1:1 mixture of diastereoisomers of the mercapto carboxylic acid **25** which was immediately converted into a mixture of diastereoisomers of the corresponding thiolactone **27** (Scheme 7). The diastereoisomers of **27** could be easily



Scheme 7 *Reagents*: i, H_2S, $Ti(OPr^i)_4$; ii, $NCP(O)(OEt)_2$; iii, H_2S, Et_3N; iv, $FeCl_3$

separated by routine chromatography. Finally, when each diastereoisomer of **27** was treated with hydrogen sulfide–triethylamine and then aqueous ferric chloride, satisfying yields of the diastereoisomeric spiro-fused 1,2-dithiolane **26** were secured. Work is now in progress to develop this chemistry in the direction of a total synthesis of leinamycin **1**.

Experimental

For general experimental details see ref. 17. *J* Values are in Hz.

3-*Benzylthio*-3-*methylbutanoic Acid* **11**.—A mixture of 3-methylbut-2-enoic acid (10.0 g, 0.1 mol), freshly distilled toluene-α-thiol (12.4 g, 11.7 cm^3, 0.1 mol) and dry piperidine (20 cm^3) was heated under reflux for 24 h. The mixture was cooled (ice–salt bath) and then acidified with cold, dilute hydrochloric acid. The resulting suspension was extracted with diethyl ether (2 × 100 cm^3) and the combined ether extracts were then washed with saturated aqueous sodium hydrogen carbonate (3 × 100 cm^3). The aqueous washings were acidified with conc. HCl and then re-extracted with diethyl ether. The organic extracts were dried and the solvent was then evaporated under reduced pressure to leave a pale yellow oil. Distillation gave the *acid* (20.2 g, 90%) as a colourless oil, b.p. 167–170 °C (1.6 mmHg) which crystallised as white prisms, m.p. 33–35 °C (pentane) (Found: C, 64.1; H, 7.4. $C_{12}H_{16}O_2S$ requires C, 64.25; H, 7.19%); λ_{max}(EtOH)/nm 196 and 234; $\nu_{max}(CHCl_3)/cm^{-1}$ 3458, 1708 (CO), 1460, 1436, 1282, 1138 and 732; δ_H (250 MHz) 1.50 (6 H, s, 2 × CH_3), 2.65 (2 H, s, CH_2CO_2H), 3.80 (2 H, s, CH_2Ph) and 7.40 (5 H, br, ArH); δ_C(67.8 MHz) 28.6 (q), 33.3 (t), 43.6 (s), 46.9 (t), 126.9 (d), 128.5 (d), 129.0 (d), 137.5 (s) and 176.9 (s); *m/z* 224.0833 (M^+, $C_{12}H_{16}O_2S$ requires 224.0871, 4.8%), 124 (10), 123 (36), 91 (100) and 59 (27).

3-*Mercapto*-3-*methylbutanoic Acid* **12**.—The benzylthio acid **11** (11.2 g, 50 mmol) was added in one portion to a stirred aliquot of freshly distilled liquid ammonia (40 cm^3), and then finely divided sodium metal (2.3 g, 0.1 mol) was added over a period of 30 min. The solution was stirred at 25 °C for 2 h and then a stream of nitrogen was passed through the mixture to remove unchanged ammonia. The solid residue was dissolved in dilute HCl and the solution was then extracted with diethyl ether. The ether extract was washed with saturated aqueous Na_2CO_3 (3 × 20 cm^3) and the basic extracts were then acidified with conc. HCl and extracted with chloroform (3 × 30 cm^3). The combined chloroform extracts were dried, and the solvent was then removed under reduced pressure to leave a colourless oil which crystallised with time to provide the *mercapto acid* (6.4 g, 95%) as a low-melting solid, m.p. 21–24 °C; λ_{max}(EtOH)/nm 194; $\nu_{max}(CHCl_3)/cm^{-1}$ 2965, 1709 (CO), 1238, 1131 and 672; δ_H(270 MHz) 1.46 (6 H, s, 2 × CH_3), 2.28 (1 H, s, SH), 2.68 (2 H, s, CH_2CO_2H) and 11.57 (1 H, br s, CO_2H); δ_C(67.8 MHz) 32.1 (q), 41.1 (s), 50.2 (t) and 177.3 (s); *m/z* 134.0404 (M^+, $C_5H_{10}O_2S$ requires 134.0401, 20%), 116 (16), 101 (12), 75 (10) and 59 (100).

