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Xanthates derived from 1,3-dithiane and its monosulfoxide; one-carbon radical equivalents

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Dedicated with respect and admiration to Professor Dieter Seebach, recipient of last year's Tetrahedron Prize

Abstract—The behaviour and synthetic scope of the C-2 centred radicals derived from 1,3-dithiane and 1,3-dithiane 1-oxide have been studied. Both radicals are available from the corresponding xanthates and have proved suitable substrates for the xanthate transfer reaction. However, the synthetic scope of the former is severely limited by the fact that it does not add to unactivated olefins. The latter on the other hand is a more promising radical precursor and undergoes smooth radical addition to a wide range of alkenes. Furthermore, subsequent transformations of some of the radical adducts confirm its utility as a synthetic equivalent of both the methyl and the formyl radical.

1. Introduction

Over the past few decades, dithioacetals have become common intermediates in organic synthesis. They are widely used as protecting groups for carbonyl compounds and provide a powerful method to make the normally electrophilic carbonyl carbon behave as a nucleophile.[1,2] The first reagent of this type that found general use was 1,3-dithiane, which on lithiation provides a powerful nucleophilic acyl equivalent that reacts with a wide range of alkyl halides, carbonyl compounds and other electrophilic reagents.[3] On the other hand, when halogenated, it provides an electrophilic acyl equivalent that is reactive towards a variety of carbon and heteroatom nucleophiles.[4,5]

Bearing these results in mind, it may be anticipated that the C-2 centred radical derived from 1,3-dithiane represents an interesting synthetic equivalent of the formyl radical and other one-carbon radicals, such as methyl and carboxyl. Despite its promising synthetic potential, however, the radical chemistry of 1,3-dithiane and derivatives has remained relatively unexplored and hence offers an interesting opportunity to further extend the synthetic scope of this heterocycle.[6–13]

Our approach is summarised in Scheme 1 and relies on a radical process that has been thoroughly developed over the past few years by our laboratory and is commonly referred to as the xanthate transfer reaction.[14–16] In contrast with other common radical processes, this method is characterised by the fact that the major competing pathway is degenerate. As a consequence, the intermediate radicals acquire an extended effective lifetime and are able to interact with a variety of relatively unreactive traps. Accordingly, the radical derived from xanthate **1** is expected to react with olefins **2** to give radical adducts **3**. The latter can then be further manipulated using established 1,3-dithiane chemistry, such as hydrolysis (path A), reduction (path B), or alkylation, followed by hydrolysis (path C) or reduction (path D). In this paper, we provide a full account of the progress that we have made while studying the subject.

2. Results and discussion

In order to access xanthate **1**, we relied on a procedure that was developed in the late 1970s by Kruse et al.[4,5] This procedure aims at transforming 1,3-dithiane into its 2-chlorinated derivative which is subsequently trapped by a suitable nucleophile. Thus, treatment of commercially available 1,3-dithiane **4** with sulfuryl chloride, followed directly by slow addition of the resulting 2-chloro-1,3-dithiane **5** to a solution of potassium *O*-ethyl xanthate in acetone gave **1** in quantitative yield (Scheme 2). This two-step-one-pot procedure turned out to be an effective and reliable method to prepare large quantities of **1**.

Subsequent attempts to use **1** in some intermolecular radical

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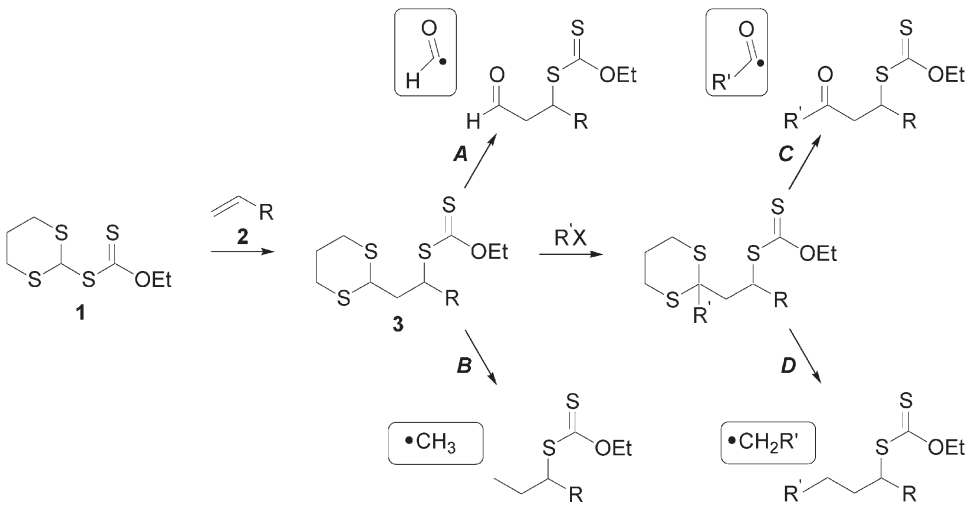
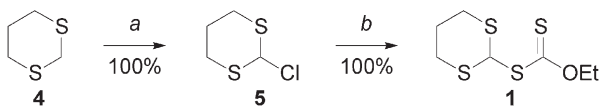


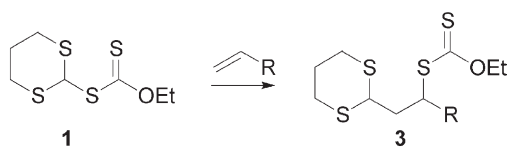
Scheme 1. Radical addition of xanthate **1** to olefins **2** and some of the conceivable transformations of the resulting radical adducts **3**.

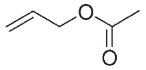
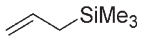
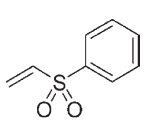
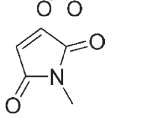


Scheme 2. Reagents and conditions: (a) SO_2Cl_2 (1.05 equiv.), dry $CHCl_3$, −40 °C→rt; (b) $EtOC(S)S^-$, K^+ (1.1 equiv.), acetone, −10 °C→rt.

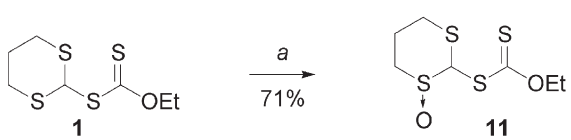
additions under standard reaction conditions gave disappointing results (Table 1, entries a–c). For example, when heating **1** with 2 equiv. of either allyl acetate **6**, or allyltrimethyl-silane **7** in refluxing 1,2-dichloroethane in the presence of lauroyl peroxide (DLP), no reaction was observed, despite the fact that 0.3 equiv. of initiator had been added. Similar results were obtained when phenylvinyl-sulfone **8** was used as olefin. Although in this case, some reaction took place, no radical adduct could be detected in the crude reaction product and a considerable amount of **1** was still present, despite the fact that 0.8 equiv. of DLP had been added. Slightly discouraged by these results, we were relieved to confirm that **1** is nonetheless a valid radical precursor, by trapping the corresponding radical with *N*-methyl maleimide **9** (Table 1, entry d). Thus, heating **1** with 2 equiv. of **9** in refluxing 1,2-dichloroethane afforded the expected radical adduct **10** in 52% yield after addition of 0.25 equiv. of initiator.

Table 1. Radical addition of xanthate **1**



Entry	Olefin		Radical adduct (%)
a		**6**	—
b		**7**	—
c		**8**	—
d		**9**	**10** (52)

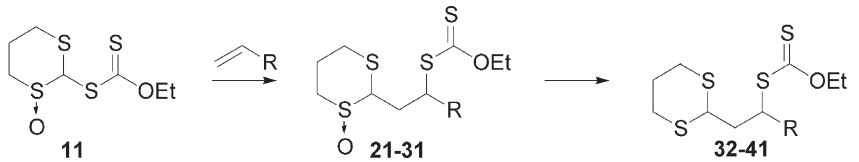
These results suggest that the radical derived from **1** is relatively electron-rich and needs highly activated traps in order to undergo efficient radical addition. It is interesting to note that Byers et al. made similar observations when they studied the photolytic addition of 2-phenylseleno-1,3-dithiane.[9] This reaction was successful only when electron-deficient alkenes were employed. In order to change the electronic properties of **1** and to achieve reversed reactivity, we decided to transform **1** into the corresponding monosulfoxide **11** (Scheme 3). As opposed to the radical derived from **1**, the radical derived from **11** is susceptible to take benefit from the captodative effect. Introduced in the late 1970s by Viehe et al. this concept states that the combined action of an electron-withdrawing and an electron-releasing substituent on a radical centre leads to enhanced stabilisation.[17] Selective oxidation was achieved by slow addition of 1 equiv. of *m*CPBA to a solution of **1** in dichloromethane. Under these conditions **11** was obtained in 71% yield as a solid 10:11 mixture of separable diastereomers. Although the isomers were isolated for identification purposes, the mixture was used as such in subsequent radical reactions, because of the fact that both diastereomers give rise to the same radical.

