Formation of Enol Ethers by Radical Decarboxylation of α-Alkoxy β-Phenylthio Acids

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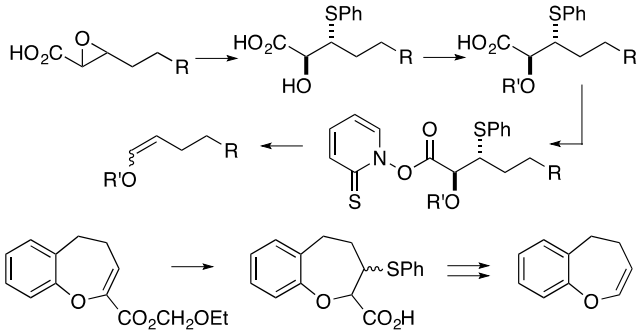
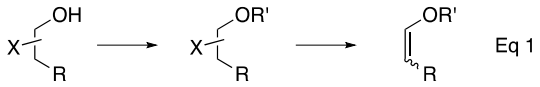


ABSTRACT

Enol ethers are formed by radical decarboxylation of α-alkoxy β-phenylthio acids via the corresponding Barton esters. The phenylthio acids were usually made by the known regioselective reaction of α,β-epoxy acids with PhSH in the presence of $InCl_3$, followed by *O*-alkylation of the resulting alcohol. In one case thiol addition to an α,β-unsaturated ethoxymethyl ester was used.

INTRODUCTION

In connection with synthetic work related to the anticancer antibiotic MPC1001,[1] which contains a cyclic enol ether substructure, we needed to prepare an alcohol that was functionalized in a way that would allow etherification of the hydroxyl and, at a later stage, formation under mild conditions of an enol ether, along the lines expressed by (eq 1).



Eq 1

This requirement resulted from our present approach to MPC1001 which is based on cyclization of an alcohol onto a β-amino enone by addition-elimination, followed by introduction of a double bond (eq 2).

Eq 2

Procedures for making enol ethers were reviewed several years ago[2] but recent publications have provided a number of more modern examples. Apart from methods that involve transfer of a vinyl group to an alcohol,[3] or elaboration of an existing simple enol ether,[4] the classical preparation is the acid- or Lewis acid-catalyzed elimination of an alcohol from an acetal.[5] A very versatile route is the Birch reduction or palladium-mediated reduction of vinyl phosphate ethers, which are available from esters and lactones.[6] Another powerful method is the

methylenation of an ester carbonyl with the Tebbe or Petasis reagents.[7] This procedure can be combined with ring-closing metathesis to afford cyclic enol ethers.[8] Reaction of aldehydes and ketones with Wittig or Horner-Wadsworth-Emmons reagents carrying an alkoxy group also give enol ethers.[9] Similarly, the Peterson olefination, using α-alkoxysilanes[10] and the Julia olefination with α-alkoxysulfones[11] both serve to generate enol ethers.

A number of elimination processes are known in which a saturated ether bearing suitable groups at either or both the α and β positions are converted into enol ethers by base treatment[12] or by reduction.[13] Selenoxide fragmentation has also been used to convert a saturated ether into an enol ether.[1, 14]

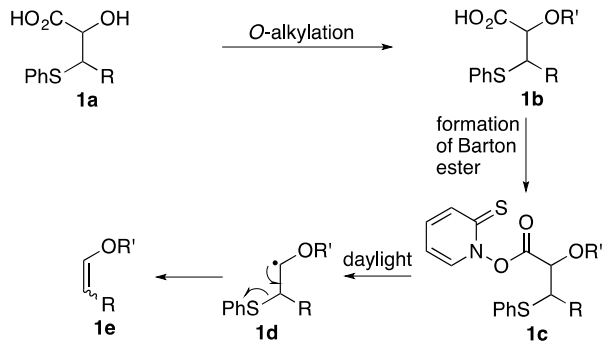
An approach involving a different principle is the isomerization of allyl ethers to enol ethers, a process that has sometimes been combined with initial ring-closing metathesis of allyl ethers.[15] Acetylenic ethers, on semihydrogenation, give enol ethers,[16] and acetylenes can undergo monoaddition of an alcohol in a process promoted by a metal salt.[17]

Michael addition of an alcohol to an α,β-acetylenic ester has been used to generate enol ethers,[18] and there are also a number of metal-mediated cross-coupling procedures for forming a C—O bond between a vinyl halide, triflate or boronic acid or by CH activation.[19]

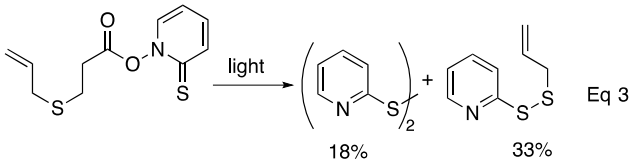
RESULTS AND DISCUSSION

None of the existing methods appeared to be appropriate for our needs and so we have explored the process summarized in Scheme 1. The key step of our approach is radical fragmentation of the Barton ester **1c**, our working hypothesis being that radical decarboxylation (**1c→1d**) would be followed by rapid expulsion[20] of a thiyl radical. In connection with this Scheme we can find only one report[21] of the collapse of a Barton ester made from a carboxylic

SCHEME 1. Principle of the present enol ether synthesis

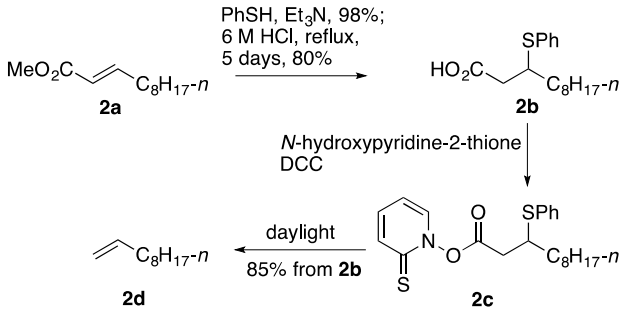


acid carrying a β-thio substituent (eq 3). In that case two disulfides were isolated in yields of 18% and 33%. Evidently, ethylene must have been released, but to establish if the yield of olefin can be synthetically useful, we first added thiophenol to the unsaturated ester **2a** (Scheme 2),



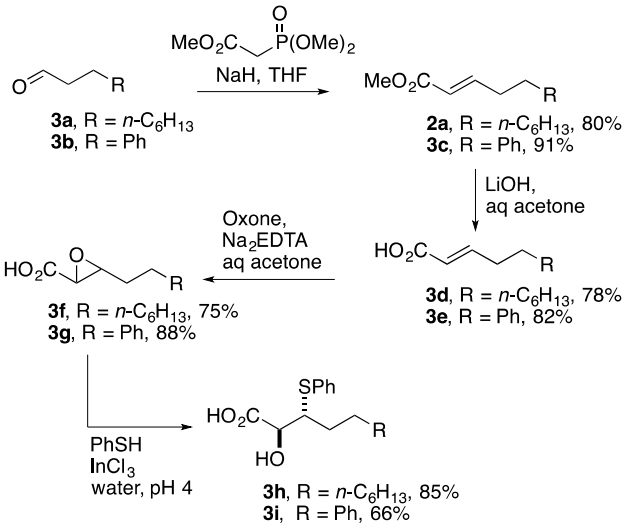
hydrolyzed the adduct to the parent acid **2b**, and then formed the Barton ester **2c** by DCC-mediated coupling with *N*-hydroxypyridine-2(1*H*)-thione. Exposure of the Barton ester to daylight for about 15 min resulted in smooth collapse to dec-1-ene which was isolated in 85% yield.

SCHEME 2. Simple test of the planned radical fragmentation



With the efficiency of alkene formation established, two β-phenylthio α-hydroxy acids were generated from epoxy acids using a literature procedure (Scheme 3). The precursors to the phenylthio compounds were the epoxy acids **3f** and **3g**, and both were made as shown in Scheme 3 by the sequence of Horner-Wadsworth-Emmons olefination, ester hydrolysis and epoxidation[22] with Oxone. Each of these steps proceeded without incident and the regioselective epoxide opening with PhSH in the presence of $InCl_3$[23] (**3f**→**3h**, **3g**→**3i**) under the reported[23] conditions

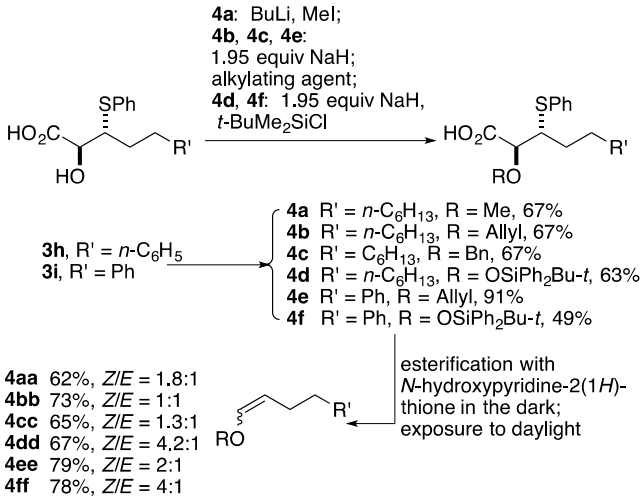
SCHEME 3. Synthesis of α-hydroxy β-phenylthio acids



was also satisfactory. The intermediate olefinic acids **3d** and **3e** were isolated stereochemically pure in 78% and 82% yield, respectively by hydrolysis of their methyl esters and, as expected, the subsequent hydroxy phenylthio acids **3h** (85%) and **3i** (66%) were each a single stereoisomer.

The next step was the *O*-alkylation of the secondary hydroxyl. In the case of **4a** (Scheme 4), deprotonation of **3h** with BuLi (2 equiv) and addition of Me_2SO_4 was found to give the desired product (67%). For the other examples we examined a variety of conditions and established that satisfactory results could be obtained by treating the hydroxy acids **3h** and **3i** with 1.95 equiv (*not* 1 equiv) of NaH at 0 °C, adding the alkylating agent at 0 °C and allowing the mixture to warm to room temperature. In two cases (**3h**→**4b**; **3h**→**4c**), the mixture was refluxed after adding the alkylating agent. During alkylation of the hydroxyl we did not observe formation of any alkyl ester and little, if any, must have been formed.[24] We also prepared the *O*-silylated compounds **4d** and **4f** (Scheme 4) and only in these cases was the whole sequence of hydroxyl deprotonation and protection done at 0 °C to room temperature, a modification needed in order to minimize carboxyl silylation.

