A New Iron-Mediated Strategy for the Synthesis of α-Lipoic Acid and Analogues

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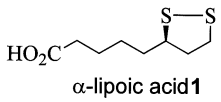
Dithioester **10** was synthesized in 6 steps from tricarbonyl-(diene)iron complex **3**. Compound **10** is not only a key intermediate for the synthesis of methyl lipoate (**13**) but could also be of interest for the preparation of various labelled compounds and structural analogues.

Introduction

(*R*)-(+)-α-lipoic acid[1] (**1**) (Scheme 1) is widely distributed in plant and animal tissues.[2] As lipoamide, it functions as a cofactor in the oxidative decarboxylation of α-keto acids.[3] It is also a growth factor for many bacteria and protozoa.[4]

Scheme 1



α-lipoic acid **1**

Lipoic acid exhibits antioxidant functions[5]: it scavenges hydroxyl radicals, hypochlorous acid, and singlet oxygen, and also chelates transition metals. Lipoic acid and its reduced form (dihydrolipoic acid) appeared to be able to regenerate other antioxidants such as ascorbate and vitamin E. Thanks to these antioxidant properties, lipoic acid is useful or potentially useful for the treatment of various diseases[5]: α-lipoic acid has beneficial effects in prevention and treatment of both type-I and type-II diabetes; α-lipoic acid and dihydrolipoic acid have been reported to be effective in ameliorating or preventing damage in myocardial and cerebral ischemia-reperfusion injury in rat; α-lipoic acid also protects against damages produced by radiation exposure.

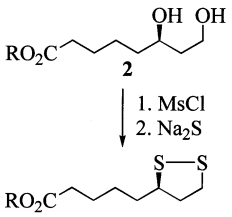
It has also be shown to be potentially useful for the treatment of heavy-metal poisoning, degenerative diseases of the central nervous system, AIDS, and diabetic cataractogenesis.

High doses of α-lipoic acid are approved in Germany for the treatment of diabetic polyneuropathy.[5]

Lipoic acid is then a biologically important molecule. Its extraction from natural sources yields only small quantities of material, and so its synthesis has been largely investigated[6] since its isolation in 1951.[1] In the asymmetric syntheses reported, the chirality is introduced either directly from the "chiral pool"[6b][6d][6e], or by using chiral auxiliaries[6a][6c], and by asymmetric epoxidation[6f]; enzymatic methods have been also used: reduction[6g][6j], oxidation[6h][6k] or resolution.[6i]

Sulfur atoms are usually introduced in two steps from the key intermediate **2** (Scheme 2).

Scheme 2



We planned a new strategy that would permit the synthesis of labelled derivatives and structural analogues which would be very useful in biochemical experiments. We believed that a strategy using tricarbonyl(diene)iron complexes could offer an original and powerful access to lipoic acid and analogues (Scheme 3). Indeed, intermediate **10** should allow access to many analogues of lipoic acid by 1,4- and 1,6-additions to the diene or to labelled compounds by deuteration or tritiation (at a *late* stage in the synthesis).[7]

Tricarbonyl(diene)iron complexes have already found many applications in the asymmetric synthesis of organic molecules.[8] Indeed, their preparation is easy and these complexes are stable under a large variety of experimental conditions, the $Fe(CO)_3$ moiety acting as an efficient protective group for the 1,3-diene. They are chiral and complex **3**, for example, can be obtained in optically active form after resolution.[9] So, starting from an optically pure **3**, it would be possible to obtain both enantiomers of lipoic acid. Finally, due to the properties of tricarbonyl(η^5-pentadie-

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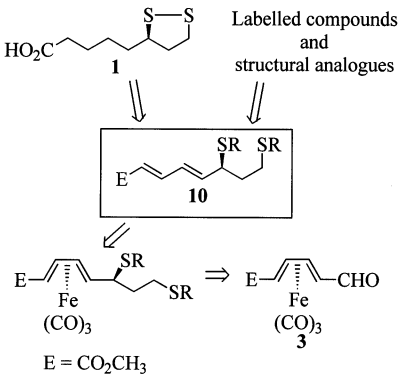
Scheme 3



nyl)iron cations[10] the stereocontrolled formation of the C−S bond may be envisaged.

We have first investigated the synthesis of racemic methyl lipoate to validate our strategy and we report here the corresponding results.