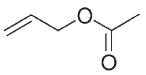
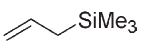
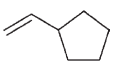
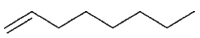
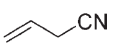
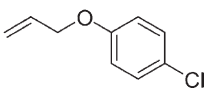
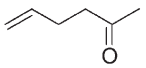
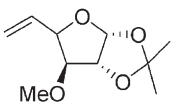
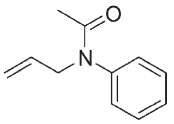
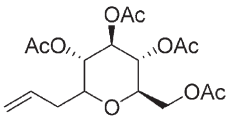
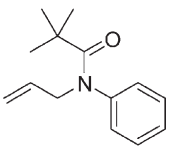


Scheme 3. Reagents and conditions: (a) *m*CPBA (1.06 equiv.), CH_2Cl_2, 0 °C→rt.

To our delight, **11** turned out to be a much more promising radical precursor than **1**, as is reflected by the fact that it underwent smooth radical addition to a wide range of alkenes (Table 2, entries a–k). The corresponding radical adducts **21**–**31** were normally obtained in reasonably good yields (60–75%), although some exceptions were observed

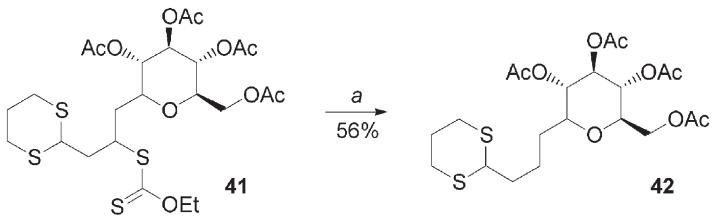
Table 2. Radical addition of xanthate **11**



Entry	Olefin		DLP (equiv.)	**21**–**31** (%)	**32**–**41** (%)
a		**6**	0.45	**21** (70)	**32** (63)
b		**7**	0.30	**22** (75)	**33** (88)
c		**12**	0.45	**23** (56 (63[a]))	**34** (67)
d		**13**	0.35	**24** (69)	**35** (69)
e		**14**	0.85	**25** (32)	**36** (89)
f		**15**	0.50	**26** (69)	**37** (77)
g		**16**	0.80	**27** (34)	**38** (66)
h		**17**	0.45	**28** (66 (72[a]))	**39** (67)
i		**18**	0.55	**29** (75)	**40** (77)
j		**19**	0.75	**30** (39)	**41** (60)
k		**20**	0.65	**31** (61)	[b]

[a] Yield based on recovered starting material.
[b] Radical adduct **31** was not reduced, but characterised after cyclisation and subsequent reduction.

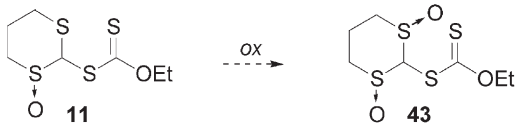
(Table 2, entries e, g, and j). The radical reaction proceeds under mild conditions and tolerates various functional groups commonly encountered in organic synthesis. It is worth noting that **11** displays a behaviour that is slightly different from that observed for most other xanthates.[14] Although it added correctly to most alkenes tested, its radical additions needed significantly more than catalytic quantities of peroxide to reach completion. In some cases (entries i and k), trace amounts of cylised reaction product were detected (TLC analysis), implying that some of the initiator had been used for rearomatisation purposes. For the other cases, the reason for this deviant behaviour is not fully understood. Another difficulty stems from the fact that **11** contains two non-fixed stereocenters and that a third stereocenter is created in a non-controlled way during the radical process. As a consequence, all reaction products **21**–**31** were obtained as complicated mixtures of diastereomers. Although several attempts have been made to characterise each isomer separately, it was judged much more convenient to subject the mixture to reductive conditions, which would considerably facilitate the task of characterisation since two stereocenters are removed in a single reaction step. Among several available methods for the transformation of sulfoxides into sulfides,[18–21] the use of trifluoroacetic anhydride and sodium iodide in dry acetone proved particularly suitable for our purpose.[18] This method allowed rapid reduction of sulfoxides **21**–**31** under mild conditions and gave the corresponding dithianes **32**–**41** in good yields (63–89%) after purification by flash chromatography on silica gel (Table 2, entries a–j). Dithiane **41** (Table 2, entry j) was obtained as an inseparable mixture of diastereomers and had to be further reduced in



Scheme 4. Reagents and conditions: (a) $(Me_3Si)_3SiH$ (2 equiv.), AIBN (cat.), heptane, reflux.

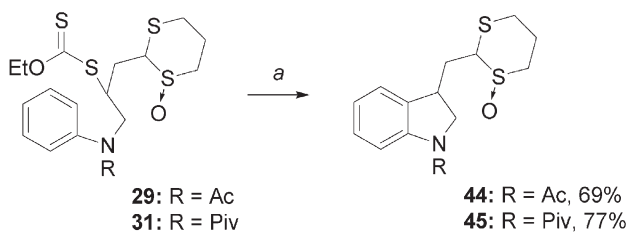
order to allow its full characterisation. Although other methods are available,[22] clean reduction was achieved by exposing **41** to 2 equiv. of tris(trimethylsilyl)silane and a small amount of AIBN in refluxing heptane, which afforded **42** in 56% yield (Scheme 4).

The difficulties related to moderate reactivity and stereochemical complexity may be overcome by transforming **11** into a symmetric and more electrophilic derivative. The most convenient way to do so seems to be the oxidation of **11** to the corresponding bis-sulfoxide **43** (Scheme 5). Initial attempts to carry out this transformation have revealed that the xanthate and the endocyclic sulfide show comparable reactivity toward most common oxidising agents and selective oxidation has become a challenge that we are still addressing.



Scheme 5. Transformation of **11** into the corresponding bis-sulfoxide **43**.

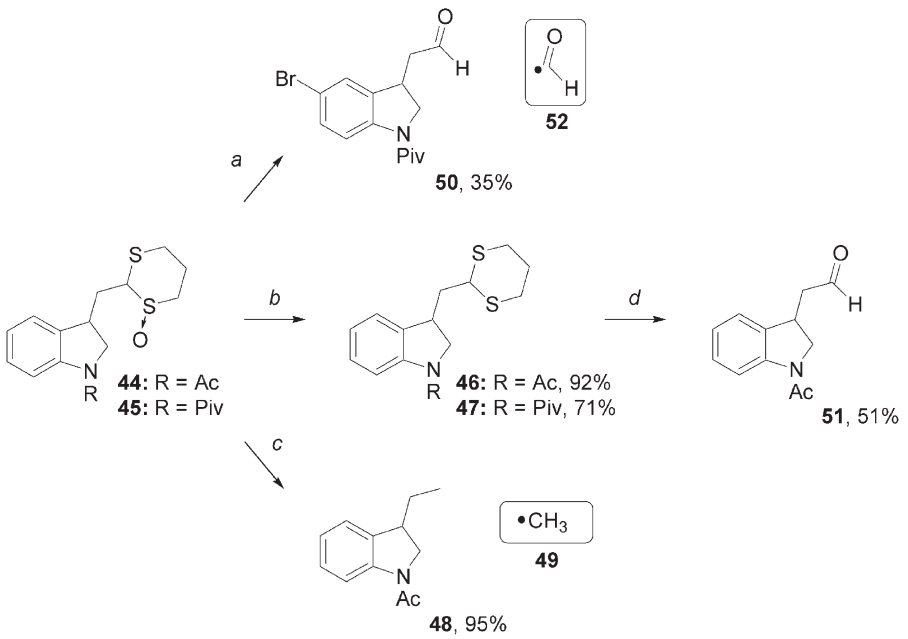
One of the major assets of the xanthate transfer reaction is that its reaction products still contain the xanthate. At this stage it may either serve to allow access to other functional groups or be used in a second radical transformation.[23–25] In order to exemplify the latter, we exposed adducts **29** and **31** to stoichiometric amounts of DLP in refluxing 1,2-dichloroethane (Scheme 6). In both cases, the reaction proceeded as expected and cyclisation onto the aromatic ring provided indolines **44** and **45** in 69 and 77% yield, respectively. As was the case for radical adducts **21**–**31**, both reaction products were obtained as complicated mixtures of diastereomers and had to be reduced as discussed previously in order to be fully characterised (Scheme 7).



