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Iterative polyketide synthesis via consecutive carbonyl-protecting strategy

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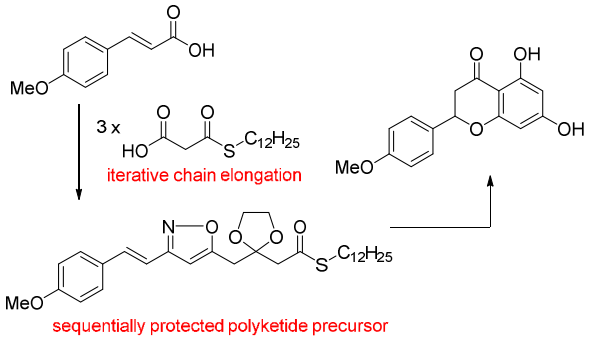
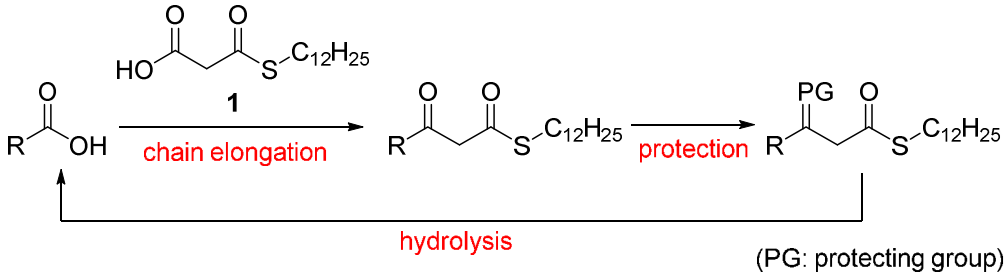


ABSTRACT: To address the difficulty in protecting a ß-polycarbonyl compound, a method for the sequential protection of elongating carbonyl groups was demonstrated. The iterative chain elongation of a carboxylic acid with malonic acid half thioester followed by the protection of the resulting ß-ketothioester was performed via the stepwise formation of an isoxazole ring using an O-protected oxime functionality. Yangonin and isosakuranetin were synthesized according to this procedure.

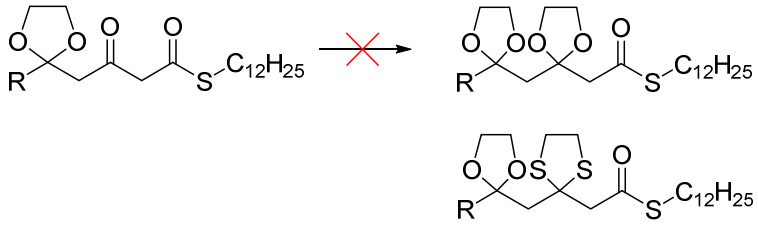
Polyketides are recognized as one of the most important compound classes from the viewpoint of biological activity and the application to pharmaceuticals. In the field of organic synthesis, much

effort has been devoted to the synthesis of polyketides, and various methods for producing complex polyketides have been established to date.[1] Notable examples are iterative synthetic methods, in which same reactions are used repeatedly for the construction of molecular structures.[2] The primary advantage of iterative synthesis is that a series of related molecules can be obtained by a uniform protocol using only a few types of reactions. Hence, it is potentially applicable to automated synthesis and solid-phase synthesis.[3] Recently, we reported an iterative method for polyketide synthesis via decarboxylative C-C bond formations with malonic acid half thioester (MAHT).[4,5] The method includes diversification steps in each iterative cycle; thus, the structure and oxidation state of linear polyketide precursors can be easily varied. When the method was applied to the synthesis of non-reduced polyketides typically produced by type III polyketide synthases, we faced the difficulty in constructing a protected β-polyketone structure. In our method (Scheme 1), a carboxylic acid is subjected to the chain elongation with MAHT **1**, and the β-carbonyl group of the resulting ketothioester is protected as 1,3-dioxolane or 1,3-dithiolane, which is then hydrolyzed to a carboxylic acid for the next chain elongation. However, in the case that a β-ketothioester had the 1,3-dioxolane protection at the δ-position, the attempt to protect the β-carbonyl group failed (Scheme 2).[6] The construction of a β,δ-bis(dithiolane) structure was also unsuccessful because of a low yield. The difficulty in the sequential carbonyl protection can be ascribed to the formation of an unstable non-protected tricarbonyl intermediate in the equilibrium of the carbonyl/acetal exchange. Although it was possible to introduce the 1,3-dioxolane protection to a δ-dithiolane-protected β-ketothioester,[4] a further protection of an extended carbonyl group is not feasible.

Scheme 1. Cycle for the iterative chain elongation with MAHT 1



Scheme 2. Limitation in the sequential protection of carbonyl groups



Another problem should be addressed in the iterative synthesis of coumaroyl-CoA-derived natural products such as yangonin and isosakuranetin (Figure 1). When 4-methoxycinnamic acid was employed as a starting substrate in our method, the strategy using a dioxolane or dithiolane protection was not applicable owing to the unsaturated aromatic structure with the electron-donating group (Schemes S1a and S1b in the Supporting Information). Another choice for the chain elongation with MAHT is Shair's aldol reaction using an aldehyde substrate and a copper catalyst.[7] However, the aldol reaction did not proceed for the substrate with a methoxy group (Scheme S1c in the Supporting Information). Harris and co-workers intensively studied on the synthesis of polyketones by a sequential carbonyl elongation.[8] In their method, for example, a tricarbonyl compound is converted into a trianion under strongly basic conditions, and subjected to the reaction with a carbonyl source to produce a tetracarbonyl compound. Presumably because a multivalent anionic intermediate is involved in the reaction, the yields for the chain elongation are

moderate to low, and the synthesis of a tetracarbonyl compound from the tricarbonyl substrate with an electron-donating group is not reported.[9] Although non-reduced polyketides including yangonin[10] and isosakuranetin[11] have been synthesized in different ways,[12] a new strategy is desirable for producing polycarbonyl compounds by a sequential chain elongation.