SCHEME 4. Conversion of α-hydroxy β-phenylthio acids to enol ethers

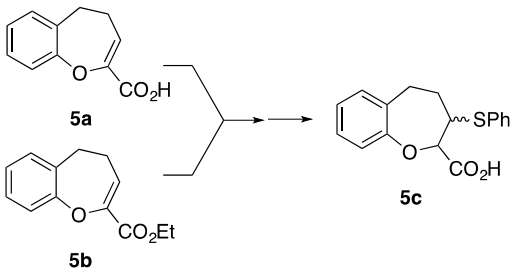


Each of the acids **4a-f** was converted into its Barton ester and, for this purpose, we found (based on experiments with **4e**) that the use of DCC in the presence of DMAP for coupling the acid with *N*-hydroxypyridine-2(1*H*)-thione gave better yields than experiments run in the absence of DMAP.[25] We also tried reaction of the sodium salt of *N*-hydroxypyridine-2(1*H*)-thione with the acid chloride[25] derived from **4b**, but the yield was poor. Each of the Barton esters underwent very rapid reaction when a solution in a mixture of EtOAc and hexane was exposed to daylight; the process appeared to be complete within 15 min, leading to the *Z*/*E* enol ethers **4aa**–**4ff** in yields of 62-79%. In our first photolysis (formation of **2d**) we irradiated a dichloromethane solution, but in the experiments with **4a-f** we found it convenient to generate the Barton ester in CH_2Cl_2 (radical decarboxylation has been reported in this solvent[26]) and to pass the reaction mixture through a short column of silica gel, using EtOAc-hexane (all done with protection from light), and the eluate was then exposed to daylight directly without evaporating the solvent.

We next applied the above method to a cyclic system and, after a number of preliminary experiments in which we explored routes to 7-membered oxygen heterocycles,[27] we chose the

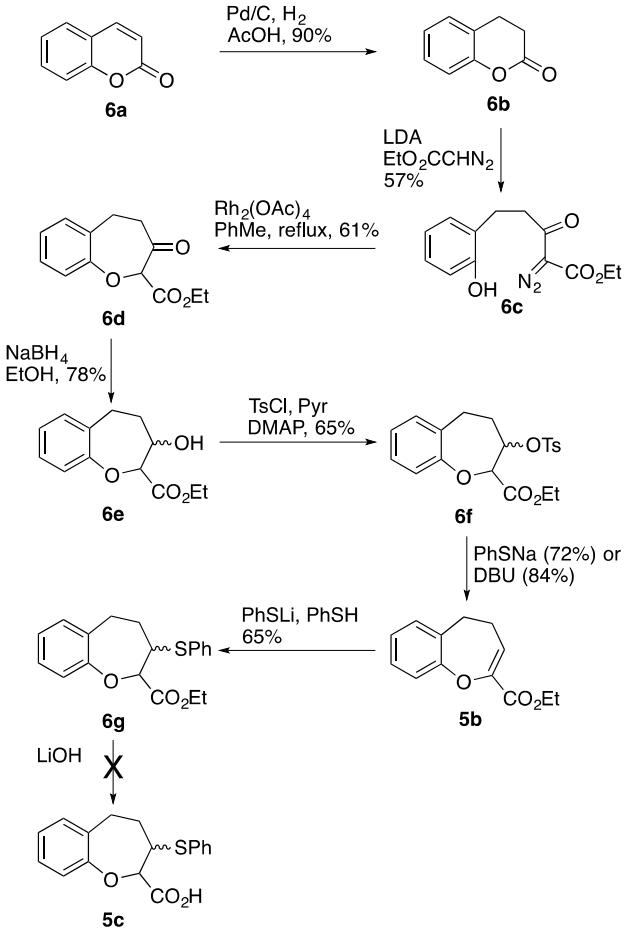
phenylthio acid **5c** as a suitable starting material (Scheme 5). Our intention was to add PhSH to the corresponding unsaturated acid **5a** which we expected to be available by hydrolysis of ester **5b**. Alternatively, we could add the thiol to the ester and do the hydrolysis as the second step.

SCHEME 5. Planned route to a cyclic model β-phenylthio acid



We decided to use a general cyclization method developed by Moody and Taylor[28] to prepare the keto ester **6d** (Scheme 6) and convert that into the desired acid **5a** or ester **5b**. To this end coumarin was hydrogenated over Pd/C in AcOH[29] (**6a→6b**) and the product was mixed with EtO_2CCHN_2 and treated with LDA, following the literature procedure.[28] This experiment gave

SCHEME 6. First approach to a cyclic β-phenylthio acid

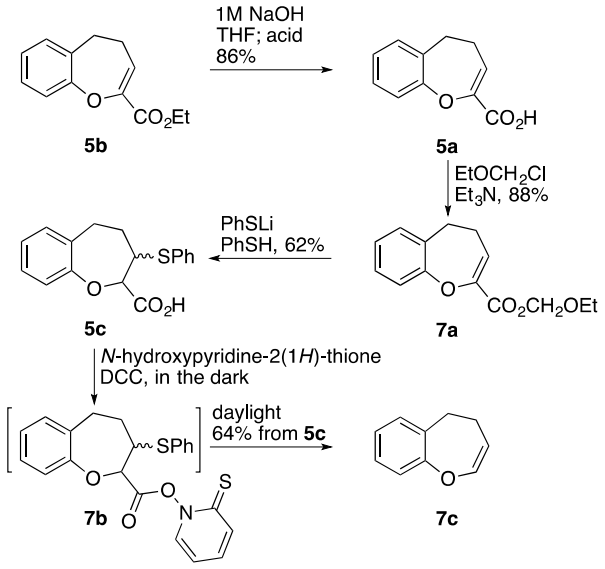


the reported diazo compound **6c** which underwent the desired cyclization (**6c→6d**) in refluxing benzene in the presence of catalytic $Rh_2(OAc)_4$.[28] This sequence worked well on a multigram scale.

Reduction of the ketone carbonyl of **6d**, which existed as a mixture of keto enol tautomers, was initially troublesome. We tried $NaBH_4/CeCl_3.7H_2O$, L-Selectride, DIBAL-H and Pd/C but eventually found that the use of 0.5 mole $NaBH_4$ per mole **6d** in EtOH at –78 °C worked satisfactorily and gave the expected hydroxy esters **6e** as an inconsequential mixture of epimers (78%). The alcohols were easily tosylated and we next sought to displace the tosyloxy group by treatment with PhSNa. Surprisingly, the product (72%) was the unsaturated ester **5b**.

This compound was subsequently obtained by treatment of the tosylate with DBU (84%). The phenylthio group could then be added by exposure of the unsaturated ester to a 10:1 mixture of PhSH and PhSLi,[30] conditions that provide a powerful nucleophile (PhS^-) as well as a source of protons (PhSH). Unfortunately, the resulting phenylthio ester **6g** could not be hydrolyzed to form acid **5a** without extensive elimination of the PhS group. Evidently, a more easily removable protecting group for the carboxyl was required.

SCHEME 7. Formation of a cyclic β-phenylthio acid and conversion to cyclic enol ether

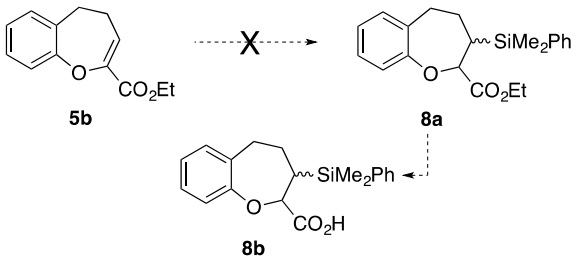


Ester **5b** was hydrolyzed to acid **5a** (Scheme 7). We were unable to add PhSH to the acid[31] and so the acid was protected (88%) by treatment with $EtOCH_2Cl$ in DMF in the presence of Et_3N (**5a**→**7a**).[32] Although esters of the type $RCOOCH_2OR'$ are often not stable to silica gel,[33] compound **7a** could be subjected to standard flash chromatography over silica gel. Addition of thiophenol, again using a 10:1 mixture of PhSH and PhSLi,[30] proceeded without incident and we obtained directly the desired phenylthio acid **5c**. We did not establish the point

(which could be during the reaction, during aqueous acidic workup, or on exposure to silica gel) that the $EtOCH_2$ group was lost in the formation of **5c**. With that acid in hand, we made the Barton esters **7b** and found that they behaved in the same way as our other examples, giving **7c** in 64% yield over the two steps from acid **5c**. The efficiency is probably higher as the oxepine is fairly volatile[6b] but we did not determine the yield by a method involving an internal standard.[6b]

Because of the difficulty in hydrolyzing the phenylthio ester **6g**, we considered a related process that would more easily accommodate ester hydrolysis. The plan (Scheme 8) was to effect conjugate addition of a $PhMe_2Si$ group[34] to **5b** in the expectation, based on extensive precedent,[35] that base hydrolysis of the product **8a** would afford the β-silyl acid **8b**. Several β-silyl acids, made by totally different routes, have been oxidized electrochemically[36] or with $Pb(OAc)_4$[37] to alkenes. However, this plan was thwarted by the fact that ester **5b** does not undergo conjugate addition of a $PhMe_2Si$ group from a cuprate[34, 38] or an organocopper reagent under conditions that are successful with unsaturated esters that are not also enol ethers.[34, 38, 39]

SCHEME 8. Attempted formation of a β-silyl acid



5b **8a** **8b**

CONCLUSION

Barton esters derived from α-alkoxy-β-phenylthio acids decompose within 15 to 30 min on

exposure to visible light to afford enol ethers. The parent β-phenylthio carboxylic acids are available either by way of regioselective opening of α,β-epoxy acids with PhSH in the presence of $InCl_3$, or by conjugate addition of PhSLi in the presence of PhSH to ethoxymethyl esters of α-alkoxy α,β-unsaturated acids. The use of the ethoxymethyl ester instead of an ethyl ester is crucial to allow ester hydrolysis without loss of the PhS group.

EXPERIMENTAL SECTION

Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230−400 mesh). Dry solvents were prepared under an inert atmosphere (N_2) and transferred by syringe or cannula. The symbols s, d, t, and q used for $^{13}C\{^1H\}$ NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum, and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometric analyses were done with an orthogonal time-of-flight analyzer, and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer.

