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Bioinspired Metal-Catalysed Doebner–Knoevenagel Condensations between Malonic Acid Half Thioesters and Aldehydes

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Inspired by polyketide biosynthesis, unprecedented metal-catalysed Doebner–Knoevenagel condensations between Malonic Acid Half Thioesters (MAHTs) and various aldehydes have been achieved through the use of $Yb(OTf)_3$ as catalyst, mimicking a five-domain polyketide synthase module for the first time. In the presence of 5-methoxybenzimidazole, stereo- and regiocontrol of the reaction proved to be high.

Introduction

Polyketides represent a vast class of natural products with large chemical diversity and diverse biological activities.[1] The common features that link polyketides as a specific chemical class are the sequence of reactions they originate from, and the related intermediates of these reactions. Each polyketide is produced by a unique PolyKetide Synthase (PKS), made up of several enzymes or modules.[2] In each module, all of which contain at least the three domains Keto Synthase (KS), Acyl Transferase (AT), and Acyl Carrier Protein (ACP), the reaction sequence begins with a decarboxylative Claisen condensation between two thioesters (derived from acetyl-CoA) to afford the corresponding β-ketothioester. In more complex modules the condensation step can be followed by a reduction process induced by the insertion of a Keto Reductase (KR) domain to yield a β-hydroxy thioester. If the reduction process includes both KR and an additional DeHydratase (DH) domain, subsequent dehydration of the β-hydroxy thioester affords an unsaturated thioester in either the α,β or the β,γ positions (Scheme 1).[3]

Inspired by this biosynthetic pathway, a variety of carbon–carbon bond-forming reactions that enable the synthesis of complex polyketides have been developed.[4] Nevertheless, these successive reactions are often time- and reagent-consuming and always require the use of reactive intermediates that yield various by-products.[5] We therefore decided to devote our efforts to a bioinspired chemical strategy towards polyketide precursors based on a simple chemical iterative process satisfying the following requirements: (1) mimicry of each PKS module of type I, II and III reactions, (2) selective metal catalysis (M_1, M_2 and M_3, respectively), (3) mild conditions, and (4) no or few by-products. Malonic Acid Half Thioesters (MAHTs) were selected as carbon-centred nucleophiles because of their natural occurrence and their typical reactivity.

Using such intermediates, Kobuke and co-workers demonstrated thirty years ago that a decarboxylative Claisen condensation, corresponding to the type I reaction, was feasible through the use of Mg^{II} catalysis (M_1) and imidazole in an enzyme-free system.[6] The Kobuke reactions contrast with the harsher conditions required for other synthetic approaches to polyketide synthesis. They were recently improved upon by Matile and co-workers, who discovered that benzimidazole derivatives in association with Mg^{II} salts can serve as efficient base catalysts in this reaction.[7] Very recently, Shair and co-workers described a mild and catalytic thioester aldol reaction of type II, involving Cu^{II} catalysis (M_2) and aldehydes as substrates,[8] whilst the same aldolisation was also shown to proceed with simple thioesters and stoichiometric Mg^{II}.[9] Inspired by these efficient synthetic strategies, we focused on the type III reaction, known as the Doebner–Knoevenagel condensation, and largely applied to malonic acid half oxoesters.[10] Mild conditions using 4-(dimethylamino)pyridine (DMAP) catalysis have been described only recently,[11] but no simple procedure for MAHTs has been proposed to date. Here we report the first metal-catalysed Doebner–Knoevenagel condensations between MAHTs and aldehydes, mimicking a five-domain module (Scheme 1). This reaction offers a route to iterative metal-catalysed condensations of thioesters to afford complex polyketides.

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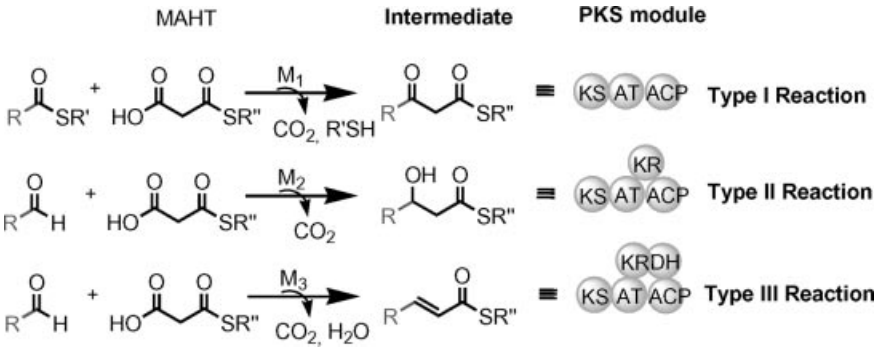
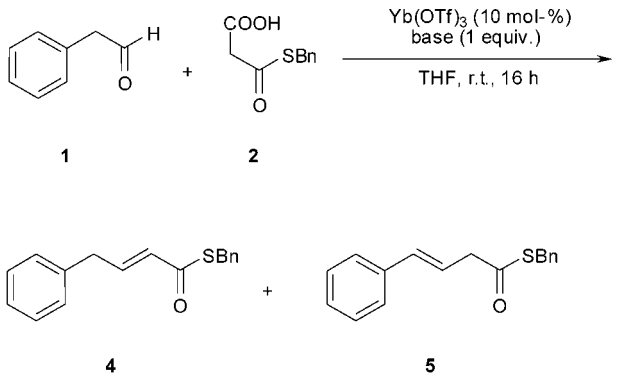