4,4-*Dimethylthietan*-2-*one* **13**.—A solution of the mercapto acid **12** (4.2 g, 31 mmol) and dry triethylamine (3.1 g, 4.3 cm^3, 31 mmol) in dry dichloromethane (50 cm^3) was stirred at −6 °C and treated dropwise with freshly distilled isobutyl chloroformate (8.47 g, 7.90 cm^3, 62 mmol). The mixture was stirred at −6 °C for a further 10 min and then diluted with dichloromethane (50 cm^3) and washed successively with cold hydrochloric acid (2 mol dm^{-3}, 4 × 20 cm^3), water (50 cm^3). The dried organic phase was evaporated under reduced pressure to leave a pale yellow oil which was distilled to give the *thietanone* (2.8 g, 79%) as a colourless oil, b.p. 30 °C (1.0 mmHg); λ_{max}(EtOH)/nm 210 and 236; ν_{max}(film)/cm^{-1} 1750, 1420, 1380, 1260, 1030 and 680; δ_H(270 MHz) 1.81 (6 H, s, 2 × CH_3) and 3.72 (2 H, s, CH_2CO); δ_C(67.8 MHz) 21.2 (q), 21.8 (q), 49.1 (t), 64.8 (s) and 202.1 (s); *m/z* 116.0312 (M^+, $C_5H_{10}O_2S$ requires 116.0296, 5%), 83 (11), 74 (27) and 56 (100).

3,4,4-*Trimethylthietan*-2-*one* **14**.—A solution of the thietanone **13** (580 g, 5 mmol) in dry tetrahydrofuran (THF) (10 cm^3) was maintained under an atmosphere of nitrogen and cooled to 0 °C (ice–salt bath). Sodium hydride (50% dispersion in mineral oil; 360 mg, 7.5 mmol) was added portionwise, and the mixture was then stirred at −20 °C for 1 h. A solution of freshly distilled methyl iodide (1.45 g, 0.64 cm^3, 10 mmol) in dry THF (5 cm^3) was added dropwise *via* a syringe, and the resulting solution was then allowed to warm to room temp. over 1 h. Ethanol (1 cm^3) was added very slowly, followed by water (10 cm^3), and the resulting turbid solution was then extracted repeatedly with diethyl ether. The ether extracts were dried and filtered, and then evaporated under reduced pressure at 0 °C to leave the thietanone (470 mg, 72%) as a sweet smelling, volatile liquid; λ_{max}(EtOH)/nm 210 and 236; ν_{max}(film)/cm^{-1} 1748, 1420, 1380, 1260, 1030 and 680; δ_H(80 MHz) 1.31 (3 H, s, CH_3), 1.38 (3 H, s, CH_3), 1.41 (3 H, d, *J* 3.2, $CHCH_3$) and 4.21 (1 H, q, *J* 3.2, $CHCH_3$). Attempts to purify the liquid by distillation or by chromatography resulted in considerable loss of material and the compound was used directly in the next stage.

3-*Hydroxy*-3,4,4-*trimethylthietan*-2-*one* **9**.—*Method* (a): *α-oxygenation of the thiolactone* **14**. A rigorously dried flask containing a nitrogen atmosphere was charged with an aliquot of potassium hydride (40% dispersion in mineral oil; 280 mg, 5 mmol) which was subsequently rendered oil-free. Dry THF (15 cm^3) was added and the resulting suspension was then cooled to −20 °C (acetonitrile–CO_2). A solution of the crude trimethylthietanone **14** (470 g, 3.6 mmol) in dry THF (5 cm^3) was added dropwise over 0.5 h and the pale yellow solution was then stirred at −20 °C for 1 h. MoO_5·Py·DMPU complex (2.2 g, 6 mol) was added as a single portion *via* a Schlenk tube, and the resulting yellow suspension was then stirred at −20 °C for 4 h before warming to room temp. Saturated aqueous NH_4Cl (20 cm^3) was added dropwise, with great care, and the mixture was then extracted with diethyl ether (3 × 15 cm^3).

The extracts were washed successively with HCl (2 mol dm^{-3}), water and brine. The combined organic extracts were dried, and the solvent was then removed under reduced pressure to leave a pale green oil. Purification by column chromatography using light petroleum–ethyl acetate (5:1) as eluent gave the *thietanone* (320 mg, 61%) as a colourless oil; λ_{max}(EtOH)/nm 214 and 240; ν_{max}($CHCl_3$)/cm^{-1} 3591 (OH), 3351, 1783 (CO), 1739 (CO), 1461, 1376, 1111, 956 and 893; δ_H(270 MHz) 1.64 (3 H, s, CH_3), 1.70 (3 H, s, CH_3), 1.80 (3 H, s, CH_3) and 3.92 (1 H, br s, OH); δ_C(67.8 MHz) 21.2 (q), 24.6 (q), 27.4 (q), 54.7 (s), 94.9 (s) and 198.8 (s); *m/z* (EI) 118.0452 ($M^+ - CO$, $C_5H_{10}OS$ requires 118.0452, 11%), 113 (19), 86 (11) and 75 (100).