Methyl (2*E*)-Undec-2-enoate (2a).[40] NaH (60%w/w in oil, 2.18 g, 0.054 mol) was suspended in THF (75 mL) (N_2 atmosphere). Methyl diethylphosphonoacetate (10 mL, 54 mmol) was added dropwise over 5 min and stirring at room temperature was continued for ca 15 min. Nonanal (8.4 mL, 49 mmol) was then added dropwise and stirring was continued for 2 h. The solution was diluted with Et_2O (75 mL), and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated.

Flash chromatography of the residue over silica gel (5.0 × 20 cm), using 15:1 hexane-EtOAc, afforded **2a** as a colorless oil (7.7 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.28–1.33 (m, 10 H), 1.45–1.48 (m, 2 H), 2.20 (qd, *J* = 7.6, 1.6 Hz, 2 H), 3.74 (s, 3 H), 5.83 (dt, *J* = 15.7, 1.7 Hz, 1 H), 6.97 (dt, *J* = 15.6, 7.1 Hz, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 28.0, 29.14, 29.19, 29.35, 31.8, 32.2, 51.4, 120.8, 149.8, 167.2.

***rac*-3-(Phenylsulfanyl)undecanoic acid (2b).** (a) ***rac*-Methyl 3-(Phenylsulfanyl)-undecanoate.** The following experiment was modeled on a general literature procedure.[41] Ester **2a** (1.0 g, 5 mmol) was dissolved in THF (5 mL) (N_2 atmosphere) and PhSH (2.6 mL, 25 mmol) was added dropwise to the solution, followed by Et_3N (0.70 mL, 5 mmol). The slightly yellow solution was stirred at room temperature for ca 20 h, diluted with Et_2O (20 mL), washed with 5% hydrochloric acid (20 mL), water (20 mL), and brine (20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 × 15.0 cm), using 50:1 hexane-EtOAc, afforded *rac*-methyl 3-(phenylsulfanyl)undecanoate as a colorless oil (1.4 g, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3 H), 1.20–1.33 (m, 10 H), 1.45–1.65 (m, 4 H), 2.56 (ddd, *J* = 27.6, 15.6, 6.9 Hz, 2 H), 3.47 (ddd, *J* = 14.4, 7.3, 5.6 Hz, 1 H), 3.66 (s, 3 H), 7.25–7.37 (m, 3 H), 7.43–7.45 (m, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 26.8, 29.2, 29.3, 29.4, 31.8, 34.6, 40.4, 45.1, 51.7, 127.3, 128.9, 132.9, 134.0, 172.1; exact mass (ESI) *m*/*z* calcd for $C_{18}H_{28}NaO_2S$ $(M + Na)^+$ 331.1702, found 331.1703.

(b) ***rac*-3-(Phenylsulfanyl)undecanoic acid (2b).** *rac*-Methyl 3-(phenylsulfanyl)undec-anoate (1.0 g, 3.2 mmol) was covered with hydrochloric acid (6 M, 20 mL) and the mixture was refluxed for 5 days, cooled and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 cm × 15 cm), using 9:1 hexane-EtOAc containing 0.1%v/v AcOH, afforded **2b** as a

colorless oil (0.76 g, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.1 Hz, 3 H), 1.20–1.36 (m, 10 H), 1.40–1.70 (m, 4 H), 2.60 (ddd, *J* = 27.7, 16.1, 6.8 Hz, 2 H), 3.46 (ddd, *J* = 14.4, 7.3, 7.3 Hz, 1 H), 7.24–7.33 (m, 3 H), 7.43–7.47 (m, 2 H), 10.4 (br s, 1 H), (OH signal not observed); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 26.8, 29.2, 29.3, 29.4, 31.8, 34.5, 40.3, 44.8, 127.5, 128.9, 133.0, 133.7, 177.6; exact mass (ESI) *m*/*z* calcd for $C_{17}H_{25}O_2S$ $(M - H)^-$ 293.1581, found 293.1577.

Dec-1-ene (2d).[42] A general literature procedure[43] was followed to prepare the intermediate Barton ester. Acid **2b** (0.057 g, 0.19 mmol) was dissolved in CH_2Cl_2 (2 mL) and the flask was wrapped with aluminum foil. The solution was cooled to 0 °C (ice bath) and DCC (0.041 g, 0.19 mmol) and 1-*N*-hydroxypyridine-2(1*H*)-thione (0.025 g, 0.19 mmol) were added. The ice bath was removed and stirring was continued for 4 h. A pad of silica gel (2 × 4 cm) was prepared in a foil-wrapped chromatography column and the reaction mixture was passed through it using 4:1 hexane-EtOAc. The yellow fractions were exposed to sunlight and, once colorless (ca 15 min), were combined and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipette, 0.5 × 4.0 cm), using hexane, gave **2d** (0.027 g, 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3 H), 1.27–1.32 (m, 10 H), 1.34–1.40 (m, 2 H), 2.03 (q, *J* = 7.6 Hz, 2 H), 4.91–5.02 (m, 2 H), 5.81 (ddt, *J* = 10.3, 6.8, 6.7, 1 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 29.0, 29.2, 29.3, 29.5, 31.9, 33.8, 114.1, 139.3.

(2*E*)-Undec-2-enoic acid (3d).[44] Ester **2a** (1.0 g, 5.0 mmol) was dissolved in acetone (90 mL), and an aqueous solution of LiOH (1.0 M, 50 mL) was added dropwise. Stirring was continued for 24 h and the acetone was evaporated. The residue was covered with Et_2O (100 mL) and the mixture was shaken with 10% aqueous $NaHCO_3$ (2 x 50 mL). The combined aqueous phases were acidified using concentrated hydrochloric acid (5 mL) and extracted with

Et_2O (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford **3d** as a colorless oil (0.70 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.0 Hz, 3 H), 1.23–1.39 (m, 10 H), 1.42–1.52 (m, 2 H), 2.21–2.27 (m, 2 H), 5.83 (dt, *J* = 15.6, 1.0 Hz, 1 H), 7.09 (dt, *J* = 15.6, 7.0 Hz, 1 H), (OH signal not observed); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.6 (t), 27.9 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.8 (t), 32.3 (t), 120.7 (d), 152.4 (d), 172.0 (s).

***rac*-*Trans*-3-Octyloxirane-2-carboxylic acid (3f).**[45] A literature procedure[22] for epoxidation was followed. Acid **3d** (5.60 g, 30.4 mmol) was dissolved in a mixture of acetone (10 mL) and water (10 mL). Solid $NaHCO_3$ (10.2 g, 122 mmol) was added and a solution of Oxone (20.0 g, 64 mmol) and Na_2EDTA (10 mg) in water (90 mL) was added over 2 h by syringe pump. The reaction mixture was stirred for a further 2 h, before being cooled to 0 °C and quenched with 10% aqueous H_2SO_4. The mixture was extracted with EtOAc (3 x 25 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated to afford pure **3f** as colorless crystals (4.56 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.23–1.40 (m, 10 H), 1.42–1.53 (m, 2 H), 1.59–1.68 (m, 2 H), 3.21 (ddd, *J* = 6.2, 4.9, 2.0 Hz, 1 H), 3.28 (s, 1 H), (OH signal not observed); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.6, 29.1, 29.2, 29.4, 31.4, 31.8, 52.6, 59.1, 174.1.

***rac*-(2*R*,3*S*)-2-Hydroxy-3-(phenylsulfanyl)undecanoic acid (3h).** The general procedure reported by Fringuelli *et. al*.[23] was followed. The pH of a mixture of PhSH (2.35 mL, 23 mmol), $InCl_3$ (0.46 g, 2.1 mmol) and water (45 mL) was carefully adjusted to 4.0 using an aqueous solution of NaOH (0.5 M). The mixture was stirred and heated at 35 °C (oil bath) and a solution of epoxy acid **3f** (4.2 g, 20.9 mmol) in acetone (1 mL) was added at a fast dropwise rate. The solution was stirred for an additional 2 h at 35 °C, after which it was cooled to 0 °C and

quenched with 10% aqueous H_2SO_4. The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.0 × 20 cm), using 3:2 PhMe-EtOAc containing 0.01%v/v AcOH, afforded **3h** as a colorless oil (5.51 g, 85%): FTIR (film) 3433, 2927, 2855, 1724, 1584, 1466, 1439, 1231, 1128, 1097, 1025, 747, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–0.91 (m, 3 H), 1.22–1.40 (m, 11 H), 1.42–1.47 (m, 1 H), 1.60–1.66 (m, 2 H), 3.58 (ddd, *J* = 8.4, 5.7, 2.9 Hz, 1 H), 4.33 (d, *J* = 2.9 Hz, 1 H), 7.27–7.35 (m, 3 H), 7.48–7.50 (m, 2 H), (CO_2H signal not observed); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 27.4, 29.17, 29.21, 29.27, 29.3, 31.8, 53.2, 72.0, 127.7, 129.3, 132.2, 133.7, 175.8; exact mass (ESI) *m*/*z* calcd for $C_{17}H_{25}O_3S$ $(M - H)^-$ 309.1530, found 309.1532.

***rac*-(2*R*,3*S*)-2-Methoxy-3-(phenylsulfanyl)undecanoic acid (4a).** Freshly titrated *n*-BuLi (2.1 M in hexane, 0.44 mL, 0.917 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **3h** (0.135 g, 0.437 mmol) in THF (5 mL). Stirring was continued for 10 min and freshly distilled Me_2SO_4 (0.09 mL, 0.917 mmol) was added dropwise. The cold bath was left in place, but not recharged, and stirring was continued for 20 h during which the mixture reached room temperature. An aqueous solution of NH_4OH (5%w/v, 10 mL) was added and stirring was continued for 10 min. The mixture was quenched with 10% aqueous hydrochloric acid (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 × 15 cm), using 4:1 PhMe-EtOAc containing 0.01%v/v AcOH, afforded **4a** as a colorless oil (0.096 g, 67%): FTIR (film) 2956, 2926, 2855, 1716, 1465, 1261, 1105, 798, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3 H), 1.20–1.38 (m, 10 H), 1.41–1.47 (m, 1 H), 1.60–1.75 (m, 3 H), 3.49–3.53 (s, 3 H and m, 1 H), 3.89 (d, *J* = 3.9 Hz, 1 H), 7.23–7.28 (m, 1 H), 7.30–7.38 (m, 2 H), 7.45–7.50 (m, 2

H), (OH signal not observed); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 27.2 (t), 29.21 (t), 29.30 (t), 29.36 (t), 29.47 (t), 31.8 (t), 51.3 (d), 60.0 (q), 82.5 (d), 127.2 (d), 129.1 (d), 131.9 (d), 134.7 (s), 174.9 (s); exact mass (ESI) *m*/*z* calcd for $C_{18}H_{27}O_3S$ $(M - H)^-$ 323.1686, found 323.1688.