Scheme 1. Metal-catalysed reactions mimicking PKS modules.

Results and Discussion

Phenylacetaldehyde (**1**) was chosen as a substrate in our preliminary investigations because of its natural occurrence and its putative role as a precursor of various polyketides, including some new spiculoic acids that we had isolated and characterized from the marine sponge *Plakortis zyggompha*.[12] Our interest came from the postulated biosynthetic pathway of these metabolites, in which the dehydration step is believed to occur unexpectedly in the β,γ-position of the additional unit. The first attempts with phenylacetaldehyde (**1**) involved combining Cu^{II} 2-ethylhexanoate (20 mol-%), 5-methoxybenzimidazole (22 mol-%) and *S*-benzyl MAHT (**2**) in THF at room temperature.[8] In good agreement with Shair's results, only the β-hydroxy thioester **3** was formed under these conditions. After a screening of various metallic salts, the first catalytic Doebner–Knoevenagel condensation of MAHT was achieved with 10 mol-% of $Zn(OTf)_2$ or $Mg(OTf)_2$ to afford, in moderate 45% and 55% yields, mixtures of the α,β- and β,γ-unsaturated thioesters **4** and **5** in 1:1 and 3:7 ratios, respectively. Remarkably, no formation of the β-hydroxy thioester **3** was observed. A more interesting result was obtained with the use of a catalytic amount of $Yb(OTf)_3$ in the presence of a stoichiometric amount of 5-methoxybenzimidazole. Indeed, the yield was raised to 75% with this catalyst, whilst the regioselectivity was higher than 95% in favour of the biomimetic β,γ-unsaturated product **5**. This satisfactory outcome with $Yb(OTf)_3$ prompted us to study the influence of other parameters, in particular the role of the base (Table 1).

Table 1. Influence of the base on the condensation between MAHT **2** and phenylacetaldehyde (**1**).



Entry	Base	% isol. yield	**4/5**[a]
1	5-methoxybenzimidazole	75	<5:>95
2	imidazole	37	22:78
3	triethylamine	18	11:89
4	2,6-lutidine	98	<5:>95
5	*N*-methylmorpholine	63	11:89
6	DBU	–	–
7	2,6-di-*tert*-butylpyridine	35	<5:>95
8	4-(dimethylamino)pyridine	–	–
9[b]	5-methoxybenzimidazole	10	41:59
10[b]	2,6-lutidine	35	<5:>95

[a] Determined by ^1H NMR spectroscopy. [b] No catalyst, in 68 h.

Every attempt to reduce the amount of base always resulted in a significant decrease in the reaction yield. These results underlined the subtle conditions necessary for this condensation to be efficient. Indeed, poor results were obtained with the stronger bases Et_3N, DBU and DMAP (Table 1, Entries 3, 6, and 8), the only product detectable under these conditions being the *S*-benzyl thioester acetate, a product of MAHT **2** decarboxylation, isolated in quantitative yield in the presence of DMAP. This result was unexpected, since DMAP is known to catalyse direct aldol additions of malonic acid half oxoesters.[11] On comparison of the results obtained with 2,6-lutidine and 2,6-di-*tert*-butylpyridine (Table 1, Entries 4 and 7), it is clear that steric effects are prone to alter the course of the reaction. A very interesting result was obtained with 2,6-lutidine, which selectively afforded the biomimetic β,γ-unsaturated thioester **5** in quantitative yield. In order to assess the role of the base in the reaction mechanism, experiments in the absence of metal catalyst were conducted with 5-methoxybenzimidazole and 2,6-lutidine, which had previously given the best results. The yield of the reaction was drastically decreased, even after 68 h reaction time, which underlines the catalytic role of the metal. Moreover, with 5-methoxybenzimidazole (Table 1, Entry 9) the regioselectivity almost disappeared, but with 2,6-lutidine (Table 1, Entry 10) compound **5** remained the only product of the reaction. It could be speculated that the catalysed reaction could involve chelation of the metal with the leaving hydroxy group and the thioester

carbonyl in a putative six-membered ring transition state. Such activation should induce the higher yields and shorter reaction times observed in the catalysed reaction.