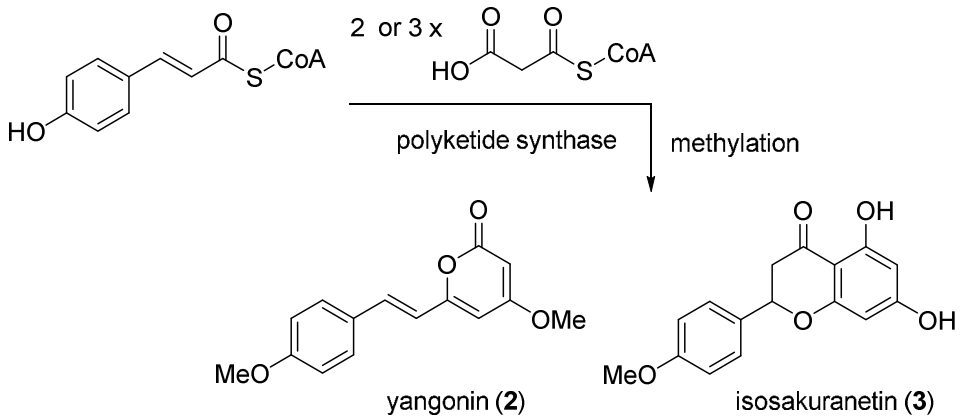
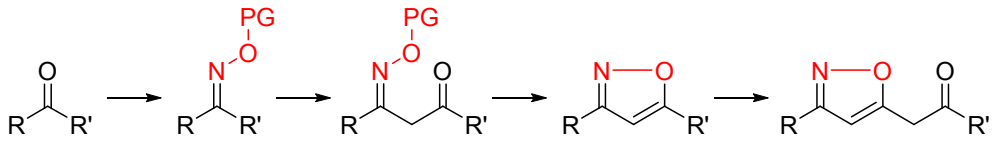


Figure 1. Natural products synthesized from coumaroyl-CoA in biological system.

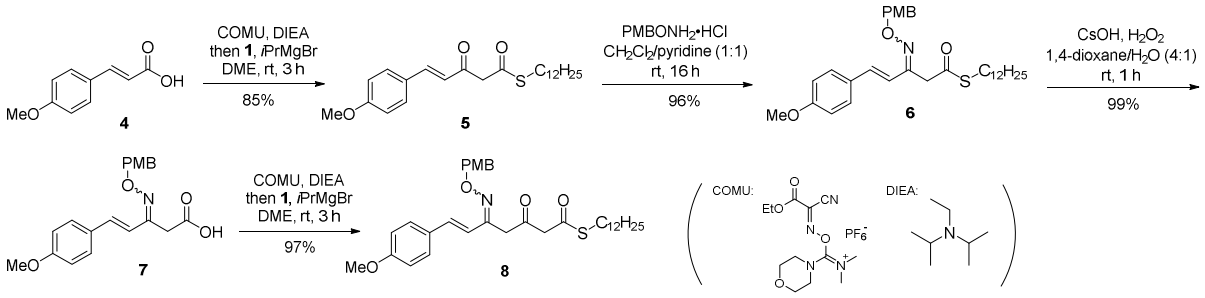
Based on the fact that an isoxazole ring has been used as the synthetic equivalent to a 1,3-dicarbonyl structure,[13] we propose the stepwise formation of isoxazole for the protection of elongating carbonyl groups (Scheme 3).[14] First, a carbonyl group is converted to an O-protected oxime. This is then subjected to the chain elongation. Finally, the newly generated carbonyl group is protected as the isoxazole ring via the removal of the O-protection and dehydration. The isoxazole-protected compound is expected to be used for a further chain elongation. To demonstrate the viability of this sequential strategy, the synthesis of yangonin and isosakuranetin by assembling 4-methoxycinnamic acid and two or three malonic acid units was performed.

Scheme 3. Proposed strategy for the consecutive protection of carbonyl groups



ß-Ketothioester **5** was obtained by decarboxylative dehydration condensation between carboxylic acid **4** and MAHT **1** (Scheme 4).[15] This ketothioester was reacted with hydroxylamine having a p-methoxybenzyl (PMB) group on the oxygen atom. The protecting reaction of the ß-carbonyl group proceeded to afford the diastereomixture (7:3) of oxime **6**. This PMB-oxime protection was stable under the conditions for hydrolysis of the thioester and the second chain elongation with **1**. These reactions produced tricarbonyl equivalent **8**. Other types of protection such as dioxolane, azide, and enol ether formation were not tolerated for the hydrolysis and condensation. The attempt for the introduction of a 1,3-dithiolane protection to the ß-carbonyl group of compound **8** was unsuccessful, indicating the difficulty in the sequential protection in a conventional manner.

