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Functionalized esters as bis-electrophiles in a silicon-induced domino synthesis of annulated carbocycles

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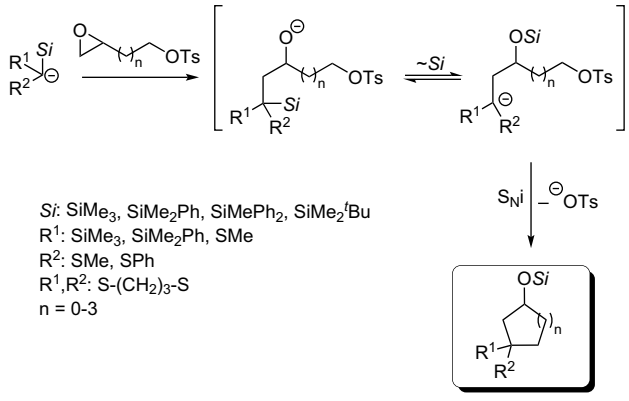
ABSTRACT

The reaction of silyl-substituted carbanion **1b** with arene-1,2-dicarboxylates **6**, **15** yields indenone derivatives **11**, **16** in a domino process involving silyl C→O migration and elimination. However, in a competing pathway, the initial addition of **1b** leads to lactone formation (**8**, **17**). Substrates **26**, **38** containing an ester group and a bromine substituent react with **1b** under substitution of the halogen not allowing silyl migration. But desilylation with TBAF gives reactive carbanions providing benzo-annulated cycloalkanones **29**, **40**.

1. Introduction

The silicon-induced domino reaction which we have developed has proven to be a versatile synthetic method for the preparation of various functionalized 4- to 7-ring carbocycles.[1] In this one-pot reaction, a reversible C→O silyl migration (Brook rearrangement)[2] is the key step. In Scheme 1, the method is illustrated for a silyl-substituted carbanion to react with an epoxy-tosylate as bis-electrophile.

Besides epoxy-tosylates, also bis-epoxides,[3] vinyl-epoxides,[4] or epoxy-aziridines[5] have been used in the domino process. In all these cases, the epoxy oxygen is the acceptor for the migrating silyl residue. We now considered other oxygen-containing functional groups as silicon acceptor and here report our results on the ester group.



Scheme 1. The silicon-induced domino process with epoxy-tosylates leads to functionalized 4–7-ring carbocycles by a [1,4]-Brook rearrangement.

2. Results and discussion

To exclude problems resulting from carbanion generation, in the first step of our investigations we did deuteration experiments to make sure that the C_1-building block **1a**, which can easily be synthesized from formaldehyde dimethylmercaptal,[6,7] is quantitatively deprotonated to carbanion **1b**. Stirring precursor **1a** in dry THF with 1.1 equiv of *n*-BuLi for 30 min at −78 °C and subsequent quenching with D_2O showed only 28% of deuteration to product **1c**, as determined by ^{1}H NMR spectroscopy. In extending literature information by Seebach et al.,[7] we found that addition of 1.1 equiv of *n*-BuLi to a 0.5 M solution of the precursor **1a** in dry THF at −78 °C, stirring for 30 min, then dipping the flask for 30 min into ice/water, followed by 15 min stirring at room temp are optimal conditions for quantitative lithiation to **1b**; the carbanion solution is then immediately used for reactions (Scheme 2).

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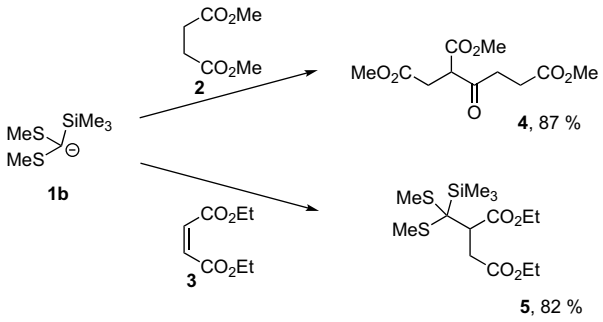
Scheme 2. (a) *n*-BuLi (1.1 equiv), Me_3SiCl (2.0 equiv), THF, −70 to 0 °C, overnight; (b) *n*-BuLi (1.1 equiv), THF, 30 min at −78 °C, then 30 min at 0 °C, finally 15 min at room temp; (c) D_2O.

Initial experiments showed that CH-acidic or α,β-unsaturated esters cannot be used in the process since the basic conditions favour competing reactions.[6] In case of dimethyl succinate (**2**), the carbanion **1b** undergoes no nucleophilic attack on the ester, instead the α-carbon is deprotonated, and ester condensation is observed yielding product **4**. Interestingly, the formation of a cyclization product as it is otherwise common for the action of bases on succinates[8] is not observed. To prevent deprotonation chemistry, the unsaturated ester diethyl maleate (**3**) was used and shows Michael addition to give succinate **5** (Scheme 3).

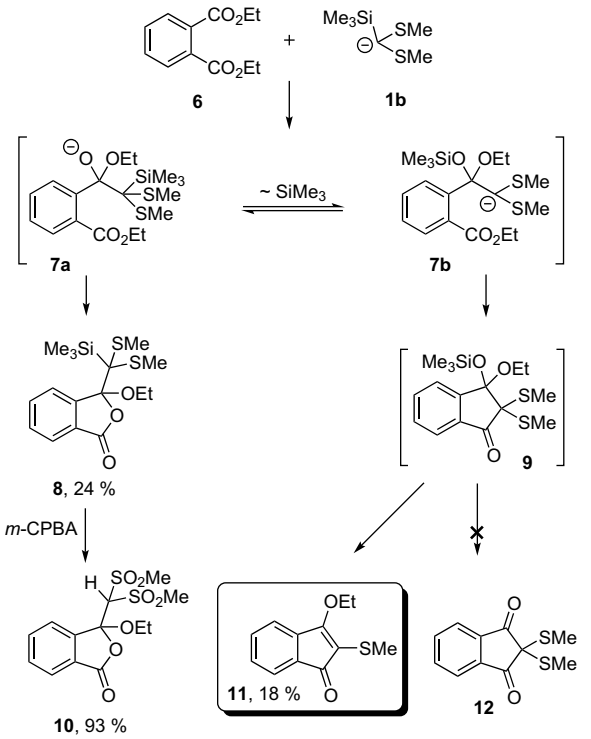


Scheme 3. CH-acidic or α,β-unsaturated esters cannot be used for the silicon-induced domino process.

For non-enolizable aromatic esters, such as phthalates, silicon migration should be possible and eventually lead to annulated rings. Therefore these esters are promising starting materials for the synthesis of new carbocyclic products by a [1,3]-Brook rearrangement.

Starting from diethyl phthalate (**6**), the desired nucleophilic addition of the silyl-substituted carbanion **1b** onto the ester function is indeed observed. However, this reaction yields two different products: γ-lactone **8** is isolated besides indenone **11**.[6] So at the stage of intermediate **7a**, lactonization competes with the C→O silyl shift to **7b**. Nevertheless, isolation of indenone **11** demonstrates that silyl migration to **7b** must have taken place, followed by ring-closure, providing intermediate **9**, which could not be isolated nor the expected product **12**. Instead, indenone **11** is formed as result of an uncommon elimination (Scheme 4). Thioacetal **8** was oxidized to sulfone **10**, which gave single crystals and allowed structural proof by X-ray analysis (Fig. 1).

The unusual formal elimination of a silyl methanesulfenate leading to indenone **11** called for a rigorous proof of structure. Unfortunately, product **11** is an oil and derivatization to the corresponding sulfone or 2,4-dinitrophenylhydrazone gave no suitable crystals for X-ray study. So in an independent synthesis (Scheme 5) 1,3-indandione (**13**) is first converted into 2,2-(bismethylthio)-1,3-indandione (**12**). The thioacetal function is then reduced by a method of Grossert and Dubey,[9] using ethanethiol and an excess of sodium hydride. From this reaction after acidification, sulfide **14** is isolated. Finally acid-catalyzed ethoxylation with triethyl orthoformate as water scavenger in dry ethanol[10] affords the previously obtained product **11** confirming the suggested structure.



Scheme 4. Competing reaction pathways in the reaction of phthalate **6** with carbanion **1b**.

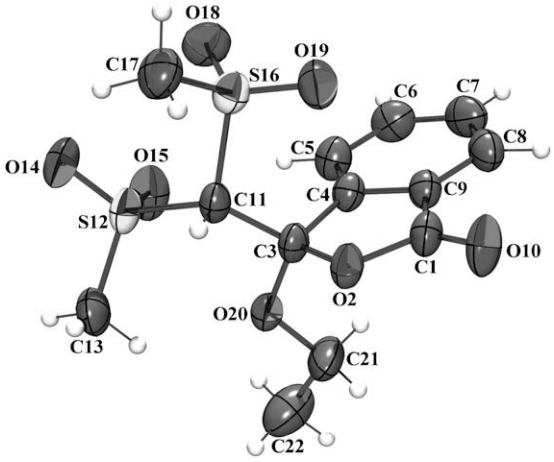
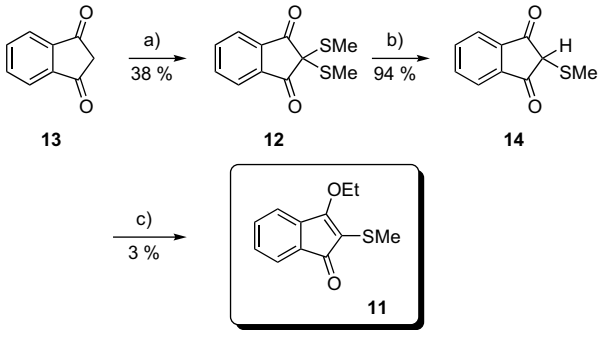


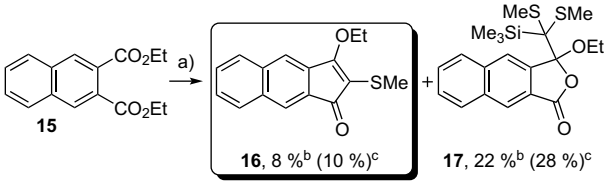
Figure 1. X-ray structure of γ-lactone **10**.[6]



Scheme 5. Independent synthesis of indenone **11**: (a) NaH (2.1 equiv), $MeSSO_2Me$ (2.1 equiv), THF, reflux, 7 h; (b) EtSH (3.0 equiv), NaH (4.0 equiv), THF, 0 °C to room temp, 3 h, then HCl, H_2O; (c) *p*-TsOH (5 mol %), $(EtO)_3CH$ (3.0 equiv), EtOH, reflux, 12 h.

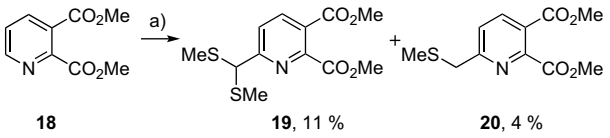
Dimethyl phthalate as starting material gave no better yields than ester **6**. Warming to room temp and longer stirring times neither result in higher conversions nor a better product yield. Additives such as DMPU, TMEDA or 12-crown-4 ether that have been reported to facilitate silyl migration[1b,11] did not improve the outcome of the reactions.

Furthermore, variations on the diester backbone seemed promising. Employing diethyl naphthalene-2,3-dicarboxylate (**15**) in the domino process, by analogy with the results for phthalate **6**, the reaction delivers carbocycle **16** along with lactone **17** (Scheme 6).



Scheme 6. Diethyl naphthalene-2,3-dicarboxylate: (a) **1b** (1.3 equiv), THF, −78 to −50 °C, overnight; (b) isolated yield; (c) isolated yield based on conversion, as judged by the amount of recovered starting material.