Method (b): *thiolactonisation of the mercapto acid* **18**. Diethyl cyanophosphonate (815 mg, 0.75 cm^3, 5 mmol) was added dropwise over 15 min to a stirred solution of the mercapto acid **18** (820 mg, 5 mmol) in dry DMF (25 cm^3) under a nitrogen atmosphere at −20 °C, and the mixture was then stirred at −20 °C for 10 min. Freshly distilled triethylamine (505 mg, 0.7 cm^3, 5 mmol) was added dropwise, and the resulting pale green solution was stirred initially at −20 °C for 30 min and then at ambient temperature for 4 h. The mixture was diluted with ethyl acetate (50 cm^3) and benzene (50 cm^3), and then washed successively with 2 mol dm^{-3} HCl (25 cm^3), cold water (50 cm^3) and brine (50 cm^3). The separated organic phase was dried and then evaporated under reduced pressure to leave a pale yellow gum which was purified by chromatography using ethyl acetate–light petroleum (1:9) as eluent to give the thietanone (511 mg, 70%) as a colourless oil, which showed spectroscopic data which were identical with those described previously.

Method (c): *hydrolysis of the acetate* **21**. Potassium cyanide (32 mg, 0.5 mmol) was added to a stirred solution of the acetate **21** (880 mg, 5 mmol) in dioxane (2.5 cm^3) and water (2.5 cm^3), and the mixture was stirred at ambient temperature for 48 h. It was then diluted with water (20 cm^3) and extracted with diethyl ether (3 × 10 cm^3). The ether extracts were dried and evaporated under reduced pressure to leave a pale green oil which was purified by chromatography using ethyl acetate–light petroleum (1:9) as eluent to give the thietanone (700 mg, 95%) as a colourless oil, which showed spectroscopic data identical with those described previously.

Method (d): [2 + 2]*cycloaddition using thiophosgene*. A solution of 3-methyl-2-trimethylsiloxybut-2-ene[18] (7.9 g, 50 mmol) and thiophosgene (1.15 g, 0.76 cm^3, 10 mmol) in dry, degassed toluene (100 cm^3) was placed in a Pyrex photochemical reaction vessel. The cooling jacket was constantly charged with cold $Na_2Cr_2O_7$ solution (0.5 mol dm^3) containing Na_2CO_3 (10% w/w) (circulated by means of a peristaltic pump and cooled with an acetone–CO_2 bath) which served as a filter for light of wavelength <360 nm. The reaction vessel was fitted with a double surface reflux condenser and maintained under nitrogen whilst the solution was irradiated with a 450 W medium pressure Hanovia immersion lamp. Irradiation was continued for 48 h, and after this time the solvent was removed under reduced pressure to leave a dark, foul smelling oil containing the dichlorothietane **23**. The material was immediately passed down an acid-washed silica column using ethyl acetate–light petroleum (1:9) as eluent. Upon contact with the acidic silica, gas bubbles were formed, and the solvent was found to be acidic to indicator paper. The major product eluted from the column was the thietanone (222 mg, 15%), isolated as a colourless oil, which showed spectroscopic data identical with those described earlier.

2-*Hydroxy*-3-*mercapto*-2,3-*dimethylbutanethioic Acid* **15**.—A stirred solution of the thiolactone **9** (292 mg, 2 mmol) in dry carbon tetrachloride (10 cm^3) was cooled to −78 °C and then saturated with dry hydrogen sulfide gas. The mixture was stirred at −78 °C for 30 min and then freshly distilled triethylamine (404 mg, 0.66 cm^3, 4 mmol) was added dropwise *via* a syringe. The resulting solution was maintained at −78 °C, and constantly saturated with hydrogen sulfide gas for a further 7 h. Unchanged gas was expelled by bubbling a steady stream of nitrogen through the mixture for a further 1 h. The solution was washed with deionised water (3 × 15 cm^3), and the pale yellow washings were then combined and acidified to pH 2 with conc. HCl. The cloudy aqueous phase was extracted with warm chloroform (5 × 10 cm^3), and the extracts were then dried and evaporated under reduced pressure to leave the *thioic acid* (260 mg, 72%) as a foul-smelling, pale yellow viscous oil which was not purified further; λ_{max}(EtOH)/nm 205 and 227; ν_{max}($CHCl_3$)/cm^{-1} 3496, 2573, 1697 (CO), 1460, 1371, 1136, 1001, 888 and 643; δ_H(270 MHz) 1.39 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 1.92 (1 H, s, SH), 3.10 (1 H, br s, COSH) and 3.42 (1 H, br s, OH); δ_C(67.8 MHz) 21.8 (q), 27.6 (q), 28.5 (q), 52.5 (s), 83.9 (s) and 205.2 (s); *m/z* 106.0071 (EI) ($M^+ - Me_2CS$, $C_3H_6O_2S$ requires 106.0088, 4.8%), 77 (100) and 57 (18).