Scheme 6. Reagents and conditions: (a) DLP (1.1–1.3 equiv.), 1,2-dichloroethane, reflux; (b) trifluoroacetic anhydride (2.4–2.6 equiv.), NaI (2.4 equiv.), dry acetone, 0 °C→rt.

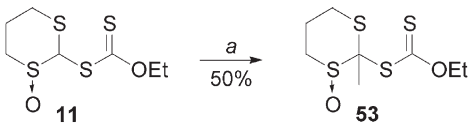
In order to validate our approach (Scheme 1), we next turned our attention to exploring some of the chemistry of the 1,3-dithiane 1-oxide moiety. For example, clean and efficient desulphurisation was achieved by treating **44** with excess Raney nickel in refluxing ethanol (Scheme 7). Inspection of the way **48** has been obtained reveals that the overall sequence is equivalent to the addition of a methyl radical **49** to **18**. Methyl radicals are reactive intermediates and it is worth noting that their generation and clean capture by unactivated olefins is not generally feasible. As is the case for 1,3-dithianes, 1,3-dithiane 1-oxides represent masked carbonyl compounds and are expected to undergo deprotection upon hydrolysis. Inspection of the literature reveals that 1,3-dithiane 1-oxides are most commonly hydrolysed by treatment with aqueous solutions of NBS.[26] Indeed, hydrolysis was achieved by treating **45** with excess NBS (8 equiv.) in aqueous acetone, but in modest yield and not without brominating the aromatic ring (Scheme 7). Attempts to achieve better selectivity by using less NBS and performing the reaction at lower temperature were only moderately successful. The best results were obtained by using 4 equiv. of NBS and carrying out the reaction at −20 °C. In this case, **50** was obtained in 15% yield along with an equimolar amount of its non-brominated derivative. When other reagents such as aqueous solutions of methyl iodide, Dess–Martin periodinane,[27] trifluoroacetic anhydride,[28] or bis(trifluoroacetoxy)iodobenzene[29] were used, no hydrolysis at all was observed. Clean hydrolysis was finally achieved by way of a two-step procedure. Thus, reduction of **44** followed by alkylative hydrolysis of the intermediate 1,3-dithiane **46**, gave the expected reaction product **51** in 47% overall yield (Scheme 7). These results led us to conclude that **11** is a valid synthetic equivalent of the formyl radical **52**.

In order to further extend the synthetic scope of **11**, we decided to attempt the alkylation of the 1,3-dithiane 1-oxide moiety present in indoline **45**. When followed by successful hydrolysis to give the corresponding ketone (similar to Scheme 1, path C), **11** provides a useful synthetic equivalent of acyl radicals. Furthermore, when followed by successful desulphurisation, **11** provides a synthetic equivalent of primary alkyl radicals (similar to Scheme 1, path D). Compared to the case of 1,3-dithianes, literature examples of successful alkylation of 1,3-dithiane 1-oxides are relatively scarce.[30–35] According to Carey et al. metalation of 2-substituted 1,3-dithiane 1-oxides is best carried out with lithium diisopropylamide (LDA).[32] However, when **45** was exposed to an equimolar amount of LDA, followed by excess methyl iodide, no alkylation was observed and most of the starting material was recovered unreacted. Inversion of the order of events, involving alkylation of **11** instead of **45**, seemed to be more promising. Thus, treatment of **11** with an equimolar amount of LDA and excess methyl iodide afforded the expected reaction product **53** as a 1:5 mixture



Scheme 7. Reagents and conditions: (a) NBS (8.3 equiv.), aqueous acetone, 0 °C; (b) trifluoroacetic anhydride (2.4–2.6 equiv.), NaI (2.4 equiv.), dry acetone, 0 °C→rt; (c) W2 Ra-Ni (excess), abs. EtOH, reflux; (d) MeI (50 equiv.), CH_2Cl_2, aqueous acetone, 45 °C.

of separable diastereomers in 50% yield (unoptimised) (Scheme 8). Unfortunately, **53** did not behave as expected when heated with 2 equiv. of **18** in refluxing 1,2-dichloroethane in the presence of DLP. Although some reaction took place, no radical adduct could be detected in the crude reaction product and a small amount of **53** was still present, despite the fact that 1.0 equiv. of DLP had been added at the end of the reaction. The reason for this failure is not clear, although it may be anticipated that the presence of the electron-releasing methyl group partially cancels the effect that the electron-withdrawing sulfoxide has on the reactivity of the corresponding radical.



Scheme 8. Reagents and conditions: (a) LDA (1.1 equiv.), MeI (2.4 equiv.), dry THF, −78 °C→rt.

3. Conclusion

In contrast with its anionic and cationic counterparts, the C-2 centred radical derived from 1,3-dithiane has revealed itself as being of rather limited synthetic scope. The corresponding monosulfoxide on the other hand has proved more useful. It is a suitable substrate for the xanthate transfer reaction and as such adds to a wide range of unactivated alkenes under mild, neutral conditions that are compatible with most functional groups encountered in modern organic synthesis. Furthermore, subsequent transformations of some of the radical adducts confirmed its utility as a synthetic equivalent of both the methyl and the formyl radical. Finally, we believe that the results presented in this paper justify the statement that our xanthate-based methodology allows considerable broadening of the synthetic scope of 1,3-dithiane chemistry and nicely complements the well-established ionic chemistry of this class of compounds.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercial sources and used as supplied or purified using standard methods. Silica gel 60 Å C.C. 40-63 (SDS) was used for flash chromatography. TLC analysis was done on silica gel 60 F_{254} TLC plates (Merck). Petroleum ether refers to the fractions with bp 40–60 °C. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 instrument. ^1H and ^{13}C chemical shifts are given with respect to the solvent as internal standard. IR spectra were measured on a Perkin–Elmer FT 1600 as solutions in CCl_4. Low resolution mass spectra were recorded at a HP 5989B mass spectrometer. Microanalyses were carried out by the microanalytical laboratory of the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette.

4.1.1. Dithiocarbonic acid *S*-[1,3]dithian-2-yl ester *O*-ethyl ester (1). A solution of 1,3-dithiane **4** (12.1 g, 100 mmol) in dry $CHCl_3$ (250 mL) was cooled to −40 °C under a nitrogen atmosphere, before dropwise addition of a solution of freshly distilled sulfuryl chloride (8.4 mL, 105 mmol) in dry $CHCl_3$ (50 mL). The yellow suspension thus obtained was allowed to warm to room temperature. The initially formed precipitate went into solution and the resulting orange solution was slowly transferred to a cooled (−10 °C) solution of dithiocarbonic acid *O*-ethyl ester potassium salt (17.6 g, 110 mmol) in acetone (250 mL). The yellow suspension thus obtained was stirred at −10 °C for another 60 min before being warmed to room temperature. The precipitate was removed by filtration and the resulting yellow solution was concentrated under reduced pressure

before addition of Et_2O (250 mL). The organic phase was extracted with water (2×150 mL), washed with brine (1×100 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded **1** (23.9 g, 100%) as a yellow oil which was sufficiently pure to be used directly in the next step. Analytical samples and samples appropriate for radical reactions were obtained by recrystallisation (petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 2.01–2.12 (m, 1H), 2.15–2.22 (m, 1H), 2.73–2.79 (m, 2H), 3.23 (ddd, J=2.8, 11.8, 14.2 Hz, 2H), 4.67 (q, J=7.2 Hz, 2H), 5.65 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.66 (CH_3), 25.01 (CH_2), 26.72 (2×CH_2), 49.84 (CH), 70.12 (CH_2), 211.07 (C=S) ppm. IR (CCl_4): 2985, 2955, 2939, 2904, 1442, 1432, 1424, 1414, 1388, 1363, 1292, 1280, 1229, 1148, 1111, 1045 cm^{-1}. MS (CI/NH_3): 119 (M−$C_3H_5OS_2$), 241 (MH^+), 258 (MNH_4^+). Anal. calcd C, 34.97; H, 5.03; found C, 35.48; H, 5.16.

