2,2-Dimethyl-1,3-oxathiane 3,3-Dioxide: A γ-Hydroxypropyl Anion Equivalent[1]

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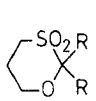
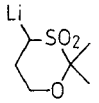
Received 18 October 1991; revised 12 December 1991

The reaction of 4-lithio-2,2-dimethyl-1,3-oxathiane 3,3-dioxide with various electrophiles is presented. Acylation of the anion provided labile 4-acyl-2,2-dimethyl-1,3-oxathiane 3,3-dioxides which underwent desulfonation with silica gel to produce γ-hydroxy ketones with three carbon unit elongation. Thus, 4-lithio-2,2-dimethyl-1,3-oxathiane 3,3-dioxide was shown to be a useful synthetic equivalent of a γ-hydroxypropyl anion. Methyl esters proved to be the best acylating agents in this reaction. Synthetic utility of this carbon chain elongation was illustrated by the syntheses of *dl*-lanceol and *dl*-dihydrojasmone.

α-Sulfonyl carbanions have been shown to be useful for C–C bond formation and their chemistry has been reviewed extensively.[2] As a part of our investigation on the chemical reactivities of 1,3-oxathiane and its derivatives,[3] the reactivity of 1,3-oxathiane 3,3-dioxide (**1**) toward base was studied.[4] Though 1,3-oxathiane itself is known to generate a carbanion at C-2,[5] preferential formation (ca. 2:1) of anion at C-4 over C-2 was observed with **1**.[4] To explore the synthetic potential of this ring system as a nucleophilic C_3-unit, we selected 2,2-dimethyl-1,3-oxathiane 3,3-dioxide (**2**), in which undesired anion formation at C-2 was blocked. Here we present a full account of the reactivity of 4-lithio-2,2-dimethyl-1,3-oxathiane 3,3-dioxide (**3**) toward electrophiles and the synthetic utility of **3**, particularly as a synthetic equivalent for the γ-hydroxypropyl anion.[6]



1 R = H
2 R = Me



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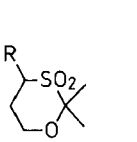
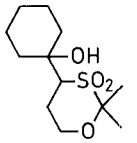
Oxidation of 2,2-dimethyl-1,3-oxathiane[7] with *m*-chloroperbenzoic acid (MCPBA) afforded 2,2-dimethyl-1,3-oxathiane 3,3-dioxide (**2**) in 82% yield. An anion **3** was generated easily in tetrahydrofuran with butyllithium as a base. The reaction of the anion **3** with electrophiles proceeded smoothly to afford the corresponding products (Table 1). A nucleophilic substitution of **3** with alkyl halides or trimethylsilyl chloride gave 4-substituted 2,2-dimethyl-1,3-oxathiane 3,3-dioxides **4** in good yield. Nucleophilic additions of **3** to carbonyl compounds took place easily to afford the corresponding adducts. Preferential 1,2-addition of the anion **3** occurred with α,β-unsaturated ketones (entries 7 and 8), while 1,4-addition products were obtained with α,β-unsaturated esters (entries 9 and 10). Methyl cinnamate afforded a γ-hydroxy ketone **10** as a minor product (entry 10) after chromatography over silica gel. The 1,2-addition of **3** followed by desulfonation of the resulting β-oxo sulfone **15** may account for the formation of **10**. If this is the case, cyclic β-hydroxy sulfones resulting from the reaction of **3** with aldehydes should be a suitable precursor for γ-hydroxy ketones. Thus, the Jones oxidation of secondary alcohols **11**–**14** followed by treatment with silica gel gave the corresponding γ-hydroxy ketones **22** (51–91% yield) (Scheme 1). The treatment of crude products with silica gel was necessary to complete desulfonation.



4a R = D
b R = Me
c R = Et
d R = $SiMe_3$
e R = CH_2Ph



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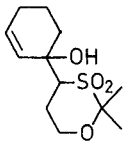

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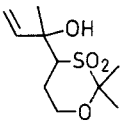

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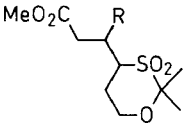
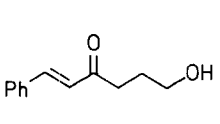


8 R = Me
9 R = Ph



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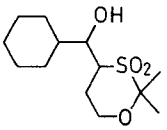

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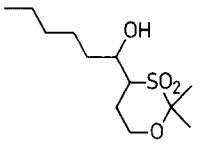

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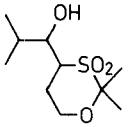

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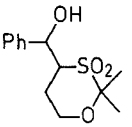

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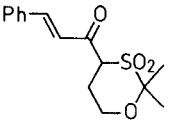
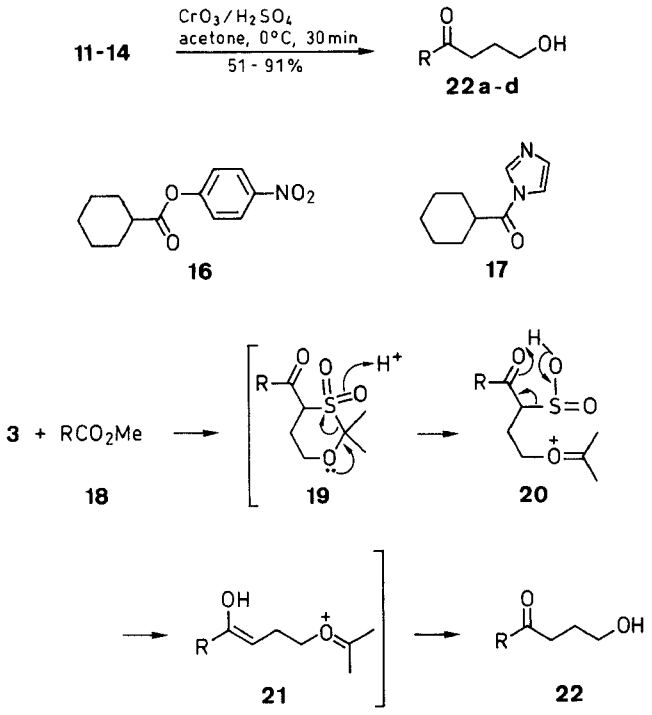