Additional promising targets for carbanion **1b** appeared to be hetarene-1,2-dicarboxylates. But in a complex reaction mixture a tendency for reaction at the hetarene ring rather than at the ester unit is seen in the reaction of pyridine derivative **18**, which with carbanion **1b** gives a nucleophilic aromatic substitution reaction at carbon 6 providing thioacetal **19**. The hydride, which must be formed at the same time partially reduces the thioacetal to sulfide **20**, which is isolated as well (Scheme 7).

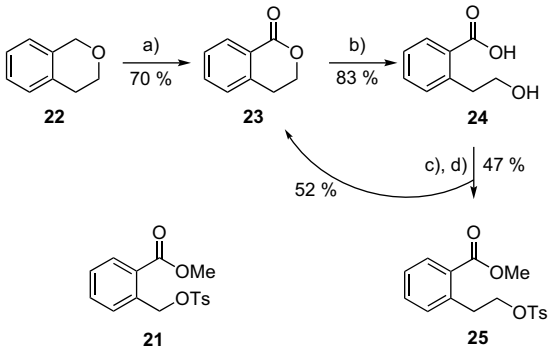


Scheme 7. Reactions of hetarenes: (a) **1b** (1.3 equiv), THF, −78 to −50 °C.

In addition to bis-esters as bis-electrophiles, we employed ester tosylates by analogy to epoxy-tosylates, which have already shown successful applications in the domino process (Scheme 1). The unknown methyl 2-(tosyloxymethyl)benzoate (**21**) appeared to be a promising candidate, but we were unable to tosylate the alcohol precursor methyl 2-(hydroxymethyl)benzoate due to competing phthalide formation.[13]

We were more successful in the synthesis of homologue **25**, a C_5-building block, which would eventually lead to annulated cyclohexanes ($C_5+C_1\rightarrow C_6$) by the silicon-induced domino reaction. Starting from isochromane (**22**) we obtained 1-isochromanone (**23**) after oxidation with selenium dioxide on a multigram-scale.[14] Saponification of δ-lactone **23**, followed by cautious acidification and conscientious exclusion of heat (to avoid recyclization)[15] affords hydroxy acid **24**. Methylation of the ester by TMS-diazomethane[12] and subsequent tosylation[16] of the crude product gives ester tosylate **25**, aside from recyclization to δ-lactone **23**, which could not be avoided (Scheme 8). Single crystals of the new bis-electrophile **25** allowed an X-ray structural analysis (Fig. 2).

The reaction of **1b** with ester tosylate **25** gave only minor conversion and no well-defined products. So as before the ester function shows low reactivity towards carbanion **1b**. Substitution of the tosyloxy group by chloride did not show better results. So bromide **26** was synthesized from the tosylate. In the reaction of **1b** with ester-bromide **26** we observed substitution of the



Scheme 8. Ester-tosylates. Synthesis of an ester-tosylate as C_5-building block, starting from isochromane: (a) SeO_2 (2.0 equiv), xylene, reflux, 42 h; (b) KOH (3.6 equiv), Et_2O, room temp, 36 h, then HCl, H_2O; (c) $TMSCHN_2$ (1.3 equiv), MeOH/THF (1:1), room temp, 15 min; (d) TsCl (2 equiv), pyridine (3 equiv), $CHCl_3$, 0 °C to room temp, 14 h.

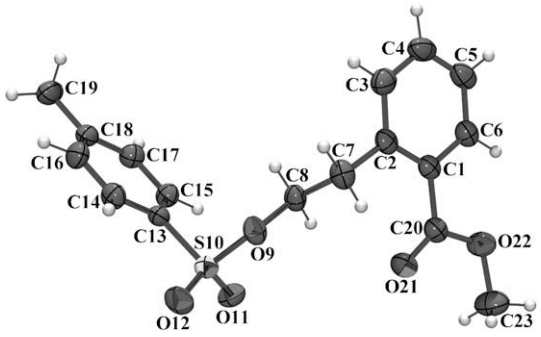
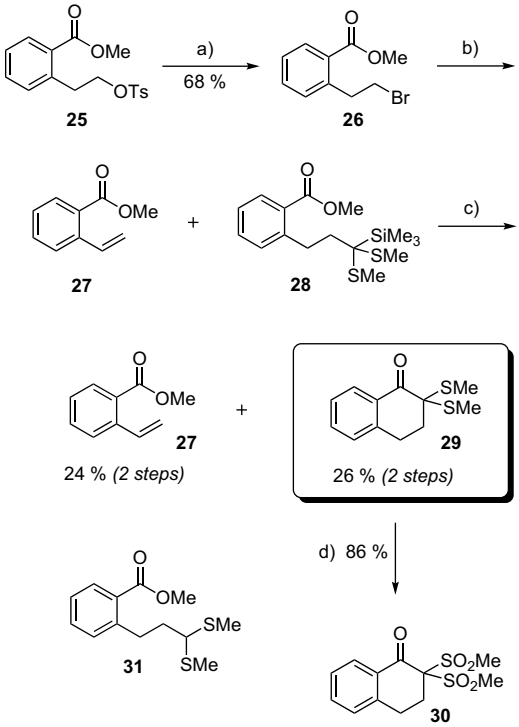


Figure 2. X-ray structure of ester tosylate **25**.



Scheme 9. C_5+C_1 annulation protocol: (a) LiBr (1.9 equiv), acetone, reflux, 12 h; (b) **1b** (1.3 equiv), THF, −78 °C to room temp, overnight (products **27**, **28** not separable); (c) anhydrous TBAF, THF, −78 °C to room temp, overnight (use of standard TBAF containing H_2O leads to desilylated product **31**; (d) *m*-CPBA (6.4 equiv), $CHCl_3$, room temp, 4 days.

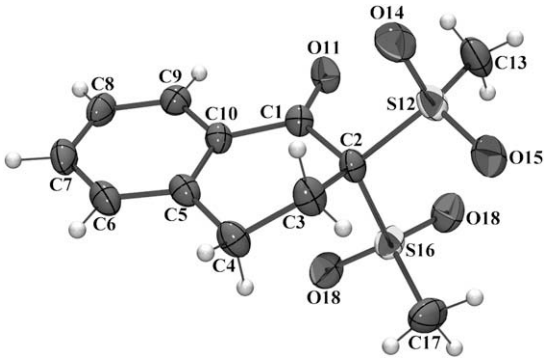


Figure 3. X-ray structure of 2,2-bis(methylsulfonyl)-1-tetralone (**30**).

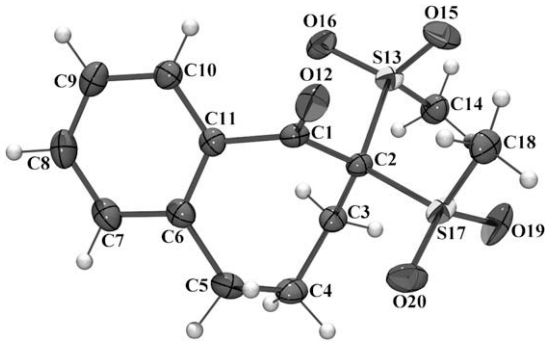
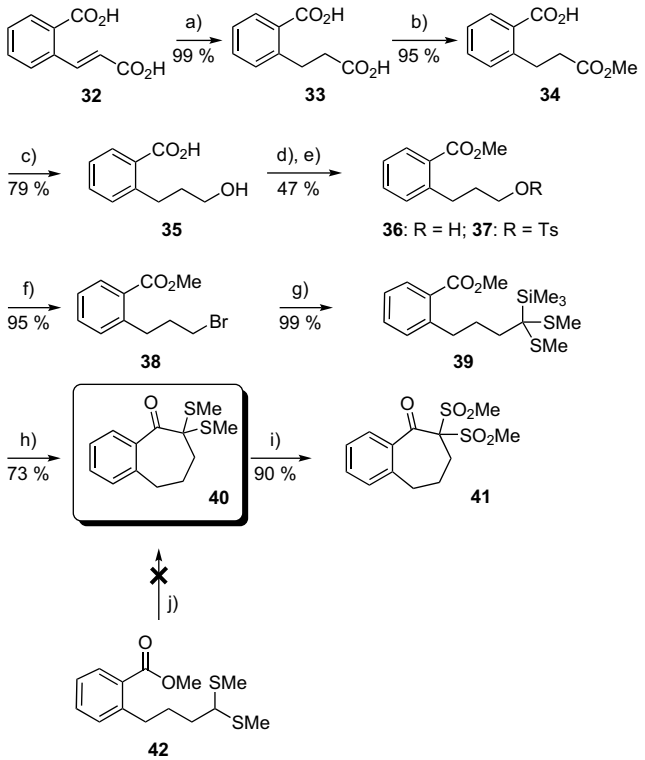


Figure 4. X-ray structure of 2,2-bis(methylsulfonyl)-1-benzosuberone (**41**).

bromide affording silylated compound **28** in an inseparable mixture with elimination product **27** (Scheme 9). In this substitution reaction of the bromide, silyl migration is not possible; so the ring-closure reaction was attempted via desilylation. Using dry TBAF[17] the new carbocycle **29** could successfully be isolated. Elimination product **27** and tetralone derivative **29** could now be separated. Analogous use of commercial TBAF gives only desilylated product **31**. Thioacetal **29** was oxidized to the corresponding sulfone **30**. The stability of compound **30** at room temp is limited, but single crystals could be grown for an X-ray structural analysis (Fig. 3).

As to the corresponding C_6-building block (Scheme 10), a literature report by Meise et al.[18a] revealed a multi-step procedure to get alcohol **36** from diacid **33**. Acid **33** is commercially available, but rather expensive; so we started one step back from the cheaper 2-carboxycinnamic acid (**32**). A method of Arterburn et al.[19] was adopted to reduce the double bond where saturated compound **33** is quantitatively obtained by a palladium-catalyzed hydrogenation using formic acid as hydride donor. Carboxylic acid **33** is selectively converted into the mono methyl ester by esterification in methanol at room temp. The ester is reduced to the corresponding alcohol by lithium borohydride in dioxane.[18a] We then combined two steps, not esterifying the benzoic acid **35** as described, but methylating it with TMS-diazomethane,[12] continuing the reaction simply after having evaporated the solvents in vacuo. Subsequent tosylation of the alcohol **36** afforded the novel ester tosylate **37**. This tosylate is more stable than its congener **25**.



Scheme 10. C_6+C_1 annulation protocol: (a) $PdCl_2$ (10 mol %), HCOOH (4 equiv), NaOH/H_2O, 65 °C, 24 h; (b) H_2SO_4 (cat.), MeOH, room temp, 30 min; (c) $LiBH_4$ (2.5 equiv), dioxane, 100 °C, 20 min, then HCl, H_2O; (d) $TMSCHN_2$ (1.7 equiv), MeOH/THF (1:1), 0 °C, 15 min; (e) TsCl (2 equiv), pyridine (3 equiv), $CHCl_3$, 0 °C to room temp, 14 h; (f) LiBr (2.0 equiv), acetone, reflux, 17 h; (g) **1b** (1.3 equiv), THF, −78 °C to room temp, overnight; (h) anhydrous TBAF, THF, −78 °C to room temp, overnight; (i) *m*-CPBA (10 equiv), $CHCl_3$, room temp, 4 days; (j) desilylated product **42** cannot be cyclized to **40** neither using *n*-BuLi nor *t*-BuLi.

Neither ester tosylate **37** nor the corresponding chloride reacted in the domino process with carbanion **1b** just as we had experienced with the analogous C_5-building block **25** and its chloride. The tosyloxy function can be displaced by bromide as well, using lithium bromide in acetone yielding bromo-ester **38**. The reaction of **38** with carbanion **1b** shows quantitative substitution of the bromide affording silylated product **39**. Treatment of **39** with anhydrous TBAF[17] gives a novel carbocycle, benzosuberone derivative **40**. With commercial TBAF, desilylated compound **42** is isolated, which could not be forced to cyclize neither by *n*-BuLi nor *t*-BuLi. Thioacetal **40** was oxidized to the corresponding sulfone **41** for an X-ray structural analysis (Scheme 10 and Fig. 4).