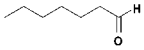
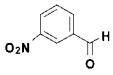
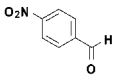
In order to evaluate the relative thermodynamic stabilities of the two isomers **4** and **5**, the dehydration step was performed under standard synthetic conditions, starting from the β-hydroxy thioester **3**. Dehydration was achieved through the formation of the methanesulfonyl ester by treatment with MsCl in CH_2Cl_2/pyridine (9:1) to afford the unsaturated compounds **4** and **5** in a 9:1 ratio. When the reaction was carried out in [D_5]pyridine at 20 °C, however, the composition of the mixture as monitored by ^{1}H NMR evolved, ending up after 6 h with pure compound **5** as the thermodynamic product of the reaction. This result demonstrated that pyridine and derivatives are basic enough to isomerise **4** into the thermodynamically more stable compound **5** whereas 5-methoxybenzimidazole is less efficient in this regard. Two distinct mechanisms leading to **5** were thus demonstrated for the catalytic Doebner–Knoevenagel condensation: (1) addition/dehydration to give **4**, followed by isomerisation into **5** in the presence of pyridine derivatives, and (2) addition/dehydration to afford **5** directly in the presence of 5-methoxybenzimidazole.

Using both sets of conditions (2,6-lutidine and 5-methoxybenzimidazole), we investigated the scope of the reaction with a variety of aldehydes as potential polyketide biosynthesis starter units. Surprisingly, the production of the dehydrated product was much more efficient with 5-methoxybenzimidazole in all cases; with saturated aliphatic aldehydes the dehydrated products were not even isolated when 2,6-lutidine was used. We then focused on 5-methoxybenzimidazole as a base for further experiments (Table 2).

With arylacetaldehydes in the presence of 5-methoxybenzimidazole, conversion into unsaturated thioesters occurred in high yields (Table 2, Entries 1–2), with the regioselectivity always in favour of the β,γ-conjugated thioesters. Interestingly, the reaction was also amenable to the use of an aliphatic β,γ-unsaturated aldehyde with the same efficiency and again with the same regioselectivity, involving conjugation with the cyclohexenyl substituent (Table 2, Entry 3). The case of 2-phenylpropionaldehyde appeared to be an exception, with a yield reduced to 35% and a reverse regioselectivity in favour of the α,β-unsaturated product (Table 2, Entry 4), though the same trend was also observed with saturated aliphatic aldehydes and arylcarboxaldehydes (Table 2, Entries 5–10). The strongly electron-withdrawing effect of *para* nitro substitution on the aromatic ring even resulted in total inhibition of the reaction, while the *meta* isomer reacted to give a 31% yield (Table 2, Entries 9–10). It is worth noting that the stereoselectivity was always totally in favour of the (*E*) stereoisomer, as shown by the large coupling constants of the vinylic protons in the ^{1}H NMR spectra of the reaction products.

Subsequent experiments were performed in order to gain new insights into the reaction mechanism. When all reagents with the exception of the aldehyde were mixed together, no decarboxylation occurred, suggesting that the addition is not induced by prior decarboxylation. With copper salts, the first putative β-hydroxy intermediate **A** undergoes a fast decarboxylative process to afford the β-hydroxy thioester **3**, as described by Shair and co-workers (Scheme 2).[8]

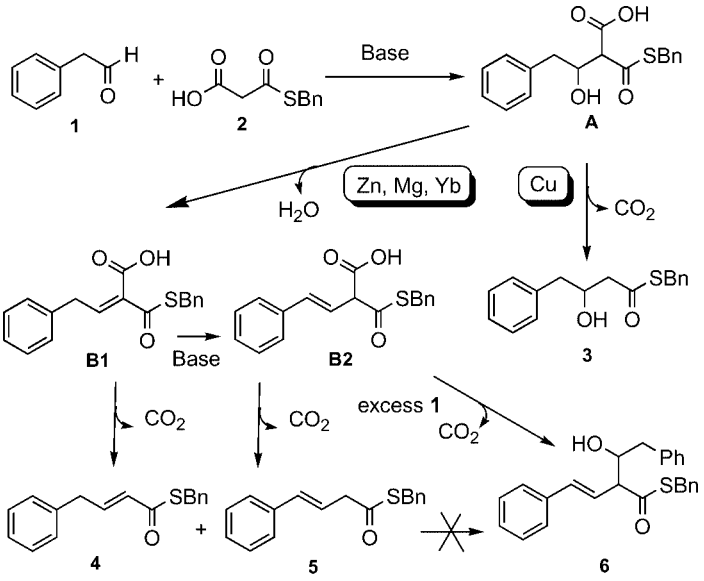
Table 2. Catalytic Doebner–Knoevenagel condensations between MAHT **2** and various aldehydes.[a]