4-*Hydroxy*-4,5,5-*trimethyl*-1,2-*dithiolan*-3-*one* **8**.—*Method* (a): *cyclisation of the mercaptothioic* 5-*acid* **15**. An aqueous solution of iron(III) chloride (0.05 mol dm^{-3}; 10 cm^3) was added over 0.5 h to a vigorously stirred solution of the mercaptothioic acid **15** (225 mg, 1.25 mmol) in methanol at 25 °C. The mixture was stirred at ambient temperature for 1 h and the resulting orange solution was then extracted with diethyl ether (3 × 10 cm^3). The dried extracts were evaporated under reduced pressure to leave a pale yellow oil which was purified by chromatography using light petroleum–ethyl acetate (19:1) as eluent to give the *dithiolanone* (202 mg, 91%) as a colourless glassy solid, m.p. 19–22 °C; λ_{max}(EtOH)/nm 205 and 277; ν_{max}($CHCl_3$)/cm^{-1} 3543, 1693, 1458, 1370, 1340, 950 and 898; δ_H(270 MHz) 1.33 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.43 (3 H, s, CH_3) and 2.97 (1 H, br s, OH); δ_C(67.8 MHz) 18.9 (q), 22.0 (q), 22.2 (q), 57.9 (s), 83.2 (s) and 208.2 (s); *m/z* 178.0123 (M^+, $C_6H_{10}O_2S_2$ requires 178.0122, 8%), 150 (37), 86 (100), 85 (40), 71 (72) and 43 (57).

Method (b): *methylation and hydroxylation of the dithiolane* **16**. A solution of the dithiolane **16** (296 mg, 2 mmol) in dry THF (5 cm^3) was added dropwise over 15 min to an ice-cold, dry flask containing a nitrogen atmosphere and oil-free potassium hydride (40% dispersion in mineral oil; 300 mg, 3 mmol). The pale yellow solution was stirred at 0 °C for 20 min and then methyl iodide (435 mg, 0.2 cm^3, 3 mmol) was added dropwise over 10 min. The resulting clear, pale yellow solution was stirred at 0 °C for 2 h before being transferred by means of a cannula to a second dry flask containing a further equivalent of oil-free potassium hydride under a nitrogen atmosphere. The resulting dark yellow solution was maintained under an atmosphere of nitrogen and stirred at 0 °C for 30 min. The mixture was cooled to *ca.* −20 °C and MoO_5·Py·DMPU (1.1 g, 3 mmol) was then added as a single portion *via* a Schlenk tube. The resulting suspension was stirred at −20 °C for 4 h and then the cooling bath was removed and the mixture was quenched by *very* slow addition of saturated aqueous NH_4Cl (30 cm^3). The mixture was extracted with diethyl ether (3 × 10 cm^3) and the extracts were then washed successively [HCl (2 mol dm^{-3}), water, brine]. The ether solution was dried and evaporated under reduced pressure to leave a pale green oil which was purified by chromatography using light petroleum–ethyl acetate (5:1) as eluent to yield the dithiolanone (153 mg, 43%) as a glass-like solid, m.p. 17–19 °C which showed spectroscopic data which were in agreement with those recorded previously.

Method (c): *disulfuration of the glycidate* **19**. A stirred mixture of sodium sulfide nonahydrate (1.2 g, 5 mmol) and elemental sulfur (160 mg, 5 mmol) in ethanol (10 cm^3) was heated under

reflux for 1 h. The resulting deep-red solution was allowed to cool, and then added dropwise to a stirred solution of the glycidate **19** (900 mg, 5 mmol) in ethanol (10 cm^3) over a period of 10 min. The mixture was warmed to 50 °C and maintained at this temperature for 72 h. The dark mixture was cooled to 25 °C and then diluted with water (100 cm^3) and extracted with diethyl ether (5 × 20 cm^3). The ether extracts were dried and evaporated under reduced pressure to leave a brown gum which was purified by chromatography using light petroleum–ethyl acetate (9:1) as eluent to give the dithiolanone (115 mg, 13%) as a colourless glass, m.p. 19–20 °C which showed spectroscopic data identical with those obtained previously.