15

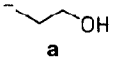
These results suggest that direct acylation of **3** followed by treatment of the intermediate oxo sulfone **19** with silica gel constitutes a more versatile method for the preparation of γ-hydroxy ketones **22** (Scheme 1). Direct acylation was examined with cyclohexanecarboxylic acid derivatives **16**, **17** and **18** (R = cyclohexyl). A stoichiometric reaction of **3** with methyl cyclohexanecarboxylate (**18**, R = cyclohexyl) afforded a labile β-oxo sulfone **19** (R = cyclohexyl) which was immediately treated with wet silica gel in dichloromethane to provide the desired product **22a** in 59% yield (entry 1 in Table 2). More reactive acylating agents **16** and **17** did not increase the yield. The low yield of the product should be due to the rapid proton transfer from the product **19** to the starting sulfonyl anion **3** under the reaction conditions. Using two

equivalents **2** (Method A), or addition of two equivalents of lithium diisopropylamide (LDA) to a 1:1 mixture of the methyl ester **18** and **2** (Method B) improved the yield (entries 2 and 3 in Table 2). Use of **16** or **17** as acylating agent resulted in a less satisfactory yield than that of the methyl ester **18** (R = cyclohexyl) even by the method A or B. The results of acylation of **3** with various methyl esters are given in Table 2. Though the yield was not optimized, all the reactions attempted afforded the desired γ-hydroxy ketones **22** in fair to good yield.



Scheme 1

The Jones oxidation of β-oxo sulfones **11–14** or the direct acylation of **2** with methyl esters **18** established a versatile new method for the preparation of γ-hydroxy ketones **22**. Thus, the sulfonyl anion **3** can be regarded as a synthetic equivalent of the γ-hydroxypropyl anion **a**. Direct acylation of **2** is particularly useful because it does not require acid halides or activated esters but requires methyl esters as acylating agents. The virtue of this method is the facile desulfonation of the intermediate β-oxo sulfone **19** under mild conditions. It takes place very easily by stirring **19** with wet silica gel in dichloromethane, though reductive conditions are generally required for other desulfonations.[8] A plausible stepwise mechanism is shown in Scheme 1. Protonation at the oxygen of the sulfonyl group in **19** is followed by the C–S bond cleavage to generate an intermediate oxonium ion **20**. Elimination of sulfur dioxide from **20** yields **21** which is easily converted into the γ-hydroxy ketone **22**. An alternative version involving concerted elimination may also be possible. The oxygen atom in the ring system plays a crucial role for the easy cleavage of the carbon–sulfur bond in either case.



a

The synthetic use of this method is illustrated by formal total syntheses of a sesquiterpene alcohol, (±)-lanceol (**26**) (Scheme 2) and a common intermediate **29** for prostaglandin synthesis.[9] Methyl 4-methyl-3-cyclohex-

Table 1. Reaction of **3** with Various Electrophiles

Entry	Electrophile	Product	Yield (%)
1	AcOD	**4a**	79
2	MeI	**4b**	83
3	EtI	**4c**	80
4	Me_3SiCl	**4d**	81
5	$PhCH_2Cl$	**4e**	68
6	cyclohexanone	**5**	87
7	2-cyclohexenone	**6**	93[a]
8	methyl vinyl ketone	**7**	88[a]
9	methyl crotonate	**8**	62
10	methyl cinnamate	**9**	60
		10	17
11	cyclohexylcarbaldehyde	**11**	80[a]
12	$C_5H_{11}CHO$	**12**	86[a]
13	Me_2CHCHO	**13**	74[a]
14	PhCHO	**14**	68[a]

[a] A mixture of two diastereoisomers.

Table 2. γ-Hydroxy Ketones **22** Prepared

Entry	Substrate	R	Reaction conditions[a]	Product	Yield (%)
1	**18**	cyclohexyl	A[b]	**22a**	59
2	**18**	cyclohexyl	A	**22a**	80
3	**18**	cyclohexyl	B	**22a**	72
4	**16**	–	A	**22a**	68
5	**16**	–	B	**22a**	62
6	**17**	–	A	**22a**	75
7	**17**	–	B	**22a**	25[c]
8	**18**	*i*-Pr	A	**22c**	59
9	**18**	C_5H_{11}	A	**22b**	64
10	**18**	C_7H_{15}	A	**22e**	77
11	**18**	C_7H_{15}	B	**22e**	62
12	**18**	C_9H_{19}	A	**22f**	69
13	**18**	C_9H_{19}	B	**22f**	78
14	**18**	$C_{13}H_{27}$	A	**22g**	53
15	**18**	Ph	A	**22d**	61
16	**18**	Ph	B	**22d**	50
17	**18**	4-MeC_6H_4	A	**22h**	78
18	**18**	4-MeC_6H_4	B	**22h**	76
19	**18**	4-$MeOC_6H_4$	A	**22i**	68
20	**18**	4-$MeOC_6H_4$	B	**22i**	89

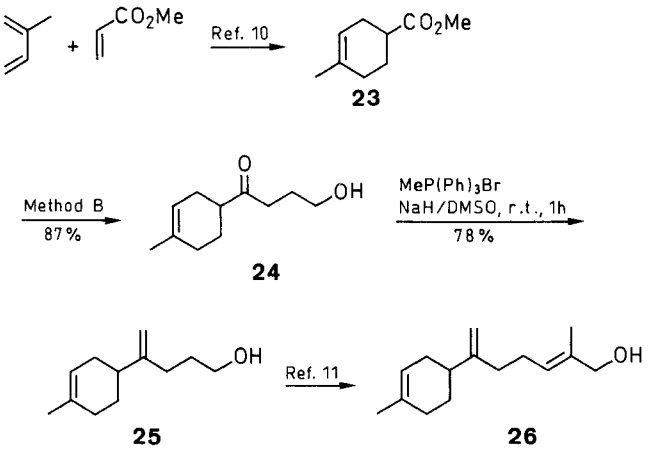
[a] See text.
[b] A 1.1 mol equivalent of **3** was used.
[c] A 55% yield of **2** was recovered.