(*Z*)-1-Methoxydec-1-ene and (*E*)-1-Methoxydec-1-ene (4aa).[46] Acid **4a** (0.080 g, 0.25 mmol) was dissolved in CH_2Cl_2 (2 mL) and the flask was wrapped with aluminum foil. The solution was cooled to 0 °C (ice bath) and DCC (0.053 g, 0.26 mmol) and *N*-hydroxypyridine-2(1*H*)-thione (0.031 g, 0.25 mmol) were added. The ice bath was removed and stirring was continued for 4 h. A pad of silica gel (1.5 × 4 cm) was prepared in a foil-wrapped chromatography column and the reaction mixture was passed through it using 4:1 hexane-EtOAc (subdued laboratory lighting). The yellow fractions were exposed to sunlight for 15 min and, once colorless, were combined and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 100:1 hexane-EtOAc afforded **4aa** (0.026 g, 62%) as a colorless oil that was a mixture of isomers: FTIR (film) 2955, 2855, 1725, 1656, 1465, 1261, 1126, 1108, 1026, 933, 803, 739, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3 H, both isomers), 1.22–1.39 (m, 12 H, both isomers), 1.90–1.95 (m, 2 H, major isomer), 2.03–2.10 (m, 2 H, minor isomer), 3.52 (s, 3 H, major isomer), 3.59 (s, 3 H, minor isomer), 4.35 (dt, *J* = 7.3, 6.5 Hz, 1 H, minor isomer), 4.74 (dt, *J* = 14.7, 7.3 Hz, 1 H, major isomer), 5.88 (dt, *J* = 6.2, 1.2 Hz, 1 H, minor isomer), 6.29 (dt, *J* = 12.6, 1.2 Hz, 1 H, major isomer); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 23.9 (t), 27.7 (t), 29.0 (t), 29.30 (t), 29.31 (t), 29.33 (t), 29.47 (t), 29.48 (t), 29.9 (t), 30.8 (t), 30.9 (t), 31.90 (t), 31.91 (t), 55.9 (q), 59.5 (q), 103.3 (d), 107.2 (d), 145.9 (d), 146.9 (d); exact mass (EI) *m*/*z* calcd for $C_{11}H_{22}O$ $(M)^+$ 170.1671, found 170.1672.

***rac*-(2*R*,3*S*)-3-(Phenylsulfanyl)-2-(prop-2-en-1-yl)undecanoic acid (4b).** Acid **3h**

(0.157 g, 0.51 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C. NaH (60%w/w in oil, 0.04 g, 0.99 mmol) was added as a solid and the mixture was stirred for 15 min at 0 °C. The ice bath was removed and stirring was continued for 1 h, during which the mixture reached room temperature. Freshly distilled allyl bromide (0.044 mL, 0.53 mmol) was added and the reaction mixture was then refluxed for 8 h. The mixture was cooled, quenched with 5% hydrochloric acid (30 mL), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 × 15 cm), using 3:1 hexane-EtOAc, followed by 1:1 hexane-EtOAc, afforded **4b** as a colorless oil (0.12 g, 67%): FTIR (film) 2956, 2926, 2856, 1716, 1466, 1439, 1260, 1095, 1025, 928, 798, 747, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3 H), 1.27–1.31 (m, 10 H), 1.43–1.49 (m, 1 H), 1.60–1.72 (m, 3 H), 3.55 (ddd, *J* = 9.6, 4.0, 4.0 Hz, 1 H), 4.07 (d, *J* = 4.0 Hz, 1 H), 4.15 (dddd, *J* = 12.5, 5.8, 1.3, 1.3 Hz, 2 H), 5.20–5.28 (m, 2 H), 5.90 (ddt, *J* = 17.2, 10.3, 5.9 Hz, 2 H), 7.21–7.28 (m, 1 H), 7.30–7.37 (m, 2 H), 7.44–7.47 (m, 2 H), (OH signal not observed); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 27.2 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.6 (t), 31.8 (t), 51.3 (d), 73.2 (t), 79.7 (d), 118.8 (s), 127.1 (d), 129.1 (d), 131.6 (d), 133.2 (d), 134.9 (t), 174.6 (s); exact mass (ESI) *m*/*z* calcd for $C_{20}H_{29}O_3S$ $(M - H)^-$ 349.1843, found 349.1843.

(1*Z*)-1-(Propen-1-yloxy)dec-1-ene and (1*Z*)-1-(Propen-1-yloxy)dec-1-ene (4bb). Acid **4b** (0.099 g, 0.28 mmol) was dissolved in CH_2Cl_2 (2 mL) and the flask was wrapped with aluminum foil. The solution was cooled to 0 °C (ice bath) and DCC (0.061 g, 0.29 mmol) and *N*-hydroxypyridine-2(1*H*)-thione (0.037 g, 0.29 mmol) were added. The ice bath was removed and stirring was continued for 4 h. A pad of silica gel (2 × 4 cm) was prepared in a foil-wrapped chromatography column and the reaction mixture was passed through it using 4:1 hexane-EtOAc

(subdued laboratory lighting. The yellow fractions were exposed to sunlight and, once colorless (ca 15 min), were combined and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 100:1 hexane-EtOAc, afforded **4bb** (0.040 g, 73%) as a colorless oil which was a mixture of isomers: FTIR (film) 2956, 2926, 2856, 1716, 1466, 1439, 1260, 1095, 1025, 928, 798, 747, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3 H, both isomers), 1.27–1.37 (m, 12 H, both isomers), 1.89–1.94 (m, 2 H, major isomer), 2.07–2.13 (m, 2 H, minor isomer), 4.19 (dt, *J* = 5.4, 1.5 Hz, 1 H, major isomer), 4.26 (dt, *J* = 5.4, 1.5 Hz, 1 H, minor isomer), 4.39 (dt, *J* = 7.3, 6.5 Hz, 1 H, minor isomer), 4.83 (dt, *J* = 12.4, 7.2 Hz, 1 H, major isomer), 5.20–5.24 (m, 2 H, minor isomer), 5.29–5.35 (m, 2 H, major isomer), 5.88–6.01 (m, 3 H, one H of minor isomer and two other H of both isomers), 6.22 (dt, *J* = 12.6, 1.2 Hz, 1 H, major isomer); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 24.0 (t), 27.7 (t), 29.0 (t), 29.32 (t), 29.33 (t), 29.34 (t), 29.4 (t), 29.5 (t), 29.8 (t), 30.7 (t), 31.91 (t), 31.93 (t), 70.1 (t), 72.5 (t), 105.2 (d), 107.6 (d), 117.1 (t), 117.3 (t), 133.8 (d), 134.2 (d), 144.2 (d), 145.5 (d); exact mass (EI) *m*/*z* calcd for $C_{13}H_{24}O$ $(M)^+$ 196.1827, found 196.1828.

***rac*-(2*R*,3*S*)-2-(Benzyloxy)-3-(phenylsulfanyl)undecanoic acid (4c).** Acid **3h** (0.157 g, 0.51 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C. NaH (60%w/w in oil, 0.04 g, 0.99 mmol) was added and the mixture and stirred for 15 min at 0 °C. The ice bath was removed and stirring was continued for 1 h during which the mixture reached room temperature. Freshly distilled BnBr (0.063 mL, 0.53 mmol) was added and the reaction mixture was refluxed for 8 h. The mixture was cooled, quenched with 5% hydrochloric acid (30 mL), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 × 15 cm), using 3:1 hexane-EtOAc, followed by 1:1 hexane-EtOAc, afforded **4c** as a colorless oil (0.12 g, 67%): FTIR

(film) 3061, 2926, 2855, 1717, 1497, 1455, 1439, 1280, 1244, 1139, 1106, 1026, 744, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.0 Hz, 3 H), 1.31–1.37 (m, 10 H), 1.41–1.56 (m, 1 H), 1.67–1.81 (m, 3 H), 3.63 (ddd, *J* = 9.5, 4.0, 4.0 Hz, 1 H), 4.19 (d, *J* = 4.0 Hz, 1 H), 4.69 (AB q, *J* = 11.4, $\Delta\nu_{AB}$ = 37.1 Hz, 2 H), 7.27–7.47 (m, 10 H), (OH signal not observed); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (two signals coincide) δ 14.1 (q), 22.7 (t), 27.2 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.7 (t), 31.9 (t), 51.6 (d), 74.2 (t), 80.0 (d), 127.2 (d), 128.2 (d), 128.5 (d), 129.1 (d), 131.8 (d), 134.9 (s), 136.7 (s), 174.6 (s); exact mass (ESI) *m*/*z* calcd for $C_{24}H_{31}O_3S$ $(M - H)^-$ 399.1999, found 399.1998.

{[(1*Z*)-Dec-1-en-1-yloxy]methyl}benzene and {[(1*E*)-Dec-1-en-1-yloxy]methyl}-benzene (4cc).[47] Acid **4c** (0.105 g, 0.26 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and the flask was wrapped with aluminum foil. The solution was cooled to 0 °C (ice bath) and DCC (0.081 g, 0.39 mmol), *N*-hydroxypyridine-2(1*H*)-thione (0.040 g, 0.31 mmol), and DMAP (0.048, 0.39 mmol) were added. The ice bath was removed and stirring was continued for 4 h. A pad of silica gel (2 × 4 cm) was prepared in a foil-wrapped chromatography column and the reaction mixture was passed through it using 4:1 hexane-EtOAc (subdued laboratory lighting). The yellow fractions were exposed to sunlight and, once colorless (ca 15 min), were combined and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 100:1 hexane-EtOAc, afforded **4cc** (0.042 g, 65%) as a colorless oil which was a mixture of isomers: FTIR (film) 3033, 2956, 2925, 2854, 1665, 1654, 1455, 1378, 1154, 1132, 1099, 931, 734, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.2 Hz, 3 H, both isomers), 1.28–1.35 (m, 12 H, both isomers), 1.91–1.96 (m, 2 H, minor isomer), 2.10–2.16 (m, 2 H, major isomer), 4.41 (dt, *J* = 7.3, 6.2 Hz, 1 H, major isomer), 4.73 (s, 2 H, minor isomer), 4.81 (s, 2 H, major isomer), 4.91 (dt, *J* = 12.6, 7.4 Hz, 1 H, minor isomer), 6.02 (dt, *J* = 6.2, 1.5 Hz, 1 H, major isomer), 6.33 (dt, *J*

= 12.6, 1.5 Hz, 1 H, minor isomer), 7.28–7.38 (m, 5 H, both isomers); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 22.7 (t), 24.1 (t), 27.8 (t), 29.0 (t), 29.30 (t), 29.33 (t), 29.35 (t), 29.50 (t), 29.51 (t), 29.8 (t), 30.7 (t), 31.91 (t), 31.93 (t), 71.1 (t), 73.5 (t), 105.4 (d), 108.1 (d), 127.3 (d), 127.5 (d), 127.7 (d), 127.8 (d), 128.42 (d), 128.45 (d), 137.4 (s), 137.9 (s), 144.4 (d), 145.8 (d); exact mass (EI) *m*/*z* calcd for $C_{17}H_{26}O$ $(M)^+$ 246.1984, found 246.1985.