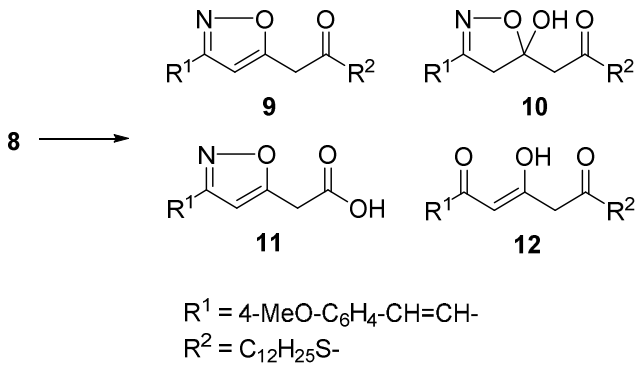
Scheme 4. Formation of a PMB-protected oxime followed by hydrolysis and chain elongation



Next, the conditions for the removal of the PMB group and the formation of the isoxazole

ring from compound **8** were screened (Table 1). In this step, it is necessary to avoid possible side reactions such as hydrolysis of the thioester and oxime functionalities. The use of an oxidant resulted in preferential reaction of the thioester part, and the formation of isoxazole **9** was not observed. (entry 1). Under acidic conditions with trifluoroacetic acid or boron trifluoride, the reaction tuned into a complex mixture, and the yield of product **9** was low (entries 2 and 3). A moderate yield was attained by the reaction with hydrochloric acid at 50 °C (entry 4). In this case, however, hydrolyzed compounds **11** and **12** were obtained. The yield was not improved by lowering the temperature and elongating the reaction time (entry 5). By using a 1,4-dioxane solution of hydrogen chloride, the formation of product **9** proceeded smoothly at room temperature without bringing about hydrolysis to **11** and **12** (entry 6). The addition of a small amount of water slightly increased the yield (entry 7).

Table 1. Formation of an isoxazole ring



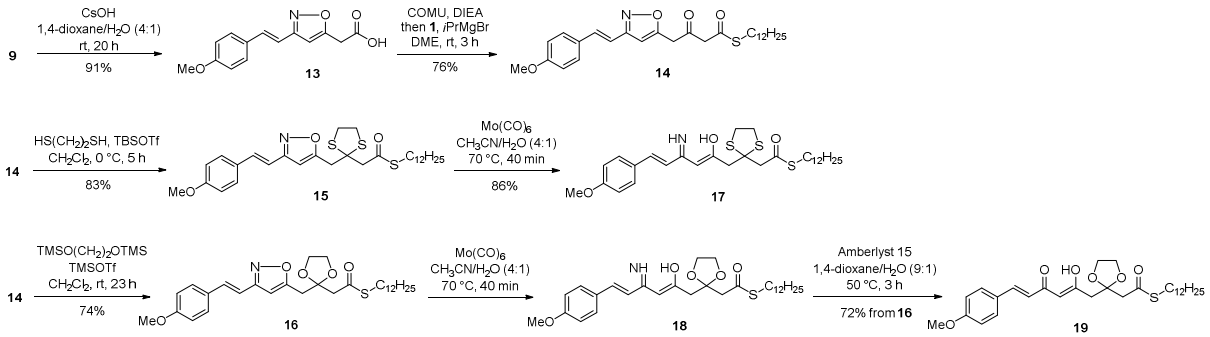
entry	conditions	yield[a]
1	DDQ (3 equiv.), CH_3CN/H_2O (9:1), rt, 20 min	**10**: 8%
2	CF_3CO_2H/CH_2Cl_2 (1:9), rt, 10 min	**9**: 22%
3	$BF_3 \cdot OEt_2$ (5 equiv.), CH_2Cl_2, rt, 10 min	**9**: 25%, **10**: 9%
4	conc. HCl aq./1,4-dioxane (1:9), 50 °C, 22 h	**9**: 56%, **11**: 18%, **12**: 6%

5	conc. HCl aq./1,4-dioxane (1:9), 40 °C, 40 h	**9**: 53%, **11**: 6%, **12**: 5%
6	4 M HCl in 1,4-dioxane, rt, 3 h	**9**: 75% (isolated yield)
7	4 M HCl in 1,4-dioxane, H_2O (3 equiv.), rt, 3 h	**9**: 82% (isolated yield)

[a] Yield was estimated by the NMR measurement of a crude mixture, unless otherwise noted as isolated yield.

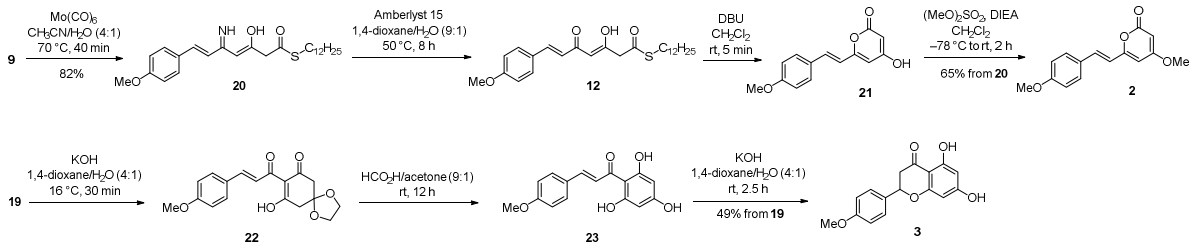
Tetracarbonyl equivalent **14** was obtained via hydrolysis of **9** and the third chain elongation (Scheme 5). To test the utility of the isoxazole formation, the protection of the ß-carbonyl group of compound **14** was conducted. Both 1,3-dithiolane and 1,3-dioxolane were successfully introduced to afford compounds **15** and **16**, respectively. It is also notable that, in the presence of the 1,3-dithiolane or 1,3-dioxolane functionality, the selective deprotection of isoxazole was possible. Reductive dissociation of the isoxazole ring of compound **15** proceeded with molybdenum hexacarbonyl[16] in an aqueous solvent system, while other reduction conditions using Raney nickel or titanium(III) chloride were not applicable. In the case of compound **16** with the acid-labile 1,3-dioxolane group, selective hydrolysis of the resulting imine is also necessary. It was found that the use of Amberlyst 15 as an acid catalyst could suppress the removal of the dioxolane protection to afford compound **19**.