Table 3. Compounds **35** Prepared[a]

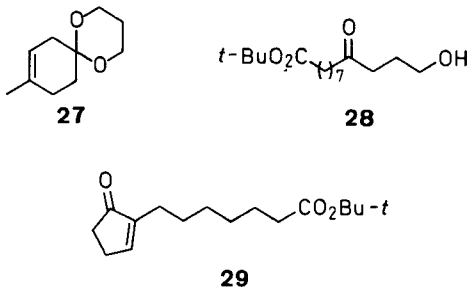
Product	R	Yield[b] (%)
35a	*i*-Bu	42
35b	C_7H_{15}	50
35c	C_9H_{19}	44
35d	Ph	53
35e	4-MeC_6H_4	82

[a] Method A.
[b] Not optimized.

enecarboxylate (**23**)[10] was treated with **2** by the method A to afford **24** in 87% yield. The Wittig reaction of **24** provided 78% yield of **25**, which had been converted to (±)-lanceol (**26**) previously.[11] The diene **25** was also previously prepared from **27** through four steps in 22% overall yield.[12] The γ-hydroxy ketone **28** was prepared from **2** by acylation of **3** with *tert*-butyl methyl azelate in 71% yield. Oxidation of **28** followed by cyclization under basic conditions afforded the cyclopentenone **29** in 45% yield.

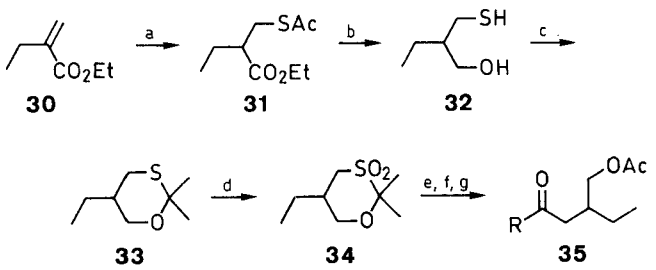


Scheme 2



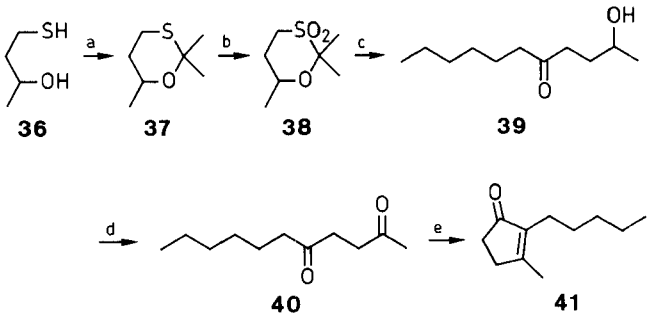
Substituted 2,2-dimethyl-1,3-oxathiane 3,3-dioxides such as **34** and **38** can be easily prepared from the corresponding γ-hydroxy thiols **32** and **36**, respectively. The 1,4-addition of thioacetic acid on ethyl 2-ethylacrylate[13] (**30**) afforded 62% yield of **31**, which was reduced with lithium aluminum hydride to give **32** in 81% yield. Acetalization of **32** with 2,2-dimethoxypropane followed by the oxidation with MCPBA gave the cyclic sulfone **34** in 71% overall yield (Scheme 3). Though the acylation of **34** with methyl esters proceeded smoothly, attempted desulfonation with wet silica gel in dichloromethane resulted in a mixture of unidentified products. Heating the crude product in a mixture of acetic acid and water (1:1) at 70°C effected the desired desulfonation to yield γ-acetoxyketone **35** after acetylation (Table 3). The reaction of **34** with methyl isopentanoate is worthy of note, because it gives rise to the product **35a** with the head-to-tail connection of two isoprene units.

2,2,6-Trimethyl-1,3-oxathiane 3,3-dioxide (**38**) was prepared from the corresponding γ-hydroxy thiol **36** in 50% overall yield by the sequence similar to that for **34** (Scheme 4). Reaction of **38** with methyl heptanoate by the method A afforded γ-hydroxyketone **39** in 62% yield. Jones oxidation of **39** gave undecan-2,5-dione (**40**) which has been converted to dihydrojasmone (**41**).[13]



(a) AcSH, Δ. (b) $LiAlH_4/Et_2O$. (c) 2,2-dimethoxypropane/$Et_2O \cdot BF_3$. (d) MCPBA/CH_2Cl_2. (e) Lithium diisopropylamide (LDA, 2 equivs), then **18**. (f) AcOH(H_2O, Δ. (g) Ac_2O/Py.

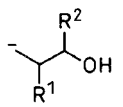
Scheme 3



(a) 2,2-dimethoxypropane/$Et_2O \cdot BF_3$. (b) MCPBA/CH_2Cl_2. (c) LDA (2 equivs); methyl heptanoate, then silica gel. (d) Jones oxidation (e) Ref. 14.

Scheme 4

In conclusion, 2,2-dimethyl-4-lithio-1,3-oxathiane 3,3-dioxide (**3**) has been shown to be a versatile building block for a γ-hydroxypropyl group. The advantage of the cyclic sulfone includes easy desulfonation of the products under non-reductive conditions. Since γ-hydroxy thiols can be easily prepared from the corresponding α,β-unsaturated carbonyl compounds, a variety of substituted 1,3-oxathiane 3,3-dioxides are available for the nucleophilic γ-hydroxypropyl unit **b** substituted at the β- and/or γ-position to the anionic carbon.



b

Melting points were determined with a Yanagimoto micro apparatus and uncorrected. ^1H NMR spectra were obtained in $CDCl_3$ solution with a JEOL JMN-FX100 spectrometer. Chemical shifts are given relative to internal TMS. IR spectra were obtained with a Jasco IR-810 spectrophotometer. Mass spectra were determined on a JEOL JMS-DX300 mass spectrometer. All reactions involving organolithium reagents were carried out in an atmosphere of dry N_2. THF was predistilled over Cu_2SO_4, dried with NaOH, and distilled from sodium benzophenone ketyl before use. All the crystalline derivatives of 1,3-oxathiane 3,3-dioxide were recrystallized from CH_2Cl_2/hexane.

2,2-Dimethyl-1,3-oxathiane 3,3-Dioxide (2):
To 3-mercaptopropanol (16.3 g, 0.177 mol) were added 2,2-dimethoxypropane (3 mL, 2.0 equivs) and a catalytic amount of $Et_2O \cdot BF_3$ at 0 °C under a N_2 atmosphere. After stirring overnight, the mixture was poured into aq Na_2CO_3 and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to leave a crude residue, which was purified by distillation to afford 2,2-dimethyl-1,3-oxathiane as a colorless oil; yield: 10.6 g (45 %); bp 55 °C/15 Torr.