4.1.2. Dithiocarbonic acid *S*-(4-[1,3]dithian-2-yl-1-methyl-2,5-dioxo-pyrrolidin-3-yl) ester *O*-ethyl ester (10). A solution of **1** (158 mg, 0.657 mmol) and **9** (148 mg, 1.33 mmol) in 1,2-dichloro-ethane (1.0 mL) was refluxed for 30 min DLP (0.05 equiv.) was then added and additional DLP (0.025 equiv.) was added every 90 min until complete consumption of **1**. After addition of 0.25 equiv. of DLP the mixture was cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (Et_2O–petroleum ether, 30:70 to 50:50 v/v) to afford **10** (104 mg, 52%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (t, J=7.2 Hz, 3H), 1.77–1.88 (m, 1H), 2.10–2.17 (m, 1H), 2.87–2.91 (m, 2H), 2.99 (ddd, J=2.4, 12.4, 14.4 Hz, 2H), 3.09 (s, 3H), 3.58 (dd, J=3.6, 5.6 Hz, 1H), 4.32 (d, J=5.6 Hz, 1H), 4.57 (q, J=7.2 Hz, 2H), 4.84 (d, J=3.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.48 (CH_3), 24.66 (CH_2), 25.57 (CH_3), 30.01 (CH_2), 30.95 (CH_2), 46.64 (CH), 47.04 (CH), 51.77 (CH), 172.37 (C=O), 173.52 (C=O), 209.12 (C=S) ppm. IR (CCl_4): 2940, 2903, 1790, 1719, 1432, 1379, 1288, 1240, 1222, 1198, 1176, 1118, 1113, 1054 cm^{-1}. MS (CI/NH_3): 352 (MH^+), 369 (MNH_4^+). Anal. calcd C, 41.00; H, 4.87; found C, 41.49; H, 5.01.

4.1.3. Dithiocarbonic acid *O*-ethyl ester *S*-(1-oxo-1λ^4-[1,3]dithian-2-yl) ester (11). A solution of **1** (23.9 g, 100 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 °C under a nitrogen atmosphere, before dropwise addition of a solution of *m*CPBA (24.9 g, 106 mmol) in CH_2Cl_2 (225 mL). The white suspension thus obtained was stirred at 0 °C for another 60 min before being warmed to room temperature. The mixture was then extracted with a saturated solution of $NaHCO_3$ (3×200 mL), washed with brine (1×150 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded crude **11** (24.8 g, 97%) as an orange oil. Purification was carried out in two steps. Flash chromatography on silica gel (Et_2O–petroleum ether, 25:75 v/v to Et_2O–EtOAc, 25:75 v/v) yielded nearly pure reaction product, which was further purified by recrystallisation (EtOAc–petroleum ether, 9:10 v/v) to afford **11** (18.4 g, 71%) as a solid 10:11 mixture (NMR analysis) of separable diastereomers. Analytical samples of both isomers were obtained by flash chromatography on silica gel (Et_2O–EtOAc, 60:40 v/v).

Less polar isomer (*major*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 2.24–2.35 (m, 1H), 2.38–2.45 (m, 1H), 2.51 (dt, J=3.6, 14.4 Hz, 1H), 2.74 (ddd, J=2.8, 12.0, 14.4 Hz, 1H), 2.84 (dt, J=3.2, 12.8 Hz, 1H), 3.08–3.13 (m, 1H), 4.70 (dq, J=1.2, 7.2 Hz, 2H), 6.13 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.76 (CH_3), 25.62 (CH_2), 27.99 (CH_2), 48.74 (CH_2), 66.22 (CH), 71.60 (CH_2), 208.78 (C=S) ppm. IR (CCl_4): 2985, 2957, 2939, 2911, 2866, 2844, 1462, 1436, 1425, 1415, 1388, 1365, 1292, 1243, 1181, 1150, 1111, 1089, 1073, 1043 cm^{-1}. MS (CI/NH_3): 257 (MH^+), 274 (MNH_4^+).

More polar isomer (*minor*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 1.79–1.86 (m, 1H), 2.52–2.57 (m, 1H), 2.60–2.71 (m, 1H), 2.88 (ddd, J=2.4, 11.6, 14.0 Hz, 1H), 2.90–2.95 (m, 1H), 3.04 (ddd, J=2.8, 12.0, 14.8 Hz, 1H), 4.68 (q, J=7.2 Hz, 2H), 5.54 (brs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.75 (CH_3), 15.65 (CH_2), 25.98 (CH_2), 43.35 (CH_2), 63.04 (CH), 71.60, 207.62 (C=S) ppm. IR (CCl_4): 2985, 2958, 2940, 2910, 2870, 1471, 1460, 1442, 1425, 1406, 1388, 1365, 1293, 1241, 1150, 1110, 1077, 1040 cm^{-1}. MS (CI/NH_3): 257 (MH^+), 274 (MNH_4^+).

4.2. Radical addition of (11). General procedure

A solution of **11** (1.0 equiv.) and olefin (1.2–3.0 equiv.) in 1,2-dichloro–ethane (1.0 mL/mmol of **11**) was refluxed for 15 min DLP (0.1 equiv.) was then added and additional DLP (0.1 equiv.) was added every 90 min until complete consumption of **11**. The mixture was then cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the reaction products as complicated mixtures of diastereomers that were used as such in the next reaction step.

4.2.1. Acetic acid 2-ethoxythiocarbonylsulfanyl-3-(1-oxo-1λ^4-[1,3]dithian-2-yl)-propyl ester (21). The reaction was carried out with a solution of **11** (125 mg, 0.49 mmol) and **6** (0.16 mL, 1.5 mmol) and needed 0.45 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O, then MeOH–EtOAc, 5:95 v/v) afforded **21** (121 mg, 70%).

4.2.2. Dithiocarbonic acid *O*-ethyl ester *S*-[2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-1-trimethylsilanylmethyl-ethyl] ester (22). The reaction was carried out with a solution of **11** (262 mg, 1.0 mmol) and **7** (0.48 mL, 3.0 mmol) and needed 0.30 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then Et_2O–EtOAc, 80:20 to 40:60 v/v) afforded **22** (282 mg, 75%).

4.2.3. Dithiocarbonic acid *S*-[1-cyclopentyl-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (23). The reaction was carried out with a solution of **11** (257 mg, 1.0 mmol) and **12** (288, 3.0 mmol) and needed 0.45 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then

Et_2O–EtOAc, 60:40 to 0:100 v/v, then MeOH–EtOAc, 5:95 v/v) afforded **23** (150 mg, 56%).

4.2.4. Dithiocarbonic acid *O*-ethyl ester *S*-[1-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-heptyl] ester (24). The reaction was carried out with a solution of **11** (254 mg, 0.99 mmol) and **13** (0.47 mL, 3.0 mmol) and needed 0.35 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then Et_2O–EtOAc, 80:20 to 40:60 v/v) afforded **24** (252 mg, 69%).

4.2.5. Dithiocarbonic acid *S*-[2-cyano-1-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-ethyl] ester *O*-ethyl ester (25). The reaction was carried out with a solution of **11** (255 mg, 1.0 mmol) and **14** (0.24 mL, 3.0 mmol) and needed 0.85 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O, then MeOH–EtOAc, 0:100 to 10:90 v/v) afforded **25** (105 mg, 32%).

4.2.6. Dithiocarbonic acid *S*-[1-(4-chloro-phenoxymethyl)-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (26). The reaction was carried out with a solution of **11** (254 mg, 0.99 mmol) and **15** (338 mg, 2.0 mmol) and needed 0.50 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then Et_2O–EtOAc, 85:15 to 20:80 v/v) afforded **26** (291 mg, 69%).

4.2.7. Dithiocarbonic acid *O*-ethyl ester *S*-[4-oxo-1-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-pentyl] ester (27). The reaction was carried out with a solution of **11** (256 mg, 1.0 mmol) and **16** (0.35 mL, 3.0 mmol) and needed 0.80 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 3:97 to 10:90 v/v) afforded **27** (119 mg, 34%).

4.2.8. Dithiocarbonic acid *O*-ethyl ester *S*-[1-(6-methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester (28). The reaction was carried out with a solution of **11** (259 mg, 1.0 mmol) and **17** (398, 2.0 mmol) and needed 0.45 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 0:100 to 5:95 v/v) afforded **28** (300 mg, 66%).

4.2.9. Dithiocarbonic acid *S*-[1-[(acetyl-phenyl-amino)-methyl]-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (29). The reaction was carried out with a solution of **11** (437 mg, 1.71 mmol) and **18** (600 mg, 3.43 mmol) and needed 0.55 equiv. of DLP to go to completion. Flash chromatography on silica gel (MeOH–EtOAc, 0:100 to 10:90 v/v) afforded **29** (557 mg, 75%).