Results and Discussion

Synthesis of the Key Intermediate 10 (Scheme 4)

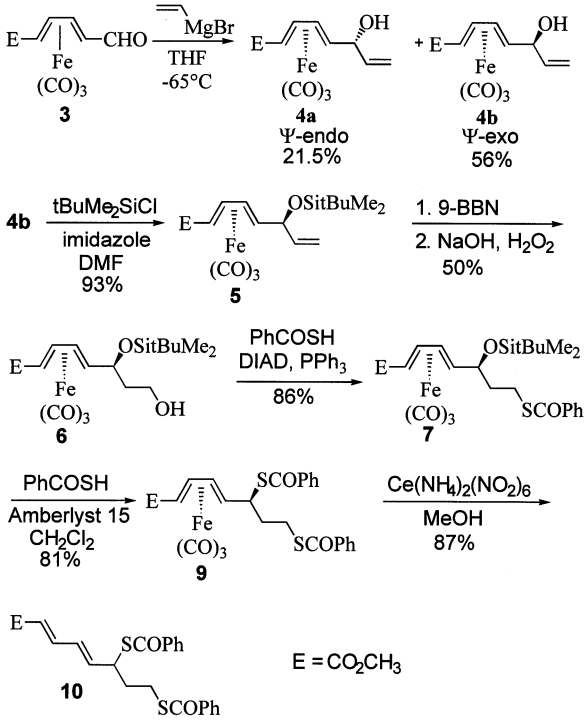
The addition of vinylmagnesium bromine to readily available[9] complex **3** gave a mixture of easily separable alcohols Ψ-*endo*-**4a** (22%) and Ψ-*exo*-**4b** (56%). The stereochemistry of the major, more polar, isomer was attributed according to previous studies[8][11] in that field. After protecting the OH group of **4b** as a *tert*-butyldimethylsilyl ether **5**, the latter compound was subjected to an hydroboration/oxidation sequence to afford alcohol **6** in 47% overall yield. The first sulfur atom was then introduced by a Mitsunobu reaction: **6** treated with PPh_3 and DIAD and then with thiobenzoic acid afforded thiobenzoate **7** in high yield (86%).

We planned to introduce stereoselectively the sulfur atom in the secondary position by allowing an appropriate sulfur nucleophile to react with the tricarbonyl(η^5-pentadienyl)iron cation **8t** (Scheme 5). It is well-known[8][10] that tricarbonyl(η^5-pentadienyl)iron cations are usually prepared by the acid-assisted dehydration of alcohol or ether precursors such as **7**. This cation may exist in two forms: transoid **8t** and cisoid **8c** (Scheme 5).

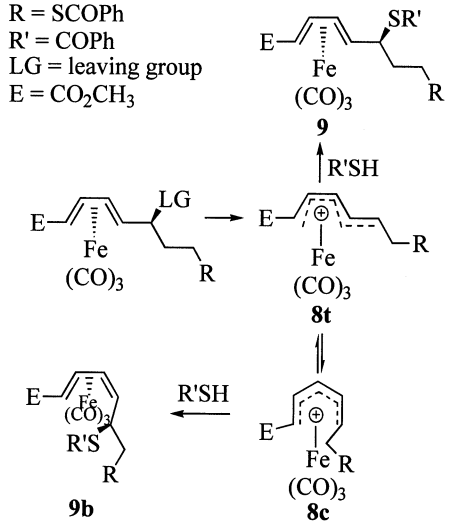
Addition of nucleophiles to such cations is usually highly stereoselective; therefore, addition of thiobenzoic acid in our case could a priori give two products; attack of the transoid form leading to (*E*,*E*) complex **9**, and attack of the cisoid form leading to (*E*,*Z*) compound **9b**. However, it is known that under the "in situ" reaction conditions, the (*E*,*E*) complexes are usually obtained. Thus, compound **7** was treated with Amberlyst® 15 and a large excess (ca. 50 equiv.) of thiobenzoic acid to afford only the (*E*,*E*)-diene complex **9** in high yield[12] (81%).

X-ray crystallographic analysis[13] confirmed the expected stereochemistry (Figure 1): departure of the leaving group and the attack of the nucleophile occur on the face opposite to the carbonyliron unit[8][10] so that the reaction proceeds with overall retention of configuration.