$C_6H_{10}OS$ calc. C 54.50 H 9.15
(130.2) found 54.77 8.90.

IR ($CHCl_3$): ν = 2930, 1070 cm^{-1}.

^1H NMR: δ = 1.16 (s, 6H), 1.68–1.94 (m, 2H), 2.89 (t, 2H, J = 6 Hz), 3.92 (t, 2H, J = 5.5 Hz).

A solution of 2,2-dimethyl-1,3-oxathiane (1.3 g) in CH_2Cl_2 (100 mL) was added to 5% aq Na_2CO_3 (100 mL). MCPBA (4.4 g) was added gradually with stirring. After 30 min, the organic layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. Recrystallization from CH_2Cl_2/hexane afforded pure **2**; yield: 1.1 g (82%); mp 63–65 °C.

$C_6H_{10}O_3S$ calc. C 43.88 H 7.37
(161.1) found 43.73 7.12

IR ($CHCl_3$): ν = 1305, 1105 cm^{-1}.

^1H NMR: δ = 1.64 (s, 6H), 2.32 (m, 2H), 3.22 (t, 2H, J = 6 Hz), 3.90 (t, 2H, J = 6 Hz).

Reaction of 3 with Electrophiles; General Procedures:
To a solution of **2** (100 mg, 0.6 mmol) in THF (5 mL) was added 1.5 M hexane solution of BuLi (0.44 mL, 1.1 equiv) at – 78 °C. After 10 min the appropriate electrophile was added at – 78 °C and stirred for 1 h at the same temperature. The mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with brine, and dried (Na_2SO_4). Solvent was removed by evaporation to give a crude residue, which was purified by recrystallization or chromatography over silica gel (eluent: CH_2Cl_2/hexane).

4-Deuterio-2,2-dimethyl-1,3-oxathiane 3,3-Dioxide **(4a)**: mp 65–66 °C.

$C_6H_{11}DO_3S$ calc. C 43.62 H 6.71
(165.2) found 43.32 7.02

IR ($CHCl_3$): ν = 1300, 1100 cm^{-1}.

^1H NMR: δ = 1.64 (s, 6H), 2.20–2.48 (m, 1H), 3.22 (br t, 1H, J = 6 Hz), 3.89 (t, 2H, J = 5 Hz).

2,2,4-Trimethyl-1,3-oxathiane 3,3-Dioxide **(4b)**: mp 64–66 °C.

$C_7H_{14}SO_3$ calc. C 47.14 H 7.92
(178.2) found 47.56 7.59

IR ($CHCl_3$): ν = 1305, 1105 cm^{-1}.

^1H NMR: δ = 1.38 (d, 3H, J = 6 Hz), 1.56 (s, 3H), 1.72 (s, 3H), 1.76–2.32 (m, 2H), 3.20–3.62 (m, 1H), 3.68–4.16 (m, 2H).

2,2-Dimethyl-4-ethyl-1,3-oxathiane 3,3-Dioxide **(4c)**: mp 33–35 °C.

$C_8H_{16}O_3S$ calc. C 49.7 H 8.39
(192.3) found 49.74 8.11

IR ($CHCl_3$): ν = 2960, 1300, 1100, 1070 cm^{-1}.

^1H NMR: δ = 1.06 (t, 3H, J = 6 Hz), 1.53 (s, 3H), 1.71 (s, 3H), 1.90–2.44 (m, 4H), 2.92–3.32 (m, 1H), 3.80–4.00 (m, 2H).

2,2-Dimethyl-4-trimethylsilyl-1,3-oxathiane 3,3-Dioxide **(4d)**: mp 77–79 °C.

$C_9H_{20}O_3SSi$ calc. C 45.73 H 8.53
(236.1) found 45.91 8.03

IR ($CHCl_3$): ν = 1300, 1100, 850 cm^{-1}.

^1H NMR: δ = 0.28 (s, 9H), 1.52 (s, 3H), 1.73 (s, 3H), 1.92 (br d, 1H, J = 14 Hz), 2.12–2.70 (m, 1H), 2.84 (dd, 1H, J = 13, 4 Hz), 3.80–3.96 (m, 2H).

4-Benzyl-2,2-dimethyl-1,3-oxathiane 3,3-Dioxide **(4e)**: colorless oil.

$C_{13}H_{18}O_3S$ calc. C 61.39 H 7.13
(254.3) found 61.17 6.97

IR ($CHCl_3$): ν = 1310, 1300, 1100 cm^{-1}.

^1H NMR: δ = 1.60 (s, 3H), 1.72 (s, 3H), 1.80–2.92 (m, 3H), 3.24–3.60 (m, 2H), 3.76–3.92 (m, 2H), 7.08–7.44 (m, 5H).

2,2-Dimethyl-4-(1-hydroxycyclohexyl)-1,3-oxathiane 3,3-Dioxide **(5)**: mp 121–123 °C.

$C_{12}H_{22}O_4S$ calc. C 54.94 H 8.45
(262.4) found 54.74 8.24

IR ($CHCl_3$): ν = 3530, 2940, 1340, 1100, 670 cm^{-1}.

^1H NMR: δ = 1.51 (s, 3H), 1.58 (s, 1H, OH), 1.72 (s, 3H), 1.40–3.04 (m, 12H), 3.32 (dd, 1H, J = 13, 4 Hz), 3.84–4.04 (m, 2H).

2,2-Dimethyl-4-(1-hydroxy-2-cyclohexenyl)-1,3-oxathiane 3,3-Dioxide **(6)**: recrystallization from CH_2Cl_2 hexane afforded the major isomer; mp 114–116 °C.

$C_{12}H_{20}O_4S$ calc. C 55.36 H 7.74
(260.4) found 55.07 7.52

IR ($CHCl_3$): ν = 1300, 1100 cm^{-1}.

^1H NMR: δ = 1.47 (s, 3H), 1.68 (s, 3H), 1.80–2.10 (m, 8H), 3.32 (br s, 1H), 3.42 (dd, 1H, J = 13.4 Hz), 3.84–4.00 (m, 2H), 5.56–6.04 (m, 2H).

2,2-Dimethyl-4-(1-hydroxy-1-methyl-2-propenyl)-1,3-oxathiane 3,3-Dioxide **(7)**: diastereomeric mixture; colorless oil.