***rac*-(2*R*,3*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-3-(phenylsulfanyl)undecanoic acid (4d).**

Acid **3h** (0.270 g, 0.87 mmol) was dissolved in THF (8 mL) and the reaction mixture was cooled to 0 °C. NaH (60%w/w in oil, 0.04 g, 0.99 mmol) was added and the mixture was stirred for 15 min at 0 °C, and then cooled to –78 °C. Freshly distilled *t*-$BuPh_2SiCl$ (0.22 mL, 0.87 mmol) was added dropwise. The cold bath was removed and stirring was continued for 2 h during which the mixture reached room temperature. The mixture was quenched with 5% hydrochloric acid (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 × 15 cm), using 3:1 hexane-EtOAc, followed by 1:1 hexane-EtOAc, afforded **4d** as a colorless oil (0.30 g, 63%): FTIR (film) 3073, 3051, 2955, 2930, 2857, 1723, 1588, 1472, 1439, 1428, 1148, 1113, 823, 739, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.1 Hz, 3 H), 1.09 (s, 9 H), 1.19–1.38 (m, 11 H), 1.40–1.49 (m, 1 H), 1.54–1.64 (m, 1 H), 1.65–1.79 (m, 1 H), 3.24 (ddd, *J* = 9.4, 4.8, 3.4 Hz, 1 H), 4.42 (d, *J* = 3.4 Hz, 1 H), 7.19–7.26 (m, 5 H), 7.30–7.38 (4 H), 7.39–7.45 (m, 2 H), 7.55–7.65 (m, 4 H), (OH signal not observed); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1 (q), 19.4 (s), 22.6 (t), 26.9 (q), 27.2 (t), 29.18 (t), 29.22 (t), 29.36 (t), 30.6 (t), 31.8 (t), 53.3 (d), 75.7 (d), 126.8 (d), 127.67 (d), 127.70 (d), 128.9 (d), 130.07 (d), 130.10 (d), 131.4 (d), 132.08 (s), 132.15 (s), 135.3 (s), 135.9 (d), 136.1 (d), 173.7 (s); exact mass (ESI) *m*/*z* calcd for $C_{33}H_{43}O_3SSi$ $(M - H)^-$ 547.2708, found 547.2707.

***tert*-Butyl[(1*Z*)-dec-1-en-1-yloxy]diphenylsilane and *tert*-Butyl[(1*E*)-dec-1-en-1-yloxy]diphenylsilane (4dd).**[48] Acid **4d** (0.123 g, 0.23 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and the flask was wrapped with aluminum foil. The solution was cooled to 0 °C (ice bath) and DCC (0.070 g, 0.34 mmol), *N*-hydroxypyridine-2(1*H*)-thione (0.034 g, 0.27 mmol), and DMAP (0.041, 0.34 mmol) were added. The ice bath was removed and stirring was continued for 4 h. A pad of silica gel (2 × 4 cm) was prepared in a foil-wrapped chromatography column and the reaction mixture was passed through it using 4:1 hexane-EtOAc (subdued laboratory lighting). The yellow fractions were exposed to sunlight and, once colorless (ca 15 min), were combined and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 100:1 hexane-EtOAc, afforded **4dd** (0.060 g, 67%) as a colorless oil which was a mixture of isomers: FTIR (film) 3072, 3000, 2927, 2856, 1657, 1464, 1428, 1259, 1114, 1095, 823, 740, 710, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (two overlapping t, *J* = 7.2 Hz, 3 H, both isomers), 1.06 (s, 9 H, minor isomer), 1.08 (s, 9 H, major isomer), 1.21–1.42 (m, 12 H, both isomers), 1.78–1.81 (m, 2 H, minor isomer), 2.21–2.25 (m, 2 H, major isomer), 4.45 (dt, *J* = 7.3, 5.9 Hz, 1 H, major isomer), 5.05 (dt, *J* = 11.9, 7.3 Hz, 1 H, minor isomer), 6.18 (dt, *J* = 5.8, 1.6 Hz, 1 H, major isomer), 6.22 (dt, *J* = 12.0, 1.2 Hz, 1 H, minor isomer), 7.38–7.49 (m, 6 H, both isomers), 7.69–7.74 (m, 4 H, both isomers); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.09 (q), 14.11 (q), 19.2 (s), 19.3 (s), 22.66 (t), 22.69 (t), 23.8 (t), 26.55 (q), 26.57 (q), 27.2 (t), 28.9 (t), 29.3 (t), 29.36 (t), 29.40 (t), 29.42 (t), 29.54 (t), 29.7 (t), 30.3 (t), 31.87 (t), 31.92 (t), 110.7 (d), 112.0 (d), 127.66 (d), 127.70 (d), 129.7 (d), 129.8 (d), 133.0 (s), 133.1 (s), 135.4 (d), 135.5 (d), 138.7 (d), 140.2 (d); exact mass (EI) *m*/*z* calcd for $C_{26}H_{38}OSi$ $(M)^+$ 394.2692, found 394.2695.

Methyl (2*E*)-5-Phenylpent-2-enoate (3c).[49] Methyl diethylphosphonoacetate (2.8 mL, 15.2 mmol) was added dropwise over 5 min to a stirred suspension of NaH (60%w/w in oil, 0.61

g, 15.2 mmol) in THF (20 mL) (N_2 atmosphere). Stirring at room temperature was continued for ca 15 min and hydrocinnamaldehyde (1.8 mL, 14 mmol) was then added dropwise. Stirring was continued for 2 h and the solution was diluted with Et_2O (75 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.0 × 20 cm), using 15:1 hexane-EtOAc, afforded **3c** as a colorless oil (2.64 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54–2.57 (m, 2 H), 2.78–2.82 (m, 2 H), 3.75 (s, 3 H), 5.87 (dt, *J* = 15.7, 1.6 Hz, 1 H), 7.03 (dt, *J* = 15.7, 6.8 Hz, 1 H), 7.19–7.23 (m, 3 H), 7.30–7.32 (m, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 33.9 (t), 34.4 (t), 51.4 (q), 121.5 (d), 126.2 (d), 128.3 (d), 128.5 (d), 140.8 (s), 148.4 (d), 167.0 (s).

(2*E*)-5-Phenylpent-2-enoic acid (3e).[50] Ester **3c** (2.64 g, 13.9 mmol) was dissolved in acetone (270 mL), and an aqueous solution of LiOH (1.0 M, 132 mL, 13.2 mmol) was added dropwise. Stirring was continued for 24 h and the acetone was evaporated. The residue was partitioned between Et_2O (100 mL) and 10% aqueous $NaHCO_3$ (2 x 50 mL). The combined aqueous base solutions were acidified using concentrated hydrochloric acid (5 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford **3e** as a colorless oil (2.01 g, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57–2.60 (m, 2 H), 2.80–2.83 (m, 2 H), 5.87 (dt, *J* = 15.7, 1.5 Hz, 1 H), 7.16 (dt, *J* = 15.7, 6.8 Hz, 1 H), 7.19–7.28 (m, 3 H), 7.30–7.38 (m, 2 H), (OH signal not observed); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 34.0 (t), 34.2 (t), 121.3 (d), 126.3 (d), 128.3 (d), 128.5 (d), 140.6 (s), 151.0 (d), 172.0 (s).

***rac-Trans*-3-(2-Phenylethyl)oxirane-2-carboxylic acid (3g).**[51] Acid **3e** (1.23 g, 6.98 mmol) was dissolved in a mixture of acetone (5 mL) and water (5 mL). Solid $NaHCO_3$ (2.34 g, 27.9 mmol) was added and a solution of Oxone (4.51 g, 14.6 mmol) and Na_2EDTA (10 mg) in

water (50 mL) was added over 2 h by syringe pump. The reaction mixture was stirred for a further 2 h, before being cooled to 0 °C and quenched with 10% aqueous H_2SO_4. The mixture was extracted with EtOAc (3 x 25 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated to afford pure **3g** as a colorless oil (1.18 g, 88%): FTIR (film) 3062, 3027, 2929, 1723, 1496, 1454, 1250, 900, 752, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90–2.04 (m, 2 H), 2.78–2.90 (m, 2 H), 3.26–3.28 (m, 2 H) 7.20–7.26 (m, 3 H), 7.31–7.35 (m, 2 H) 10.2 (br s, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 31.9 (t), 33.2 (t), 52.6 (d), 58.4 (d), 126.4 (d), 128.3 (d), 128.7 (d), 140.3 (s), 174.8 (s); exact mass (ESI) *m*/*z* calcd for $C_{11}H_{11}O_3$ $(M - H)^-$ 191.0714, found 191.0713.

***rac*-(2*R*,3*S*)-2-Hydroxy-5-phenyl-3-(phenylsulfanyl)pentanoic acid (3i).** The pH of a mixture of PhSH (0.9 mL, 8.6 mmol), $InCl_3$ (0.17 g, 0.78 mmol) and water (20 mL) was adjusted to 4.0 using an aqueous solution of NaOH (0.5 M). The mixture was stirred and heated at 35 °C (oil bath) and a solution of epoxy acid **3g** (1.5 g, 7.8 mmol) in acetone (1 mL) was added at a fast dropwise rate. The solution was stirred for an additional 2 h at 35 °C, after which it was cooled to 0 °C and quenched with 10% aqueous H_2SO_4. The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.0 × 20 cm), using 3:2 PhMe-EtOAc containing 0.01%v/v AcOH, afforded **3i** as a colorless oil (1.55 g, 66%): FTIR (film) 3413, 3048, 2927, 2860, 1725, 1583, 1454, 1438, 1261, 1099, 1078, 1024, 739, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94–2.01 (m, 2 H), 2.77 (dt, J = 14.0, 8.5, 8.3 Hz, 1 H), 2.98–3.00 (m, 1 H), 3.53 (ddd, J = 8.1, 7.0, 3.0 Hz, 1 H), 4.33 (d, J = 3.0 Hz, 1 H), 7.18–7.23 (m, 3 H), 7.25–7.33 (m, 5 H), 7.42–7.49 (m, 2 H), (both OH signals not observed); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 31.0 (t), 33.3 (t), 52.4 (d), 72.4 (d), 126.2 (d), 127.6 (d), 128.5 (d), 128.6

(d), 129.3 (d), 132.2 (d), 133.8 (s), 140.9 (s), 176.3 (s); exact mass (ESI) *m*/*z* calcd for $C_{17}H_{17}O_3S$ $(M - H)^-$ 301.0904, found 301.0896.