4.2.10. Acetic acid 3,5-diacetoxy-2-acetoxymethyl-6-[2-ethoxythiocarbonylsulfanyl-3-(1-oxo-1λ^4-[1,3]dithian-2-yl)-propyl]-tetrahydro-pyran-4-yl ester (30). The reaction was carried out with a solution of **11** (59 mg, 0.23 mmol) and **19** (104, 0.28 mmol) and needed 0.75 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 4:96 v/v) afforded **30** (55 mg, 39%).

4.2.11. Dithiocarbonic acid *S*-[1-{[(2,2-dimethyl-propionyl)-phenyl-amino]-methyl}-2-(1-oxo-1λ^4-[1,3]dithian-2-yl)-ethyl] ester *O*-ethyl ester (31). The reaction was carried out with a solution of **11** (256 mg, 1.0 mmol) and **20** (439, 2.0 mmol) and needed 0.65 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 0:100 to 5:95 v/v) afforded **31** (288 mg, 61%).

4.3. Reduction of radical adducts (21)–(31). General procedure

A solution of sulfoxide (1.0 equiv.) and NaI (2.4 equiv.) in dry acetone (5.2 mL/mmol of sulfoxide) was cooled to 0 °C before dropwise addition of a solution of TFAA (2.4–2.6 equiv.) in dry acetone (2.0 mL/mmol TFAA). The red brown solution thus obtained was allowed to warm to room temperature and diluted with Et_2O. The mixture was extracted twice with a saturated solution of $Na_2S_2O_3$, washed once with water, and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified as specified below.

4.3.1. Acetic acid 3-[1,3]dithian-2-yl-2-ethoxythiocarbonylsulfanyl-propyl ester (32). The reaction was carried out with **21** (99 mg, 0.28 mmol), TFAA (0.10 mL, 0.73 mmol), and NaI (102 mg, 0.67 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 15:185 to 10:90 v/v) afforded **32** (60 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.45 (t, J=7.2 Hz, 3H), 1.85–1.95 (m, 1H), 2.05–2.25 (m, 3H), 2.09 (s, 3H), 2.85–2.90 (m, 4H), 4.17 (dd, J=6.0, 9.2 Hz, 1H), 4.22–4.28 (m, 2H), 4.34–4.39 (m, 1H), 4.66 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.67 (CH_3), 20.74 (CH_3), 25.66 (CH_2), 29.67 (CH_2), 29.91 (CH_2), 35.77 (CH_2), 43.92 (CH), 46.00 (CH), 65.07 (CH_2), 70.25 (CH_2), 170.56 (C=O), 211.98 (C=S) ppm. IR (CCl_4): 2984, 2939, 2902, 1749, 1462, 1441, 1423, 1380, 1362, 1227, 1112, 1051 cm^{-1}. MS (CI/NH_3): 341 (MH^+), 358 (MNH_4^+).

4.3.2. Dithiocarbonic acid *S*-(2-[1,3]dithian-2-yl-1-trimethylsilanylmethyl-ethyl) ester *O*-ethyl ester (33). The reaction was carried out with **22** (111 mg, 0.30 mmol), TFAA (0.11 mL, 0.78 mmol), and NaI (109 mg, 0.72 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 2:98 v/v) afforded **33** (93 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=0.10 (s, 9H), 1.07 (dd, J=8.4, 14.8 Hz, 1H), 1.18 (dd, J=6.8, 14.8 Hz, 1H), 1.44 (t, J=7.2 Hz, 3H), 1.84–1.94 (m, 1H), 2.03 (ddd, J=5.6, 8.4, 14.4 Hz, 1H), 2.09–2.16 (m, 2H), 2.81–2.92 (m, 4H), 4.04–4.11 (m, 1H), 4.15 (dd, J=5.6, 8.4 Hz, 1H), 4.61–4.69 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=−0.69 (3×CH_3), 13.77 (CH_3), 23.29 (CH_2), 25.76 (CH_2), 29.94 (CH_2), 30.08 (CH_2), 41.99 (CH_2), 44.63 (CH), 45.42 (CH), 69.62 (CH_2), 213.51 (C=S) ppm. IR (CCl_4): 2956, 2900, 1423, 1276, 1250, 1216, 1111, 1051 cm^{-1}. MS (CI/NH_3): 233 ($MH^+-C_3H_6OS_2$), 355 (MH^+). Anal. calcd C, 44.02; H, 7.39; found C, 44.13; H, 7.35.

4.3.3. Dithiocarbonic acid *S*-(1-cyclopentyl-2-[1,3]dithian-2-yl-ethyl) ester *O*-ethyl ester (34). The

reaction was carried out with **23** (72 mg, 0.20 mmol), TFAA (74 μL, 0.52 mmol), and NaI (72 mg, 0.48 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 2:98 v/v) afforded **34** (45 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22–1.39 (m, 2H), 1.43 (t, J=7.2 Hz, 3H), 1.47–1.68 (m, 4H), 1.75–1.92 (m, 3H), 2.01–2.15 (m, 3H), 2.19–2.29 (m, 1H), 2.82–2.92 (m, 4H), 4.09–4.14 (m, 1H), 4.17 (dd, J=5.6, 8.8 Hz, 1H), 4.64 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73 (CH_3), 25.23 (CH_2), 25.48 (CH_2), 25.78 (CH_2), 29.57 (CH_2), 29.78 (CH_2), 30.05 (CH_2), 30.29 (CH_2), 39.18 (CH_2), 43.78 (CH), 44.43 (CH), 52.55(CH), 69.90 (CH_2), 213.99 (C=S) ppm. IR (CCl_4): 2955, 2903, 2869, 1433, 1424, 1387, 1362, 1292, 1276, 1216, 1145, 1112, 1051 cm^{-1}. MS (CI/NH_3): 337 (MH^+). Anal. calcd C, 49.96; H, 7.19; found C, 49.64; H, 7.16.

4.3.4. Dithiocarbonic acid *S*-(1-[1,3]dithian-2-ylmethyl-heptyl) ester *O*-ethyl ester (35). The reaction was carried out with **24** (89 mg, 0.24 mmol), TFAA (90 μL, 0.63 mmol), and NaI (87 mg, 0.58 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 3:197 v/v) afforded **35** (58 mg, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.4 Hz, 3H), 1.22–1.51 (m, 8H), 1.44 (t, J=7.2 Hz, 3H), 1.65–1.76 (m, 2H), 1.85–1.95 (m, 1H), 2.04–2.16 (m, 3H), 2.82–2.92 (m, 4H), 3.95–4.02 (m, 1H), 4.16 (t, J=7.6 Hz, 1H), 4.66 (dq, J=2.0, 7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.74 (CH_3), 14.00 (CH_3), 22.48 (CH_2), 25.77 (CH_2), 26.50 (CH_2), 28.93 (CH_2), 29.86 (CH_2), 29.99 (CH_2), 31.56 (CH_2), 34.07 (CH_2), 39.29 (CH_2), 44.42 (CH), 47.82 (CH), 69.76 (CH_2), 213.59 (C=S) ppm. IR (CCl_4): 2957, 2929, 2857, 2359, 1458, 1424, 1379, 1276, 1218, 1145, 1112, 1052 cm^{-1}. MS (CI/NH_3): 353 (MH^+), 370 (MNH_4^+). Anal. calcd C, 51.09; H, 8.00; found C, 50.92; H, 8.05.

4.3.5. Dithiocarbonic acid *S*-(2-cyano-1-[1,3]dithian-2-ylmethyl-ethyl) ester *O*-ethyl ester (36). The reaction was carried out with **25** (100 mg, 0.31 mmol), TFAA (0.11 mL, 0.81 mmol), and NaI (112 mg, 0.74 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 10:90 to 20:80 v/v) afforded **36** (85 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.45 (t, J=7.2 Hz, 3H), 1.88–1.98 (m, 1H), 2.09–2.16 (m, 1H), 2.28 (ddd, J=2.8, 6.8, 8.8 Hz, 2H), 2.81–3.04 (m, 6H), 4.14 (dd, J=6.4, 8.4 Hz, 1H), 4.16–4.23 (m, 1H), 4.67 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.69 (CH_3), 23.63 (CH_2), 25.52 (CH_2), 29.28 (CH_2), 29.56 (CH_2), 37.18 (CH_2), 43.33 (CH), 43.44 (CH), 70.58 (CH_2), 116.76 (CN), 211.29 (C=S) ppm. IR (CCl_4): 2984, 2938, 2903, 2250, 1423, 1363, 1292, 1276, 1231, 1148, 1112, 1052 cm^{-1}. MS (CI/NH_3): 308 (MH^+), 325 (MNH_4^+). Anal. calcd C, 42.96; H, 5.57; found C, 42.82; H, 5.57.