Scheme 4



Scheme 5



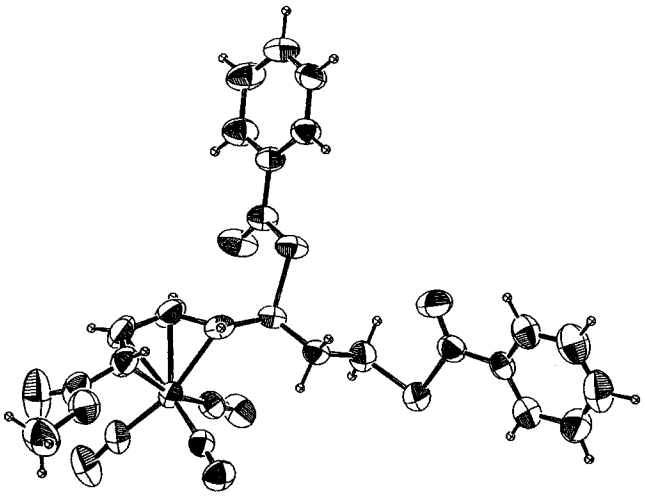
Finally, oxidative decomplexation with ceric ammonium nitrate gave diene **10** in 87% yield. This key intermediate should open the route to labelled derivatives and analogues of lipoic acid.

Synthesis of Methyl Lipoate (13) (Scheme 6)

The first step was the reduction of a diene in a molecule containing two sulfur atoms. The difficulty of reducing a double or triple bond in a molecule containing a sulfur atom is well-known, so this step proved to be challenging.

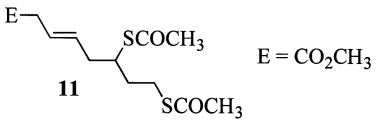
We first tried to perform the catalytic hydrogenation of the diene over palladium on charcoal or platinum oxide. The reaction led only to recovery of the starting material.

Figure 1. Crystal structure of **9**



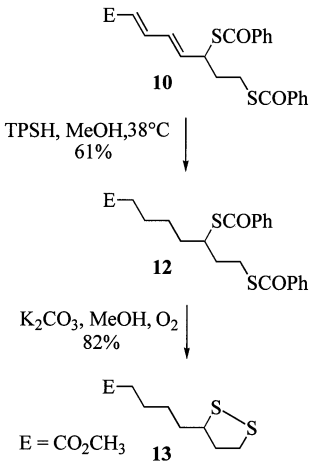
Photodecomplexation using an improved[14] variant of the Franck-Neumann reaction[15] was attempted with the dithioacetate complex. The reaction yielded a complex mixture of compounds where the expected β,γ-unsaturated ester complex **11** (Figure 2) was clearly identified. Unfortunately, the separation of the products was very difficult. Moreover, the yield of expected compound **11** was low (< 50%) and this approach was abandoned.

Figure 2. β,γ-Unsaturated ester **11**



Though we were not able to find any example reported of the reduction of unsaturated carbon−carbon bonds by diimide in the presence of a sulfur atom, this reagent seemed a priori promising. The two main ways to generate diimide were tried: 2,4,6-triisopropylbenzenesulfonyl hydrazide (TPSH) in MeOH[16] was found to be more effective than potassium azodicarboxylate/acetic acid in CH_2Cl_2.[17]

Scheme 6



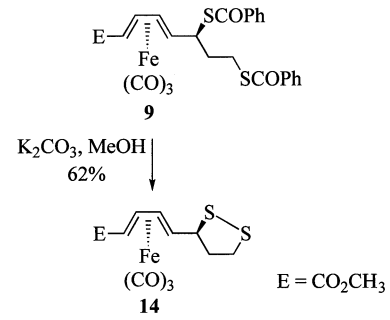
Thus, treatment of diene **10** with a large excess of TPSH in MeOH at 38°C during 12 days gave saturated compound **12** in 61% yield.