3. Conclusion

The isolation of indenone derivatives **11**, **16** confirms that addition of silyl-substituted carbanion **1b** to one ester moiety in phthalate **6** or naphthalene-2,3-dicarboxylate **15** may be followed by C→O silyl migration to give a new carbanion, ring-closure and finally, by a noteworthy 1,2-elimination step, carbocycles **11**, **16** (Schemes 4 and 6). This corresponds to a four-step domino process (Scheme 4). However, we were not able to suppress the competing cyclization to lactones **10**, **17** after the initial addition of carbanion **1b**. Furthermore, the reactions did not go to completion. The reluctance of the ester unit to add carbanion **1b** is also seen in the lack of ester reactivity in esters **26**, **38** with an additional bromine substituent. Here, the bromine is displaced and cyclization occurs only after TBAF-induced desilylation. However, products **29**, **40** are identical with the products, which would be formed by reaction of **1b** with the ester, silyl migration, cyclization and finally hydrolysis. Lack of ester reactivity is furthermore seen in the reaction of hetarene **18** with carbanion **1b**. Also the desilylated derivates **31**, **42** of **28**, **39** do not cyclize after deprotonation with alkyl lithiums. A special role of the tetrabutylamonium cation is apparent, which has also been seen in other work.[20]

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-200 and AMX-400 instruments in the solvents $CDCl_3$, DMSO-d_6 or MeOD as indicated. Chemical shifts are reported in δ (ppm) and coupling constants J in hertz. Unless otherwise stated, for NMR spectra the solvent peak (^{1}H NMR: $CDCl_3$=7.26, DMSO=2.50, MeOD=3.34; ^{13}C NMR: $CDCl_3$=77.4, DMSO=40.4, MeOD=49.9) was used as reference. The degree of substitution (C, CH, CH_2, CH_3) was determined by the DEPT-135 method. Melting points are uncorrected. IR spectra were recorded on a Bruker Vektor 22 FTIR spectrometer in the range of 400 to 4000 cm^{-1}. Elemental analyses were performed by the Institut für Pharmazeutische Chemie, Technische Universität Braunschweig. The GC–MS spectra (EI) were recorded either with a GC Hewlett-Packard 5980, Serie II/MS Hewlett Packard 5989 B, or a Varian GC3900 with SAT2100T mass spectrometer. The ESI mass spectra were measured with an Agilent LCMSD Series HP1100 with APIES. Samples were sprayed from methanol at a fragmentor voltage of 0 V, unless otherwise noted. HRMS spectra were measured at the *Institut für Organische Chemie, Leibniz Universität Hannover*. X-ray structural analysis of compound **10** was performed at *Mineralogisch-Petrographisches Institut, Universität Hamburg*; and of compounds **25**, **30** and **41** at the *Institut für Anorganische und Analytische Chemie, Technische Universität Clausthal*. TLC was performed on Merck 60 F_{254} precoated silica plates, spots were detected either by UV (254 nm, 366 nm) or dipping into a permanganate [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5 mL, 5% in H_2O), H_2O (300 mL)] or an anisaldehyde solution [3% *p*-methoxybenzaldehyde and 1% H_2SO_4 in MeOH] and heating. Flash chromatography was performed with silica gel 60 (Merck, 40–63 μm); the given mass is for the amount of silica gel used. Boiling range of petroleum ether: 60–70 °C. Absolute solvents (abs) were dried by standard laboratory methods and kept under nitrogen.

4.2. Synthesis and analytics

4.2.1. Lithio-bis(methylthio)(trimethylsilyl)methane (*1b*): optimized procedure for quantitative deprotonation

In an oven-dried Schlenk flask compound **1a**[6,7] (1.0 equiv) is placed under an inert and dry atmosphere, generated by at least three short evacuations (volatile compound!) with an oil pump, alternately ventilating with nitrogen; then dissolving in abs THF (0.5 M). To this solution *n*-BuLi (1.1 equiv) is added dropwise via syringe at −78 °C. The solution is stirred at −78 °C for 30 min, then 30 min at 0 °C and finally 15 min at room temp. The pale yellow solution of the carbanion is then immediately used for reactions.

4.2.2. Deutero-bis(methylthio)(trimethylsilyl)methane (*1c*)

A solution of carbanion **1b** (obtained using 100 mg, 0.55 mmol, of **1a**) was quenched by D_2O (1 mL). The mixture was diluted with Et_2O and washed with water. The organic layer was dried over Na_2SO_4 and the solvents removed in vacuo obtaining **1c** (89 mg, 89%) as a colourless liquid. $C_6H_{15}DS_2Si$; 181.41 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.16 (s, 6H, SCH_3), 0.17 (s, 9H, $SiMe_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=41.4 (t, J=21 Hz, 1C, CD), 15.2 (2C, SCH_3), −1.3 (3C, $SiMe_3$).

4.2.3. General procedure for reactions of carbanion *1b* with bis-electrophiles

The bis-electrophile (1.0 equiv) is placed in an oven-dried, rubber septum sealed Schlenk flask, evacuated by an oil pump and alternately ventilated with nitrogen at least 3×. Then abs THF is added to give a 0.25 M solution, which is cooled to −78 °C. A simultaneously prepared solution of carbanion **1b** (0.5 M, using 1.3 equiv of **1a** and 1.4 equiv *n*-BuLi as described above) is added dropwise via cannula or syringe. After complete addition, the temperature is slowly raised and the mixture stirred at −50 °C overnight. The reaction is quenched at −50 °C by water and the mixture is allowed to warm to room temp. After multiple extractions with Et_2O or CH_2Cl_2, the combined organic layers are dried over Na_2SO_4 and the solvents are removed on a rotary evaporator followed by purification of the crude product by flash chromatography.

4.2.4. Trimethyl 3-oxopentane-1,2,5-tricarboxylate (*4*)[6]

Under nitrogen at room temp, a solution of thioacetal **1a** (192 mg, 1.06 mmol, 1.0 equiv) in abs THF (7 mL) was treated dropwise with *n*-BuLi (1.6 M in hexane, 0.70 mL, 1.12 mmol, 1.1 equiv). After 5 min the solution was cooled to −80 °C, and DMPU (0.08 mL, 0.62 mmol, 0.6 equiv) was added. The obtained solution was then added to a solution of dimethyl succinate (**2**, 156 mg, 1.06 mmol, 1.0 equiv) in abs THF (27 mL) at −80 °C. The mixture was allowed to warm to −30 °C, observing a brightly yellow colour. After completion, the reaction was quenched with water, extracted with CH_2Cl_2, the combined organic layers dried over Na_2SO_4 and the solvents evaporated on a rotary evaporator. Purification of the crude product by flash chromatography (petroleum ether/EtOAc=10:1) afforded compound **4** (120 mg, 87%) as a colourless oil. $C_{11}H_{16}O_7$; 260.24 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.04 (dd, J=7.7, 6.8 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.14–2.80 (m, 4H, CH_2), 2.62 (t, J=6.6 Hz, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=202.7 (1C, C=O), 173.1 (1C, CO_2Me), 172.1 (1C, CO_2Me), 169.0 (1C, CO_2Me), 54.1 (1C, CH), 53.3 (1C, OCH_3), 52.5 (1C, OCH_3), 52.2 (1C, OCH_3), 37.7 (1C, CH_2), 32.5 (1C, CH_2), 28.1 (1C, CH_2). IR (film): ν_{max}=2957, 1739, 1438, 1167, 913, 745 cm^{-1}. MS (ESI$^+$): m/z=283 $[M+Na]^+$. Elemental analysis: found C 51.42%, H 6.42%, calcd C 50.77%, H 6.20%.

4.2.5. Diethyl 2-(bis(methylthio)(trimethylsilyl)methyl)-succinate (*5*)[6]

Under nitrogen at 0 °C, a solution of thioacetal **1a** (100 mg, 0.55 mmol, 1.1 equiv) in abs THF (4 mL) was treated with *n*-BuLi (1.6 M in hexane, 0.41 mL, 0.66 mmol, 1.3 equiv). After 30 min DMPU (0.08 mL, 0.62 mmol, 1.2 equiv) was added, the solution stirred at 0 °C for further 60 min and cooled to −78 °C. This solution was then added dropwise to a solution of diethyl maleate (**3**, 86 mg, 0.50 mmol, 1.0 equiv) in abs THF (5 mL) at −60 °C, the mixture turning yellow, then becoming darker. The reaction mixture was allowed to come to room temp, quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and the solvents evaporated on a rotary evaporator. Purification of the crude product by flash chromatography (petroleum ether/EtOAc=30:1) afforded compound **5** (144 mg, 82%) as a colourless oil. $C_{14}H_{28}O_4S_2Si$; 352.59 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=4.17 (q, J=7.0 Hz, 2H, OCH_2), 4.11 (q, J=7.1 Hz, 2H, OCH_2), 3.27 (dd, J=7.6, 6.5 Hz, 1H, CH), 3.18–2.95 (m, 2H, CH_2), 2.14 (s, 3H, SCH_3), 2.09 (s, 3H, SCH_3), 1.29 (t, J=7.1 Hz, 3H, CH_3), 1.24 (t, J=7.1 Hz, 3H, CH_3), 0.26 (s, 9H, $SiMe_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=173.1 (1C, C=O), 172.5 (1C, C=O), 61.4 (1C, OCH_2), 61.1 (1C, OCH_2), 49.1 (1C, CH), 48.3 (1C, C), 35.8 (1C, CH_2), 14.5 (1C, CH_3), 14.4 (1C, CH_3), 13.5 (1C, CH_3), 12.2 (1C, CH_3), 0.9 (3C, $SiMe_3$). IR (film): ν_{max}=2982, 2360, 1735, 1249, 913, 743 cm^{-1}. MS (ESI$^+$): m/z=375 $[M+Na]^+$. HRMS (ESI$^+$): $[M+Na]^+$ found 375.1093, calcd 375.1096.

4.2.6. 3-(Bis(methylthio)(trimethylsilyl)methyl)-3-ethoxyphthalide (*8*) and 3-ethoxy-2-(methylthio)-1-indenone (*11*)