4.3.6. Dithiocarbonic acid *S*-[1-(4-chloro-phenoxymethyl)-2-[1,3]dithian-2-yl-ethyl] ester *O*-ethyl ester (37). The reaction was carried out with **26** (128 mg, 0.30 mmol), TFAA (0.11 mL, 0.78 mmol), and NaI (110 mg, 0.73 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 2:98 v/v) afforded **37** (95 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43 (t, J=7.2 Hz, 3H), 1.87–1.96 (m, 1H), 2.10–2.15 (m, 1H), 2.20 (ddd, J=6.0, 9.2, 14.8 Hz, 1H), 2.44 (ddd, J=5.6, 9.2, 14.8 Hz, 1H), 2.81–2.89 (m, 4H), 4.09 (dd, J=6.4, 10.0 Hz, 1H), 4.18 (dd, J=5.6, 8.8 Hz, 1H), 4.27 (dd, J=3.6, 9.6 Hz, 1H), 4.36–4.43 (m, 1H), 4.66 (q, J=7.2 Hz), 6.86 (d, J=9.2 Hz, 2H), 7.24 (d, J=9.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.73 (CH_3), 25.69 (CH_2), 29.52 (CH_2), 29.79 (CH_2), 35.68 (CH_2), 43.98 (CH), 46.70 (CH), 69.31 (CH_2), 70.27 (CH_2), 115.91 (CH), 126.02 (C), 129.26 (CH), 156.84 (C), 212.62 (C=S) ppm. IR (CCl_4): 2978, 2935, 2901, 2867, 1597, 1583, 1492, 1464, 1424, 1381, 1276, 1240, 1170, 1148, 1112, 1094, 1052 cm^{-1}. MS (CI/NH_3): 406 (M^+-H_2, $C_{16}H_{21}^{35}ClO_3S_4$), 408 ($M^+-H_2$, $C_{16}H_{21}^{37}ClO_3S_4$), 409 ($MH^+$, $C_{16}H_{21}^{35}ClO_3S_4$), 411 ($MH^+$, $C_{16}H_{21}^{37}ClO_3S_4$), 426 ($MNH_4^+$, $C_{16}H_{21}^{35}ClO_3S_4$), 428 ($MNH_4^+$, $C_{16}H_{21}^{37}ClO_3S_4$). Anal. calcd C, 46.98; H, 5.17; found C, 46.61; H, 5.21.

4.3.7. Dithiocarbonic acid *S*-(1-[1,3]dithian-2-ylmethyl-4-oxo-pentyl) ester *O*-ethyl ester (38). The reaction was carried out with **27** (119 mg, 0.34 mmol), TFAA (0.12 mL, 0.87 mmol), and NaI (121 mg, 0.81 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 0:100 to 15:85 v/v) afforded **38** (76 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.44 (t, J=7.2 Hz, 3H), 1.82–1.93 (m, 2H), 2.00–2.19 (m, 4H), 2.17 (s, 3H), 2.64 (t, J=8.0 Hz, 2H), 2.84–2.92 (m, 4H), 3.95–4.02 (m, 1H), 4.16 (t, J=7.6 Hz, 1H), 4.65 (q, J=7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.70 (CH_3), 25.68 (CH_2), 27.57 (CH_2), 29.81 (CH_2), 29.89 (CH_2), 30.00 (CH_3), 39.77 (CH_2), 40.57 (CH_2), 44.18 (CH), 47.36 (CH), 70.08 (CH_2), 208.34 (C=O), 212.96 (C=S) ppm. IR (CCl_4): 2984, 2937, 2902, 1721, 1442, 1423, 1367, 1276, 1217, 1162, 1112, 1050 cm^{-1}. MS (CI/NH_3): 339 (MH^+), 356 (MNH_4^+). Anal. calcd C, 46.12; H, 6.55; found C, 46.36; H, 6.55.

4.3.8. Dithiocarbonic acid *S*-[2-[1,3]dithian-2-yl-1-(6-methoxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*]-[1,3]dioxol-5-yl)-ethyl] ester *O*-ethyl ester (39). The reaction was carried out with **28** (135 mg, 0.30 mmol), TFAA (0.11 mL, 0.77 mmol), and NaI (113 mg, 0.75 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 13:87 to 20:80 v/v) afforded **39** (88 mg, 67%) as a 8:5 mixture (NMR analysis) of separable diastereoisomers.

Less polar isomer (*major*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.32 (s, 3H), 1.44 (t, J=7.2 Hz, 3H), 1.48 (s, 3H), 1.86–1.96 (m, 1H), 2.04–2.12 (m, 1H), 2.25 (ddd, J=4.8, 9.6, 14.8 Hz, 1H), 2.53 (ddd, J=4.0, 10.0, 14.4 Hz), 2.72–2.92 (m, 4H), 3.38 (s, 3H), 3.79 (d, J=3.2 Hz, 1H), 4.15–4.21 9M, 2H), 4.44 (dd, J=3.2, 8.8 Hz, 1H), 4.54 (d, J=3.6 Hz, 1H), 4.62–4.70 (m, 2H), 5.91 (d, J=3.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.74 (CH_3), 25.76 (CH_2), 26.15 (CH_3), 26.74 (CH_3), 28.78 (CH_2), 29.20 (CH_2), 36.98 (CH_2), 43.80 (CH), 45.96 (CH), 57.75 (CH_3), 70.05 (CH_2), 81.02 (2×CH), 84.26 (CH), 105.15 (CH), 111.59 (C), 212.43 (C=S) ppm. IR (CCl_4): 2989, 2934, 2901, 2830,

1454, 1443, 1423, 1382, 1373, 1293, 1275, 1220, 1164, 1113, 1082, 1052, 1021 cm^{-1}. MS (CI/NH_3): 441 (MH^+).

More polar isomer (*minor*). ^1H NMR (400 MHz, $CDCl_3$): δ=1.32 (s, 3H), 1.43 (t, J=7.2 Hz, 3H), 1.48 (s, 3H), 1.84–1.93 (m, 1H), 2.05–2.13 (m, 2H), 2.30–2.37 (m, 1H), 2.75–2.92 (m, 4H), 3.41 (s, 3H), 3.79 (d, J=3.2 Hz), 4.18 (dd, J=4.0, 10.0 Hz, 1H), 4.40–4.51 (m, 2H), 4.57 (d, J=3.6 Hz, 1H), 4.66 (q, J=7.2 Hz, 2H), 5.92 (d, J=3.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.72 (CH_3), 25.77 (CH_2), 26.23 (CH_3), 26.80 (CH_3), 29.30 (CH_2), 29.89 (CH_2), 34.90 (CH_2), 44.24 (CH), 46.39 (CH), 57.56 (CH_3), 70.02 (CH_2), 79.81 (CH), 81.06 (CH), 84.69 (CH), 104.97 (CH), 111.61 (C), 212.77 (C=S) ppm. IR (CCl_4): 2990, 2933, 2830, 2359, 1454, 1423, 1382, 1373, 1294, 1276, 1220, 1165, 1110, 1081, 1053 cm^{-1}. MS (CI/NH_3): 441 (MH^+).

4.3.9. Dithiocarbonic acid *S*-{1-[(acetyl-phenyl-amino)-methyl]-2-[1,3]dithian-2-yl-ethyl} ester *O*-ethyl ester (40). The reaction was carried out with **29** (272 mg, 0.63 mmol), TFAA (0.21 mL, 1.5 mmol), and NaI (227 mg, 1.5 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 25:75 v/v) afforded **40** (203 mg, 77%).

^1H NMR (400 MHz, $CDCl_3$): δ=1.21 (t, J=7.2 Hz, 3H), 1.81–1.90 (m, 4H), 1.99–2.13 (m, 2H), 2.23 (ddd, J=4.0, 10.8, 14.8 Hz, 1H), 2.78–2.91 (m, 4H), 3.61 (dd, J=5.6, 13.6 Hz, 1H), 3.92–4.00 (m, 1H), 4.19 (dd, J=4.0, 10.8 Hz, 1H), 4.40–4.49 (m, 3H), 7.23–7.25 (m, 2H), 7.35–7.38 (m, 1H), 7.42–7.45 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.41 (CH_3), 22.64 (CH_3), 25.75 (CH_2), 29.92 (CH_2), 30.28 (CH_2), 35.94 (CH_2), 44.50 (CH), 45.47 (CH), 51.02 (CH_2), 69.84 (CH_2), 128. 17 (CH), 128.30 (CH), 129.69 (CH), 142.01 (C), 170.89 (C=O), 212.12 (C=S) ppm. IR (CCl_4): 3066, 3038, 2984, 2937, 2902, 1668, 1596, 1496, 1472, 1452, 1433, 1424, 1414, 1389, 1364, 1288, 1276, 1219, 1112, 1052 cm^{-1}. MS (CI/NH_3): 416 (MH^+), 433 (MNH_4^+).