Finally, **12** was converted into racemic methyl lipoate (**13**) by treatment with potassium carbonate in MeOH (82%): the intermediate bis-thiolate was probably further oxidized by oxygen dissolved in the solvent to afford the cyclic disulfide. ^{1}H- and ^{13}C-NMR spectral values were in excellent agreement with literature data.[6k] Conversion of methyl lipoate to lipoic acid has already been reported in the literature.[6d]

Synthesis of Analogue 14 (Scheme 7)

The preparation of a carbonylmetal derivative of lipoic acid could be biologically interesting since a cold FT-IR assay technique has been developed which relies on the strong carbonyl IR absorbance of organometallic species.[18] Thus, the same reaction that yielded **13** was performed with complex **9** to give the tricarbonyl(diene)iron analogue **14** of methyl lipoate in 62% yield.

Scheme 7



Conclusion

We have shown that tricarbonyl(diene)iron chemistry furnishes a new stereoselective route to **10**, diene analogue of protected dihydrolipoic acid. We have already synthesized racemic methyl lipoate in only 8 steps from readily available complex **3**, together with its interesting carbonyl(diene)iron analogue **14**. Starting from optically active **3** it should be possible to obtain optically active **10** which could be converted into various analogues of (*R*)-(+)-α-lipoic acid.

We thank Dr. *P. Guenot* (*CRMPO, Rennes*) for performing the mass-spectral experiments.

Experimental Section

General: THF was distilled from sodium benzophenone, CH_2Cl_2 from P_2O_5 or CaH_2. MeOH was distilled from Na and stored over molecular sieves while DMF was dried over 4-Å molecular sieves. − Melting points are uncorrected. − IR spectra were recorded with a Nicolet 205 spectrometer. − ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker ARX 400 instrument (internal standard TMS, δ_H and $\delta_C = 0$ or $CDCl_3$, $\delta_H = 7.26$ and $\delta_C = 77.0$). The coupling constants (*J*) are in Hertz (Hz). High-resolution mass measurements were performed at the CRMPO (Rennes) with a Varian Mat 311 spectrometer. − Microanalyses were performed at the "Service de Microanalyse" I.C.S.N.-

C.N.R.S., Gif-sur-Yvette, France. − Crystallographic data were obtained using a CAD4 ENRAF-NONIUS diffractometer. Crystal data are given in Table 1[13].

Table 1. Crystallograpic data for **9**

formula	$C_{26}H_{23}FeS_2O_7$	radiation	Mo-K_α
mol. wt.	567.44	μ (Mo-$K\alpha$) [cm^{-1}]	7.73
cryst. system	monoclinic	variance of standards	0.2%
space group	$P2_1/n$	t_{max} (for one neasure) [s]	60
crystal size	0.22×0.25×0.33	range of *h; k; l*	−47/47; 0/7; 0/15
$\rho_{calcd.}$ [g cm^{-3}]	1.448	reflections measured	5072
a [Å]	34.516(4)	refl. observed [$I > \sigma(I)$]	2856 (4σ)
b [Å]	5.956(1)	R_{int} (merging equiv. refl.)	0.011
c [Å]	12.707(2)	*R* (isotropic)	0.082
β [°]	94.93	*R* (anisotropic)	0.062
V [$Å^3$]	2603(1)	Fourier difference	0.46−0.15
Z	4	*N*(obs)/*N*(var)	2856/391
F(000)	1172	final *R*	0.029
T [K]	294	*Rw*[a]	0.028
$2\Theta_{max}$ [°]	50	*Sw*	1.116
scan	ω/2θ = 1	max. resid. e $Å^{-3}$, Δ/σ	0.28, 0.12

[a] $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04\ F_o^2)^2]^{-1/2}$.

Alcohols **4a** *and* **4b**: To a solution of aldehyde **3** (2.72 g, 9.7 mmol) in THF (80 ml) was added at −65°C, a solution of vinylmagnesium bromide (10 M, 15 ml, 15 mmol). The reaction mixture was warmed to −45°C over a period of 50 min and quenched with a saturated aqueous NH_4Cl solution then diluted with ether. The organic layer was washed with water, then dried ($MgSO_4$). The solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel (petroleum ether/ether, 3:2) to furnish alcohol **4a** as a yellow oil (0.65 g, 22%) then alcohol **4b** as a yellow solid (1.68 g, 56%).