$C_{10}H_{18}O_4S$ calc. C 51.25 H 7.74
(234.3) found 51.10 7.58

2,2-Dimethyl-4-(2-methoxycarbonyl-1-methylethyl)-1,3-oxathiane 3,3-Dioxide **(8)**: recrystallization from CH_2Cl_2/hexane afforded roughly a 1:1 mixture of diastereoisomers; mp 63–65 °C.

$C_{11}H_{20}O_5S$ calc. C 49.98 H 7.63
(264.3) found 49.52 7.54

2,2-Dimethyl-4-(2-methoxycarbonyl-1-phenylethyl)-1,3-oxathiane 3,3-Dioxide **(9)**: recrystallization from CH_2Cl_2/hexane afforded the major isomer; mp 98–99 °C.

$C_{16}H_{22}O_5S$ calc. C 58.89 H 6.79
(326.4) found 59.15 6.73

IR ($CHCl_3$): ν = 1730, 1300, 1100 cm^{-1}.

^1H NMR: δ = 1.53 (s, 3H), 1.67 (s, 3H), 1.70–3.08 (m, 4H), 3.28–3.60 (m, 1H), 3.75 (s, 3H), 3.79–3.94 (m, 2H), 4.20 (dt, 1H, J = 10, 4 Hz), 7.22–7.65 (m, 5H).

6-Hydroxy-1-phenyl-1-hexen-3-one **(10)**: colorless oil.

$C_{12}H_{14}O_2$ calc. C 75.76 H 7.42
(190.2) found 75.50 7.43

IR ($CHCl_3$): ν = 1660, 1610 cm^{-1}.

^1H NMR: δ = 1.80–2.20 (m, 3H), 2.82 (t, 2H, J = 6 Hz), 3.68 (t, 2H, J = 6 Hz), 6.64–7.72 (m, 7H).

4-(Cyclohexylhydroxymethyl)-2,2-dimethyl-1,3-oxathiane 3,3-Dioxide **(11)**: recrystallization from CH_2Cl_2/EtOAc afforded the major isomer; mp 81–83 °C.

$C_{13}H_{24}O_4S$ calc. C 56.49 H 8.75
(276.4) found 56.46 8.52

IR ($CHCl_3$): ν = 3530, 2920, 1295, 1100 cm^{-1}.

^1H NMR: δ = 1.56 (s, 3H),1.72 (s, 3H), 0.80–3.12 (m, 14H), 3.28–3.68 (m, 1H), 3.84–4.08 (m, 2H), 4.20 (br d, 1H, J = 8 Hz).

2,2-Dimethyl-4-(1-hydroxyhexyl)-1,3-oxathiane 3,3-Dioxide **(12)**: recrystallization from CH_2Cl_2/hexane afforded the major isomer; mp 50–51 °C.

$C_{12}H_{24}O_4S$ calc. C 54.21 H 9.15
(264.4) found 54.04 8.82

IR ($CHCl_3$): ν = 3530, 2920, 1295, 1100 cm^{-1}.

^1H NMR: δ = 0.93 (m, 3H), 1.20–2.12 (m, 9H), 1.55 (s, 3H), 1.72 (s, 3H), 2.40–2.92 (m, 2H), 3.16 (ddd, 1H, J = 13, 4, 1 Hz), 3.88–4.08 (m, 2H), 4.44–4.64 (m, 1H).

2,2-Dimethyl-4-(1-hydroxy-2-methylpropyl)-1,3-oxathiane 3,3-Dioxide **(13):**

Recrystallization from CH_2Cl_2/hexane afforded roughly a 3:1 mixture of diastereoisomers: mp 56–58 °C.

$C_{10}H_{20}O_4S$ calc. C 50.28 H 8.53
(236.3) found 50.41 8.28

2,2-Dimethyl-4-(α-hydroxybenzyl)-1,3-oxathiane 3,3-Dioxide Diastereomers **(14a, b)**:

Column chromatographic separation over silica gel with EtOAc/hexane (1:1) yielded the major isomers **14a** and **14b**.

14a: mp 123.5–125 °C.

$C_{13}H_{18}O_4S$ calc. C 57.76 H 6.71
(270.3) found 57.44 6.87

IR ($CHCl_3$): ν = 3520, 1295, 1100 cm^{-1}.

^1H NMR: δ = 1.59 (s, 3H), 1.72 (s, 3H), 1.60–1.88 (m, 2H), 2.47–3.00 (m, 1H), 3.30 (ddd, 1H, J = 2, 4, 13 Hz), 3.81 (br s, 1H), 3.90 (d, 1H, J = 2 Hz), 5.78 (br s, 1H), 7.36 (br s, 5H).

14b: mp 123.5–125 °C.

$C_{13}H_{18}O_4S$ calc. C 57.76 H 6.71
(270.3) found 57.27 6.63

IR ($CHCl_3$): ν = 3520, 1295, 1100 cm^{-1}.

^1H NMR: δ = 1.60 (s, 3H), 1.78 (s, 3H), 1.22 (br d, 1H, J = 12 Hz), 1.80–2.32 (m, 1H), 3.36 (br s, 1H), 3.40–3.86 (m, 3H), 5.28 (d, 1H, J = 6 Hz, 7.35 (br s, 5H).

γ-Hydroxy Ketones 22a–d by oxidation of 11–14; General Procedure:

To a solution of the alcohol **11–14** (10 mg) in acetone (10 mL) was added a few drops of Jones reagent at 0 °C with stirring. After 30 min *i*-PrOH was added to the mixture. After filtering the undissolved material, the solvent was removed under reduced pressure to leave crude residue, which was purified by preparative TLC to give **22a–d**, respectively.

1-Cyclohexyl-4-hydroxybutan-1-one **(22a)**: yield: 91 %; colorless oil.

$C_{10}H_{18}O_2$ calc. C 70.55 H 10.66
(170.2) found 70.76 10.84

IR ($CHCl_3$): ν = 3450, 2950, 2925, 1700 cm^{-1}.

^1H NMR: δ = 1.00–2.48 (m, 14H), 2.58 (t, 2H, J = 6 Hz), 3.63 (t, 2H, J = 6 Hz).

1-Hydroxynonan-4-one **(22b):** yield: 87 %; colorless oil.

IR ($CHCl_3$): ν = 3450, 2950, 2925, 1700 cm^{-1}.

^1H NMR: δ = 0.80–2.00 (m, 12H), 2.36–2.68 (m, 4H), 3.64 (t, 2H, J = 4 Hz).