Scheme 5. Synthesis of protected tetraketides and reductive cleavage of the isoxazole ring



Finally, the obtained intermediates were transformed into natural products (Scheme 6). Reduction of the isoxazole ring of compound **9** gave imine **20**. Through hydrolysis of the imine, cyclization with a base, and methylation, yangonin was obtained in 34% overall yield from carboxylic acid **4**. Meanwhile, upon treatment of compound **19** in a potassium hydroxide aqueous solution, Claisen-type cyclization proceeded to afford compound **22**. By removing the 1,3-dioxolane protection, a chalcone structure formed. This was then subjected to intramolecular Michael addition under basic conditions to produce isosakuranetin. From starting carboxylic acid **4**, the overall yield of isosakuranetin was 12%. In the reported synthesis of isosakuranetin,[11] trihydroxybenzene derivatives were employed as a starting material. The most different feature in our case is that the aromatic ring was constructed by assembling malonic acid units. Although the synthetic procedure seems less efficient, the present iterative method is expected to be applied to a wider range of polyketide synthesis in the uniform protocol.

Scheme 6. Derivatization into natural products



In conclusion, the sequential protecting method via the stepwise formation of an isoxazole ring was demonstrated. The isoxazole protection was compatible with other protecting groups such as 1,3-dithiolane and 1,3-dioxolonae. To control the cyclization mode of a polycarbonyl compound, the combination of these protecting groups is considered to be effective. The present protecting technique is expected to be applied not only to the synthesis of more complex polyketides, but also to other synthetic schemes for obtaining polycarbonyl compounds.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively on a JEOL JNM-LA400 spectrometer, and chemical shifts were referenced to internal tetramethylsilane (TMS, δ = 0.0 ppm) for ^{1}H and the central line of $CDCl_3$ (δ = 77.0 ppm) or CD_3OD (δ = 49.0 ppm) for ^{13}C. High-resolution FAB-MS measurements were performed on JEOL JMS-600H, a double-focusing magnetic sector mass spectrometer. Unless otherwise noted, the data were collected in a positive-ion mode. 3-Nitrobenzylalcohol was used as a matrix, and polyethylene glycol 400 or 600 was added to the matrix as an internal mass calibrant.

S-Dodecyl (E)-5-(4-methoxyphenyl)-3-oxopent-4-enethiolate, S-Dodecyl (2Z,4E)-3-hydroxy-5-(4-methoxyphenyl)penta-2,4-dienethioate (***5***). To a suspension of 4-methoxycinnamic acid (178.6 mg) and COMU (429.4 mg) in DME (2.5 mL), DIEA (175 μL) was added, and the mixture was stirred for 15 min. In another flask, to a solution of MAHT **1** (433.6 mg) in DME (2.5 mL), a THF solution (1 M) of isopropylmagnesium bromide (2.0 mL) was added at 0 °C. The solution was allowed to warm to room temperature, and stirred for 3 min. This was added to the flask containing the activated carboxylic acid. After stirring the solution for 2 h, an aqueous solution (10 w%) of citric acid was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 4:1) to afford β-ketothioester **5** (343.9 mg, 85%) as a yellow solid. Keto/enol ratio = 35:65. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, J = 16.0 Hz, 0.35H), 7.54-7.41 (m, 2.65H), 6.94-6.87 (m, 2H), 6.71 (d, J = 16.0 Hz, 0.35H), 6.23 (d, J = 16.0 Hz, 0.65H), 5.55 (s, 0.65H), 3.89 (s, 0.7H), 3.85 (s, 1.05H), 3.84 (s, 1.95H), 2.96 (t, J = 7.4 Hz, 1.3 H), 2.93 (t, J = 7.4 Hz, 0.7 H), 1.67-1.56 (m, 2H), 1.43-1.19 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.5, 192.4,

191.1, 166.9, 162.0, 160.8, 144.9, 138.1, 130.4, 129.2, 128.0, 126.7, 122.8, 118.9, 114.4, 114.3, 101.0, 56.1, 55.4, 55.3, 31.9, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 29.1, 28.8, 28.8, 28.3, 22.7, 14.1. **HRMS** (FAB) *m/z*: calculated for $C_{24}H_{37}O_3S$ $[M+H]^+$: 405.2463, found 405.2457.