Alcohol **4a**: ^{1}H NMR ($CDCl_3$): δ = 0.98 (d, 1 H, *J* = 7.9, C*H*E), 1.32 (t, 1 H, *J* = 7.5, CH=C*H*CHOH), 1.92 (br. s, 1 H, OH), 3.66 (s, 3 H, E), 4.16 (br. t, 1 H, *CH*OH), 5.16 (d, 1 H, *J* = 10.3, CH=CH_2), 5.26 (d, 1 H, *J* = 17.0, CH=CH_2), 5.43 (dd, 1 H, *J* = 5.1, 8.3, ECH=C*H*), 5.82 (dd, 1 H, *J* = 5.3, 7.5, ECH=CHC*H*), 5.91 (m, 1 H, *J* = 6.2, 10.2, 16.8, C*H*=CH_2). − ^{13}C NMR ($CDCl_3$): δ = 45.6, 51.7, 67.6, 74.0, 83.2, 83.8, 114.8, 140.6, 172.7. − HRMS: calcd. for $C_{12}H_{12}FeO_6$ 307.9983; found 307.9987.

Alcohol **4b**: M.p. 65°C (hexane/ethyl acetate). − IR (nujol): $\tilde{\nu}$ = 2064, 1999, 1966, 1712 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.08 (dd, 1 H, *J* = 1.1, 8.1, C*H*E), 1.27 (dt, 1 H, *J* = 1.1, 8.2, CH=C*H*CHOH), 1.87 (d, 1 H, *J* = 3.7, OH), 3.67 (s, 3 H, E), 3.99 (br. dt, 1 H, *J* ≈ 3.5, 7.5, C*H*OH), 5.19 (td, 1 H, *J* = 0.9, 10.2, CH=CH_2), 5.29 (td, 1 H, *J* = 1.1, 17.1, CH=CH_2), 5.51 (ddd, 1 H, *J* = 0.9, 5.0, 8.5, C*H*=CHCHOH), 5.85 (ddd, 1 H, *J* = 1.1, 5.0, 8.1, *E*CH=C*H*), 5.96 (m, 1 H, *J* = 7.2, 10.2, 17.1, C*H*=CH_2). − ^{13}C NMR ($CDCl_3$): δ = 46.1, 51.7, 64.7, 75.2, 84.4, 85.2, 115.8, 139.5, 172.5. − HRMS: calcd. for $C_{12}H_{12}FeO_6$ 307.9983; found 307.9987.

Silyl Ether **5**: To a solution of alcohol **4b** (1.48 g, 4.80 mmol) in anhydrous DMF (4 ml) was added imidazole (1.14 g, 16.7 mmol) and *tert*-butyldimethylsilyl chloride (1.59 g, 10.5 mmol). The reaction mixture was stirred at room temperature for 1 h then diluted (Et_2O). The organic layer was washed with a saturated solution of NH_4Cl and with water, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography on silica gel (petroleum ether/ether, 97:3) to give **5** as a yellow solid (1.89 g, 94%). − IR (nujol): $\tilde{\nu}$ = 2064, 2006, 1988, 1722 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.05 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.89 (s, 9 H, *t*Bu), 1.08 (dd, 1 H, *J* = 1.1, 8.1, EC*H*), 1.33 (dt, 1 H, *J* = 1.1, 8.4, CH=C*H*CHOH), 3.66 (s, 3 H, E), 3.90 (br. tdd, 1 H, *J* ≈ 1, 7, 8, C*H*OSi*t*Bu), 5.12 (ddd, 1 H, *J* = 0.8, 1.4, 10.2 CH=CH_2), 5.19 (ddd, 1 H, *J* = 1.1, 1.4, 17.1, CH=CH_2), 5.36 (ddd, 1 H, *J* = 0.8, 5.0, 8.5, ECH=CHC*H*=CH), 5.80 (ddd, 1 H, *J* = 1.1, 5.0, 8.1, ECH=C*H*CH=CH), 5.89 (m, 1 H, *J* = 7.2, 10.2, 17.1, C*H*=CH_2). − ^{13}C NMR ($CDCl_3$): δ = −4.4, −4.1, 18.1, 25.8, 46.2, 51.7, 67.0, 76.2, 83.9, 85.6, 114.8, 140.1, 172.5. − $C_{18}H_{26}FeO_6Si$ (422.3): calcd. C 51.19, H 6.20; found C 51.29, H 6.23.