4-*Hydroxy*-4,5,5-*trimethyl*-1,2-*dithiolan*-3-*one* 1-*Oxide* **6**.—A freshly distilled solution of dimethyldioxirane in acetone (0.1 mol dm^{-3}; 5 cm^3), was added in one portion to a solution of the dithiolanone **8** in AnalaR acetone at room temp. The mixture was stirred at room temp. for 2 h after which the excess of acetone was removed under reduced pressure to leave a pale glass-like solid. The solid was purified by chromatography using pentane–ethyl acetate (4:1) as eluent to give the *dithiolanone* s-*oxide* (157 mg, 81%) as a colourless semi-solid, m.p. 20–24 °C, which was shown by GC to be a 1:1 mixture of diastereoisomers; λ_{max}(EtOH)/nm 195 and 214; ν_{max}($CHCl_3$)/cm^{-1} 3490, 1728 (CO), 952 (SO) and 896; δ_H(270 MHz) 1.12 and 1.20 (3 H, s, CH_3), 1.31 and 1.52 (3 H, s, CH_3), 1.55 and 1.67 (3 H, s, CH_3) and 3.02 and 4.75 (1 H, br s, OH); δ_C(67.8 MHz) 16.8 and 17.15 (q), 18.8 and 19.15 (q), 20.1 and 24.4 (q), 84.7 and 84.9 (s) and 202.4 (s); *m/z* 102.0671 (M^+ – COS, $C_5H_{10}O_2$ requires 102.0681, 4%), 91 (28), 86 (66), 85 (23), 80 (51), 71 (62) and 43 (100).

4,4-*Dimethyl*-1,2-*dithiolan*-3-*one* **16**.—A solution of the thiolactone **14** (580 mg, 5 mmol) in dry chloroform (6 cm^3) was cooled to −78 °C and a steady stream of dry H_2S gas was then bubbled through the mixture for 30 min. A solution of triethylamine (606 mg, 0.8 cm^3, 6 mmol) in chloroform (4 cm^3) was added dropwise, and the passage of H_2S was continued for a further 7 h at −78 °C. The solution was allowed to stand at room temp. for 8 h and then cold water (15 cm^3) was added. The aqueous layer was separated and then washed with chloroform. The aqueous medium was acidified with dilute HCl and then extracted with chloroform (3 × 10 cm^3). The combined chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a pale green oil. The oil was taken up in methanol (2 cm^3) and the resulting solution was stirred vigorously as a solution of iron(III) chloride (0.05 mol dm^{-3}; 200 cm^3, 10 mmol) was added dropwise over a period of *ca.* 20 min. The resulting suspension was stirred at room temp. for a further 90 min and then extracted with diethyl ether (3 × 50 cm^3). Evaporation of the dried extracts under reduced pressure left a green oil which was purified by chromatography using ethyl acetate and light petroleum (1:19) as eluent to give the dithiolanone (460 mg, 62%) as a pale green oil; λ_{max}(EtOH)/nm 221 and 275; ν_{max}($CHCl_3$)/cm^{-1} 1703 (CO), 1479, 1369, 1035, 630, 587 and 556; δ_H(270 MHz) 1.82 (6 H, s, 2 × CH_3) and 2.88 (2 H, s, CH_2); δ_C(67.8 MHz) 26.6 (q), 52.85 (s), 56.8 (t) and 205.9 (s); *m/z* 147.9962 (EI) (M^+, $C_5H_8OS_2$ requires 148.0016, 44%), 83 (100), 56 (21) and 55 (48).

Ethyl 2,3-*Epoxy*-2,3-*dimethylbutanoate* **19**.—A solution of freshly distilled ethyl 2-chloropropionate (13.6 g, 0.1 mol) in AnalaR acetone (5.8 g, 0.1 mol) was vigorously stirred under an atmosphere of nitrogen at 0–2 °C. A solution of potassium *tert*-butoxide (12.3 g, 0.11 mol) in dry THF (150 cm^3) was added dropwise to the mixture over 1.5 h and the resulting pale yellow solution was then stirred at room temp. for a further 1 h. Water (100 cm^3) was added slowly and the mixture was then extracted with diethyl ether (3 × 50 cm^3). The combined extracts were dried and evaporated under reduced pressure to leave a pale green oil which was distilled to give the *epoxide* (14.9 g, 94%) as a colourless oil, b.p. 112–115 °C (15 mmHg) (Found: C, 60.7; H, 8.95. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92%); ν_{max}(liq. film)/cm^{-1} 1750 and 1728 (CO), 1464, 1447, 1390, 1127 and 1023; δ_H(270 MHz) 1.17 (3 H, t, *J* 7, CH_3CH_2O), 1.19 (3 H, s, CH_3), 1.27 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 4.13 (2 H, q, *J* 7, OCH_2CH_3); δ_C(67.8 MHz) 14.3 (q), 16.3 (q), 19.8 (t), 20.7 (q), 61.0 (t), 62.1 (s), 63.7 (s) and 171.1 (s); *m/z* (EI) 198 (M^+, 1%), 127 (96), 99 (100) and 81 (60).