HRMS: calc. $C_9H_{18}O_2$ 158.1307, found 158.1307.

6-Hydroxy-2-methylhexan-3-one **(22c)**: yield: 51 %; colorless oil.

IR ($CHCl_3$): ν = 3425, 2970, 1700 cm^{-1}.

^1H NMR: δ = 1.11 (d, 6H, J = 3 Hz), 1.40–2.00 (m, 3H), 2.40–2.72 (m, 1H), 2.62 (t, 2H, J = 6 Hz), 3.66 (t, 2H, J = Hz).

HRMS: calc. for $C_7H_{14}O_2$ 130.0994, found 130.0984.

4-Hydroxy-1-phenylbutan-1-one **(22d)**: yield: 69 %; colorless oil.

IR ($CHCl_3$): ν = 3425, 1680, 1600, 1450 cm^{-1}.

^1H NMR: δ = 1.40–2.22 (m, 2H), 3.15 (t, 2H, J = 6 Hz), 3.76 (t, 2H, J = 6 Hz), 4.16 (br s, 1H), 7.32–8.20 (m, 5H).

HRMS: calc. for $C_{10}H_{12}O_2$ 164.0838, found 164.0854.

γ-Hydroxy Ketones 22a–i; General Procedures:

Method A: To a solution of **2** (100 mg, 0.6 mmol) in THF (10 mL) was added a 1.5 N hexane solution of BuLi (1.1 equiv) at −78 °C under N_2 atmosphere. A solution of the appropriate acylating agent (0.5 equiv) Table 2 in THF (5 mL) was added after 10 min and the mixture was stirred for 30 min. Usual extractive workup with CH_2Cl_2 afforded a crude product. This was dissolved in a small amount of CH_2Cl_2 and stirred with silica gel (ca. 1 g) for 30 min. After the solvent was removed under reduced pressure, the product adsorbed on the silica gel was eluted directly with EtOAc/hexane (1:1) by dry column chromatography to afford γ-hydroxy ketone **22**.

Method B: To a mixture of **2** (82.0 mg, 0.5 mmol) and acylating agent (1.0 equiv) in THF (5 mL) was added lithium diisopropylamide (2.1 equiv) in THF (1 mL) at −78 °C under a N_2 atmosphere and the mixture was stirred for 30 min. The same workup as described above gave **22**.

The spectral and analytical data of compounds **22a–d** has been described above.

1-Hydroxyundecan-4-one **(22e)**: colorless oil.

IR ($CHCl_3$): ν = 3450, 1700 cm^{-1}.

^1H NMR: δ = 0.86 (t, 3H, J = 6 Hz), 1.16–2.00 (m, 13H), 2.36–2.68 (m, 4H), 3.64 (t, 2H, J = 6 Hz).

HRMS: calcd for $C_{11}H_{22}O_2$ 186.1616, found 186.1595.

1-Hydroxytridecan-4-one **(22f)**: colorless oil.

$C_{13}H_{26}O_2$ calc. C 72.84 H 12.23
(214.3) found 72.85 12.47

IR ($CHCl_3$): ν = 3470, 1705 cm^{-1}.

^1H NMR: δ = 0.89 (t, 3H, J = 6 Hz), 1.16–2.00 (m, 17H), 2.28–2.64 (m, 4H), 3.62 (t, 2H, J = 6 Hz).

1-Hydroxyheptadecan-4-one **(22g)**: mp 58–59 °C (CH_2Cl_2/hexane).

IR ($CHCl_3$): ν = 3440, 1705 cm^{-1}.

^1H NMR: δ = 0.89 (t, 3H, J = 6 Hz), 1.04–2.00 (m, 25H), 2.28–2.64 (m, 4H), 3.64 (t, 2H, J = 6 Hz).

HRMS: calcd for $C_{17}H_{34}O_2$ 270.2558, found 270.2515.

4-Hydroxy-1-(p-tolyl)buan-1-one **(22h)**: mp 36–37 °C (CH_2Cl_2/hexane).

$C_{11}H_{14}O_2 \cdot 0.5H_2O$ calc. C 70.47 H 8.19
(187.2) found 70.77 7.75

IR ($CHCl_3$): ν = 3450, 1675, 1605 cm^{-1}.

^1H NMR: δ = 1.80 (br s, 1H), 2.00 (quint, 2H, J = 6 Hz), 2.20 (s, 3H), 3.09 (t, 2H, J = 6 Hz), 3.72 (t, 2H, J = 6 Hz), 7.23 (d, 2H, J = 8 Hz), 7.84 (d, 2H, J = 8 Hz).

4-Hydroxy-1-(p-methoxyphenyl)butan-1-one **(22i)**: mp 41–43 °C (CH_2Cl_2/hexane).

$C_{11}H_{14}O_3$ calc. C 68.02 H 7.26
(194.2) found 67.72 7.34

IR ($CHCl_3$): ν = 3450, 1670, 1600 cm^{-1}.

^1H NMR: δ = 2.00 (quint, 2H, J = 6 Hz), 2.16 (br s, 1H), 3.08 (t, 2H, J = 6 Hz), 3.73 (t, 2H, J = 6 Hz), 3.84 (s, 3H), 6.92 (d, 2H, J = 8 Hz), 7.95 (d, 2H, J = Hz).

4-Hydroxy-1-(4-methyl-3-cyclohexenyl)butan-1-one (24):

2,2-Dimethyl-1,3-oxathiane 3,3-dioxide (**2**; 820 mg, 5 mmol) reacted with methyl 4-methyl-3-cyclohexenecarboxylate (**23**; 765 mg, 5 mmol) by method B to provide **24**; yield: 792 mg (87 %); colorless oil.

$C_{11}H_{18}O_2$ calc. C 72.49 H 9.96
(182.3) found 72.40 10.05

IR ($CHCl_3$): ν = 2920, 1700 cm^{-1}.

^1H NMR: δ = 1.80–2.28 (m, 12H), 2.40–2.70 (m, 1H), 2.62 (t, 2H, J = 6 Hz), 3.63 (t, 2H, J = 6 Hz), 5.39 (br s, 1H).