Alcohol **6**: To a solution of **5** (296 mg, 0.701 mmol) in THF (5 ml) was added at 0°C a solution of 9-BBN in THF (0.5 M, 2.9 ml, 1.45 mmol). After the solution was stirred at room temperature for 8 h, an aqueous solution of NaOH (1 N, 2 ml, 2 mmol), then a 35% solution of H_2O_2 (240 ml, 2.74 mmol) was added dropwise at 0°C. The reaction mixture was further stirred at room temperature for 15 min, then poured into a saturated NH_4Cl solution and extracted with ether. The organic layer was washed with a saturated NH_4Cl solution and water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/ether, 75:25) to give **6** as a yellow solid (154 mg, 50%). − IR (nujol): $\tilde{\nu}$ = 3532, 2063, 1989, 1980, 1689 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.14 (2s, 6 H, 2 $SiCH_3$), 0.89 (s, 9 H, Si*t*Bu), 1.16 (dd, 1 H, *J* = 0.9, 8.1, EC*H*), 1.42 (dt, 1 H, *J* = 0.8, 8.9, CH=C*H*CHOSi), 1.80−1.89 (m, 1 H, CH_2), 1.93−2.02 (m, 1 H, CH_2), 2.10 (t, 1 H, *J* = 5.2, OH), 3.67 (s, 3 H, E), 3.70 (ddd, 1 H, *J* = 3.3, 7.4, 9.2, C*H*OSi), 3.75−3.91 (m, 2 H, CH_2OH), 5.32 (ddd, 1 H, *J* = 1.0, 5.1, 8.6, C*H*=CHCHOSi), 5.82 (ddd, 1 H, *J* = 1.0, 5.1, 8.1, ECH=C*H*). − ^{13}C NMR ($CDCl_3$): δ = −4.4, −3.7, 18.0, 25.7, 40.9, 46.7, 51.7, 59.5, 66.2, 73.8, 84.0, 86.2, 172.3. − $C_{18}H_{28}FeO_7Si$ (440.3): calcd. C 49.10, H 6.41; found C 48.82, 6.39.

Thioester **7**: To a solution of PPh_3 (2.8 g, 10.6 mmol) in THF (40 ml) was added dropwise at 0°C DIAD (2.1 ml, 10.7 mmol). The reaction mixture was stirred 20 min at 0°C. Then a solution of alcohol **6** (2.35 g, 5.3 mmol) in THF (40 ml) and thiobenzoic acid (1.3 ml, ca. 10 mmol) were added dropwise. The reaction mixture was stirred 1 h at 0°C then concentrated under reduced pressure. The resulting residue was filtered through silica gel (petroleum ether/ether, 95:5), then purified by flash chromatography on silica gel (petroleum ether/ether, 95:5) to give thioester **7** (2.55 g, 85%) as a yellow syrup. − IR (film): $\tilde{\nu}$ = 2050, 1995, 1988, 1715, 1666 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.14 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$) 0.91 (s, 9 H, Si*t*Bu), 1.12 (dd, 1 H, *J* = 0.8, 8.1, EC*H*), 1.36 (dt, 1 H, *J* = 0.8, 8.6, CH=C*H*CHOSi), 1.93−2.09 (m, 2 H, CH_2), 3.04 (td, 1 H, *J* = 7.9, 13.3, CH_2S), 3.29 (m, 1 H, *J* = 4.8, 7.6, 13.3, CH_2S), 3.61 (dt, 1 H, *J* = 3.5, 8.4, C*H*OSi), 3.66 (s, 3 H, E), 5.33 (ddd, 1 H, *J* = 0.8, 5.1, 8.6, C*H*=CHCHOSi), 5.80 (ddd, 1 H, *J* = 1.0, 5.1, 8.1, ECH=C*H*), 7.41−7.47 (m, 2 H, Ph), 7.53−7.59 (m, 1 H, Ph), 7.91−7.96 (m, 2 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = −4.2, −3.5, 18.1, 25.4, 25.8, 38.8, 46.6, 51.7, 66.5, 73.6, 83.8, 86.1, 127.1, 128.5, 133.2, 137.1, 172.3, 191.7. − $C_{25}H_{32}FeO_7SSi$ (560.5): calcd. C 53.57, H 5.75; found C 53.84, H 5.99.