***rac*-(2*R*,3*S*)-5-Phenyl-3-(phenylsulfanyl)-2-(propen-1-yloxy)pentanoic acid (4e).** Acid **3i** (0.269 g, 0.89 mmol) was dissolved in THF (20 mL) and the solution was cooled to 0 °C. NaH (60%w/w in oil, 0.04 g, 0.99 mmol) was added and the mixture was stirred for 15 min at 0 °C. The ice bath was removed and stirring was continued for 1 h during which the mixture reached room temperature. Freshly distilled allyl bromide (0.077 mL, 0.94 mmol) was added and the mixture was refluxed for 8 h. The mixture was cooled, quenched with 5% hydrochloric acid (30 mL), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 × 15 cm), using 3:1 hexane-EtOAc, followed by 1:1 hexane-EtOAc, afforded **4e** as a colorless oil (0.28 g, 91%): FTIR (film) 3061, 3027, 2927, 1719, 1583, 1481, 1439, 1243, 1127, 1083, 1026, 996, 930, 746, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90–2.10 (m, 2 H), 2.76 (ddd, *J* = 13.8, 9.5, 7.2 Hz, 1 H), 3.02 (ddd, *J* = 13.8, 9.5, 4.9 Hz, 1 H), 3.55 (ddd, *J* = 9.5, 4.0, 4.0 Hz, 1 H), 4.09 (d, *J* = 4.0 Hz, 1 H), 4.12 (ddt, *J* = 12.4, 5.9, 1.0 Hz, 1 H), 4.21 (ddt, *J* = 12.4, 5.9, 1.0 Hz, 1 H), 5.19–5.29 (m, 2 H), 5.88 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1 H), 7.18–7.21 (m, 3 H), 7.22–7.33 (m, 5 H), 7.41–7.47 (m, 2 H), (OH signal not observed); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 31.4, 33.2, 50.7, 73.2, 79.9, 118.8, 126.0, 127.3, 128.4, 128.5, 129.2, 131.8, 133.2, 134.5, 141.1, 173.9; exact mass (ESI) *m*/*z* calcd for $C_{20}H_{21}O_3S$ $(M - H)^-$ 341.1217, found 341.1223.

[(3*Z*)-4-(Prop-2-en-1-yloxy)but-3-en-1-yl]benzene and [(3*Z*)-4-(Prop-2-en-1-yloxy)-but-3-en-1-yl]benzene (4ee).[52] Acid **4e** (0.030 g, 0.09 mmol) was dissolved in CH_2Cl_2 (2 mL) and the flask was wrapped with aluminum foil. The solution was cooled to 0 °C (ice bath) and DCC (0.027 g, 0.13 mmol), *N*-hydroxypyridine-2(1*H*)-thione (0.013 g, 0.11 mmol), and DMAP

(0.016 g, 0.13 mmol) were added. The ice bath was removed and stirring was continued for 4 h. A pad of silica gel (1.5 × 4 cm) was prepared in a foil-wrapped chromatography column and the reaction mixture was passed through it using 4:1 hexane-EtOAc (subdued laboratory lighting). The yellow fractions were exposed to sunlight and, once colorless (ca 15 min), were combined and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 100:1 hexane-EtOAc, afforded **4ee** (0.013 g, 79%) as a colorless oil which was a mixture of isomers: FTIR (film) 2959, 2927, 2855, 1723, 1463, 1265, 1126, 805, 742 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 2.29 (q, *J* = 7.4 Hz, 2 H, minor isomer), 2.41 (q, *J* = 7.5 Hz, 2 H, major isomer), 2.64 (t, *J* = 7.9 Hz, 2 H, minor isomer), 2.67 (t, *J* = 7.9 Hz, 2 H, major isomer), 4.15 (d, *J* = 5.4 Hz, 2 H, minor isomer), 4.25 (d, *J* = 5.3 Hz, 2 H, major isomer), 4.40 (q, *J* = 6.8 Hz, 1 H, major isomer), 4.83 (dt, *J* = 12.5, 7.4 Hz, 1 H, minor isomer), 5.17–5.21 (m, 2 H, minor isomer), 5.25–5.30 (m, 2 H, major isomer), 5.85–5.90 (m, 1 H, both isomers), 5.93 (d, *J* = 6.2 Hz, 1 H, major isomer), 6.22 (d, *J* = 12.5 Hz, 1 H, minor isomer), 7.15–7.20 (m, 3 H, both isomers), 7.25–7.28 (m, 2 H, both isomers); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 25.7 (t), 29.8 (t), 35.9 (t), 37.3 (t), 70.1 (t), 72.5 (t), 104.1 (d), 106.3 (d), 117.1 (t), 117.3 (t), 125.6 (d), 125.8 (d), 128.20 (d), 128.24 (d), 128.48 (d), 128.50 (d), 133.6 (d), 134.1 (d), 141.9 (s), 142.3 (s), 144.8 (d), 146.1 (d).

***rac*-(2*R*,3*S*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-5-phenyl-3-(phenylsulfanyl)pentanoic acid (4f).** Acid **3i** (0.309 g, 1.02 mmol) was dissolved in THF (25 mL) and the solution was cooled to 0 °C. NaH (60%w/w in oil, 0.08 g, 1.99 mmol) was added and the mixture and stirred for 15 min at 0 °C, and then cooled to –78 °C. Freshly distilled *t*-$BuPh_2SiCl$ (0.28 mL, 1.07 mmol) was added dropwise. The cold bath was removed and stirring was continued for 2 h, during which the mixture reached room temperature. The mixture was quenched with 5% hydrochloric acid (30 mL), and extracted with EtOAc (3 x 15 mL). The combined organic

extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 × 15 cm), using 10:1 hexane-EtOAc, followed by 4:1 hexane-EtOAc, afforded **4f** as a colorless oil (0.271 g, 49%): FTIR (film) 3071.9, 2932, 2894, 2858, 1722, 1454, 1428, 1138, 1113, 822, 739, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9 H), 1.88–2.00 (m, 1 H), 2.06–2.15 (m, 1 H), 2.62–2.71 (ddd, *J* =13.8, 9.5, 7.2 Hz, 1 H), 2.83–2.92 (ddd, *J* = 13.8, 9.5, 4.9 Hz, 1 H), 3.34 (ddd, *J* = 9.5, 4.0, 4.0 Hz, 1 H), 4.42 (d, *J* = 3.6 Hz, 1 H), 7.11–7.64 (m, 20 H), (OH signal not observed); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 19.5 (s), 27.0 (q), 32.0 (t), 33.2 (t), 52.5 (d), 75.7 (d), 126.0 (d), 126.9 (d), 127.65 (d), 127.67 (d), 128.41 (d), 128.46 (d), 128.9 (d), 130.03 (d), 130.06 (d), 131.6 (d), 132.3 (s), 134.9 (s), 136.0 (d), 136.1 (d), 141.2 (s), 174.5 (s); exact mass (ESI) *m*/*z* calcd for $C_{33}H_{35}O_3SSi$ $(M - H)^-$ 539.2082, found 539.2091.

***tert*-Butyldiphenyl{[(1*Z*)-4-phenylbut-1-en-1-yl)silane and *tert*-Butyldiphenyl{[(1*E*)-4-phenylbut-1-en-1yl)silane (4ff).** Acid **4f** (0.109 g, 0.20 mmol) was dissolved in CH_2Cl_2 (4 mL) and the flask was wrapped with aluminum foil. The solution was cooled to 0 °C (ice bath) and DCC (0.062 g, 0.30 mmol), *N*-hydroxypyridine-2(1*H*)-thione (0.031 g, 0.24 mmol), and DMAP (0.037, 0.30 mmol) were added. The ice bath was removed and stirring was continued for 4 h. A pad of silica gel (2 × 4 cm) was prepared in a foil-wrapped chromatography column and the reaction mixture was passed through it using 4:1 hexane-EtOAc (subdued laboratory lighting). The yellow fractions were exposed to sunlight and, once colorless (ca 15 min), were combined and evaporated. Flash chromatography of the residue over silica gel (1.5 × 10 cm), using 100:1 hexane-EtOAc, afforded **4ff** (0.0601 g, 78%) as a colorless oil which was a mixture of isomers: FTIR (film) 3028, 3000, 2931, 2858, 1657, 1428, 1262, 1114, 1030, 823, 741, 711, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9 H, minor isomer), 1.12 (s, 9 H, major isomer), 2.16–2.19 (m, 2 H, minor isomer), 2.57–2.64 (m, 2 H, both isomers), 2.74–2.79 (m, 2 H,

major isomer), 4.53 (dt, *J* = 7.3, 5.9 Hz, 1 H, major isomer), 5.15 (dt, *J* = 11.9, 7.3 Hz, 1 H, minor isomer), 6.21 (dt, *J* = 5.9, 1.6 Hz, 1 H, major isomer), 6.26 (dt, *J* = 11.9, 1.6 Hz, 1 H, minor isomer), 7.12–7.49 (m, 11 H, both isomers), 7.66–7.69 (m, 4 H, both isomers); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 19.3 (s), 25.8 (t), 26.6 (q), 35.9 (t), 109.5 (d), 125.7 (d), 127.72 (d), 127.77 (d), 127.78 (d), 127.784 (d), 128.2 (d), 128.5 (d), 129.9 (d), 133.0 (s), 135.40 (d), 135.49 (d), 139.4 (d), 142.5 (s); exact mass calcd (EI) *m*/*z* for $C_{26}H_{30}OSi$ 386.2066, found 386.2075.