4.3.10. Acetic acid 3,5-diacetoxy-2-acetoxymethyl-6-(3-[1,3]dithian-2-yl-2-ethoxythiocarbonylsulfanyl-propyl)-tetrahydro-pyran-4-yl ester (41). The reaction was carried out with **30** (55 mg, 0.088 mmol), TFAA (33 μL, 0.23 mmol), and NaI (33 mg, 0.22 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 30:70 v/v) afforded **41** (32 mg, 60%) as a liquid 10:13 mixture (NMR analysis) of inseparable diastereoisomers.

IR (CCl_4): 2953, 2902, 1756, 1432, 1367, 1276, 1220, 1146, 1112, 1051 cm^{-1}. MS (CI/NH_3): 613 (MH^+), 630 (MNH_4^+).

4.3.11. Acetic acid 3,5-diacetoxy-2-acetoxymethyl-6-(3-[1,3]dithian-2-yl-propyl)-tetrahydro-pyran-4-yl ester (42). A solution of **41** (31 mg, 0.051 mmol) and tris(trimethylsilyl) silane (31 μL, 0.10 mmol) in heptane (1 mL) was refluxed for 15 min before addition of a few crystals of AIBN. The solution was kept at reflux temperature and stirred for another 2 h before it was cooled to room temperature. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc–petroleum ether, 27:73 v/v) to afford **42** (14 mg, 56%) as a slightly yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ=1.45–1.54 (m, 2H), 1.66–1.91 (m, 5H), 2.03 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.10–2.17 (m, 1H), 2.11 (s, 3H), 2.80–2.93 (m, 4H), 3.82 (ddd, J=2.4, 5.2, 9.2 Hz, 1H), 4.04–4.11 (m, 2H), 4.16 (ddd, J=3.6, 5.6, 11.2 Hz, 1H), 4.23 (d, J=5.2, 12.0 Hz, 1H), 4.97 (t, J=9.2 Hz, 1H), 5.07 (d, J=5.6, 9.2 Hz, 1H), 5.31 (t, J=9.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 20.76 (CH_3), 20.81 (CH_3), 20.84 (CH_3), 20.90 (CH_3), 22.19 (CH_2), 25.02 (CH_2), 26.00 (CH_2), 30.48 (2×CH_2), 35.00 (CH_2), 47.27 (CH), 62.37 (CH_2), 68.76 (CH), 68.86 (CH), 70.43 (CH), 70.48 (CH), 72.47 (CH), 169.65 (C=O), 169.76 (C=O), 170.30 (C=O), 170.86 (C=O) ppm. IR (CCl_4): 2952, 2902, 2831, 1757, 1455, 1424, 1367, 1226, 1099, 1065, 1031 cm^{-1}. MS (CI/NH_3): 494 (MH^+), 511 (MNH_4^+).

4.4. Radical cyclisation of adducts (29) and (31). General procedure

A solution of cyclisation precursor in 1,2-dichloro-ethane (10 mL/mmol of cyclisation precursor) was refluxed for 15 min DLP (0.1 equiv.) was then added and additional DLP (0.1 equiv.) was added every 90 min until complete consumption of starting material. The mixture was then cooled to room temperature and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the reaction products as complicated mixtures of diastereomers that were used as such in the next reaction step.

4.4.1. 1-[3-(1-Oxo-1λ^4-[1,3]dithian-2-ylmethyl)-2,3-dihydro-indol-1-yl]-ethanone (44). The reaction was carried out with a solution of **29** (638 mg, 1.48 mmol) and needed 1.1 equiv. of DLP to go to completion. Flash chromatography on silica gel (MeOH–EtOAc, 0:100 to 25:75 v/v) afforded **44** (310 mg, 69%).

4.4.2. 2,2-Dimethyl-1-[3-(1-oxo-1λ^4-[1,3]dithian-2-ylmethyl)-2,3-dihydro-indol-1-yl]-propan-1-one (45). The reaction was carried out with a solution of **31** (3.1 g, 6.4 mmol) and needed 1.3 equiv. of DLP to go to completion. Flash chromatography on silica gel (Et_2O–petroleum ether, 50:50 v/v, then MeOH–EtOAc, 5:95 to 10:90 v/v) afforded **45** (1.7 g, 77%).

4.5. Reduction of cyclisation products (44)–(45). General procedure

A solution of sulfoxide (1.0 equiv.) and NaI (2.4 equiv.) in dry acetone (5.2 mL/mmol of sulfoxide) was cooled to 0 °C before dropwise addition of a solution of TFAA (2.4–2.6 equiv.) in dry acetone (2.0 mL/mmol TFAA). The red brown solution thus obtained was allowed to warm to room temperature and diluted with Et_2O. The mixture was extracted twice with a saturated solution of $Na_2S_2O_3$, washed once with water, and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified as specified below.

4.5.1. 1-(3-[1,3]Dithian-2-ylmethyl-2,3-dihydro-indol-1-yl)-ethanone (46). The reaction was carried out with **44** (464 mg, 1.5 mmol), TFAA (0.51 mL, 3.6 mmol), and NaI

(540 mg, 3.6 mmol). Recrystallisation of the crude reaction product from acetone afforded **46** (404 mg, 92%).

Major conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.82–2.04 (m, 2H), 2.14–2.26 (m, 2H), 2.24 (s, 3H), 2.84–2.98 (m, 4H), 3.70–3.78 (m, 2H), 4.14 (t, *J*=6.8 Hz, 1H), 4.23 (t, *J*=8.8 Hz, 1H), 7.04 (t, *J*=7.2 Hz, 1H), 7.19–7.24 (m, 2H), 8.20 (d, *J*=8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.17 (CH_3), 25.66 (CH_2), 30.29 (2×CH_2), 37.36 (CH), 41.02 (CH_2), 45.16 (CH), 55.15 (CH_2), 116.96 (CH), 123.61 (CH), 123.75 (CH), 128.13 (CH), 133.69 (C), 142.50 (C), 168.53 (C=O) ppm. IR (CCl_4): 2939, 2904, 2252, 1653, 1598, 1482, 1461, 1406, 1358, 1338, 1290, 1277, 1244, 1177, 1132, 1032 cm^{-1}. MS (CI/NH_3): 294 (MH^+), 311 (MNH_4^+). Anal. calcd C, 61.39; H, 6.53; found C, 59.91; H, 6.43.

4.5.2. 1-(3-[1,3]Dithian-2-ylmethyl-2,3-dihydro-indol-1-yl)-2,2-dimethyl-propan-1-one (47). The reaction was carried out with **45** (177 mg, 0.50 mmol), TFAA (0.18 mL, 1.3 mmol), and NaI (184 mg, 1.2 mmol). Flash chromatography on silica gel (EtOAc–petroleum ether, 10:90 v/v) afforded **47** (120 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 9H), 1.85–2.01 (m, 2H), 2.13–2.21 (m, 2H), 2.83–2.99 (m, 4H), 3.59–3.66 (m, 1H), 4.00 (dd, *J*=5.2, 10.4 Hz, 1H), 4.13 (t, *J*=7.6 Hz, 1H), 4.37 (dd, *J*=8.4, 10.4 Hz, 1H), 7.05 (t, *J*=7.2 Hz, 1H), 7.21–7.25 (m, 2H), 8.22 (d, *J*=7.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.76 (CH_2), 27.76 (3×CH_3), 30.32 (CH_2), 30.47 (CH_2), 38.51 (CH), 40.12 (CH_2), 40.17 ($C(CH_3)_3$), 45.42 (CH), 55.91 (CH_2), 118.53 (CH), 123.68 (CH), 123.76 (CH), 128.07 (CH), 133.52 (C), 144.30 (C), 176.50 (C=O) ppm. IR (CCl_4): 2933, 2903, 1652, 1598, 1477, 1460, 1432, 1423, 1414, 1400, 1372, 1360, 1334, 1288, 1276, 1242, 1186, 1107, 1090, 1026 cm^{-1}. MS (CI/NH_3): 336 (MH^+), 353 (MNH_4^+).