Dithioester **9**: To a solution of thioester **7** (300 mg, 0.53 mmol) in CH_2Cl_2 (10 ml) was added at 0°C, thiobenzoic acid (3 ml, ca. 25 mmol) and Amberlyst® 15 (600 mg). The reaction mixture was stirred at 0°C for 4.5 h then filtered, poured into a saturated aqueous $NaHCO_3$ solution and extracted with ether. The organic layer

was washed successively three times with saturated aqueous $NaHCO_3$, solution then with water, dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (petroleum ether/ether, 4:1) to give compound **9** (245 mg, 81%) as a yellow foam which was crystallized from hexane, m.p. 94−96°C (hexane). − IR (film): $\tilde{\nu}$ = 2058, 1996, 1990, 1716, 1666, 1662 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.08 (dd, 1 H, *J* = 1.0, 8.2, C*H*E), 1.47 (ddd, 1 H, *J* = 0.9, 8.3, 10.4, CH=C*H*CHS), 2.15−2.36 (m, 2 H, CH_2), 3.06 (td, 1 H, *J* = 8.1, 13.7, CH_2S), 3.38 (ddd, 1 H, *J* = 4.3, 7.9, 13.5; CH_2S), 3.66 (s, 3 H, E), 3.84 (dt, 1 H, *J* = 3.5, 10.7, C*H*S), 5.68 (ddd, 1 H, *J* = 0.9, 5.2, 8.5, CH=CH), 5.79 (ddd, 1 H, *J* = 1.1, 5.2, 8.2, CH=CH), 7.41−7.51 (m, 4 H, Ph), 7.54−7.63 (m, 2 H, Ph), 7.92−8.01 (m, 4 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 26.5, 35.7, 46.3, 47.0, 51.8, 66.8, 84.2, 85.6, 127.2, 127.5, 128.6, 128.7, 133.4, 133.8, 136.6, 136.9, 172.2, 190.8, 191.5. − $C_{26}H_{22}FeO_7S_2$ (566.4): calcd. C 55.13, H 3.91; found C 55.35, H 3.98.

Diene **10**: To a solution of complex **9** (1.0 g, 1.76 mmol) in MeOH (130 ml) was added at 0°C ceric ammonium nitrate (3.55 g, 6.48 mmol). The reaction mixture was stirred at 0°C for 1.5 h, poured into H_2O and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ether 4:1) to give diene **10** (685 mg, 91%) as a colorless oil. − IR (film): $\tilde{\nu}$ = 1719, 1664 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 2.12−2.27 (m, 2 H, CH_2CH_2S), 3.17 (t, 2 H, *J* = 7.4, CH_2S), 3.74 (s, 3 H, E), 4.52 (q, 1 H, *J* = 7.8, C*H*S), 5.93 (d, 1 H, *J* = 15.3, EC*H*), 6.14 (dd, 1 H, *J* = 8.6, 15.1, CH=C*H*CHS), 6.52 (dd, 1 H, *J* = 11.1, 15.1, CH=C*H*C*H*=CH), 7.27 (ddd, 1 H, *J* = 0.5, 11.1, 15.2, CH=C*H*C*H*=CH), 7.43−7.49 (m, 4 H, Ph), 7.55−7.61 (m, 2 H, Ph), 7.92−7.99 (m, 4 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 26.5, 33.8, 44.7, 51.5, 121.6, 127.2, 127.3, 128.6, 128.7, 130.0, 133.4, 133.6, 136.6, 136.8, 140.5, 143.7, 167.2, 190.1, 191.4. − $C_{23}H_{22}O_4S_2$ (426.6): calcd. C 64.76, H 5.20; found C 64.89, H 5.31.