Addition of carbanion **1b** [obtained using **1a** (529 mg, 2.93 mmol, 1.3 equiv), abs THF (6 mL), *n*-BuLi (1.6 M in hexane, 2.0 mL, 3.2 mmol, 1.4 equiv)] to a solution of diethyl phthalate (**6**, 500 mg, 2.25 mmol, 1.0 equiv) in abs THF (9 mL) showed

incomplete conversion and gave 780 mg of a red liquid as crude product. Purification by flash chromatography (78 g, petroleum ether/EtOAc=20:1) afforded excess of **1a** in an inseparable mixture with further nonpolar undefined side products; a mixture of **8** and **11** as a red oil (315 mg) and the recovered phthalate **6** (185 mg, 37%). Separation of **8** and **11** was achieved by a second flash chromatography (25 g, toluene/CH_2Cl_2=1:1) delivering lactone **8** (196 mg, 24%) as a slightly orange oil, and carbocycle **11** (90 mg, 18%) as a slowly solidifying orange oil. *Lactone* ***8***: $C_{16}H_{24}O_3S_2Si$; 356.58 g/mol. Mp 35–40 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.10–8.02 (m, 1H, $H_{ar.}$), 7.95–7.86 (m, 1H, $H_{ar.}$), 7.67–7.54 (m, 2H, $H_{ar.}$), 3.44–3.02 (m, 2H, OCH_2), 2.36 (s, 3H, SCH_3), 1.27 (s, 3H, SCH_3), 1.17 (t, J=7.0 Hz, 3H, CH_3), 0.38 (s, 9H, $SiMe_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=167.9 (1C, C=O), 145.0 (1C, $C_{ar.}$), 133.1 (1C, $CH_{ar.}$), 131.1 (1C, $CH_{ar.}$), 130.2 (1C, $C_{ar.}$), 126.4 (1C, $CH_{ar.}$), 125.3 (1C, $CH_{ar.}$), 115.8 (1C, C_{acetal}), 60.7 (1C, OCH_2), 50.9 (1C, C), 16.7 (1C, SCH_3), 15.3 (1C, SCH_3), 12.1 (1C, CH_3), 1.5 (3C, $SiMe_3$). IR (KBr): ν_{max}=2979, 2923, 1777, 1466, 1260, 1128, 1105, 919, 845 cm^{-1}. GC–MS (EI): m/z=356 [100%, M^+], 341 [20%], 311 [72%], 179 [32%]. HRMS (EI): [M^+] found 356.0935, calcd 356.0934. *Indenone* ***11***: $C_{12}H_{12}O_2S$; 220.29 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.44–7.22 (m, 4H, $H_{ar.}$), 4.98 (q, J=7.0 Hz, 2H, OCH_2), 2.32 (s, 3H, SCH_3), 1.51 (t, J=7.2 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ=194.0 (1C, C=O), 175.6 (1C, COEt), 140.6 (1C, $C_{ar.}$), 132.9 (1C, $CH_{ar.}$), 132.5 (1C, $C_{ar.}$), 130.5 (1C, $CH_{ar.}$), 121.4 (1C, $CH_{ar.}$), 119.2 (1C, $CH_{ar.}$), 102.6 (1C, CSMe), 68.9 (1C, OCH_2), 19.6 (1C, SCH_3), 15.8 (1C, CH_3). IR (KBr): ν_{max}=2981, 2923, 1712, 1613, 1553, 1467, 1377, 1350, 1296, 1156, 1079, 1007, 875, 769, 712, 691 cm^{-1}. GC–MS (EI): m/z=220 [100%, M^+]. HRMS (EI): [M^+] found 220.0559, calcd 220.0558.

4.2.7. 3-(Bis(methylsulfonyl)methyl)-3-ethoxy-phthalide (*10*)

Lactone **8** (100 mg, 0.28 mmol, 1.0 equiv) and *m*-CPBA (70%, 760 mg, 3.08 mmol, 11 equiv) were stirred in $CHCl_3$ (20 mL) at room temp for 12 h. An aqueous solution of $Na_2S_2O_3$ was added to destroy excess *m*-CPBA. The mixture was extracted with CH_2Cl_2 (3×20 mL), the combined organic layers were washed with satd $NaHCO_3$ (2×10 mL) and water (20 mL), dried over Na_2SO_4 and the solvents removed on a rotary evaporator. Purification of the residue by flash chromatography (petroleum ether/EtOAc=1:1) afforded sulfone **10** (91 mg, 93%) as a colourless solid. $C_{13}H_{16}O_7S_2$; 348.39 g/mol. Mp 134 °C. ^{1}H NMR (200 MHz, DMSO): δ=8.10–7.56 (m, 4H, $H_{ar.}$), 6.65 (s, 1H, CH), 3.36 (s, 3H, SO_2CH_3), 3.33 (s, 3H, SO_2CH_3), 3.30–2.87 (m, 2H, OCH_2), 1.10 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR (50 MHz, DMSO): δ=167.3 (1C, C=O), 143.2 (1C, $C_{ar.}$), 135.5 (1C, $CH_{ar.}$), 132.5 (1C, $CH_{ar.}$), 128.8 (1C, $C_{ar.}$), 125.8 (1C, $CH_{ar.}$), 125.5 (1C, $CH_{ar.}$), 105.7 (1C, C^{acetal}), 82.8 (1C, CH), 59.8 (1C, OCH_2), 49.7 (1C, SO_2CH_3), 46.7 (1C, SO_2CH_3), 15.1 (1C, CH_3). IR (film): ν_{max}=3419, 2936, 2916, 1770, 1330, 1135, 928, 784, 719 cm^{-1}. MS (ESI$^+$): m/z=371 [M+Na]$^+$.

4.2.8. X-ray analysis of *10*[6]

A suitable single crystal of the title compound was selected under a polarization microscope and mounted in a glass capillary (d=0.5 mm). The crystal structure was determined by X-ray diffraction analysis. Single crystal intensity data were collected by use of an Enraf-Nonius Kappa CCD equipped with a rotating anode (MoKα radiation, λ=0.71073 Å) [T=293(2) K]. The crystal structure was solved by Direct Methods using SHELXS-97[21a] and refined using alternating cycles of least squares refinements against F^2 (SHELXL-97).[21a] All non-H atoms were located in Difference Fourier maps and were refined with anisotropic displacement parameters. The H positions were determined by a final Difference Fourier Synthesis. For the presentation of the structure drawings the programs ORTEP[21b] and POV-Ray[21c] were applied. $C_{13}H_{16}O_7S_2$; M=348.39 g mol^{-1} crystallized in the monoclinic space group $P2_1/c$ with lattice parameters a=9.005(1) Å, b=22.292(1) Å, c=14.131(1) Å, β=147.03(1)°, V=1543.7(2) Å^3, Z=4, d_{calcd}=1.499 g cm^{-3}, F(000)=728 using 3449 independent reflections and 220 parameters. $R1$=0.0498, $wR2$=0.1208 [$I>2\sigma(I)$], goodness of fit on F^2=1.074, residual electron density=0.399 and −0.330 e Å^{-3}. Further details of the crystal structure investigations have been deposited with the Cambridge Crystallographic Data Center, CCDC-699488. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223) 336 033; e-mail: fileserv@ccdc.ac.uk; www.ccdc.cam.ac.uk).

4.2.9. 2,2-Bis(methylthio)-1,3-indandione (*12*)

Under nitrogen, a solution of 1,3-indandione (**13**, 500 mg, 3.42 mmol, 1.0 equiv) and *S*-methyl methanethiosulfonate (906 mg, 7.18 mmol, 2.1 equiv) in abs THF (10 mL) was added to a suspension of sodium hydride (60% in mineral oil, 287 mg, 7.18 mmol, 2.1 equiv) in abs THF (10 mL). A spontaneous black-violet tinct was observed. After heating at reflux for 7 h and stirring for additional 16 h at room temp, the dark reaction mixture was poured into water and extracted 3× with CH_2Cl_2 (red aqueous phase). The combined organic layers were dried over Na_2SO_4, filtrated and the solvents removed on a rotary evaporator. Purification of the oily brown residue by flash chromatography (70 g, petroleum ether/EtOAc=5:1) afforded thioacetal **12** (310 mg, 38%) as a beige solid. $C_{11}H_{10}O_2S_2$; 238.33 g/mol. Mp 74–76 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.03–7.84 (m, 4H, $H_{ar.}$), 2.34 (s, 6H, SCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ=193.4 (2C, C=O), 138.8 (2C, $C_{ar.}$), 136.8 (2C, $CH_{ar.}$), 124.8 (2C, $CH_{ar.}$), 60.4 (1C, SCS), 12.6 (2C, SCH_3). IR (KBr): ν_{max}=2919, 1741, 1704, 1589, 1417, 1351, 1328, 1252, 1157, 1087, 1024, 943, 865, 845, 765, 649, 614, 531 cm^{-1}. GC–MS (EI): m/z=238 [100%, M^+], 191 [42%]. HRMS (EI): [M^+] found 238.0123, calcd 238.0122.

4.2.10. 2-(Methylthio)-1,3-indandione (*14*)

NaH (60% in mineral oil, 504 mg, 12.6 mmol, 4.0 equiv) was suspended in abs THF (20 mL) under nitrogen and cooled by ice/water. Ethanethiol (0.70 mL, 9.45 mmol, 3.0 equiv) was added dropwise, and the mixture was stirred until the formation of gas ceased (5 min). Then a solution of thioacetal **12** (750 mg, 3.15 mmol, 1.0 equiv) in abs THF (20 mL) was added slowly via syringe, obtaining an ochre reaction mixture. The ice was removed, followed by additional stirring at room temp for 3 h. The suspension was poured into water (30 mL), and the resulting red mixture acidified by 1 M HCl (30 mL), observing a change of colour to orange. It was extracted with Et_2O (3×50 mL) until complete decolouration of the aqueous layer was reached. The combined organic layers were dried over Na_2SO_4 and the solvents removed on a rotary evaporator, obtaining a brown residue. Washing with petroleum ether (3×2 mL) and subsequent drying in vacuo gave **14** (568 mg, 94%) as a pale yellow powder. $C_{10}H_8O_2S$; 192.23 g/mol. Mp 133–135 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.06–7.84 (m, 4H, $H_{ar.}$), 3.85 (s, 1H, CH), 2.22 (s, 3H, SCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ=196.3 (2C, C=O), 142.0 (2C, $C_{ar.}$), 136.6 (2C, $CH_{ar.}$), 124.1 (2C, $CH_{ar.}$), 52.2 (1C, CH), 14.5 (1C, SCH_3). IR (KBr): ν_{max}=2905, 1707, 1582, 1429, 1246, 1160, 780, 754, 655, 492 cm^{-1}. MS (ESI$^+$): m/z=407 [2 M+Na]$^+$, 215 [M+Na]$^+$. HRMS (ESI$^+$): [M+H]$^+$ found 193.0328, calcd: 193.0323; no analytical data in the references.[22]

4.2.11. 3-Ethoxy-2-(methylthio)-1-indenone (*11*): independent synthesis

Sulfide **14** (100 mg, 0.52 mmol, 1.0 equiv) and *p*-TsOH·H_2O (5 mg, 0.03 mmol, 5 mol %) were dissolved in abs EtOH (5 mL) under nitrogen. Triethyl orthoformate (0.26 mL, 1.56 mmol, 3.0 equiv) was added and the mixture heated at reflux for 12 h. The red reaction mixture was diluted with Et_2O (50 mL) in spite of incomplete conversion. The mixture was washed 3× with satd $NaHCO_3$, the yellow organic layer dried over Na_2SO_4 and the solvents were

removed on a rotary evaporator. Purification of the crude product (9 mg) by flash chromatography (1 g, petroleum ether/EtOAc=11:1) afforded indenone **11** (3 mg, 3%) as a red oil (*for analytical data see above*).

4.2.12. 3-Ethoxy-2-(methylthio)-1H-cyclopenta[b]-naphthalen-1-one (**16**) and 3-(bis(methylthio)(trimethylsilyl)methyl)-3-ethoxynaphtho[2,3-c]furan-1(3H)-one (**17**)