3,4-Dihydro-2*H*-1-benzopyran-2-one (6b).[29] 10%Pd/C (729 mg) was added to a stirred solution of **6a** (10 g, 68.42 mmol) in AcOH (200 mL) and the mixture was stirred under H_2 (balloon) for 2 days and then filtered through a pad of Celite (w × h = 5 × 4 cm), using EtOAc as a rinse. The solvent was evaporated and the residue was taken up in Et_2O. The resulting solution was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated to give **6b** (9.1 g, 90%) which was pure enough for the next step. The material had: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75–2.79 (m, 2 H), 2.97–3.01 (m, 2 H), 7.01–7.10 (m, 2 H), 7.18–7.28 (m, 2 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 23.7 (t), 29.2 (t), 117.0 (d), 122.7 (s), 124.4 (d), 128.1 (d), 128.3 (d), 152.0 (s), 168.7 (s).

Ethyl 2-diazo-5-(2-hydroxyphenyl)-3-oxopentanoate (6c).[28] A stock solution of LDA was made by addition of BuLi (2.5 M, 8 mL, 20.24 mmol) to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (2.83 mL, 20.24 mmol) in THF (50 mL). Stirring was continued for 30 min at –78 °C and the whole solution was taken up into a syringe and added at a fast dropwise rate to a stirred and cooled (–78 °C) solution of **6b** (2 g, 13.49 mmol) and EtO_2CCHN_2 (2.12 mL, 20.24 mmol) in THF (40 mL). Stirring at –78 °C was continued for 5 h and then a solution of AcOH (4 mL) in Et_2O (16 mL) was added rapidly. The cold bath was removed and stirring was continued for 15 min at which point the mixture had reached room temperature. Water (40 mL)

was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm), using 1:3 EtOAc-hexane, gave **6c** (2.0 g, 57%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.0 Hz, 3 H), 2.90 (t, *J* = 6.5 Hz, 2 H), 3.20 (t, *J* = 6.5 Hz, 2 H), 4.30 (q, *J* = 7.0 Hz, 2 H), 6.85–6.92 (m, 2 H), 7.10–7.28 (m, 2 H), 7.71 (br s, 1 H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.3 (q), 24.1 (t), 42.2 (t), 61.8 (t), 117.4 (d), 120.6 (d), 127.1 (s), 128.1 (d), 130.6 (d), 154.5 (s), 161.2 (s), 194.3 (s). The carbon bearing the N_2-group was not visible due to quadrupole coupling and relaxation effects.

Ethyl 3-oxo-2,3,4,5-tetrahydro-1-benzoxepine-2-carboxylate (6d).[28] A solution of **6c** (2.0 g, 7.62 mmol) in dry PhH (200 mL) was added over 45 min (syringe pump) to a stirred and refluxing suspension of $Rh_2(OAc)_4$ (68 mg, 0.15 mmol) in PhH (200 mL). Refluxing was continued for 1 h after the addition, and the mixture was then cooled and filtered through a pad of Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4 × 20 cm), using 1:3 EtOAc-hexane, gave **6d** (1.1 g, 61%) as an oil which was a 2:1 keto-enol mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.5 Hz, 3 H, keto), 1.42 (t, *J* = 7.5 Hz, 1.7 H, enol), 2.71–2.78 (m, 2 H), 3.00–3.07 (m, 2 H), 3.13–3.19 (m, 1 H), 3.22–3.28 (m, 1 H), 4.29 (q, *J* = 7.0 Hz, 2 H), 4.34 (q, *J* = 7.0 Hz, 1 H), 4.97 (s, 1 H), 7.06–7.12 (m, 2 H), 7.14–7.19 (m, 4 H), (OH signal not observed); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.0 (q), 14.3 (q), 26.7 (t), 27.2 (t), 31.1 (t), 40.0 (t), 61.2 (t), 62.0 (t), 86.3 (d), 120.4 (d), 122.0 (d), 124.7 (d), 124.9 (d), 127.3 (s), 127.5 (d), 128.1 (d), 130.0 (d), 130.4 (s), 130.5 (d), 133.0 (s), 156.3 (s), 160.0 (s), 165.3 (s), 165.4 (s), 169.3 (s).

Ethyl 3-hydroxy-2,3,4,5-tetrahydro-1-benzoxepine-2-carboxylate (6e).[53] $NaBH_4$ (80 mg, 2.11 mmol) was added in one lot to a stirred and cooled (–78 °C) solution of **6d** (1.00 g, 4.23

mmol) in anhydrous EtOH (40 mL) and stirring was continued at –78 °C for 2 h at which point all **6d** had reacted (tlc, silica, 1:1 EtOAc-hexane). Saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:1 EtOAc-hexane, gave **6e** (790 mg, 78%) as a colorless oil which was a 1:3.8 (^{1}H NMR) mixture of isomers: FTIR (film) 3501, 2937, 1758, 1489, 1303, 1275, 1101, 1080, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.0 Hz, 3 H, major isomer), 1.38 (t, *J* = 7.5 Hz, 3 H, minor isomer), 1.62–1.70 (m, 1 H, minor isomer), 1.79–1.85 (m, 1 H, major isomer), 1.90–2.22 (m, 1 H, major isomer), 2.31–2.36 (m, 1 H, minor isomer), 2.56 (ddd, *J* = 6.5, 2.0 Hz, 1 H, major isomer), 2.78 (t, *J* = 6.5 Hz, 1 H, minor isomer), 2.84 (d, *J* = 9.0 Hz, 1 H, major isomer), 3.01 (d, *J* = 4.0 Hz, 1 H, minor isomer), 3.21 (t, *J* = 13.5 Hz, 1 H, major isomer), 3.63 (t, *J* = 6.0 Hz, 1 H, minor isomer), 3.97 (d, *J* = 9.5 Hz, 1 H, minor isomer), 4.30–4.36 (m, 2 H, both isomers), 4.43–4.46 (m, 1 H, major isomer), 6.99–7.18 (m, 4 H, both isomers), (OH signal not observed); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.14 (q), 14.21 (q), 26.4 (t), 27.8 (t), 32.7 (t), 33.3 (t), 61.7 (t), 61.8 (t), 70.8 (d), 71.9 (d), 82.8 (d), 83.6 (d), 121.3 (d), 121.5 (d), 124.5 (d), 124.7 (d), 127.7 (d), 127.8 (d), 130.20 (d), 130.22 (d), 134.8 (s), 158.2 (s), 169.6 (s), 170.8 (s), two small impurity signals were present at ca 26 and 117 ppm; exact mass (ESI) *m*/*z* calcd for $C_{13}H_{16}NaO_4$ 259.0941, found 259.0941.

Ethyl 3-[(4-methylbenzenesulfonyl)oxy]-2,3,4,5-tetrahydro-1-benzoxepine-2-carboxylate (6f). A solution of **6e** (790 mg, 3.34 mmol) and pyridine (15 mL) in CH_2Cl_2 (30 mL) was added at a fast dropwise rate to a stirred mixture of solid TsCl (956 mg, 5.01 mmol) and solid DMAP (40 mg, 0.33 mmol). Stirring was continued overnight (N_2 atmosphere). The mixture was diluted with Et_2O (40 mL) and washed with dilute hydrochloric acid (1 M, 200 mL).

The aqueous phase was extracted with CH_2Cl_2 and all the organic extracts (CH_2Cl_2 and Et_2O) were combined and washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 EtOAc-hexane, gave **6f** (850 mg, 65%) as a colorless oil which was a 1:4 mixture of isomers probably containing minor impurities: FTIR (film) 2982, 2941, 1762, 1489, 1370, 1213, 1190, 1176, 1097, 924, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3 H, minor isomer), 1.30 (t, *J* = 7.5 Hz, 3 H, major isomer), 1.85 (t, *J* = 13.0 Hz, 1 H, major isomer), 2.34–3.07 [series of m, 2 H (major isomer), 4 H (minor isomer), 3 H (both isomers)], 3.28 (t, *J* = 13.5 Hz, 1 H, major isomer), 4.06–4.11 (m, 2 H, major isomer), 4.11–4.19 (m, 2 H, minor isomer), 4.32 (s, 1 H, major isomer), 4.34 (s, 1 H, minor isomer), 5.16 (dt, *J* = 8.0, 3.5 Hz, 1 H, minor isomer), 5.47 (s, Hz, 1 H, major isomer), 7.02–7.05 (m, 1 H, both isomers), 7.09–7.17 (m, 3 H, both isomers), 7.34–7.38 (m, 2 H, both isomers), 7.81–7.84 (m, 2 H, both isomers); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 13.9 (q), 14.1 (q), 21.66 (q), 21.69 (q), 26.4 (t), 27.0 (t), 31.0 (t), 31.2 (t), 61.8 (t), 62.0 (t), 80.00 (d), 80.02 (d), 81.2 (d), 81.4 (d), 121.4 (d), 121.9 (d), 124.7 (d), 124.8 (d), 127.80 (d), 127.83 (d), 127.9 (d), 129.7 (d), 129.8 (d), 130.10 (d), 130.11 (d), 133.2 (s), 134.0 (s), 134.3 (s), 144.8 (s), 144.9 (s), 157.2 (s), 157.9 (s), 167.6 (s), 167.7 (s); exact mass (ESI) *m*/*z* calcd for $C_{20}H_{22}NaO_6S$ 413.1029, found 413.1031.

Ethyl 4,5-dihydro-1-benzoxepine-2-caboxylate (5b).[54] PhSH (37 μL, 0.352 mmol) was injected into dry DMF (0.75 mL) and the solution was cooled (0 °C). NaH (60%w/w, 14 mg, ca 0.350 mmol) was tipped in and stirring at 0 °C was continued for 30 min (N_2 atmosphere). A solution of **6f** (55 mg, 0.140 mmol) in DMF (0.75 mL) was then injected at a fast fast dropwise rate. The cold bath was removed and stirring was continued overnight. Water was added and the mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and

evaporated. Flash chromatography of the residue over silica gel (15 × 1 cm), using 1:19 EtOAc-hexane, gave **5b** (25 mg, 72%) as a colorless oil, spectroscopically the same as material made by the following method.