Saturated Dithiobenzoate **12**: To a solution of diene **10** (55.5 mg, 0.130 mmol) in MeOH (25 ml) at 38°C, was added every day for 5 d triisopropylbenzenesulfonyl hydrazide (860 mg, 2.9 mmol). The reaction mixture was heated at 38°C for 6 h, then kept at room temperature for 48 h after the fifth addition. It was then diluted in CH_2Cl_2. The organic layer was treated with an aqueous $NaHCO_3$ solution. The aqueous layer was extracted three times with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$) and the solvents were evaporated. The crude residue was filtered through silica gel (petroleum ether/ether, 9:1 to 3:1). The colorless crude syrup obtained was taken up in MeOH (25 ml). To the solution heated at 38°C was added every day for 6 d TPSH (850 mg, 2.8 mmol). The reaction mixture was heated at 38°C for 48 h after the sixth addition. The work-up (vide infra) gave a crude product that was purified by flash chromatography on silica gel (petroleum ether/ether, 8:1 to 4:1) to give compound **12** as a colorless oil (34 mg, 61%). − IR (film): $\tilde{\nu}$ = 2933, 2859, 1737, 1664 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.40−1,85 (m, 6 H, CH_2), 1.97−2.14 (m, 2 H, CH_2), 2.32 (t, 2 H, *J* = 7.5, CH_2E), 3.09 (ddd, 1 H, *J* = 6.6, 9.1, 13.5, CH_2S), 3.26 (ddd, 1 H, *J* = 5.3, 9.1, 13.5, CH_2S), 3.65 (s, 3 H, E), 3.89 (tt, 1 H, *J* = 5.3, 8.4, CHS), 7.41−7.48 (m, 4 H, Ph), 7.53−7.60 (m, 2 H, Ph), 7.94−8.01 (m, 4 H, Ph). − ^{13}C NMR ($CDCl_3$): δ = 24.7, 26.4, 26.5, 33.9, 34.7, 35.1, 43.7, 51.5, 127.2, 127.3, 128.6, 133.35, 133.4, 137.0, 137.1, 174.0, 191.6, 191.8. − HRMS: calcd. for $C_{16}H_{21}O_3S_2$ 325.0932; found 325.0918.

Methyl Lipoate (**13**): To a suspension of potassium carbonate (55 mg, 0.40 mmol) in MeOH (4 ml) was added for 2.5 h a solution of dithiobenzoate **12** (34.3 mg, 0.08 mmol) in MeOH (12 ml). The reaction mixture was then stirred for 3.5 h under air at room temperature. A saturated NH_4Cl solution was then added and the mixture was extracted three times with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvents were evaporated. The crude residue was purified by flash chromatography on silica gel (petroleum ether/ether 10:1) to give methyl lipoate (**13**) (14.4 mg, 82%) as a clear yellow oil. − HRMS: calcd. for $C_9H_{16}S_2O_2$ 220.0592; found 202.0586. − ^1H- and ^{13}C-NMR spectral values were comparable with those reported[6k].

Disulfur Compound **14**: To a solution of dithioester **9** (70 mg, 0.124 mmol) in MeOH (5 ml) was added K_2CO_3 (100 mg, 0.723 mmol). The reaction mixture was stirred at room temperature for 1.5 h, poured into saturated aqueous NH_4Cl solution and extracted with ether. The organic layer was washed with an aqueous $NaHCO_3$ solution and with H_2O before being dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/ether, 9:1) to give compound **14** (27.5 mg, 63%) as a yellow syrup. − IR (film): $\tilde{\nu}$ = 2055, 1979, 1712 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.17 (dd, 1 H, *J* = 1.0, 8.2, EC*H*), 1.44 (ddd, 1 H, *J* = 0.9, 8.5, 10.1, CH=C*H*CHS), 2.07−2.18 (m, 1 H, CH_2CH_2S), 2.57−2.67 (m, 1 H, CH_2CH_2S), 3.15 (ddd, 1 H, *J* = 6.5, 7.9, 11.4, CH_2S), 3.31 (m, 1 H, *J* = 4.6, 6.8, 11.4, CH_2S), 3.51 (td, 1 H, *J* = 6.9, 10.3, C*H*S), 3.67 (s, 3 H, E), 5.37 (ddd, 1 H, *J* = 1.0, 5.1, 8.5, C*H*=CHCHS), 5.84 (ddd, 1 H, *J* = 1.1, 5.1, 8.2, ECH=C*H*). −^{13}C NMR ($CDCl_3$): δ = 39.8, 42.6, 46.7, 51.8, 59.2, 63.8, 84.8, 85.7, 172.1. − HRMS: calcd. for $C_{12}H_{12}FeO_5S_2$ 355.9475; found 355.9483.

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[12] It is worth noting that the reaction carried out with the

thioacetate analogue of **7** and thioacetic acid led to the transoid dithioacetate with a lower yield (< 55%), along with a cisoid isomer when a slight excess of acid was used or with a third unidentified by-product when a large excess of acid was used.

[13] Atomic coordinates for structure **9** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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