Addition of carbanion **1b** [obtained using **1a** (87 mg, 0.48 mmol, 1.3 equiv), abs THF (1 mL), *n*-BuLi (2.4 M in hexane, 0.22 mL, 0.52 mmol, 1.4 equiv)] to a solution of diethyl ester **15** (100 mg, 0.37 mmol, 1.0 equiv) in abs THF (1.5 mL) showed incomplete conversion and gave 140 mg of a red oil as crude product. Purification by flash chromatography (14 g, petroleum ether/EtOAc=30:1) afforded lactone **17** (32 mg, 22%) as an orange oil, carbocycle **16** as an orange solid (8 mg, 8%); and recovered ester **15** (40 mg, 41%). *Carbocycle* ***16***: $C_{16}H_{14}O_2S$; 270.35 g/mol. Mp 45–73 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.47–7.45 (m, 6H, $H_{ar.}$), 5.02 (q, J=7.0 Hz, 2H, OCH_2), 2.40 (s, 3H, SCH_3), 1.55 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.7 (1C, C=O), 175.3 (1C, COEt), 135.9 (1C, $C_{ar.}$), 135.7 (1C, $C_{ar.}$), 134.5 (1C, $C_{ar.}$), 133.7 (1C, $C_{ar.}$), 130.8 (1C, $CH_{ar.}$), 129.6 (1C, $CH_{ar.}$), 128.7 (1C, $CH_{ar.}$), 127.8 (1C, $CH_{ar.}$), 122.2 (1C, $CH_{ar.}$), 118.8 (1C, $CH_{ar.}$), 108.5 (1C, CSMe), 69.0 (1C, OCH_2), 19.1 (1C, SCH_3), 15.9 (1C, CH_3). IR (film): ν_{max}=2924, 1698, 1545, 1459, 1302, 1199, 1120, 895, 779 cm^{-1}. GC–MS (EI): m/z=270 [100%, M^+]. HRMS (EI): [M^+] found 270.0715, calcd 270.0715. *Lactone* ***17***: $C_{20}H_{26}O_3S_2Si$; 406.63 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.48 (s, 1H, $H_{ar.}$), 8.45 (s, 1H, $H_{ar.}$), 8.07–8.00 (m, 2H, $H_{ar.}$), 7.72–7.58 (m, 2H, $H_{ar.}$), 3.46–3.10 (m, 2H, OCH_2), 2.40 (s, 3H, SCH_3), 1.18 (s, 3H, SCH_3), 1.18 (t, J=7.0 Hz, 3H, CH_3), 0.41 (s, 9H, $SiMe_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.0 (1C, C=O), 138.9 (1C, $C_{ar.}$), 135.6 (1C, $C_{ar.}$), 134.3 (1C, $C_{ar.}$),130.1 (1C, $CH_{ar.}$), 129.5 (1C, $CH_{ar.}$), 129.3 (1C, $CH_{ar.}$), 128.0 (1C, $CH_{ar.}$), 127.5 (1C, $C_{ar.}$), 126.3 (1C, $CH_{ar.}$), 125.6 (1C, $CH_{ar.}$), 116.0 (1C, C_{acetal}), 60.7 (1C, OCH_2), 51.1 (1C, C), 16.7 (1C, SCH_3), 15.4 (1C, CH_3), 12.3 (1C, SCH_3), 1.6 (3C, $SiMe_3$). IR (film): ν_{max}=2979, 2925, 1771, 1635, 1511, 1450, 1337, 1253, 1187, 1129, 1041, 920, 859, 751 cm^{-1}. GC–MS (EI): m/z=406 [85%, M^+], 391 [11%], 377 [23%], 359 [65%], 271 [100%, $M^+-Si(CH_3)_3-SCH_3-CH_3$], 227 [65%], 73 [44%]. HRMS (EI): [M^+] found 406.1094, calcd 406.1093.

4.2.13. Dimethyl 6-(bis(methylthio)methyl)-pyridine-2,3-dicarboxylate (**19**) and dimethyl 6-(methylthiomethyl)-pyridine-2,3-dicarboxylate (**20**)

Addition of carbanion **1b** [obtained using **1a** (265 mg, 1.47 mmol, 1.3 equiv), abs THF (3 mL), *n*-BuLi (2.4 M in hexane, 0.66 mL, 1.58 mmol, 1.4 equiv)] to a solution of dimethyl ester **18** (225 mg, 1.13 mmol, 1.0 equiv) in abs THF (4.5 mL) showed complete conversion and gave 380 mg of a yellow oil as crude product. A first flash chromatography (25 g, petroleum ether/EtOAc=4:1) afforded excess of **1a** in an inseparable mixture with non-polar undefined side products, impure **19** (70 mg) as a viscous orange to brown oil and impure **20** (100 mg) as an orange oil. Further flash chromatography of each compound afforded **19** (35 mg, 11%) as a yellow oil by (7 g, toluene/CH_2Cl_2=1:1) and **20** (13 mg, 4%) as a yellowish oil by (10 g, toluene/Et_2O=5:1). *Thioacetal* ***19***: $C_{12}H_{15}NO_4S_2$; 301.38 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.21 (d, J=8.3 Hz, 1H, $H_{ar.}$), 7.69 (d, J=8.3 Hz, 1H, $H_{ar.}$), 4.95 (s, 1H, CH), 3.99 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.15 (s, 6H, SCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ=167.0 (1C, C=O), 165.6 (1C, C=O), 163.2 (1C, $C_{ar.}$), 151.0 (1C, $C_{ar.}$), 139.1 (1C, $CH_{ar.}$), 124.7 (1C, $C_{ar.}$), 123.1 (1C, $CH_{ar.}$), 57.6 (1C, CH), 53.5 (1C, OCH_3), 53.3 (1C, OCH_3), 15.2 (2C, SCH_3). IR (film): ν_{max}=2953, 2919, 1732, 1586, 1434, 1394, 1292, 1229, 1148, 1074, 959, 911, 827, 758 cm^{-1}. GC–MS (EI): m/z=302 [10%, M^+], 270 [11%], 255 [100%, M^+-SCH_3], 223 [16%]. MS (ESI$^+$): m/z=324 [M+Na]$^+$. HRMS (ESI$^+$): [M+Na]$^+$ found 324.0343, calcd 324.0340. *Sulfide* ***20***: $C_{11}H_{13}NO_4S$; 255.29 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.65 (d, J=2.1 Hz, 1H, $H_{ar.}$), 8.10 (d, J=2.2 Hz, 1H, $H_{ar.}$), 3.99 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2), 2.00 (s, 3H, SCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ=166.7 (1C, C=O), 166.2 (1C, C=O), 152.1 (1C, $CH_{ar.}$), 149.2 (1C, $C_{ar.}$), 137.9 (1C, $CH_{ar.}$), 136.8 (1C, $C_{ar.}$), 127.2 (1C, $C_{ar.}$), 53.5 (1C, OCH_3), 53.4 (1C, OCH_3), 35.2 (1C, CH_2), 15.3 (1C, SCH_3). IR (film): ν_{max}=2954, 1731, 1562, 1435, 1298, 1137, 1078, 963, 795 cm^{-1}. GC–MS (EI): m/z=255 [16%, M^+], 224 [54%], 180 [100%, $M^+-OCH_3-CO_2CH_3$], 139 [93%]. MS (ESI$^+$): m/z=278 [M+Na]$^+$. HRMS (ESI$^+$): [M+H]$^+$ found 256.0643, calcd 256.0644.

4.2.14. 1-Isochromanone (**23**)[14]

Isochromane (6.37 g, 47.5 mmol, 1.0 equiv) and selenium dioxide (5.27 g, 47.5 mmol, 1.0 equiv) were stirred in xylene (50 mL, isomers) under reflux for 20 h. The black mixture was allowed to cool, and a second portion of selenium dioxide (5.27 g, 47.5 mmol, 1.0 equiv) was added. The mixture was heated at reflux for additional 22 h, then filtrated and the xylene was removed on a rotary evaporator. Purification of the red residue by flash chromatography (240 g, petroleum ether/EtOAc=5:1) afforded δ-lactone **23** (4.91 g, 70%) as a pale red liquid. $C_9H_8O_2$; 148.16 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.11–8.07 (m, 1H, $H_{ar.}$), 7.58–7.50 (m, 1H, $H_{ar.}$), 7.43–7.35 (m, 1H, $H_{ar.}$), 7.28–7.24 (m, 1H, $H_{ar.}$), 4.53 (t, J=6.0 Hz, 2H, OCH_2), 3.06 (t, J=6.0 Hz, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=165.5 (1C, C=O), 139.9 (1C, $C_{ar.}$), 134.0 (1C, $CH_{ar.}$), 130.8 (1C, $CH_{ar.}$), 128.0 (1C, $CH_{ar.}$), 127.6 (1C, $CH_{ar.}$), 125.7 (1C, $C_{ar.}$), 67.7 (1C, OCH_2), 28.2 (1C, CH_2).

4.2.15. 2-(2-Hydroxyethyl)benzoic acid (**24**)[15]

Powdered KOH (4.9 g, 87 mmol, 2 equiv) was added to a solution of 1-isochromanone (**23**, 6.45 g, 43.5 mmol, 1.0 equiv) in Et_2O (120 mL) and the suspension was stirred at room temp for 12 h. A second portion of powdered KOH (4.0 g, 71 mmol, 1.6 equiv) was added and the mixture stirred at room temp for additional 24 h. After complete conversion (TLC) the ethereal solution was decanted, the residue was washed with additional ether, dissolved in water (70 mL) and cooled by ice/water. The aqueous solution was acidified with 1 M HCl (130 mL), then extracted 3× with Et_2O. The combined ethereal layers were shortly dried over Na_2SO_4 and the solvents removed in vacuo without any heat. Hydroxy acid **24** (5.97 g, 83%) was obtained as a beige solid. $C_9H_{10}O_3$; 166.17 g/mol. Mp 79–81 °C (lit. *white crystals, which slowly turn into lactone when exposed to air*, mp 87 °C). ^{1}H NMR (200 MHz, DMSO): δ=12.84 (s, 1 H, CO_2H), 7.78–7.74 (m, 1 H, $H_{ar.}$), 7.49–7.41 (m, 1 H, $H_{ar.}$), 7.33–7.24 (m, 2 H, $H_{ar.}$), 4.65 (s, 1 H, OH), 3.58 (t, J=7.0 Hz, 2 H, OCH_2), 3.07 (t, J=7.0 Hz, 2 H, CH_2). ^{13}C NMR (50 MHz, MeOD): δ=172.0 (1 C, C=O), 142.4 (1 C, $C_{ar.}$), 133.8 (2 C, $CH_{ar.}$), 132.8 (1 C, $C_{ar.}$), 132.7 (1 C, $CH_{ar.}$), 128.2 (1 C, $CH_{ar.}$), 65.0 (1 C, OCH_2), 39.4 (1 C, CH_2).

4.2.16. Methyl 2-(2-tosyloxyethyl)benzoate (**25**)

Acid **24** (6.07 g, 36.5 mmol, 1.0 equiv) was dissolved in abs THF/abs MeOH (1:1, 60 mL) under nitrogen and cooled to 0 °C. $TMSCHN_2$ (2.0 M in Et_2O, 24 mL, 48 mmol, 1.3 equiv) was added within 15 min via syringe until a persistent yellowish colour was observed and the development of gas ceased. The volatile compounds were removed on a rotary evaporator without any heating (!) and the colourless oily residue was dissolved in abs $CHCl_3$ (65 mL) under nitrogen. At 0 °C, first a solution of TsCl (13.8 g, 72 mmol, 2 equiv) in abs $CHCl_3$ (20 mL) was added via syringe, immediately followed by the addition of abs pyridine (9 mL, 108 mmol, 3 equiv). The cooling bath was removed and the solution stirred at room temp for 14 h. More $CHCl_3$ was added and the mixture was washed with 0.1 M HCl (200 mL). The aqueous phase was tested for acidity (slightly acidic), then it was extracted 2× with $CHCl_3$. The combined organic layers were washed 2× with satd $NaHCO_3$ (!), dried over Na_2SO_4, filtrated and the solvents removed on a rotary evaporator at 30 °C. Purification of the crude product

(14.3 g yellow oil) by flash chromatography (250 g, petroleum ether/EtOAc=gradient, 6:1 to 2:1) afforded tosylate **25** (5.74 g, 47%) as a slowly solidifying oil, giving a waxy beige solid (mp 54–56 °C) as well as lactone **23** (2.84 g, 52%, *analytics see above*) as a yellow oil. Tosylate **25** was partially crystallized from petroleum ether/EtOAc in the cold, giving a snow-white solid (mp 60–61 °C). Especially in $CHCl_3$ its stability is limited. Single crystals (mp 60–61 °C) for X-ray analysis were grown from petroleum ether/CH_2Cl_2. *Tosylate* ***25***: $C_{17}H_{18}O_5S$; 334.39 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.88 (dd, J=7.7, 1.5 Hz, 1H, $H_{ar.}$), 7.67–7.63 (m, 2H, $H_{ar.}$), 7.42 (ddd, J=7.4, 1.6 Hz, 1H, $H_{ar.}$), 7.33–7.22 (m, 4H, $H_{ar.}$), 4.29 (t, J=6.5 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.31 (t, J=6.5 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3^{Ts}). ^{13}C NMR (50 MHz, $CDCl_3$): δ=167.8 (1C, C=O), 144.8 (1C, $C_{ar.}$), 138.6 (1C, $C_{ar.}$), 133.3 (1C, $C_{ar.}$), 132.7 (1C, $CH_{ar.}$), 132.6 (1C, $CH_{ar.}$), 131.4 (1C, $CH_{ar.}$), 130.0 (2C, $CH_{ar.}$), 129.6 (1C, $C_{ar.}$), 128.2 (2C, $CH_{ar.}$), 127.4 (1C, $CH_{ar.}$), 71.0 (1C, CH_2OTs), 52.4 (1C, OCH_3), 34.7 (1C, CH_2), 22.0 (1C, CH_3). IR (film): ν_{max}=2953, 1719, 1599, 1577, 1492, 1435, 1359, 1266, 1176, 1090, 964, 907, 817, 777, 708, 664, 555, 434 cm^{-1}. GC–MS (EI): m/z=303 [1%, M^+-OCH_3], 149 [100%, M^+-CH_2OTs], 118 [37%], 91 [31%]. HRMS (ESI^+): $[M+Na]^+$ found 357.0775, calcd 357.0773.