Entry	Aldehyde	% isol. yield of unsaturated thioesters	α,β : β,γ
1		75	< 5 : > 95
2		91	30 : 70
3		82	< 5 : > 95
4		35	> 95 : < 5
5		34	> 95 : < 5
6		35	> 95 : < 5
7		32	> 95 : < 5
8		38	> 95 : < 5
9		31	> 95 : < 5
10		–	

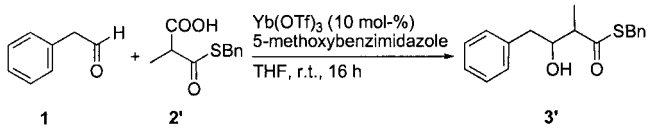
[a] Conducted under N_2 by combining 1:1:1 equiv. of aldehyde, MAHT **2** and 5-methoxybenzimidazole in the presence of $Yb(OTf)_3$ (10 mol-%) in THF at room temperature in 16 h.

With zinc, magnesium and ytterbium salts, it is assumed that the dehydration is faster than the decarboxylation process, affording the α,β-conjugated intermediate **B1**. Isomerisation followed by decarboxylation would then give product **5**. The fact that **3** is not an intermediate in the formation of **4** and **5** was demonstrated unequivocally, as no reaction occurred when **3** was subjected to our optimized conditions [$Yb(OTf)_3$, 5-methoxybenzimidazole in THF at room temp.]. The transient existence of the reactive intermediate **B1** was supported by the fact that no dehydrated product was observed with α-methyl-substituted MAHT **2′** (Scheme 3).

In this case the reaction stopped after the decarboxylative Claisen addition, providing the β-hydroxy thioester **3′** in 65% yield, just as in a type II reaction. The quaternary carbon atom at the α-position of the thioester intermediate **A′** would indeed make a dehydration process to afford the α,β-unsaturated intermediate **B1′** impossible. Furthermore, a decarboxylative isomerisation process involving **B1**, as previously described by Corey in the case of unsaturated malonic acid derivatives,[13] would by itself explain the presence of the mixtures of compounds **4** and **5**, in ratios dic-



Scheme 2. Mechanistic insights into the Doebner–Knoevenagel condensations between MAHT and aldehydes.



Scheme 3. Reaction between the α-methyl-substituted MAHT **2′** and phenylacetaldehyde (**1**).

tated by the natures of the metal catalysis and the substrates. The presence of the phenyl-conjugated intermediate **B2** in the mechanistic pathway leading to **5** was, however, demonstrated by an additional experiment. With an excess of aldehyde **1** rather than a stoichiometric quantity, we observed the formation of a large amount of the adduct **6**, the result of the addition of **B2** to a second molecule of aldehyde **1** (Scheme 2). This double addition was not observed when product **5** was subjected to the same reaction conditions. On the basis of the mechanistic proposal, we assume that the outcome of the reaction (yield and regioselectivity) is governed by the relative thermodynamic stabilities of the **B1**- and **B2**-derived carbanions. With a poorly stabilized **B1** carbanion the yield drops because of a slow decarboxylative process on **B1** (Table 2, Entries 4–8), whilst with a strongly stabilized **B1** carbanion the regioselectivity in favour of the β,γ-unsaturated thioester decreases (Table 2, Entry 2).

Conclusions

We have developed original, bioinspired, metal-catalysed Doebner–Knoevenagel condensations between MAHTs and aldehydes. The reactions can be conducted under very mild conditions with catalytic quantities of $Yb(OTf)_3$ in the presence of stoichiometric amounts of 5-methoxybenzimidazole and always proceed with high regio- and stereoselectivity. The simple reaction conditions and the accessibility of MAHTs are attractive incentives to use this reaction as a starting point in polyketide synthesis. Indeed, an iterative process using the easy reduction of thioesters into aldehydes and additional condensations using the same as electrophiles can be considered for future extensions.[14]