4.5.3. 1-(3-Ethyl-2,3-dihydro-indol-1-yl)-ethanone (48). To a suspension of freshly prepared W2 Raney Nickel (400 mg of residual material/0.1 mmol of **44**) in absolute EtOH (5 mL) was added **44** (178 mg, 0.57 mmol). The resulting mixture was refluxed for 4 h, then cooled to room temperature and filtered over Celite. Evaporation of the solvent gave analytically pure **48** (104 mg, 95%) as a white solid.

Major conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.99 (t, *J*=7.2 Hz, 3H), 1.54–1.65 (m, 1H), 1.81–1.91 (m, 1H), 2.24 (s, 3H), 3.31–3.39 (m, 1H), 3.69 (dd, *J*=6.0, 10.4 Hz, 1H), 4.16 (t, *J*=10.0 Hz, 1H), 7.04 (t, *J*=7.6 Hz, 1H), 7.17–7.23 (m, 2H), 8.21 (d, *J*=8.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.07 (CH_3), 24.16 (CH_3), 28.02 (CH_2), 41.38 (CH), 54.60 (CH_2), 116.79 (CH), 123.44 (CH), 123.70 (CH), 127.67 (CH), 134.84 (C), 142.62 (C), 168.55 (C=O) ppm. IR (CCl_4): 2963, 2931, 2876, 1670, 1599, 1482, 1461, 1400, 1353, 1332, 1286, 1274, 1173, 1131, 1096, 1030 cm^{-1}. MS (CI/NH_3): 190 (MH^+), 207 (MNH_4^+). Anal. calcd C, 76.16; H, 7.99; found C, 76.16; H, 8.09.

4.5.4. [5-Bromo-1-(2,2-dimethyl-propionyl)-2,3-dihydro-1*H*-indol-3-yl]-acetaldehyde (50). A solution of NBS (362 mg, 2.0 mmol) in a 97:3 mixture of acetone and water (10 mL) was cooled to 0 °C before dropwise addition of a solution of **45** (86 mg, 0.24 mmol) in a 97:3 mixture of acetone and water (0.5 mL). After another 10 min of stirring at 0 °C the reaction was quenched by addition of a saturated solution of Na_2SO_3 (20 mL). The aqueous mixture thus obtained was extracted with CH_2Cl_2 (3×20 mL) and the collected organic layers were extracted with water (1×30 mL), washed with brine (1×30 mL) and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc–petroleum ether, 20:80 v/v) to afford **50** (27 mg, 35%) as a slightly yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.35 (s, 9H), 2.75 (dd, *J*=9.2, 19.2 Hz, 1H), 3.02 (dd, *J*=4.0, 18.4 Hz, 1H), 3.75–3.86 (m, 2H), 4.50 (dd, *J*=8.4, 10.4 Hz, 1H), 7.25 (dd, *J*=0.8, 2.0 Hz, 1H), 7.33 (ddd, *J*=0.4, 6.0, 8.4 Hz, 1H), 8.11 (d, *J*=8.8 Hz, 1H), 9.87 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.48 (3×CH_3), 34.91 (CH), 40.12 ($C(CH_3)_3$), 48.52 (CH_2), 55.45 (CH_2), 100.54 (C), 116.06 (C), 119.86 (CH), 126.30 (CH), 130.94 (CH), 135.05 (C), 176.93 (C=O), 199.70 (C(O)H) ppm. IR (CCl_4): 2972, 2931, 2820, 2720, 1727, 1656, 1592, 1474, 1400, 1371, 1350, 1329, 1242, 1204, 1177, 1108, 1065 cm^{-1}. MS (CI/NH_3): 323 (MH^+, $C_{15}H_{18}^{79}BrNO_2$), 325 (MH^+, $C_{15}H_{18}^{81}BrNO_2$), 340 (MNH_4^+, $C_{15}H_{18}^{79}BrNO_2$), 342 (MNH_4^+, $C_{15}H_{18}^{81}BrNO_2$).

4.5.5. (1-Acetyl-2,3-dihydro-1*H*-indol-3-yl)-acetaldehyde (51). To a solution of **46** (143 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) were added methyl iodide (1.6 mL, 25 mmol), acetone (4 mL), and water (0.15 mL) and the mixture was stirred at 45 °C for 26 h. The resulting orange solution was concentrated under reduced pressure before addition of EtOAc (20 mL). The organic phase was extracted with water (1×20 mL), then with a saturated solution of NaS_2O_3 (1×20 mL), washed with brine (1×20 mL), and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (EtOAc–petroleum ether, 10:90 v/v) to afford **51** (51 mg, 51%) as a slightly yellow solid.

Major conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.22 (s, 3H), 2.80 (dd, *J*=9.6, 18.8 Hz, 1H), 3.10 (dd, *J*=4.4, 18.8 Hz, 1H), 3.61 (dd, *J*=6.0, 18.8 Hz, 1H), 3.86–3.93 (m, 1H), 4.38 (dd, *J*=9.2, 10.8 Hz, 1H), 7.05 (dt, *J*=0.8, 7.4 Hz, 1H), 7.15 (d, *J*=7.2 Hz, 1H), 7.24–7.26 (m, 1H), 8.22 (d, *J*=8.0 Hz, 1H), 9.89 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.07 (CH_3), 33.93 (CH), 49.69 (CH_2), 55.00 (CH_2), 116.85 (CH), 123.34 (CH), 123.61 (CH), 128.17 (CH), 132.87 (C), 142.40 (C), 168.54 (C=O), 200.14 (C(O)H) ppm. IR (CCl_4): 2889, 2819, 2720, 1727, 1672, 1600, 1483, 1462, 1399, 1354, 1331, 1282, 1133, 1029 cm^{-1}. MS (CI/NH_3): 204 (MH^+), 221 (MNH_4^+).

4.5.6. Dithiocarbonic acid *O*-ethyl ester *S*-(2-methyl-1-oxo-1λ^4-[1,3]dithian-2-yl) ester (53). A solution of freshly distilled diisopropyl amine (0.21 mL, 1.5 mmol) in dry THF (7mL) was cooled to −78 °C under a nitrogen atmosphere, before dropwise addition of a 1.5 M solution of *n*BuLi in hexanes (0.73 mL, 1.1 mmol). To the colourless solution thus obtained was added a solution of **11** (256 mg,

1.0 mmol) in dry THF (5 mL). After 30 min of stirring at −78 °C methyl iodide (0.15 mL, 2.4 mmol) was added and the yellow solution thus obtained was allowed to warm to room temperature. After 90 min of additional stirring at room temperature, ice-cold water (20 mL) was added and the aqueous mixture extracted with CH_2Cl_2 (3×15 mL). The collected organic layers were washed with brine (1×40 mL) and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue purified by flash chromatography on silica gel (Et_2O–EtOAc, 60:40 v/v) to afford **53** (135 mg, 50%) as a liquid 1:5 mixture (NMR analysis) of separable diastereomers.

Less polar isomer (*minor*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.48 (t, J=7.2 Hz, 3H), 2.27 (s, 3H), 2.29–2.47 (m, 3H), 3.04–3.15 (m, 2H), 3.32 (dt, J=3.2, 13.2 Hz, 1H), 4.66–4.74 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.51 (CH_3), 25.46 (CH_3), 27.03 (CH_2), 29.44 (CH_2), 48.23 (CH_2), 70.61 (CH_2), 73.82 (C), 208.20 (C=S) ppm. IR (CCl_4): 2983, 2923, 1436, 1424, 1410, 1365, 1292, 1258, 1242, 1113, 1077, 1067, 1033 cm^{-1}. MS (CI/NH_3): 271 (MH^+).

More polar isomer (*major*). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.47 (t, J=7.2 Hz, 3H), 1.71–1.78 (m, 1H), 2.03 (s, 3H), 2.38–2.45 (m, 1H), 2.47–2.55 (m, 1H), 2.97–3.02 (m, 1H), 3.18 (ddd, J=2.0, 12.4, 14.0 Hz, 1H), 3.34 (ddd, J=2.8, 13.2, 14.8 Hz, 1H), 4.59–4.72 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.43 (CH_2), 13.61 (CH_3), 24.17 (CH_3), 25.68 (CH_2), 42.58 (CH_2), 69.36 (C), 70.76 (CH_2), 208.41 (C=S) ppm. IR (CCl_4): 2984, 2980, 2918, 1442, 1424, 1404, 1364, 1292, 1242, 1113, 1068, 1034 cm^{-1}. MS (CI/NH_3): 271 (MH^+).

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