*S-Dodecyl (4E)-3-(((4-methoxybenzyl)oxy)imino)-5-(4-methoxyphenyl)pent-4-enethioate (**6**).* To a solution of ß-ketothioester **5** (202.5 mg) in dichloromethane (1.25 mL) and pyridine (1.25 mL), *O*-(4-methoxybenzyl)hydroxylamine hydrochloride (111.1 mg) was added. The mixture was stirred for 16 h, and transferred to a separation funnel with diethyl ether. The organic layer was washed with an aqueous saturated solution of ammonium chloride three times, and dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 4:1) to afford oxime **6** (258.6 mg, 96%) as a pale yellow oil. Diastereomeric ratio = 7:3. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 4.3H), 6.92-6.73 (m, 5.7H), 5.15 (s, 0.6H), 5.14 (s, 1.4H), 3.88 (s, 1.4H), 3.81 (s, 3H), 3.81 (s, 0.9H), 3.80 (s, 2.1H), 3.69 (s, 0.6H), 2.88 (t, J = 7.2 Hz, 0.6 H), 2.86 (t, J = 7.2 Hz, 1.4 H), 1.61-1.49 (m, 2H), 1.37-1.19 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.2, 194.0, 160.5, 160.0, 159.3, 152.1, 150.1, 136.3, 133.5, 129.9, 129.8, 129.7, 129.5, 129.1, 129.0, 128.7, 128.3, 122.5, 114.3, 114.1, 113.7, 113.7, 76.2, 76.1, 55.3, 55.2, 46.5, 40.0, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.2, 29.2, 29.1, 28.8, 28.8, 22.7, 14.1. **HRMS** (FAB) *m/z*: calculated for $C_{32}H_{46}NO_4S$ $[M+H]^+$: 540.3148, found 540.3156.

*(4E)-3-(((4-Methoxybenzyl)oxy)imino)-5-(4-methoxyphenyl)pent-4-enoic acid (**7**).* To a solution of oxime **6** (205.3 mg) in 1,4-dioxane (6.08 mL) and water (758 μL), an aqueous solution (30-36 w%) of hydrogen peroxide (431 μL) and an aqueous solution (50 w%) of cesium hydroxide (331 μL, 5 equiv.) were added. At this point, the concentration of **6** was 0.05 M in 1,4-dioxane/water (4:1 v/v). An aqueous solution (30-36 w%) of hydrogen peroxide (216 μL) was added twice every 20 min. After

stirring the mixture for 1 h in total, the resulting solution was transferred to a separation funnel with diethyl ether and water. Two phases were separated with the addition of brine. The aqueous layer was acidified with an aqueous solution of hydrochloric acid, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. The removal of the solvent under reduced pressure afforded carboxylic acid **7** (134.2 mg, 99%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.26 (m, 4.3H), 6.92-6.73 (m, 5.7H), 5.13 (s, 1.4H), 5.12 (s, 0.6H), 3.80 (s, 3H), 3.80 (s, 0.9H), 3.77 (s, 2.1H), 3.67 (s, 1.4H), 3.56 (s, 0.6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.4, 174.0, 160.7, 160.0, 159.4, 159.4, 152.0, 149.9, 136.4, 133.3, 130.0, 129.7, 129.3, 129.3, 129.1, 128.6, 128.4, 128.3, 122.1, 114.2, 114.1, 113.8, 113.8, 76.2, 55.3, 55.2, 55.2, 36.6, 30.8. **HRMS** (FAB, negative ion mode) *m/z*: calculated for $C_{20}H_{20}NO_5$ $[M–H]^–$: 354.1342, found 354.1340.

*S-Dodecyl (6E)-5-(((4-methoxybenzyl)oxy)imino)-7-(4-methoxyphenyl)-3-oxohept-6-enethioate, S-Dodecyl (2Z,6E)-3-hydroxy-5-(((4-methoxybenzyl)oxy)imino)-7-(4-methoxyphenyl)hepta-2,6-dienethioate (**8**)*. To a suspension of carboxylic acid **7** (118.6 mg) and COMU (179.5 mg) in DME (1.07 mL), DIEA (73.2 μL) was added, and the mixture was stirred for 12 min. In another flask, to a solution of MAHT **1** (207.7 mg) in DME (1.07 mL), a THF solution (1 M) of isopropylmagnesium bromide (0.84 mL) was added at 0 °C. The solution was allowed to warm to room temperature, and stirred for 2 min. This was added to the flask containing the activated carboxylic acid. After stirring the solution for 3 h, an aqueous solution (10 w%) of citric acid was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 2:1) to afford β-ketothioester **8** (188.4 mg, 97%) as a pale yellow solid. Keto/enol ration = 85:15. Diastereomeric ratio = 3:1 (keto) and 2:1 (enol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.26 (m, 4.3H), 6.92-6.69 (m, 5.7H), 5.47 (s, 0.05H),

5.39 (s, 0.1H), 5.13 (s, 0.1H), 5.13 (s, 0.2H), 5.11 (s, 0.42H), 5.11 (s, 1.28H), 3.81 (s, 3H), 3.81 (s, 3H), 3.77 (s, 1.28H), 3.69 (s, 0.42H), 3.65 (s, 0.42H), 3.64 (s, 1.28H), 3.54 (s, 0.2H), 3.36 (s, 0.1H), 2.92-9.84 (m, 2H), 1.62-1.49 (m, 2H), 1.39-1.19 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.9, 196.8, 195.0, 192.2, 192.1, 172.5, 170.6, 160.6, 160.5, 160.0, 160.0, 159.5, 159.4, 153.1, 152.7, 150.9, 150.3, 136.6, 136.3, 133.9, 133.5, 129.9, 129.8, 129.7, 129.7, 129.5, 129.1, 129.1, 129.0, 128.9, 128.8, 128.5, 128.3, 128.3, 122.3, 122.1, 114.1, 113.8, 113.7, 100.0, 99.7, 76.3, 76.2, 76.0, 76.0, 56.5, 55.8, 55.3, 55.2, 46.2, 40.0, 36.6, 31.9, 30.3, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.8, 28.8, 28.2, 22.6, 14.1. **HRMS** (FAB) *m*/*z*: calculated for $C_{34}H_{48}NO_5S$ $[M+H]^+$: 582.3253, found 582.3257.