Experimental Section

General: All chemicals were obtained from commercial suppliers and were used without further purification. All reactions were carried out under nitrogen with use of standard Schlenk techniques. THF was distilled from sodium/benzophenone. ^1H and ^{13}C spectra were recorded on either a Bruker Avance 500 MHz or an Avance 200 MHz NMR spectrometer with $CDCl_3$ (δ_H = 7.26 and δ_C = 77.16 ppm) as internal standards. Spectral features are tabulated in the following order: chemical shift (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = complex multiplet), number of protons, coupling constant (J in Hz), assignment. ElectroSpray Ionisation (ESI) mass spectra were run on a Bruker Esquire 3000 Plus spectrometer in the positive or negative mode. High-resolution mass spectra were obtained with a LCT Waters-Micromass mass spectrometer (ESI TOF). IR spectra were obtained with a Perkin–Elmer Paragon 1000 FT-IR spectrometer.

General Procedure for the Preparation of Malonic Acid Half Thioesters: The malonic or methylmalonic acid (50 mmol, 4 equiv.) was added to a stirred solution of the polyphosphate ester (PPE, 7.8 g) in $CHCl_3$ (65 mL) and THF (15 mL), and benzyl mercaptan (1.46 mL, 12.5 mmol, 1 equiv.) diluted in $CHCl_3$ (20 mL) was then added to the resulting white suspension by syringe. The reaction mixture was stirred at 25 °C for 16 h and the quenched with aqueous HCl (0.5 N, 200 mL). The mixture was extracted with CH_2Cl_2 (2 × 200 mL) and the organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel [*n*-hex/EtOAc (8:2), then *n*-hex/EtOAc (5:5)] afforded the pure malonic acid half thioesters.

***S*-Benzyl Malonic Acid Half Thioester 2:** White solid; purified by flash chromatography; 1.77 g or 68% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.75 (br s, OH), 7.14–7.40 (m, 5 H, Ph), 4.16 (s, 2 H, H-4), 3.61 (s, 2 H, H-2) ppm. ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 190.9 (C-3), 170.9 (C-1), 136.5, 129.0, 128.9, 127.7, 48.6 (C-2), 34.1 (C-4) ppm. IR: $\tilde{\nu}$ = 3453 (OH), 1726 (CO), 1687 (CO), 1496, 1454 cm^{-1}. MS (ESI, MeOH): *m*/*z*: 209 $[M - H]^-$.

***S*-Benzyl Methylmalonic Acid Half Thioester 2′:** Colourless oil; purified by flash chromatography; 1.79 g or 64% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 11.05 (br s, OH), 7.25–7.40 (m, 5 H, Ph), 4.23 (m, 2 H, H-4), 3.75 (q, 1 H, J = 7.3 Hz, H-2), 1.52 (d, 3 H, J = 7.3 Hz, H-5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.1 (C-3), 174.8 (C-1), 136.6, 128.8, 128.7, 127.5, 53.5 (C-2), 33.7 (C-4), 14.1 (C-5) ppm. MS (ESI, MeOH): *m*/*z*: 223 $[M - H]^-$.

Procedure for the Catalytic Aldol Reactions between MAHTs and Phenylacetaldehyde (1): 5-Methoxybenzimidazole (0.057 mmol, 0.22 equiv.) and Cu(2-ethylhexanoate)$_2$ (0.052 mmol, 0.20 equiv.) were added at 25 °C to a stirred solution of *S*-benzyl malonic acid half thioester **2** (55 mg, 0.26 mmol) in THF (5 mL). Phenylacetaldehyde (**1**, 0.26 mmol, 1 equiv.) was added after homogenisation of the solution (≈ 2 min), which was then stirred for 16 h at 25 °C and quenched with an aqueous solution of HCl (0.5 N, 10 mL). The resulting mixture was diluted with EtOAc and washed successively with aq. HCl (0.5 N), saturated aq. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel (from *n*-hex to EtOAc) to afford pure compound **3**.

***S*-Benzyl 3-Hydroxy-4-Phenylbutanethioate (3):** Colourless oil; 48 mg or 48% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.15–7.34 (m, 10 H, Ph), 4.25 (m, 1 H, 3-H), 4.08 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, 1′a-H), 4.04 (d, $^3J_{H,H}$ = 14.1 Hz, 1 H, 1′b-H), 2.70 (m, 2 H, 4-H), 2.66 (m, 2 H, 2-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.2 (C-1), 137.4, 137.1, 129.4, 128.7, 128.6, 128.5, 127.3, 126.7, 69.6 (C-3), 49.6 (C-2), 42.9 (C-4), 33.3 (C-1′) ppm. IR: $\tilde{\nu}$ = 3540 (OH), 1686 (CO), 1495, 1453 cm^{-1}. MS (ESI, pos, MeOH): *m*/*z*: 309 $[M + Na]^+$. HRMS (ESI, pos, MeOH): *m*/*z*: 309.0928 $[M + Na]^+$; 309.0925 calcd. for $C_{17}H_{18}O_2NaS$.