Sodium 2,3-*Epoxy*-2,3-*dimethylbutanoate* **17**.—Finely divided sodium metal (230 mg, 0.01 mol) was added portionwise to absolute ethanol (8 cm^3) at 0 °C. The ethyl ester **19** (1.98 g, 10 mmol) was added in one portion, followed by the addition of deionised water (0.18 cm^3, 10 mmol). The mixture was stirred vigorously for 12 h after which time a white gum had formed. Diethyl ether (10 cm^3) was added to the stirred gum whereupon it solidified to a white, insoluble powder. The powder was filtered off and dried *in vacuo* to give the sodium salt (1.43 g, 94%) as a brilliant white solid, m.p. 248–255 °C (decomp.).

2-*Hydroxy*-3-*mercapto*-2,3-*dimethylbutanoic Acid* **18**.—A solution of the glycidate **17** (1.14 g, 7.5 mmol) and sodium sulfide nonahydrate (2.4 g, 10 mmol) in dry methanol (30 cm^3) was stirred vigorously at room temp. for 4 h and then evaporated under reduced pressure to leave a green residue which was taken up in deionised water and acidified to pH 4 with conc. HCl. The aqueous solution was extracted with chloroform (3 × 30 cm^3) and the chloroform extracts were dried and evaporated under reduced pressure to leave an off-white gum. The gum crystallised from hexane–ethyl acetate to give the *acid* (824 mg, 67%) as white needles, m.p. 132–126 °C; λ_{max}(EtOH)/nm 196 and 234; ν_{max}($CHCl_3$)/cm^{-1} 3452 (OH), 3059, 1719 (CO), 1479, 1451, 1284, 1236, 1170, 1122 and 718; δ_H(270 MHz) 1.48 (6 H, s, 2 × CH_3), 1.52 (3 H, s, CH_3), 2.12 (1 H, s, SH) and 6.50 (2 H, br s, OH and CO_2H); δ_C(67.8 MHz) 21.33 (q), 27.63 (q), 28.0 (q), 50.1 (s), 79.7 (s) and 178.6 (s); *m/z* (EI) 164.0482 (M^+, $C_6H_{12}O_3S$ requires 164.0507, 2%), 151 (20), 113 (17), 85 (15) and 75 (100).

3,4,4-*Trimethyl*-2-*oxothietan*-3-*yl Acetate* **21**.—A solution of freshly prepared thioacetone[19] (1.85 g, 25 mmol) and 2-acetoxypropionyl chloride[20] (3.8 g, 25 mmol) in dry dichloromethane (75 cm^3) was introduced into a glass pressure reaction vessel and stirred gently as triethylamine (2.5 g, 3.5 cm^3, 25 mmol) was added immediately in one portion. The mixture was flushed rapidly with nitrogen gas and the vessel was then sealed. The dark solution was heated at 80 °C for 48 h and then cooled to 0 °C before the seal of the vessel was released. The mixture was poured onto cold water (100 cm^3) and extracted with dichloromethane (3 × 30 cm^3). The organic extracts were dried and evaporated under reduced pressure to leave a dark oil which was purified by chromatography, using light petroleum–ethyl acetate (1:9) as eluent to give the *acetate* (1.2 g, 25%) as a colourless oil; λ_{max}(EtOH)/nm 215 and 242; ν_{max}($CHCl_3$)/cm^{-1} 1753 (CO), 1744 (CO), 1373, 1105 and 961; δ_H(270 MHz) 1.81 (3 H, s, CH_3), 1.86 (3 H, s, CH_3), 1.90 (3 H, s, CH_3) and 2.19 (3 H, s, $COCH_3$); δ_C(67.8 MHz) 19.5 (q), 22.2 (q), 26.3 (q), 29.0 (q), 55.6 (s), 99.4 (s), 178.6 (s) and 191.2 (s); *m/z* (EI) 146.0454 (M^+ – H_2CO, $C_6H_{10}O_2S$ requires 146.0401, 6%), 117 (14), 113 (19), 86 (49), 75 (37) and 43 (100).