4.2.17. *X-ray analysis of* ***25***

A suitable single crystal of the title compound was selected under a polarization microscope and mounted in a glass capillary (d=0.3 mm). The crystal structure was determined by X-ray diffraction analysis using graphite monochromated MoKα radiation (0.71073 Å), whereas the scattering intensities were collected with a single crystal diffractometer (STOE IPDS II). The crystal structure was solved by Direct Methods using SHELXS-97[21a] and refined using alternating cycles of least squares refinements against F^2 (SHELXL-97).[21a] All non-H atoms were located in Difference Fourier maps and were refined with anisotropic displacement parameters. The H positions were determined by a final Difference Fourier Synthesis. For the presentation of the structure drawings the programs ORTEP[21b] and POV-Ray[21c] were applied. $C_{17}H_{18}O_5S$, M=334.39 g mol^{-1} crystallized in the triclinic space group P-1 with lattice parameters a=7.638(1) Å, b=8.410(1) Å, c=14.338(3) Å, α=74.14(1)°, β=84.17(1)°, γ=64.58(1)°, V=800.0(2) Å^3, Z=2, d_{calcd}=1.388 g cm^{-3}, F(000)=352 using 2767 independent reflections and 280 parameters. $R1$=0.0358, $wR2$=0.0819 [$I>2\sigma(I)$], goodness of fit on F^2=1.055, residual electron density=0.253 and −0.326 e Å^{-3}. Further details of the crystal structure investigation have been deposited with the Cambridge Crystallographic Data Center, CCDC-699489. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223) 336 033; e-mail: fileserv@ccdc.ac.uk; www.ccdc.cam.ac.uk).

4.2.18. *Methyl 2-(2-bromoethyl)benzoate (****26****)*[23]

Under nitrogen, tosylate **25** (206 mg, 0.62 mmol, 1.0 equiv) and LiBr (104 mg, 1.9 mmol, 1.9 equiv) were stirred in abs acetone (10 mL) at reflux for 12 h. The solvents were removed by a rotary evaporator. Purification by flash chromatography (10 g, petroleum ether/EtOAc=50:1) afforded bromide **26** (103 mg, 68%) as a colourless oil. $C_{10}H_{11}BrO_2$; 243.10 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.98–7.94 (m, 1H, $H_{ar.}$), 7.52–7.44 (m, 1H, $H_{ar.}$), 7.38–7.28 (m, 2H, $H_{ar.}$), 3.91 (s, 3H, OCH_3), 3.69–3.61 (m, 2H, CH_2), 3.55–3.46 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=167.8 (1C, C=O), 140.9 (1C, $C_{ar.}$), 132.6 (1C, $CH_{ar.}$), 132.3 (1C, $CH_{ar.}$), 131.5 (1C, $CH_{ar.}$), 129.7 (1C, $C_{ar.}$), 127.5 (1C, $CH_{ar.}$), 52.5 (1C, OCH_3), 38.5 (1C, CH_2), 33.4 (1C, CH_2).

4.2.19. *Methyl 2-(3,3-bis(methylthio)-3-(trimethylsilyl)-propyl)benzoate (****28****)*

Addition of carbanion **1b** [obtained using **1a** (762 mg, 4.23 mmol, 1.3 equiv), abs THF (8.5 mL), n-BuLi (2.4 M in hexane, 1.9 mL, 4.55 mmol, 1.4 equiv)] to a solution of bromide **26** (790 mg, 3.25 mmol, 1.0 equiv) in abs THF (13 mL) with the reaction temperature of the pale pink solution after 30 min at −78 °C slowly being raised to room temp in a Dewar overnight (16 h, conversion not detectable by TLC, petroleum ether/EtOAc, same R_f for starting material and product) gave 1.22 g of a yellow liquid as crude product. Excess of **1a** was separated by flash chromatography (120 g, petroleum ether/EtOAc=500:1) obtaining an inseparable mixture of **27** and **28** (680 mg, yellow oil). *Methyl 2-vinylbenzoate (****27****)*:[24] $C_{10}H_{10}O_2$; 162.19 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.91–7.86 (m, 1H, $H_{ar.}$), 7.61–7.40 (m, 3H, $H_{ar.}$), 7.32–7.28 (m, 1H, H_{vinyl}), 5.65 (dd, J=17.4, 1.8 Hz, 1H, H_{vinyl}), 5.36 (dd, J=10.9, 1.3 Hz, 1H, H_{vinyl}), 3.90 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.2 (1C, C=O), 139.9 (1C, $C_{ar.}$), 136.2 (1C, CH), 132.5 (1C, $CH_{ar.}$), 130.7 (1C, $CH_{ar.}$), 128.9 (1C, $C_{ar.}$), 127.8 (1C, $CH_{ar.}$), 127.6 (1C, $CH_{ar.}$), 116.8 (1C, CH_2), 52.5 (1C, OCH_3). *Silylated product* ***28***: $C_{16}H_{26}O_2S_2Si$; 342.59 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.89–7.22 (m, 4H, $H_{ar.}$), 3.90 (s, 3H, OCH_3), 3.21–3.16 (m, 2H, CH_2), 2.09 (s, 6H, SCH_3), 2.08–2.03 (m, 2H, CH_2), 0.28 (s, 9H, $SiMe_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4 (1C, C=O), 144.1 (1C, $C_{ar.}$), 132.4 (1C, $CH_{ar.}$), 131.3 (1C, $CH_{ar.}$), 131.0 (1C, $CH_{ar.}$), 130.1 (1C, $C_{ar.}$), 126.4 (1C, $CH_{ar.}$), 52.5 (1C, OCH_3), 47.9 (1C, C), 40.2 (1C, CH_2), 31.9 (1C, CH_2), 11.7 (2C, SCH_3), −0.5 (3C, $SiMe_3$). IR (film): ν_{max}=2952, 2919, 1723, 1685, 1601, 1575, 1484, 1434, 1257, 1133, 1083, 843, 755, 714 cm^{-1}. GC–MS (EI): m/z=327 [100%, M^+−Me], 223 [59%], 91 [78%]. MS (ESI^+): m/z=365 $[M+Na]^+$. HRMS (ESI^+): $[M+Na]^+$ found 365.1041, calcd 365.1041.

4.2.20. *2,2-Bis(methylthio)-1-tetralone (****29****)*

TBAF·3H_2O (2.88 g, 9.1 mmol, 4.6 equiv) was placed in a Schlenk flask under nitrogen, and was dissolved in abs THF (28 mL). After cooling to 0 °C, hexamethyldisilazane (HMDS, 8.5 mL, 41 mmol, 20.7 equiv) was added, the cooling bath removed and the mixture stirred at room temp for 16 h. Under intense stirring, the volatile compounds were then condensed into a cooling trap (liquid N_2) with an oil pump vacuum. The vacuum was held for several hours until a solid brownish residue was obtained. After ventilation with nitrogen, the solid was broken into small pieces by spattle in a nitrogen counter current, and the solid again conscientiously dried in vacuum until an optically dry beige solid was obtained (about 6 h). The flask was ventilated with nitrogen, the solid dissolved in abs THF (21 mL) and cooled to −78 °C. Then a solution of silylated compound **28** (*inseparable mixture from the prior reaction*, 680 mg, <1.98 mmol, <1 equiv) in abs THF (35 mL) was slowly added via syringe. The reaction temperature was slowly allowed to rise to room temp overnight. The orange solution was quenched with water (100 mL) after 16 h, observing decolouration. The mixture was extracted with CH_2Cl_2 (4×60 mL), the combined organic layers dried over Na_2SO_4 and the solvents removed on a rotary evaporator. Purification of the crude product (640 mg, brown oil) by flash chromatography (60 g, petroleum ether/EtOAc=500:1) afforded styrene **27** (210 mg, 24% *over two steps, for analytical data see above*) as a yellowish liquid; and tetralone **29** (205 mg, 26% *over two steps*) as a colourless oil. $C_{12}H_{14}OS_2$; 238.37 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.15–8.11 (m, 1H, $H_{ar.}$), 7.52–7.44 (m, 1H, $H_{ar.}$), 7.37–7.29 (m, 1H, $H_{ar.}$), 7.23–7.19 (m, 1H, $H_{ar.}$), 3.08 (t, J=6.3 Hz, 2H, CH_2), 2.60 (t, J=6.3 Hz, 2H, CH_2), 2.06 (s, 6H, SCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ=188.8 (1C, C=O), 142.4 (1C, $C_{ar.}$), 133.8 (1C, $CH_{ar.}$), 130.6 (1C, $C_{ar.}$), 129.2 (1C, $CH_{ar.}$), 128.8 (1C, $CH_{ar.}$), 127.3 (1C, $CH_{ar.}$), 65.1 (1C, C), 35.8 (1C, CH_2), 26.8 (1C, CH_2), 11.6 (2C, SCH_3). IR (film): ν_{max}=2917, 1673, 1600, 1454, 1426, 1355, 1292, 1220, 1157, 1124, 1025, 965, 889, 815, 747, 636 cm^{-1}. GC–MS (EI): m/z=238 [10%, M^+], 191 [100%, M^+-SCH_3], 163 [24%]. HRMS (EI): [M^+] found 238.0486, calcd 238.0486.

4.2.21. *2,2-Bis(methylsulfonyl)-1-tetralone (****30****)*

A solution of thioacetal **29** (50 mg, 0.21 mmol, 1.0 equiv) and m-CPBA (77%, 300 mg, 1.34 mmol, 6.4 equiv) in $CHCl_3$ (20 mL) was stirred at room temp for 4 days. The mixture was diluted with Et_2O,

washed with 10% $Na_2S_2O_3$, 2×satd $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and the solvents were removed on a rotary evaporator. Purification of the crude product by flash chromatography (15 g, petroleum ether/EtOAc=5:1) afforded sulfone **30** (53 mg, 86%) as a colourless solid. Single crystals for X-ray analysis were grown from petroleum ether/CH_2Cl_2. $C_{12}H_{14}O_5S_2$; 302.37 g/mol. Mp 147–153 °C (decomposition). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.11–8.07 (m, 1H, $H_{ar.}$), 7.63–7.55 (m, 1H, $H_{ar.}$), 7.42–7.34 (m, 1H, $H_{ar.}$), 7.30–7.26 (m, 1H, $H_{ar.}$), 3.44 (s, 6H, SO_2CH_3), 3.36 (t, J=6.4 Hz, 2H, CH_2), 3.09 (t, J=6.2 Hz, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=184.1 (1C, C=O), 142.9 (1C, $C_{ar.}$), 135.9 (1C, $CH_{ar.}$), 132.1 (1C, $C_{ar.}$), 129.3 (1C, $CH_{ar.}$), 129.0 (1C, $CH_{ar.}$), 128.0 (1C, $CH_{ar.}$), 88.5 (1C, C), 41.4 (2C, SO_2CH_3), 25.4 (1C, CH_2), 25.3 (1C, CH_2). IR (KBr): ν_{max}=3023, 2930, 1677, 1597, 1463, 1311, 1237, 1200, 1133, 954, 881, 782, 741 cm^{-1}. GC–MS (EI): m/z=302 [5%, M^+], 223 [39%], 144 [100%, $M^+-SO_2CH_3$], 115 [50%].