4-(4-Methyl-3-cyclohexenyl)-4-pentenol (25):

A mixture of NaH (214 mg, 8.9 mmol) and DMSO (4 mL) was stirred at 75–80 °C for 45 min to generate the dimsyl anion. After the mixture was cooled to 0 °C, a solution of methyltriphenylphosphonium iodide (3.6 g, 90 mmol) in DMSO (6 mL) was added and the mixture was stirred for 10 min. The Wittig reagent thus prepared was added to **24** (414 mg, 2.3 mmol) at r.t. and stirred for 1 h. Usual extractive workup with Et_2O followed by dry column chromatography over silica gel (EtOAc/hexane, 1:1) gave **25**; yield: 335 mg (78 %); colorless oil (Lit.[12] bp 87–89/0.8 Torr).

11-*tert*-Butoxycarbonyl-1-hydroxyundecan-4-one (28):
The reaction of **2** (820 mg, 5 mmol) with *tert*-butyl methyl azelate (1.3 g, 5 mmol) in THF (50 mL) by method B followed by purification by dry column chromatography over silica gel (hexane/EtOAc, 1:1) afforded **28**; yield: 1.0 g (71%); colorless oil.

$C_{16}H_{30}O_2$ calc. C 67.09 H 10.56
(254.4) found 67.02 10.41

^{1}H NMR: δ = 1.20–2.64 (m, 19H), 1.43 (s, 9H), 3.65 (t, 2H, J = 6 Hz).

IR ($CHCl_3$): ν = 2925, 1710, 1150 cm^{-1}.

***tert*-Butyl 7-(5-Oxo-1-pentenyl)heptanoate (29):**
To a solution of **28** (18.5 mg) in CH_2Cl_2 (2 mL) was added pyridinium dichromate (36.5 mg) at r.t. and the mixture was kept for 30 min. Extractive workup with CH_2Cl_2 afforded crude keto aldehyde, which was treated with 0.1 N NaOH in 20 mL of H_2O/MeOH (1:1) for 1 h. After acidification with dilute HCl, the mixture was extracted with CH_2Cl_2. The organic layer was washed successively with aq Na_2CO_3, brine, dried (Na_2SO_4), and evaporated to afford a residue. Column chromatography over alumina (CH_2Cl_2) gave **29**; yield: 7.8 mg (45%); colorless oil (Lit.[15] bp not reported).

Ethyl 2-Acetylthiomethylbutyrate (31):
To a mixture of thiolacetic acid (10 mL, 140 mmol) and ethyl 2-ethylacrylate (**30**, 10 g, 78 mmol) was added Et_3N (19.5 mL, 140 mmol) gradually. After stirring for 5 h at 70°C, the mixture was distilled under reduced pressure to afford **31**; yield: 9.9 g (62%); bp 75–80°C/3 Torr.

IR ($CHCl_3$): ν = 1720, 1990 cm^{-1}.

^{1}H NMR: δ = 0.93 (t, 3H, J = 7 Hz), 1.25 (t, 3H, J = 7 Hz), 1.64 (m, 2H), 2.30 (s, 3H), 2.50 (m, 1H), 3.06 (m, 2H), 4.14 (q, 2H, J = 7 Hz).

HRMS: calc. for $C_9H_{16}O_3S$ 204.0819, found 204.0808.

2-Hydroxymethylbutanethiol (32):
To a suspension of $LiAlH_4$ (6.2 g, 162 mmol) in anhydrous Et_2O (500 mL) was added dropwise **31** (16.6 g, 81 mmol) and the mixture was refluxed for 1 h. Usual acidic workup followed by the distillation of the crude material gave **32**; yield: 8.0 g (81%); bp 120°C/20 Torr.

$C_5H_{12}OS$ calc. C 49.98 H 10.07
(120.2) found 49.55 10.13

IR ($CHCl_3$): ν = 3620, 2960, 1460, 1040 cm^{-1}.

^{1}H NMR: δ = 0.92 (t, 3H, J = 7 Hz), 1.20–1.80 (m, 4H), 1.95 (br s, 1H), 2.56–2.76 (m, 2H), 3.52–3.82 (m, 2H).

2,2-Dimethyl-5-ethyl-1,3-oxathiane (33):
To a mixture of **32** (4.9 g, 40.5 mmol) and 2,2-dimethoxypropane (25 mL, 203 mmol) was added $Et_2O \cdot BF_3$ (0.5 mL, 0.4 mmol) and the mixture was heated at 90°C for 30 min with continuous removal of MeOH with molecular sieve 4Å. The mixture was poured into sat. Na_2CO_3 after cooling. Extractive workup with CH_2Cl_2 followed by column chromatography over silica gel (CH_2Cl_2, hexane 1:1) afforded **33**; yield: 4.9 g (75%); colorless oil; bp 93°C/23 Torr.

$C_8H_{16}OS$ calc. C 60.36 H 10.33
(128.2) found 59.98 10.07

IR ($CHCl_3$): ν = 2980, 1460, 1380, 1365, 1165, 1125, 1070 cm^{-1}.

^{1}H NMR: δ = 0.93 (t, 3H, J = 7 Hz), 1.09 (quintet, 2H, J = 7 Hz), 1.56 (s, 3H), 1.64 (s, 3H), 1.40–1.92 (m, 1H), 2.52–2.80 (m, 2H), 3.40–3.95 (m, 2H).

2,2-Dimethyl-5-ethyl-1,3-oxathiane 3,3-Dioxide (34):
MCPBA (10.8 g, 50.0 mmol) was slowly added to the two phase system consisting of a solution of **33** (4.0 g, 25.0 mmol) in CH_2Cl_2 (50 mL) and saturated Na_2CO_3 (50 mL) and stirred at r.t. for 4 h. Usual workup followed by column chromatography over silica gel (EtOAc/hexane, 1:2) afforded **34**; yield: 4.5 g (94%); mp 75–77°C (CH_2Cl_2/hexane).

$C_8H_{16}O_3S$ calc. C 49.74 H 8.40
(192.3) found 49.99 8.39

IR ($CHCl_3$): ν = 1300, 1100 cm^{-1}.

^{1}H NMR: δ = 0.95 (t, 3H, J = 7 Hz), 1.20–1.50 (m, 2H), 1.56 (s, 3H), 1.68 (s, 3H), 2.49 (m, 1H), 2.91 (dd, 1H, J = 12, 14 Hz), 3.11 (dd, 1H, J = 4, 14 Hz), 3.58 (dd, 1H, J = 11, 13 Hz), 3.81 (ddd, 1H, J = 2, 4, 13 Hz).