Ethyl 4,5-dihydro-1-benzoxepine-2-carboxylate (5b) by use of DBU.[54] DBU (0.35 mL, 2.39 mmol) was added to a solution of **6f** (850 mg, 2.17 mmol) in dry THF (20 mL) and the mixture was refluxed for 2 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm), using 1:9 EtOAc-hexane, gave **5b** (400 mg, 84%) as an oil: FTIR (film) 2981, 2906, 1701, 1655, 1489, 1268, 1233, 1075, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, *J* = 6.8 Hz, 3 H), 2.50–2.55 (m, 2 H), 3.05 (t, *J* = 6.2 Hz, 2 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 6.33 (t, *J* = 4.4 Hz, 1 H), 7.05–7.09 (m, 1 H), 7.14–7.21 (m, 3 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 14.3 (q), 27.8 (t), 29.9 (t), 61.4 (t), 119.7 (d), 120.7 (d), 124.8 (d), 127.4 (d), 129.4 (d), 134.0 (s), 144.6 (s), 158.6 (s), 163.8 (s); exact mass (ESI) *m*/*z* calcd for $C_{13}H_{14}NaO_3$ 241.08351, found 241.0834.

Ethyl 3-(phenylsulfanyl)-2,3,4,5-tetrahydro-1-benzoxepine-2-carboxylate (6g). PhSH (195 μL, 1.76 mmol) was injected into a stirred and cooled (0 °C) solution of BuLi (2.0 M in hexane, 80 μL, 1.0 mmol) in THF (0.75 mL) contained in a flask fitted with a reflux condenser. This produced a 1:10 mixture of PhSLi and PhSH. After 5 min a solution of **5b** (35 mg, 0.16 mmol) in THF (0.75 mL) was injected. The reaction flask was transferred to an oil bath and the mixture was heated at 70 °C overnight. The mixture was cooled, basified by addition of 5%w/v aqueous NaOH, and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (15 × 1 cm), using 1:19 EtOAc-hexane, gave **6g** (41 mg, 65%) as a colorless oil which was a mixture

of isomers: FTIR (film) 2982, 2937, 1760, 1728, 1604, 1488, 1236, 1201, 1100 cm^{-1}; exact mass (ESI) *m*/*z* calcd for $C_{19}H_{20}NaO_3S$ 351.1025, found 351.1027.

During the chromatography individual the individual isomers were separated, although not obtained absolutely pure, but characterization data could be obtained for both:

The less polar isomer had: ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.5 Hz, 3 H), 1.58–1.65 (m, 1 H), 2.44–2.49 (m, 1 H), 2.78–2.83 (m, 1 H), 2.95–3.00 (m, 1 H), 3.64 (dt, *J* = 10.5 Hz, 1 H), 4.1 (d, *J* = 10.5 Hz, 1 H), 4.22–4.28 (m, 2 H), 7.00–7.10 (m, 3 H), 7.13–7.17 (m, 2 H), 7.27–7.34 (m, 2 H), 7.50–7.53 (m, 2 H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 14.0 (q), 31.2 (t), 32.5 (t), 49.9 (d), 61.4 (t), 84.7 (d), 121.5 (d), 124.5 (d), 127.7 (d), 128.2 (d), 128.9 (d), 129.8 (d), 131.8 (s), 132.3 (d), 134.2 (d), 134.6 (s), 158.0 (s), 169.1 (s).

The more polar isomer had: ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.0 Hz, 3 H), 1.95–2.02 (m, 1 H), 2.25–2.30 (m, 1 H), 2.65 (dd, *J* = 15.0, 6.0 Hz, 1 H), 3.54 (t, *J* = 13.0 Hz, 1 H), 4.10 (s, 1 H), 4.13–4.20 (m, 1 H), 4.23–4.29 (m, 1 H), 4.49 (d, *J* = 2.0 Hz, 1 H), 7.03–7.07 (m, 1 H), 7.1–7.20 (m, 3 H), 7.29–7.34 (m, 3 H), 7.51–7.53 (m, 2 H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 14.1 (q), 28.9 (t), 31.9 (t), 53.9 (d), 61.6 (t), 82.9 (d), 121.6 (d), 124.5 (d), 127.3 (d), 127.6 (d), 128.9 (d), 130.3 (d), 132.4 (d), 134.8 (s), 135.1 (s), 158.5 (s), 169.2 (s).

4,5-Dihydro-1-benzoxepine-2-carboxylic acid (5a). Aqueous NaOH (1 M, 7.33 mL) was added to a stirred solution of **5b** (400 mg, 1.83 mmol) in THF (20 mL) and stirring was continued overnight. The mixture was neutralized by addition of dilute hydrochloric acid (5%) and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated to give **5a** (300 mg, 86%) as a solid: mp 87–89 °C; FTIR (film) 3062, 2951, 2978, 2920, 2857, 1701, 1651, 1489, 1235, 1100, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.56–2.60 (m, 2 H), 3.08 (t, *J* = 6.0 Hz, 2 H), 6.52 (t, *J* = 4.5 Hz, 1 H), 7.09–7.16 (m, 1 H), 7.17–7.28 (m, 3 H), (OH

signal not observed); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 28.0 (t), 29.8 (t), 120.6 (d), 122.2 (d), 125.1 (d), 127.6 (d), 129.5 (d), 133.8 (s), 143.5 (s), 158.2 (s), 167.9 (s); exact mass (ESI) *m*/*z* calcd for $C_{11}H_9O_3$ $(M - H)^-$ 189.0557, found 189.0556.

Ethoxymethyl 4,5-dihydro-1-benzoxepine-2-carboxylate (7a). Et_3N (0.11 mL, 0.78 mmol) and $EtOCH_2Cl$ (54 μL, 0.57 mmol) were added to a stirred solution of **5a** (100 mg, 0.52 mmol) in dry DMF (5 mL) and stirring was continued for 2 h. The mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 EtOAc-hexane, gave **7a** (115 mg, 88%) as an oil: FTIR (film) 2978, 2902, 1731, 1654, 1489, 1264, 1186, 1084, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.5 Hz, 3 H), 2.53–2.56 (m, 2 H), 3.07 (t, *J* = 6.0 Hz, 2 H), 3.77 (q, *J* = 7.5 Hz, 2 H), 5.45 (s, 2 H), 6.40 (t, *J* = 9.5 Hz, 1 H), 7.06–7.10 (m, 1 H), 7.15–7.28 (m, 3 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 15.1 (q), 27.9 (t), 29.8 (t), 66.2 (t), 90.1 (t), 120.70 (d), 120.74 (d), 124.9 (d), 127.4 (d), 129.4 (d), 133.9 (s), 144.2 (s), 158.5 (s), 163.2 (s); exact mass (ESI) *m*/*z* calcd for $C_{14}H_{16}NaO_4$ 271.0941, found 271.0939.

3-(Phenylsulfanyl)-2,3,4,5-tetrahydro-1-benzoxepine-2-carboxylic acid (5c). PhSH (1 mL, 9.96 mmol) was added at a fast dropwise rate to a stirred and cooled (0 °C) solution of BuLi (2.5 M in hexane, 0.36 mL, 0.90 mmol) in THF (5 mL) to generate a 10:1 mixture of PhSH and PhSLi.

A solution of **7a** (225 mg, 0.90 mmol) in THF (5 mL) was then added dropwise at (0 °C) over ca 5 min. The resulting mixture was then heated at 70 °C overnight, cooled, made alkaline (pH 8, pH paper) by addition of 5% aqueous NaOH and extracted with Et_2O. The aqueous phase was acidified to pH 6–7 with 5% hydrochloric acid and extracted with EtOAc. The combined

organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 1:19 MeOH-EtOAc, gave **5c** (200 mg, 62%) as a semisolid: FTIR (film) 3059, 2928, 2849, 1758, 1728, 1488, 1454, 1233, 1100, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major isomer only δ 1.95 (t, *J* = 7.5 Hz, 1 H), 2.23–2.29 (m, 1 H), 2.67 (dd, *J* = 14.8, 5.6 Hz, 1 H), 3.62 (t, *J* = 13.6 Hz, 1 H), 4.10 (s, 1 H), 4.51 (d, *J* = 1.6 Hz, 1 H), 7.09–7.16 (m, 2 H), 7.19–7.26 (m, 2 H), 7.27–7.34 (m, 3 H), 7.53–7.55 (m, 2 H), (OH signal not observed); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 28.6 (t), 31.5 (t), 53.9 (d), 83.8 (d), 120.9 (d), 125.4 (d), 127.8 (d), 127.9 (d), 129.0 (d), 129.1 (d), 130.9 (d), 132.9 (d), 134.3 (d), 134.6 (s), 134.7 (s), 157.3 (s), 170.9 (s); exact mass (ESI) *m*/*z* calcd for $C_{17}H_{15}O_3S$ $(M - H)^-$ 299.0747, found 299.0748.

4,5-Dihydrobenzoxepine (7c).[6b, 55] A solution of **5c** (200 mg, 0.55 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a stirred and cooled (0 °C) solution of *N*-hydroxypyridine-2(1*H*)-thione (71 mg, 0.55 mmol) and 1,3-dicylohexylcarbodiimide (117 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) (N_2 atmosphere, flask wrapped with aluminum foil). The ice bath was removed and the progress of the reaction was monitored by tlc (silica, 1:1 EtOAc-hexane). After 2 h, during which the mixture attained room temperature, the reaction was over. A pad of silica gel (2 × 4 cm) was prepared in a foil-wrapped sintered disk funnel and the reaction mixture was passed through it using EtOAc (subdued laboratory lighting). The yellow fractions (70 mL) were collected in a rack of test tubes (no aluminum foil, but laboratory lights off) and the rack was then placed on a windowsill in subdued sunlight for 30 min, at which point the original yellow color had been discharged. The combined fractions were evaporated at room temperature and flash chromatography of the residue over silica gel (2 × 20 cm), using 1:1 pentane-Et_2O, gave **7c** (52 mg, 64%) as an oil. The compound is somewhat volatile[6b] under water pump vacuum, but we did not determine a yield based, for example, on glc or NMR with an internal

standard. The compound had: FTIR (film) 3044, 2917, 1658, 1488, 1287, 1181, 1101, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35–2.40 (m, 2 H), 3.06 (t, *J* = 5.5 Hz, 2 H), 4.78–4.82 (m, 1 H), 6.42 (dt, *J* = 7.6, 2.0 Hz, 1 H), 6.99–7.05 (m, 2 H), 7.12–7.18 (m, 2 H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 27.4 (t), 32.5 (t), 108.4 (d), 120.2 (d), 123.9 (d), 127.1 (d), 129.8 (d), 133.6 (s), 143.2 (d), 158.4 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{10}O$ 146.0732, found 146.0731.

ASSOCIATED CONTENT

Supporting Information: ^{1}H and $^{13}C\{^{1}H\}$ spectra of all compounds.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

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Notes

The authors declare no competing financial interest.

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