4.2.22. *X-ray analysis of* ***30***

Procedure analogous to X-ray study of compound **25**. $C_{12}H_{14}O_5S_2$, M=302.37 g mol^{-1} crystallized in the monoclinic space group $P2_1/c$ with lattice parameters a=14.627(3) Å, b=6.0043(7) Å, c=15.082(4) Å, β=99.45(2)°, V=1306.6(4) Å^3, Z=4, d_{calcd}=1.537 g cm^{-3}, $F(000)$=632 using 2211 independent reflections and 229 parameters. $R1$=0.0433, $wR2$=0.0866 [$I>2\sigma(I)$], goodness of fit on F^2=1.076, residual electron density=0.300 and −0.327 e Å^{-3}. Further details of the crystal structure investigation have been deposited with the Cambridge Crystallographic Data Center, CCDC-699486. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(1223) 336 033; e-mail: fileserv@ccdc.ac.uk; www.ccdc.cam.ac.uk).

4.2.23. *Methyl 2-(3,3-bis(methylthio)propyl)benzoate (****31****)*

Desilylated product **31** (10 mg, 0.04 mmol) was obtained as a colourless oil after flash chromatography (petroleum ether/EtOAc=500:1), from a reaction analogous to the preparation of **29** using not conscientiously dried TBAF, but working with an oily residue. $C_{13}H_{18}O_2S_2$; 270.41 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.90–7.87 (m, 1H, $H_{ar.}$), 7.49–7.39 (m, 1H, $H_{ar.}$), 7.31–7.22 (m, 2H, $H_{ar.}$), 3.90 (s, 3H, OCH_3), 3.66 (t, J=7.2 Hz, 1H, CH), 3.22–3.14 (m, 2H, CH_2), 2.11 (s, 6H, SCH_3), 2.09–2.02 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.3 (1C, C=O), 143.5 (1C, $C_{ar.}$), 132.4 (1C, $CH_{ar.}$), 131.6 (1C, $CH_{ar.}$), 131.2 (1C, $CH_{ar.}$), 129.9 (1C, $C_{ar.}$), 126.6 (1C, $CH_{ar.}$), 54.6 (1C, CH), 52.4 (1C, OCH_3), 36.8 (1C, CH_2), 33.0 (1C, CH_2), 13.0 (2C, SCH_3). IR (film): ν_{max}=2917, 1721, 1434, 1260, 1123, 1082, 756, 710 cm^{-1}. MS (ESI$^+$): m/z=309 [M+O+Na]$^+$ (*thioacetal* ***31*** *is readily oxidized to the corresponding sulfoxide on exposition to air.*), 293 [M+Na]$^+$; HRMS (ESI$^+$): [M+O+Na]$^+$ found 309.0598, calcd 309.0595.

4.2.24. *2-(2-Carboxyethyl)benzoic acid (****33****)*[18b]

$PdCl_2$ (461 mg, 2.6 mmol, 10 mol %) was added to a solution of 2-carboxycinnamic acid (**32**, 5.00 g, 26.0 mmol, 1.0 equiv) in 2.5 M aqueous NaOH (400 mL). Formic acid (3.9 mL, 104 mmol, 4.0 equiv) was added, the flask equipped with an air cooler, and the mixture stirred at 65 °C for 24 h. The black palladium particles were removed by filtration, and the basic solution washed 2× with Et_2O. The aqueous phase was acidified to pH 1–2 with concd HCl, obtaining a fluffy white precipitate, which was dissolved by the addition of EtOAc. The mixture was extracted 4× with EtOAc, the combined organic layers dried over Na_2SO_4 and the solvents removed in vacuo. Saturated acid **33** (4.98 g, 99%) was obtained as a colourless crystalline solid. *Use of 5 mol% $PdCl_2$ under identical reaction conditions resulted in incomplete reduction*! Acids **32** and **33** are distinguishable by TLC (CH_2Cl_2/MeOH=1:1). $C_{10}H_{10}O_4$; 194.18 g/mol. Mp 167–169 °C (lit. 166–168 °C). ^{1}H NMR (200 MHz, MeOD): δ=7.96–7.91 (m, 1H, $H_{ar.}$), 7.52–7.44 (m, 1H, $H_{ar.}$), 7.37–7.27 (m, 2H, $H_{ar.}$), 3.28 (t, J=8.0 Hz, 2H, CH_2), 2.64 (t, J=8.0 Hz, 2H, CH_2). ^{13}C NMR (50 MHz, DMSO): δ=174.7 (1C, CO_2H), 169.6 (1C, CO_2H), 142.8 (1C, $C_{ar.}$), 132.7 (1C, $CH_{ar.}$), 131.7 (1C, $CH_{ar.}$), 131.4 (1C, $C_{ar.}$), 131.2 (1C, $CH_{ar.}$), 127.2 (1C, $CH_{ar.}$), 36.3 (1C, CH_2), 30.0 (1C, CH_2).

4.2.25. *2-(2-Methoxycarbonylethyl)benzoic acid (****34****)*[18a]

Acid **33** (4.98 g, 25.6 mmol, 1.0 equiv) was dissolved in MeOH (150 mL), concd H_2SO_4 (2.5 mL) was added and the solution stirred at room temp for 30 min. The solution was concentrated on a rotary evaporator at 30 °C to about 1/10 of the original volume. The residue was dissolved in water (60 mL), and 1 M NaOH (60 mL) was added while stirring. The pH value was cautiously brought to 8–9 by addition of satd $NaHCO_3$ and more 1 M NaOH. The aqueous solution was washed with Et_2O (2×100 mL) and the ethereal layers were discarded. The stirred aqueous layer was cautiously acidified with concd HCl (pH=1–2) and the milky acidic product extracted 4× with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvents removed by a rotary evaporator at 30 °C. After further drying in vacuo, ester **34** (5.04 g, 95%) was obtained as a colourless solid. $C_{11}H_{12}O_4$; 208.21 g/mol. Mp 79–81 °C (lit. 78–80 °C). ^{1}H NMR (200 MHz, DMSO): δ=12.92 (s, 1H, CO_2H), 7.83–7.78 (m, 1H, $H_{ar.}$), 7.51–7.43 (m, 1H, $H_{ar.}$), 7.35–7.27 (m, 2H, $H_{ar.}$), 3.57 (s, 3H, OCH_3), 3.16 (t, J=7.8 Hz, 2H, CH_2), 2.60 (t, J=7.8 Hz, 2H, CH_2). ^{13}C NMR (50 MHz, DMSO): δ=173.6 (1C, C=O), 169.5 (1C, C=O), 142.5 (1C, $C_{ar.}$), 132.8 (1C, $CH_{ar.}$), 131.8 (1C, $CH_{ar.}$), 131.3 (1C, $CH_{ar.}$), 131.3 (1C, $C_{ar.}$), 127.4 (1C, $CH_{ar.}$), 52.2 (1C, OCH_3), 36.0 (1C, CH_2), 30.0 (1C, CH_2).

4.2.26. *2-(3-Hydroxypropyl)benzoic acid (****35****)*[18a]

Under nitrogen, $LiBH_4$ (1.14 g, 52.5 mmol, 2.5 equiv) was suspended in abs dioxane (60 mL). To this suspension, a solution of ester **34** (4.37 g, 21.0 mmol, 1.0 equiv) in abs dioxane (40 mL) was added dropwise via cannula (nitrogen current). When the addition was complete, the reaction mixture was heated for 20 min at 100 °C, then poured into a beaker with ice (120 g) (foaming!). The mixture was cautiously acidified to pH=1 with 1 M HCl (85 mL), preventing it from foaming too much. The aqueous solution was saturated with NaCl and extracted with Et_2O (5×100 mL). The combined ethereal layers were concentrated under reduced pressure and the oily residue dissolved in 1 M NaOH (80 mL). The alkaline aqueous phase was washed 3× with CH_2Cl_2 and 1× with Et_2O, and the organic layers were discarded. The aqueous phase was acidified with 1 M HCl (120 mL) and extracted 3× with Et_2O. The combined ethereal layers were dried over Na_2SO_4 and the solvents removed in vacuo. Alcohol **35** (3.00 g, 79%) was obtained as a colourless solid. $C_{10}H_{12}O_3$; 180.20 g/mol. Mp 55–65 °C (lit. 63–65 °C). ^{1}H NMR (200 MHz, DMSO): δ=12.72 (s, 1H, CO_2H), 7.77–7.73 (m, 1H, $H_{ar.}$), 7.49–7.41 (m, 1H, $H_{ar.}$), 7.31–7.16 (m, 2H, $H_{ar.}$), 4.46 (s, 1H, OH), 3.44 (t, J=6.6 Hz, 2H, CH_2), 2.95 (t, J=7.7 Hz, 2H, CH_2), 1.79–1.68 (m, 2H, CH_2).

4.2.27. *Methyl 2-(3-tosyloxypropyl)benzoate (****37****)*

Reaction analogous to the preparation of tosylate **25**. *Methylation:* compound **35** (3.60 g, 20 mmol, 1.0 equiv), abs MeOH/abs THF (35 mL each), $TMSCHN_2$ (2.0 M in Et_2O, 17 mL, 34 mmol, 1.7 equiv). *Tosylation*: crude product **36** (colourless oil) in abs $CHCl_3$ (30 mL), TsCl (7.60 g, 40 mmol, 2 equiv) in abs $CHCl_3$ (20 mL), abs pyridine (5 mL, 60 mmol, 3 equiv), and purification of the crude product by flash chromatography (250 g, petroleum ether/EtOAc=gradient, 6:1 to 2:1) afforded tosylate **37** (3.27 g, 47% *over two steps*) as a colourless oil. $C_{18}H_{20}O_5S$; 348.41 g/mol. ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.91–7.78 (m, 3H, $H_{ar.}$), 7.42–7.12 (m, 5H, $H_{ar.}$), 4.06 (t, J=6.3 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 2.98 (t, J=7.9 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.01–1.90 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.0 (1C, C=O), 145.0 (1C, $C_{ar.}$), 142.8 (1C, $C_{ar.}$), 133.4 (1C, $C_{ar.}$),

132.4 (1C $CH_{ar.}$), 131.5 (1C, $CH_{ar.}$), 131.3 (1C, $CH_{ar.}$), 130.1 (2C, $CH_{ar.}$), 129.5 (1C, $C_{ar.}$), 128.2 (2C, $CH_{ar.}$), 126.6 (1C, $CH_{ar.}$), 70.4 (1C, OCH_2), 52.2 (1C, OCH_3), 30.8 (1C, CH_2), 30.7 (1C, CH_2), 21.9 (1C, CH_3^{Ts}). IR (film): ν_{max}=2953, 1720, 1599, 1435, 1360, 1260, 1177, 1136, 1095, 1000, 966, 928, 816, 752, 710, 664, 573, 555, 443 cm^{-1}. GC–MS (EI): *m*/*z*=317 [23%, M^+-OCH_3], 177 [76%], 148 [100%, $M^+-OTs-OCH_3$], 117 [21%]. HRMS (ESI^+): $[M+H]^+$ found 349.1107, calcd 349.1110; $[M+Na+MeCN]^+$ found 412.1189, calcd 412.1195.