*S-Dodecyl (E)-2-(3-(4-methoxystyryl)isoxazol-5-yl)ethanethioate (**9**).* To a flask containing ß-ketothioester **8** (187.4 mg) and water (17.4 μL), a 1,4-dioxane solution (4 M) of hydrogen chloride (1.61 mL) was added. After stirring the mixture for 3 h, an aqueous saturated solution of sodium bicarbonate was added. The resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 4:1) to afford isoxazole **9** (116.7 mg, 82%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.10 (d, J = 16.4 Hz, 1H), 6.97 (d, J = 16.4 Hz, 1H), 6.94-6.89 (m, 2H), 6.49 (s, 1H), 4.00 (s, 2H), 3.84 (s, 3H), 2.93 (t, J = 7.6 Hz, 2H), 1.59 (quin, J = 7.4 Hz, 2H), 1.40-1.19 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.9, 164.4, 162.2, 160.2, 135.6, 128.5, 128.4, 114.2, 113.6, 100.7, 55.3, 41.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.8, 22.7, 14.1. **HRMS** (FAB) *m*/*z*: calculated for $C_{26}H_{38}NO_3S$ $[M+H]^+$: 444.2572, found 444.2568.

*(E)-2-(3-(4-Methoxystyryl)isoxazol-5-yl)acetic acid (**13**).* Hydrolysis was performed in the absence of hydrogen peroxide. To a solution of isoxazole **9** (115.8 mg) in 1,4-dioxane (4.18 mL) and water

(817 μL), an aqueous solution (50 w%) of cesium hydroxide (227 μL, 5 equiv.) was added. After stirring the mixture for 20 h, the resulting solution was transferred to a separation funnel with diethyl ether and water. Two phases were separated with the addition of brine. The aqueous layer was acidified with an aqueous solution of hydrochloric acid, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. The removal of the solvent under reduced pressure afforded carboxylic acid **13** (61.9 mg, 91%) as a pale yellow solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.55-7.50 (m, 2H), 7.26 (d, *J*= 16.4 Hz, 1H), 6.96 (d, *J*= 16.4 Hz, 1H), 6.97-6.92 (m, 2H), 6.68 (s, 1H), 3.87 (s, 2H), 3.82 (s, 3H). **^{13}C NMR** (100 MHz, CD_3OD) δ 171.2, 167.6, 163.7, 162.0, 137.5, 129.9, 129.6, 115.3, 114.0, 101.6, 55.8, 33.1. **HRMS** (FAB, negative ion mode) *m*/*z*: calculated for $C_{14}H_{12}NO_4$ $[M–H]^–$: 258.0767, found 258.0766.

*S-Dodecyl (E)-4-(3-(4-methoxystyryl)isoxazol-5-yl)-3-oxobutanethioate, S-Dodecyl (Z)-3-hydroxy-4-(3-((E)-4-methoxystyryl)isoxazol-5-yl)but-2-enethioate (**14**).* To a suspension of carboxylic acid **13** (145.4 mg) and COMU (266.3 mg) in DME (1.4 mL), DIEA (108 μL) was added, and the mixture was stirred for 10 min. In another flask, to a solution of MAHT **1** (278.8 mg) in DME (1.4 mL), a THF solution (1 M) of isopropylmagnesium bromide (954 μL) was added at 0 °C. The solution was allowed to warm to room temperature, and stirred for 3 min. This was added to the flask containing the activated carboxylic acid. After stirring the solution for 3 h, an aqueous solution (10 w%) of citric acid was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: chloroform) to afford β-ketothioester **14** (206.9 mg, 76%) as a pale yellow solid. Keto/enol ratio = 7:3. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (d-like, *J*= 8.8 Hz, 2H), 7.10 (d, *J*= 16.6 Hz, 1H), 6.97 (d, *J*= 16.6 Hz, 1H), 6.91 (d-like, *J*= 8.8 Hz, 2H), 6.50 (s, 0.7H), 6.42 (s, 0.3H), 5.50 (s, 0.3H), 4.05 (s, 1.4H),

3.84 (s, 3H), 3.78 (s, 1.4H), 3.65 (s, 0.6H), 2.93 (t, J = 7.4 Hz, 2H), 1.59 (quin, J = 7.3 Hz, 2H), 1.40-1.21 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.4, 195.2, 191.7, 168.5, 166.0, 164.0, 162.3, 160.3, 135.7, 135.7, 128.5, 128.4, 114.3, 113.6, 113.5, 101.0, 100.8, 100.2, 57.0, 55.3, 40.7, 32.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.8, 28.4, 22.7, 14.1. **HRMS** (FAB) *m*/*z*: calculated for $C_{28}H_{40}NO_4S$ $[M+H]^+$: 486.2678, found 486.2683.