2-*Hydroxy*-2-(1-*mercapto*-4-*methylcyclohex*-3-*enyl*)*propanoic Acid* **25**.—A solution of butyllithium in hexane (2.5 mol dm^3; 20 cm^3, 50 mmol) was added dropwise *via* syringe to freshly distilled diisopropylamine (5.05 g, 50 mmol) and the resulting

gel was stirred at 0 °C for 10 min. Dry THF (150 cm^3) was added by means of a cannula, and the solution was then cooled to −80 °C. A solution of 2-chloropropanoic acid (2.71 g, 2.3 cm^3, 25 mmol) in dry THF (10 cm^3) was slowly added *via* a syringe and the resulting pale yellow mixture was then stirred at −80 °C for 5 min. A solution of 4-methylcyclohex-3-enone[21] (2.75 g, 25 mmol) in dry THF (5 cm^3) was added dropwise, and the mixture was then stirred at −80 °C for a further 5 min. The mixture was allowed to warm to 0 °C before titanium(IV) isopropoxide (14.2 g, 14.9 cm^3, 25 mmol) was added dropwise and dry hydrogen sulfide gas was bubbled through the solution for 2 h. The resulting yellow, turbid mixture was set aside at 25 °C for 8 h before water (150 cm^3) was added, and the aqueous layer was then separated and acidified with conc. HCl before extraction with ethyl acetate (3 × 50 cm^3). The organic extracts were dried and evaporated under reduced pressure to yield a pale yellow gum which was purified by chromatography using toluene–ethyl formate–acetic acid (12:6:1) as eluent to give a 1:1 mixture of diastereoisomers of the mercaptohydroxy acid (3.4 g, 63%) as a viscous oil; λ_{max}(EtOH)/nm 205.5; ν_{max}(liq. film)/cm^{-1} 3425, 1719 (CO), 1442, 1335, 1195, 1055, 917 and 732; δ_H(270 MHz) 1.46 and 1.51 (3 H, s, CH_3), 1.63 and 1.67 (3 H, d, *J* 0.35, =CCH_3), 2.19–2.36 (4 H, m, 2 × CH_2), 2.19 and 2.36 (2 H, ≈dd, *J* 2, and 0.3, CH_2CS), 5.30 and 5.45 (1 H, br s, =CH) and 6.99 (2 H, br s, CO_2H and OH); δ_C(67.8 MHz) 22.5 and 21.1 (q), 24.6 and 26.2 (q), 29.5 and 30.9 and 31.2 (t), 37.7 and 38.4 (t), 39.0 and 39.9 (t), 46.4 and 46.9 (s), 96.2 and 97.0 (s) 117.8 and 118.4 (d), 134.1 and 135.2 (s) and 169.4 and 170.2 (s).

3-*Hydroxy*-3,7-*dimethyl*-1-*thiaspiro*[3.5]*non*-6-*en*-2-*one* **27**.—A solution of the mercapto acid **25** (1.08 g, 5 mmol) in dry DMF (25 cm^3) was stirred under a nitrogen atmosphere at −20 °C. Diethyl cyanophosphonate (815 mg, 0.75 cm^3, 5 mmol) was added dropwise *via* a syringe, and the mixture was then stirred at −20 °C for 10 min. Freshly distilled triethylamine (505 mg, 0.7 cm^3, 5 mmol) was added dropwise, and the resulting pale green solution was stirred initially at −20 °C for 30 min and then at ambient temperature for 4 h. The mixture was diluted with ethyl acetate (50 cm^3) and benzene (50 cm^3), and the solution was then washed successively with HCl (2 mol dm^{-3}; 25 cm^3), cold water (50 cm^3), brine (50 cm^3). The separated organic phase was dried and evaporated under reduced pressure to leave a pale yellow gum which was purified by chromatography using ethyl acetate–light petroleum (1:9) as eluent to give a colourless oil (1:1 mixture of diastereoisomers) (703 mg, 71%); λ_{max}(EtOH)/nm 235.6; ν_{max}(liq. film)/cm^{-1} 3425, 1748 (CO), 1621, 1442, 1335, 1055, 917 and 732. Further chromatography using ethyl acetate–light petroleum (1:19) as eluent yielded: first diastereoisomer, δ_H(270 MHz) 1.49 (3 H, s, CH_3), 1.66 (3 H, d, *J* 0.35, =CCH_3), 2.19–2.36 (4 H, m, 2 × CH_2), 2.69 (2 H, ≈dd, *J* 2, 0.35, CH_2CS) and 5.15 (1 H, br s, =CH); δ_C(67.8 MHz) 22.5 (q), 24.9 (q), 30.9 (t), 38.4 (t), 84.6 (s), 99.0 (s), 119.9 (d), 136.3 (s) and 199.8 (s); and a second *diastereoisomer*, δ_H(270 MHz) 1.51 (3 H, s, CH_2), 1.68 (3 H, d, *J* 0.35, =CCH_3), 2.19–2.36 (4 H, m, 2 × CH_2), 2.72 (2 H, ≈dd, *J* 2, 0.35, CH_2CS) and 5.25 (1 H, br s, =CH); δ_C(67.8 MHz) 22.8 (q), 24.3 (q), 30.4 (t), 39.6 (t), 84.2 (s), 98.3 (s), 118.2 (d), 136.3 (s) and 198.7 (s); *m/z* (EI) 138.1019 (M^+ − COS, $C_9H_{14}O$ requires 138.1044, 6%), 95 (43) and 43 (100).