General Procedure for the Yb(OTf)$_3$-Catalyzed Doebner–Knoevenagel Condensation between MAHTs and Aldehydes: The base (0.26 mmol, 1 equiv.) and Yb(OTf)$_3$ (0.026 mmol, 10 mol-%) were added at 25 °C to a stirred solution of *S*-benzyl malonic acid half thioester **2** (55 mg, 0.26 mmol) in THF (5 mL). The aldehyde (0.26 mmol, 1 equiv.) was added after homogenization of the solution (≈ 2 min), which was then stirred for 16 h at 25 °C and concentrated under reduced pressure to yield a yellow oil. The oil was purified by flash chromatography on silica gel [*n*-hexane/CH_2Cl_2 (1:1) then CH_2Cl_2 (100%)] to afford the following unsaturated thioesters.

***S*-Benzyl (*E*)-4-Phenylbut-3-enethioate (5, Table 2, Entry 1):** Colourless oil; purified by flash chromatography; 52 mg or 75% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.15–7.50 (m, 10 H, Ph), 6.65 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, 4-H), 6.40 (dt, $^3J_{H,H}$ = 16.0, 7.3 Hz, 1 H, 3-H), 4.26 (s, 2 H, 1′-H), 3.57 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H, H-2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.9 (C-1), 137.5, 136.7, 135.1 (C-4), 129.0, 128.7, 127.9, 127.4, 126.5, 120.9 (C-3), 47.5 (C-2), 33.5 (C-1′) ppm. IR: $\tilde{\nu}$ = 1683 (CO), 1648, 1494, 1400 cm^{-1}. MS (ESI, MeOH): *m*/*z*: 269 $[M + H]^+$. HRMS (ESI, MeOH): *m*/*z*: 291.0814 $[M + Na]^+$; 291.0820 calcd. for $C_{17}H_{16}ONaS$.

***S*-Benzyl (*E*)-4-(2-Nitrophenyl)but-3-enethioate and *S*-Benzyl (*E*)-4-(2-Nitrophenyl)but-2-enethioate (Table 2, Entry 2):** Colourless oil; purified by flash chromatography; 74 mg or 91% isolated yield in a 7:3 mixture.

α,β-Unsaturated Thioester: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (dd, $^3J_{H,H}$ = 8.0, 1.5 Hz, 1 H), 7.60–7.40 (m, Ph), 7.36 (m, $^3J_{H,H}$ = 16.0 Hz, 1 H, 3-H), 7.30–7.07 (m, Ph), 6.01 (dt, $^3J_{H,H}$ = 15.5, 1.5 Hz, 1 H, 2-H), 4.09 (s, 2 H, 1′-H), 3.75 (dd, $^3J_{H,H}$ = 6.5, 1.5 Hz, 2 H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.0 (C-1), 149.0, 141.5 (C-3), 137.6, 133.6, 132.4 (C-2), 129.9, 128.9, 128.7, 128.3, 127.4, 125.3, 35.7 (C-4), 33.2 (C-1′) ppm. MS (ESI, MeOH): *m*/*z*: 336 $[M + Na]^+$.

β,γ-Unsaturated Thioester: ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (br d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.60–7.40 (m, Ph), 7.30–7.07 (m, Ph), 6.96 (d, $^3J_{H,H}$ = 15.0 Hz, 1 H, 4-H), 6.21 (dt, $^3J_{H,H}$ = 15, 7.5 Hz, 1 H, 3-H), 4.08 (s, 2 H, 1′-H), 3.47 (dd, $^3J_{H,H}$ = 7.5, 1.5 Hz, 2 H, 2-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3 (C-1), 147.7, 137.3, 133.3, 130.2 (C-4), 129.0, 128.8, 128.4, 127.5, 126.5, 124.7 (C-3), 47.5 (C-2), 33.6 (C-1′) ppm. MS (ESI, MeOH): *m*/*z*: 336 $[M + Na]^+$.