6-Acetoxymethyl-2-methyloctan-4-one (35a); Typical Procedure:
To a solution of **34** (95 mg, 0.5 mmol) and methyl 3-methylbutanoate (58 mg, 0.5 mmol) in THF (5 mL) was added LDA (2.1 eq) under N_2 and the mixture was stirred for 30 min. Usual workup gave the crude oxo sulfone which was dissolved in 50% AcOH (5 mL) and heated at 70°C for 3 h. The crude product obtained through the usual extractive workup was acetylated with Ac_2O/pyridine. Chromatography over a short column of silica gel (EtOAc/hexane, 1:4) afforded **35a**; colorless oil.

$C_{12}H_{22}O_3$ calc. C 67.25 H 10.35
(214.3) found 67.27 10.17

IR ($CHCl_3$): ν = 2960, 1725, 1715, 1250 cm^{-1}.

^{1}H NMR: δ = 0.90 (d, 6H, J = 6 Hz), 0.92 (d, 1H, J = 6 Hz), 1.32 (m, 2H), 2.00 (s, 3H), 2.10–2.48 (6H), 3.98 (m, 2H).

3-(Acetoxymethyl)dodecan-5-one (**35b**): colorless oil.

$C_{15}H_{28}O_3$ calc. C 70.27 H 11.01
(265.6) found 70.20 10.88

IR ($CHCl_3$): ν = 2960, 2925, 1730, 1710, 1250 cm^{-1}.

^{1}H NMR: δ = 0.90 (m, 6H), 1.00–1.80 (m, 13H), 2.06 (s, 3H), 2.40 (m, 4H), 4.03 (m, 2H).

3-(Acetoxymethyl)tetradecan-5-one (**35c**): colorless oil.

$C_{17}H_{32}O_3$ calc. C 71.79 H 11.34
(284.4) found 71.50 11.04

IR ($CHCl_3$): ν = 2960, 2925, 1730, 1710, 1250 cm^{-1}.

^{1}H NMR: δ = 0.90 (m, 6H), 1.08–1.80 (m, 17H), 2.03 (s, 3H), 2.39 (m, 4H), 4.00 (m, 2H).

3-Acetoxymethyl-1-phenylpentan-1-one (**35d**): colorless oil.

$C_{14}H_{18}O_3$ calc. C 71.77 H 7.74
(234.3) found 71.94 7.63

IR ($CHCl_3$): ν = 3000, 1710, 1680, 1360 cm^{-1}.

^{1}H NMR: δ = 0.95 (t, 3H, J = 7 Hz), 1.42 (m, 2H), 1.98 (s, 3H), 2.41 (septet, 1H, J = 7 Hz), 2.98 (m, 2H), 4.09 (m, 2H), 7.36–7.68 (m, 3H), 7.98 (dd, 2H, J = 8, 2 Hz).

3-Acetoxymethyl-1-p-tolylpentan-1-one (**35e**): colorless oil.

$C_{15}H_{20}O_3$ calc. C 72.55 H 8.12
(248.3) found 72.34 7.96

IR ($CHCl_3$): ν = 3010, 2960, 1730, 1680, 1605 cm^{-1}.

^{1}H NMR: δ = 0.95 (t, 3H, J = 7 Hz), 1.44 (m, 2H), 1.96 (s, 3H), 2.40 (s, 3H), 2.40 (m, 1H), 2.94 (m, 2H), 4.06 (m, 2H), 7.24 (d, 2H, J = 8 Hz), 7.84 (d, 2H, J = 8 Hz).

2,2,6-Trimethyl-1,3-oxathiane (37):
To a mixture of 3-hydroxybutanediol (**36**, 6.5 g, 61 mmol) and 2,2-dimethoxypropane (2.2 equivs) was added $Et_2O \cdot BF_3$ (1 mL) at 0°C. After stirring overnight at r.t., the mixture was worked up in a usual manner followed by the distillation under reduced pressure to give **37**; yield: 5.6 g (63%); colorless oil; bp 81°C/40 Torr.

$C_7H_{14}OS$ calc. C 57.49 H 9.65
(146.2) found 57.70 9.66

IR ($CHCl_3$): ν = 2920 cm^{-1}.

^{1}H NMR: δ = 1.16 (d, 1H, J = 6 Hz), 1.54 (s, 3H), 1.68 (s, 3H), 1.20–1.88 (m, 2H), 2.62 (dt, 1H, J = 13, 4 Hz), 3.10 (td, 1H, J = 12, 3 Hz), 3.87 (m, 1H).

2,2,6-Trimethyl-1,3-oxathiane 3,3-Dioxide (**38**) was prepared by the procedure similar to that of **2**; yield: 79%; mp 117–119°C.

$C_7H_{14}O_3S$ calc. C 47.16 H 7.92
(178.2) found 46.86 7.82

IR ($CHCl_3$): ν = 1310, 1105 cm^{-1}.

^{1}H NMR: δ = 1.24 (d, 3 H, J = 6 Hz), 1.52 (s, 3 H), 1.74 (s, 3 H), 1.88–2.60 (m, 2 H), 3.03 (dt, 1 H, J = 14, 4 Hz), 3.34 (dt, 1 H, J = 4, 12 Hz), 4.15 (m, 1 H).

2-Hydroxyundecan-5-one (39):
Reaction of **38** (178 mg) with methyl heptanoate (66 μL, 1.0 equiv) in THF (10 mL) by method B afforded **39** as colorless oil; yield: 15 mg (62%) with recovery of **38** (12.5 mg, 7%).

$C_{11}H_{22}O_2$	calc.	C 70.92	H 11.90
(186.3)	found	71.26	11.54

IR ($CHCl_3$): ν = 3400, 2925, 1700 cm^{-1}.

^{1}H NMR: δ = 0.80–2.00 (m, 17 H), 2.41 (t, 2 H, J = 7 Hz), 3.78 (septet, 1 H, J = 7 Hz).

Undecane-2,5-dione (40):
A few drops of Jones reagent was added to a solution of **39** (95.0 mg) in acetone (2 mL) and stirred for 30 min at r.t. The mixture was treated with *i*-PrOH filtered, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), evaporated to leave a crude residue which was purified by chromatography on silica gel (CH_2Cl_2) to afford **40**; yield: 93.8 mg (~ 100%); colorless oil (Lit.[14] bp not yet reported).

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