4-*Hydroxy*-4,8-*dimethyl*-1,2-*dithiaspiro*[4.5]*dec*-7-*en*-3-*one* **26**.—A stirred solution of the thiolactone **27** (1:1 mixture of diastereoisomers) (495 mg, 2.5 mmol) in dry carbon tetrachloride (20 cm^3) was cooled to −78 °C, and then saturated with dry hydrogen sulfide gas. The mixture was stirred at −78 °C for 30 min and then freshly distilled triethylamine (250 mg, 0.35 cm^3, 0.35 mmol) was added dropwise. The solution was maintained at −78 °C and constantly saturated with hydrogen sulfide gas for a further 7 h. Unchanged hydrogen sulfide was then expelled by bubbling a steady stream of nitrogen through the mixture for a further 1 h. The solution was washed with deionised water (3 × 10 cm^3), and the pale yellow washings were then combined and acidified to pH 2 with conc. HCl. The now cloudy aqueous phase was extracted with warm chloroform (5 × 10 cm^3), and the extracts were then dried and evaporated under reduced pressure to leave 2-hydroxy-2-(1-mercapto-4-methylcyclohex-3-enyl)propanethioic acid (400 mg, 69%) as a foul-smelling, pale yellow viscous oil which was used directly in the next reaction.

A solution of the mercapto thioic acid (400 mg, 1.7 mmol) in methanol (2 cm^3) was stirred vigorously and treated in a dropwise fashion over 1 h with iron(III) chloride solution (0.05 mol dm^{-3}; 30 cm^3) and then stirred at ambient temperature for 1 h. The resulting orange solution was extracted with diethyl ether (3 × 10 cm^3), and the extracts were then dried and evaporated under reduced pressure to leave a pale yellow oil. The oil was purified by chromatography using light petroleum and ethyl acetate (19:1) as eluent to give the spiro-dithiolane (344 mg, 88%) as a colourless oil; λ_{max}(EtOH)/nm 235.6 and 279; ν_{max}(liq. film)/cm^{-1} 3425, 1712 (CO), 1621, 1442, 1335, 1055, 917 and 548; δ_H(270 MHz) 1.58 (3 H, s, CH_3), 1.74 (3 H, d, *J* 0.35, CH_3), 1.78–1.90 (2 H, m, 2 × CH_2), 2.09 (2 H, ≈dd, *J* 2, 0.3, CH_2CS) and 5.22 (1 H, br s, =CH); δ_C(67.8 MHz) 22.5 (q), 24.9 (q), 30.9 (t), 38.4 (t), 66.7 (s), 92.1 (s), 119.9 (d), 136.3 (s) and 199.8 (s).

The second *diastereoisomer* (prepared from **27** in exactly the same manner) showed δ_H(270 MHz) 1.61 (3 H, s, CH_3), 1.76 (3 H, d, *J* 0.35, CH_3), 1.78–1.90 (4 H, m, 2 × CH_2), 2.10 (4 H, ≈dd, *J* 2, 0.3, CH_2CS) and 5.25 (1 H, br s, =CH); δ_C(67.8 MHz) 22.8 (q), 24.3 (q), 30.4 (t), 39.6 (t), 65.2 (s), 94.6 (s), 118.2 (d), 136.3 (s) and 198.7 (s); *m/z* (EI) 164.0825 [$M^+ - 2(H_2S)$, $C_{10}H_{12}O_2$ requires 164.0837, 22%], 151 (15), 135 (33), 85 (31) and 64 (100).

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