*S-Dodecyl (E)-2-(2-((3-(4-methoxystyryl)isoxazol-5-yl)methyl)-1,3-dithiolan-2-yl)ethanethioate (**15**)*. The reaction was performed under argon atmosphere. To a solution of β-ketothioester **14** (67.8 mg) in dichloromethane (2.8 mL), 1,2-ethandithiol (117 μL) and trimethylsilyl trifluoromethanesulfonate (96.5 μL) were added at 0 °C. After stirring the mixture for 5 h at this temperature, an aqueous saturated solution of sodium bicarbonate was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 4:1) to afford dithiolane **15** (64.8 mg, 83%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.10 (d, J = 16.6 Hz, 1H), 6.98 (d, J = 16.6 Hz, 1H), 6.93-6.88 (m, 2H), 6.46 (s, 1H), 3.83 (s, 3H), 3.66 (s, 2H), 3.36-3.25 (m, 6H), 2.93 (t, J = 7.2 Hz, 2H), 1.60 (quin, J = 7.4 Hz, 2H), 1.41-1.21 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.4, 168.8, 161.8, 160.2, 135.3, 128.6, 128.3, 114.2, 113.9, 101.0, 64.8, 55.7, 55.3, 40.4, 39.8, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 28.8, 22.7, 14.1. **HRMS** (FAB) *m*/*z*: calculated for $C_{30}H_{44}NO_3S_3$ $[M+H]^+$: 562.2483, found 562.2492.

*S-Dodecyl (E)-2-(2-((3-(4-methoxystyryl)isoxazol-5-yl)methyl)-1,3-dioxolan-2-yl)ethanethioate (**16**)*. The reaction was performed under argon atmosphere. To a solution of β-ketothioester **14** (21.1 mg) and ethylenedioxybis(trimethylsilane) (239 μL) in dichloromethane (976 μL), trimethylsilyl trifluoromethanesulfonate (26.4 μL) was added. After stirring the mixture for 23 h, an aqueous

saturated solution of sodium bicarbonate was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 2:1) to afford dithiolane **16** (17.0 mg, 74%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H), 7.09 (d, *J* = 16.4 Hz, 1H), 6.97 (d, *J* = 16.4 Hz, 1H), 6.93-6.88 (m, 2H), 6.42 (s, 1H), 4.06-3.88 (m, 4H),3.84 (s, 3H), 3.31 (s, 2H), 2.95 (s, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 1.58 (quin, *J* = 7.4 Hz, 2H), 1.41-1.21 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.0, 167.6, 162.0, 160.1, 135.2, 128.6, 128.3, 114.2, 113.9, 107.4, 100.8, 65.4, 55.3, 50.8, 35.6, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 29.1, 28.8, 22.7, 14.1. **HRMS** (FAB) *m*/*z*: calculated for $C_{30}H_{44}NO_5S$ $[M+H]^+$: 530.2940, found 530.2938.

*S-Dodecyl 2-(2-((2Z,5E)-2-hydroxy-4-imino-6-(4-methoxyphenyl)hexa-2,5-dien-1-yl)-1,3-dithiolan-2-yl)ethanethioate (**17**)*. To a flask containing dithiolane-protected isoxazole **15** (25.7 mg) and molybdenum hexacarbonyl (60.7 mg), acetonitrile (457 μL) and water (91.4 μL) were added, and the mixture was heated to 70 °C. Sublimed molybdenum hexacarbonyl on the wall of the flask was dropped to the bottom with a small amount of acetonitrile every 10 min. After stirring the mixture for 40 min in total, the flask was cooled to room temperature. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 2:1) to afford imine **17** (22.3 mg, 86%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d-like, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.90 (d-like, *J* = 8.8 Hz, 2H), 6.29 (d, *J* = 16.2 Hz, 1H), 5.27 (s, 1H), 3.83 (s, 3H), 3.59 (s, 2H), 3.40 (s, 2H), 3.29 (s, 4H), 2.86 (t, *J* = 7.2 Hz, 2H), 1.55 (quin, *J* = 7.2 Hz, 2H), 1.38-1.18 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.1, 195.8, 160.6, 157.1, 134.1, 128.8, 127.8, 122.2, 114.3, 97.3, 63.4, 55.7, 55.3, 53.7, 39.0, 31.9, 29.6, 29.5, 29.5, 29.5, 29.3, 29.1, 29.1, 28.9, 22.7, 14.1. **HRMS** (FAB) *m*/*z*: calculated for $C_{30}H_{46}NO_3S_3$ $[M+H]^+$: 564.2640, found 564.2634.