***S*-Benzyl (*E*)-4-(2,6,6-Trimethylcyclohex-1-enyl)but-3-enethioate (Table 2, Entry 3):** Colourless oil; purified by flash chromatography; 67 mg or 82% isolated yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.09–7.28 (m, 5 H, Ph), 5.98 (d, $^3J_{H,H}$ = 15.4 Hz, 1 H, 4-H), 5.40 (dt, $^3J_{H,H}$ = 15.4 7.2 Hz, 1 H, 3-H), 4.21 (s, 2 H, 1′-H), 3.28 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, 2-H), 1.90 (m, 2 H, H-3′′), 1.65–1.28 (m, 7 H, 4′′,5′′,9′′-H), 0.91 (s, 6 H, 7′′,8′′-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.6 (C-1), 137.9, 137.0 (C-1′′), 134.0 (C-4), 129.5 (C-2′′), 128.9, 128.7, 127.3, 124.5 (C-3), 48.1 (C-2), 39.5 (C-5′′), 34.2 (C-6′′), 33.4 (C-1′), 32.8 (C-3′′), 28.8 (C-7′′, C-8′′), 21.6 (C-4′′), 19.4 (C-9′′) ppm. MS (ESI, MeOH): *m*/*z*: 337 $[M + Na]^+$. HRMS (ESI, MeOH): *m*/*z*: 337.1616 $[M + Na]^+$; 337.1602 calcd. for $C_{20}H_{26}ONaS$.

***S*-Benzyl (*E*)-4-Phenylpent-2-enethioate (Table 2, Entry 4):** Colourless oil; purified by flash chromatography; 25 mg or 35% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.09–7.25 (m, 10 H, Ph), 7.00 (dd, $^3J_{H,H}$ = 15.6, 6.4 Hz, 1 H, 3-H), 6.01 (dd, $^3J_{H,H}$ = 15.6, 1.8 Hz, 1 H, 2-H), 4.10 (s, 2 H, 1′-H), 3.54 (m, 1 H, 4-H), 1.36 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.5 (C-1), 149.3 (C-3), 143.1, 137.8, 129.0, 128.9, 128.7, 127.5, 127.4, 127.0 (C-2), 42.2 (C-4), 21.9 (C-5), 37.4 (C-1′) ppm. IR: $\tilde{\nu}$ = 1671 (CO), 1627, 1493, 1452 cm^{-1}. MS (ESI, MeOH): *m*/*z*: 305 $[M + Na]^+$. HRMS (ESI, MeOH): *m*/*z*: 305.1014 $[M + Na]^+$; 305.0996 calcd. for $C_{18}H_{18}OSNa$.

***S*-Benzyl (*E*)-But-2-enethioate (Table 2, Entry 5):** Colourless oil; purified by flash chromatography; 17 mg or 34% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.24 (m, 5 H, Ph), 6.86 (dq, $^3J_{H,H}$ = 15.6, 6.9 Hz, 1 H, 3-H), 6.07 (dq, $^3J_{H,H}$ = 15.6, 1.8 Hz, 1 H, 2-H), 4.11 (s, 2 H, 1′-H), 1.80 (dd, $^3J_{H,H}$ = 6.9, 1.8 Hz, 3 H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.3 (C-1), 141.4 (C-3), 137.9, 129.9 (C-2), 129.0, 128.7, 127.3, 33.0 (C-1′), 18.1 (C-4) ppm. IR: $\tilde{\nu}$ = 1671 (CO), 1630 cm^{-1}. MS (ESI, MeOH): *m*/*z*: 215 $[M + Na]^+$. HRMS (ESI, MeOH): *m*/*z*: 215.0489 $[M + Na]^+$; 215.0507 calcd. for $C_{11}H_{12}ONaS$.

***S*-Benzyl (*E*)-Pent-2-enethioate (Table 2, Entry 6):** Colourless oil; purified by flash chromatography; 19 mg or 35% isolated yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.24 (m, 5 H, Ph), 6.90 (dt, $^3J_{H,H}$ = 15.6, 6.4 Hz, 1 H, 3-H), 6.04 (dt, $^3J_{H,H}$ = 15.6, 1.8 Hz, 1 H, 2-H), 4.12 (s, 2 H, 1′-H), 2.16 (qdd, $^3J_{H,H}$ = 6.9, 6.4, 1.8 Hz, 2 H, 4-H), 0.99 (t, $^3J_{H,H}$ = 6.8 Hz, 3 H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.5 (C-1), 147.5 (C-3), 137.9, 129.0, 128.7, 127.5 (C-2), 127.3, 33.0 (C-1′), 25.5 (C-4), 12.2 (C-5) ppm. IR: $\tilde{\nu}$ = 1673 (CO), 1631 cm^{-1}. MS (ESI, MeOH): *m*/*z*: 229 $[M + Na]^+$. HRMS (ESI, MeOH): *m*/*z*: 229.0682 $[M + Na]^+$; 229.0663 calcd. for $C_{12}H_{14}ONaS$.