4.2.28. Methyl 2-(3-bromopropyl)benzoate (**38**)[25]

Under nitrogen, tosylate **37** (820 mg, 2.35 mmol, 1.0 equiv) and LiBr (408 mg, 4.70 mmol, 2.0 equiv) were refluxed in abs acetone (20 mL) for 17 h. The solvents were removed on a rotary evaporator followed by purification of the residue by flash chromatography (50 g, petroleum ether/EtOAc=50:1) to afford bromide **38** (575 mg, 95%) as a colourless liquid. $C_{11}H_{13}BrO_2$; 257.12 g/mol. ^1H NMR (200 MHz, $CDCl_3$): δ=7.93–7.89 (m, 1H, $H_{ar.}$), 7.49–7.40 (m, 1H, $H_{ar.}$), 7.31–7.23 (m, 2H, $H_{ar.}$), 3.90 (s, 3H, OCH_3), 3.44 (t, *J*=6.6 Hz, 2H, CH_2), 3.11 (t, *J*=7.6 Hz, 2H, CH_2), 2.25–2.11 (m, 2H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.2 (1C, C=O), 143.0 (1C, $C_{ar.}$), 132.5 (1C, $CH_{ar.}$), 131.6 (1C, $CH_{ar.}$), 131.3 (1C, $CH_{ar.}$), 129.7 (1C, $C_{ar.}$), 126.7 (1C, $CH_{ar.}$), 52.4 (1C, OCH_3), 34.7 (1C, CH_2Br), 33.9 (1C, CH_2), 33.3 (1C, CH_2).

4.2.29. Methyl 2-(4,4-bis(methylthio)-4-(trimethylsilyl)-butyl)benzoate (**39**)

Addition of carbanion **1b** [obtained using **1a** (346 mg, 1.90 mmol, 1.3 equiv), abs THF (3 mL), *n*-BuLi (2.4 M in hexane, 0.86 mL, 2.10 mmol, 1.4 equiv)] to a solution of bromide **38** (380 mg, 1.48 mmol, 1.0 equiv) in abs THF (8 mL) with the reaction temperature after 30 min at −78 °C slowly being raised to room temp in a Dewar overnight, showed complete conversion after 16 h. From the pale yellow solution, 620 mg of a pale yellow liquid was obtained as crude product. Purification by flash chromatography (23 g, petroleum ether/EtOAc=500:1) afforded silylated compound **39** (527 mg, 99%) as a colourless oil. $C_{17}H_{28}O_2S_2Si$; 356.62 g/mol. ^1H NMR (200 MHz, $CDCl_3$): δ=7.87–7.83 (m, 1H, $H_{ar.}$), 7.46–7.38 (m, 1H, $H_{ar.}$), 7.28–7.20 (m, 2H, $H_{ar.}$), 3.88 (s, 3H, OCH_3), 2.97–2.90 (m, 2H, CH_2), 2.00 (s, 6H, SCH_3), 1.84–1.80 (m, 4H, CH_2), 0.14 (s, 9H, $SiMe_3$). ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.4 (1C, C=O), 144.1 (1C, $C_{ar.}$), 132.3 (1C, $CH_{ar.}$), 131.3 (1C, $CH_{ar.}$), 131.0 (1C, $CH_{ar.}$), 129.9 (1C, $C_{ar.}$), 126.3 (1C, $CH_{ar.}$), 52.3 (1C, OCH_3), 47.7 (1C, C), 37.9 (1C, CH_2), 35.1 (1C, CH_2), 29.1 (1C, CH_2), 11.5 (2C, SCH_3), −0.6 (3C, $SiMe_3$). IR (film): ν_{max}=2951, 1723, 1601, 1575, 1488, 1434, 1251, 1134, 1088, 965, 842, 753, 710, 625, 427 cm^{-1}. GC–MS (EI): *m*/*z*=341 [100%, M^+-Me], 309 [20%], 251 [37%], 163 [28%], 149 [41%], 91 [84%]. MS (ESI^+): *m*/*z*=379 $[M+Na]^+$. HRMS (ESI^+): $[M+Na]^+$ found 379.1194, calcd 379.1191.

4.2.30. 2,2-Bis(methylthio)-1-benzosuberone (**40**)

TBAF·$3H_2O$ (1.31 g, 4.1 mmol, 2.8 equiv) was placed in a Schlenk flask under nitrogen, and was dissolved in abs THF (15 mL). After cooling to 0 °C, hexamethyldisilazane (3.9 mL, 18.6 mmol, 12.6 equiv) was added, the cooling removed and the mixture stirred at room temp for 15 h. Under intense stirring, the volatile compounds were then condensed into a cooling trap (liquid N_2) with an oil pump vacuum. The vacuum was held for 6 h until an optically dry beige solid was obtained. The flask was ventilated with nitrogen, the solid dissolved in abs THF (10 mL) and cooled to −78 °C. Then a solution of silylated compound **39** (527 mg, 1.48 mmol, 1.0 equiv) in abs THF (20 mL) was slowly added via syringe. The reaction temperature was allowed to slowly rise to room temp overnight in a Dewar. The red solution was quenched with water after 20 h, observing decolouration. The mixture was extracted 4× with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4 and the solvents removed on a rotary evaporator. Purification of the crude product (400 mg, brown oil) by flash chromatography (50 g, petroleum ether/EtOAc=500:1) afforded benzosuberone **40** (272 mg, 73%) as a colourless oil, which solidified in the cold, obtaining a waxy colourless solid. $C_{13}H_{16}OS_2$; 252.40 g/mol. Mp 39–43 °C. ^1H NMR (400 MHz, $CDCl_3$): δ=7.40–7.35 (m, 2H, $H_{ar.}$), 7.29 (dd, *J*=7.3, 1.1 Hz, 1H, $H_{ar.}$), 7.12 (dd, *J*=7.1, 0.3 Hz, 1H, $H_{ar.}$), 2.86 (t, *J*=6.9 Hz, 2H, CH_2), 2.08 (s, 6H, SCH_3), 2.02–1.95 (m, 2H, CH_2), 1.90–1.86 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=199.4 (1C, C=O), 139.1 (1C, $C_{ar.}$), 137.1 (1C, $C_{ar.}$), 131.3 (1C, $CH_{ar.}$), 128.6 (1C, $CH_{ar.}$), 128.2 (1C, $CH_{ar.}$), 126.9 (1C, $CH_{ar.}$), 68.7 (1C, C), 31.8 (1C, CH_2), 31.5 (1C, CH_2), 23.0 (1C, CH_2), 12.2 (2C, SCH_3). IR (film): ν_{max}=2918, 1681, 1600, 1451, 1246, 959, 762, 675, 635 cm^{-1}. GC–MS (EI): *m*/*z*=252 [3%, M^+], 205 [72%], 177 [100%, M^+-SCH_3-CO], 133 [52%]. MS (ESI^+): *m*/*z*=527 $[2\,M+Na]^+$, 275 $[M+Na]^+$. HRMS (EI): $[M^+]$ found 252.0643, calcd 252.0643.

4.2.31. 2,2-Bis(methylsulfonyl)-1-benzosuberone (**41**)

A solution of thioacetal **40** (50 mg, 0.20 mmol, 1.0 equiv) and *m*-CPBA (77%, 448 mg, 2.0 mmol, 10 equiv) in $CHCl_3$ (10 mL) was stirred at room temp for 4 days. The mixture was diluted with Et_2O, washed with 10% $Na_2S_2O_3$, 2×satd $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4 and the solvents removed on a rotary evaporator. Purification of the colourless crude product by flash chromatography (15 g, petroleum ether/EtOAc=6:1) afforded sulfone **41** (57 mg, 0.18 mmol, 90%) as a colourless solid (mp 175–180 °C). Single crystals for X-ray analysis were grown from petroleum ether/CH_2Cl_2 (mp 192–193 °C). $C_{13}H_{16}O_5S_2$; 316.39 g/mol. ^1H NMR (400 MHz, $CDCl_3$): δ=7.47 (ddd, *J*=7.4, 1.8 Hz, 1H, $H_{ar.}$), 7.38–7.31 (m, 2H, $H_{ar.}$), 7.15 (d, *J*=7.2 Hz, 1H, $H_{ar.}$), 3.40 (s, 6H, SO_2CH_3), 3.06 (t, *J*=7.1 Hz, 2H, CH_2), 2.69 (t, *J*=6.7 Hz, 2H, CH_2), 2.24 (qui, *J*=6.9 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.5 (1C, C=O), 139.3 (1C, $C_{ar.}$), 137.4 (1C, $C_{ar.}$), 133.4 (1C, $CH_{ar.}$), 129.3 (1C, $CH_{ar.}$), 129.0 (1C, $CH_{ar.}$), 127.7 (1C, $CH_{ar.}$), 92.2 (1C, C), 41.4 (2C, SO_2CH_3), 29.9 (1C, CH_2), 24.2 (1C, CH_2), 22.3 (1C, CH_2). IR (KBr): ν_{max}=3034, 2926, 1694, 1596, 1448, 1420, 1336, 1304, 1247, 1135, 944, 883, 802, 775, 749, 604, 551, 528, 504, 483, 465 cm^{-1}. GC–MS (EI): *m*/*z*=317 [6%, M^+], 237 [100%, $M^+-SO_2CH_3$], 158 [59%].

4.2.32. X-ray analysis of **41**

Procedure analogous to X-ray study of compound **25**. $C_{13}H_{16}O_5S_2$, *M*=316.39 g mol^{-1} crystallized in the orthorhombic space group *Pbca* with lattice parameters *a*=12.036(1) Å, *b*=13.692(1) Å, *c*=16.679(1) Å, *V*=2748.5(3) $Å^3$, *Z*=8, d_{calcd}=1.529 g cm^{-3}, *F*(000)=1328 using 2435 independent reflections and 246 parameters. *R*1=0.0339, *wR*2=0.0837 [$I>2\sigma(I)$], goodness of fit on F^2=1.145, residual electron density=0.371 and −0.270 e $Å^{-3}$. Further details of the crystal structure investigations have been deposited with the Cambridge Crystallographic Data Center, CCDC-699487. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223) 336 033; e-mail: fileserv@ccdc.ac.uk; www.ccdc.cam.ac.uk).

4.2.33. Methyl 2-(4,4-bis(methylthio)butyl)benzoate (**42**)

Desilylated product **42** (64 mg, 68%) was obtained as a colourless oil after flash chromatography (10 g, petroleum ether/EtOAc=500:1), from the reaction of **39** (120 mg, 0.34 mmol) with TBAF, analogous to the preparation of **40** using not conscientiously dried TBAF, but working with an oily residue. $C_{14}H_{20}O_2S_2$; 284.44 g/mol. ^1H NMR (200 MHz, $CDCl_3$): δ=7.89–7.84 (m, 1H, $H_{ar.}$), 7.46–7.38 (m, 1H, $H_{ar.}$), 7.28–7.20 (m, 2H, $H_{ar.}$), 3.89 (s, 3H, OCH_3), 3.70–3.63 (m, 1H, CH), 3.02–2.92 (m, 2H, CH_2), 2.08 (s, 6H, SCH_3), 1.89–1.78 (m, 4H, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ=168.4 (1C, C=O), 144.2 (1C, $C_{ar.}$), 132.3 (1C, $CH_{ar.}$), 131.2 (1C, $CH_{ar.}$), 131.1 (1C, $CH_{ar.}$), 129.8 (1C, $C_{ar.}$), 126.3 (1C, $CH_{ar.}$), 54.6 (1C, CH), 52.3 (1C, OCH_3), 34.8 (1C, CH_2), 34.1 (1C, CH_2), 29.9 (1C, CH_2), 12.9 (2C, SCH_3). IR (film): ν_{max}=2917, 1723, 1601, 1575, 1488, 1434, 1261, 1189, 1121, 1084, 964, 751, 710 cm^{-1}. GC–MS (EI): *m*/*z*=237 [34%, M^+-SCH_3], 206 [100%,

$M^+-SCH_3-OCH_3$], 190 [66%]. MS (ESI^+): m/z=307 $[M+Na]^+$. HRMS (ESI^+): $[M+MeCN+K]^+$ found 364.0812, calcd 364.0807.

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