***S*-Benzyl (*E*)-Non-2-enethioate (Table 2, Entry 7):** Colourless oil; purified by flash chromatography; 22 mg or 32% isolated yield. ^1H

NMR (500 MHz, $CDCl_3$): δ = 7.30–7.10 (m, 5 H, Ph), 6.86 (dt, $^3J_{H,H}$ = 15.5, 6.5 Hz, 1 H, 3-H), 6.04 (dt, $^3J_{H,H}$ = 15.5, 1.5 Hz, 1 H, 2-H), 4.11 (s, 2 H, 1′-H), 1.60–1.10 (m, 10 H), 0.81 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, 9-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.5 (C-1), 147.5 (C-3), 137.9, 129.0, 128.7, 127.5 (C-2), 127.3, 33.0 (C-1′), 25.5 (C-4), 12.2 (C-5) ppm. MS (ESI, MeOH): *m*/*z*: 285 $[M + Na]^+$.

***S*-Benzyl (*E*)-4-Methylpent-2-enethioate (Table 2, Entry 8):** Colourless oil; purified by flash chromatography; 22 mg or 38% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.15–7.25 (m, 5 H, Ph), 6.82 (dd, $^3J_{H,H}$ = 15.6 Hz, 1 H, 3-H), 6.00 (dd, $^3J_{H,H}$ = 15.6, 1.4 Hz, 1 H, 2-H), 4.11 (s, 2 H, 1′-H), 2.37 (hd, $^3J_{H,H}$ = 6.9, 1.4 Hz, 1 H, 4-H), 0.99 (d, $^3J_{H,H}$ = 6.9 Hz, 6 H, 5,6-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.8 (C-1), 152.2 (C-3), 137.9, 129.0, 128.7, 127.3, 125.7 (C-2), 33.3 (C-1′), 31.1 (C-4), 21.3 (C-5, C-6) ppm. IR: $\tilde{\nu}$ = 1673 (CO), 1629, 1495, 1453 cm^{-1}. MS (ESI, MeOH): *m*/*z*: 243 $[M + Na]^+$. HRMS (ESI, MeOH): *m*/*z*: 243.0833 $[M + Na]^+$; 243.0820 calcd. for $C_{13}H_{16}ONaS$.

***S*-Benzyl (*E*)-3-(3-Nitrophenyl)prop-2-enethioate (Table 2, Entry 9):** Colourless oil; purified by flash chromatography; 24 mg or 31% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (s, 2′′-H), 8.16 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 4′′-H), 7.74 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, 6′′-H), 7.58 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H, 3-H), 7.50 (t, $^3J_{H,H}$ = 8.7 Hz, 1 H, 5′′-H), 7.17–7.28 (m, 5 H, Ph), 6.73 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H, 2-H), 4.21 (s, 2 H, 1′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.7 (C-1), 148.8 (C-3′′), 137.8 (C-3), 137.3, 136.0 (C-1′′), 134.1 (C-6′′), 130.2 (C-5′′), 129.0, 127.8, 127.6 (C-2′′), 127.4, 124.9 (C-4′′), 122.7 (C-2), 33.6 (C-1′) ppm. IR: $\tilde{\nu}$ = 1670 (CO), 1619, 1530 (NO), 1350 (NO) cm^{-1}. MS (ESI, MeOH): *m*/*z*: 317 $[M + NH_4]^+$. HRMS (ESI, MeOH): *m*/*z*: 322.0534 $[M + Na]^+$; 322.0514 calcd. for $C_{16}H_{13}NO_3NaS$.

Dehydration of 3 via a Methanesulfonyl Ester: Methanesulfonyl chloride (0.85 mmol, 5 equiv.) was added at 25 °C to a stirred solution of the β-hydroxy thioester **3** (48 mg, 0.17 mmol) in a mixture of pyridine (1 mL) and CH_2Cl_2 (9 mL). The solution was then stirred for 16 h at room temperature and quenched with saturated aq. $NaHCO_3$. After extraction with CH_2Cl_2 (2 × 20 mL), the organic phase was washed successively with aq. HCl (0.5 N , 20 mL), saturated aq. $NaHCO_3$ (20 mL) and brine (20 mL). It was then dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield 45 mg of a mixture of compounds **4** and **5** along with the non-eliminated methanesulfonyl derivative. When the mixture of compounds was dissolved in $[D_5]$pyridine the elimination/isomerization process was followed by ^{1}H NMR spectroscopy. After 6 h no trace of compound **4** was present in the mixture.

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