*S-Dodecyl 2-(2-((2Z,5E)-2-hydroxy-6-(4-methoxyphenyl)-4-oxohexa-2,5-dien-1-yl)-1,3-dioxolan-2-yl) ethanethioate (**19**).* To a flask containing dioxolane-protected isoxazole **16** (14.3 mg) and molybdenum hexacarbonyl (36.0 mg), acetonitrile (432 μL) and water (108 μL) were added, and the mixture was heated to 70 °C. Sublimed molybdenum hexacarbonyl on the wall of the flask was dropped to the bottom with a small amount of acetonitrile every 10 min. After stirring the mixture for 40 min in total, the flask was cooled to room temperature. After the removal of the solvent under reduced pressure, Amberlyst 15 (270 mg), 1,4-dioxane (486 μL), and water (54.0 μL) were added to the flask, and the mixture was heated to 50 °C. After stirring the mixture for 3 h, the flask was cooled to room temperature. Amberlyst 15 was filtered off and washed with chloroform. After the removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate = 9:1 → 7:3) to afford ketoenol **19** (10.3 mg, 72%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.57 (d, J = 15.8 Hz, 1H), 7.50-7.45 (m, 2H), 6.93-6.88 (m, 2H), 6.36 (d, J = 15.8 Hz, 1H), 5.75 (s, 1H), 4.06-3.98 (m, 4H),3.84 (s, 3H), 3.07 (s, 2H), 2.92 (s, 2H), 2.89 (t, J = 7.4 Hz, 2H), 1.57 (quin, J = 7.6 Hz, 2H), 1.40-1.20 (m, 18H), 0.88 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.2, 194.5, 178.4, 161.2, 140.0, 129.6, 127.7, 120.4, 114.3, 107.6, 102.2, 65.2, 55.4, 51.0, 47.9, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.1, 28.9, 22.7, 14.1. **HRMS** (FAB) *m/z*: calculated for $C_{30}H_{45}O_6S$ $[M+H]^+$: 533.2937, found 533.2943.

*S-Dodecyl (3Z,6E)-3-hydroxy-5-imino-7-(4-methoxyphenyl)hepta-3,6-dienethioate (**20**).* To a flask containing isoxazole **9** (53.1 mg) and molybdenum hexacarbonyl (158 mg), acetonitrile (0.96 mL) and water (0.24 mL) were added, and the mixture was heated to 70 °C. Sublimed molybdenum hexacarbonyl on the wall of the flask was dropped to the bottom with a small amount of acetonitrile every 10 min. After stirring the mixture for 40 min in total, the flask was cooled to room temperature. After the removal of the solvent under reduced pressure, the residue was purified by

preparative TLC on silica gel (eluent: hexanes/ethyl acetate = 2:1) to afford imine **20** (43.6 mg, 82%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.39 (m, 2H), 7.04 (d, *J* = 16.4 Hz, 1H), 6.93-6.88 (m, 2H), 6.32 (d, *J* = 16.4 Hz, 1H), 5.36 (s, 1H), 3.84 (s, 3H), 3.61 (s, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.59 (quin, *J* = 7.3 Hz, 2H), 1.40-1.20 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.9, 189.2, 160.8, 158.6, 134.9, 128.9, 127.6, 121.6, 114.3, 95.7, 57.9, 55.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.3, 29.1, 28.8, 22.6, 14.1. **HRMS** (FAB) *m*/*z*: calculated for $C_{26}H_{40}NO_3S$ $[M+H]^+$: 446.2729, found 446.2730.

*Yangonin (**2**).* To a flask containing imine **20** (24.1 mg) and Amberlyst 15 (540 mg), 1,4-dioxane (973 μL) and water (108 μL) were added, and the mixture was heated to 50 °C. After stirring the mixture for 8 h, the flask was cooled to room temperature. Amberlyst 15 was filtered off and washed with chloroform. After the removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane (1.08 mL), and DBU (8.08 μL, 1 equiv.) was added. After stirring the mixture for 5 min, an aqueous solution (1 N) of hydrochloric acid was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane (1.08 mL), and DIEA (28.3 μL, 3 equiv.) was added. The solution was cool to –78 °C, and dimethyl sulfate (25.7 μL, 5 equiv.) was added. After stirring the mixture for 5 min at this temperature, the reaction flask was allowed to warm to room temperature. After stirring the mixture for 2 h, an aqueous solution (1 N) of hydrochloric acid was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by preparative TLC on silica gel (eluent: chloroform) to afford yangonin (9.1 mg, 65% yield) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 16.2 Hz, 1H), 7.47-7.42 (m, 2H), 6.93-6.88 (m, 2H), 6.45 (d, *J* = 16.2 Hz, 1H), 5.90 (d, *J* = 2.2 Hz, 1H), 5.47 (d, *J* = 2.2 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H). **^{13}C NMR**

(100 MHz, $CDCl_3$) δ 171.2, 164.2, 160.7, 159.1, 135.4, 129.0, 128.0, 116.3, 114.3, 100.4, 88.3, 55.9, 55.3. **HRMS** (FAB) *m/z*: calculated for $C_{15}H_{15}O_4$ $[M+H]^+$: 259.0970, found 259.0969.

*Isosakuranetin (**3**).* To a solution of ketoenol **19** (9.4 mg) in 1,4-dioxane (564 μL), an aqueous solution (2.5 M) of potassium hydroxide (141 μL) was added. After stirring the mixture for 30 min at 16 °C, an aqueous solution (1 N) of hydrochloric acid was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, acetone (70 μL) and formic acid (630 μL) were added to the residue. After stirring the mixture for 12 h, the reaction solvent was removed under reduced pressure. The residue was dissolved in 1,4-dioxane (564 μL), and an aqueous solution (2.5 M) of potassium hydroxide (141 μL) was added. After stirring the mixture for 2.5 h, an aqueous solution (1 N) of hydrochloric acid was added. The resulting mixture was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate = 4:1 → 1:1) to afford isosakuranetin (2.5 mg, 49%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.1 (s, 1H), 7.41-7.36 (m, 2H), 6.98-6.93 (m, 2H), 6.00 (d, J = 2.0 Hz, 1H), 5.98 (d, J = 2.0 Hz, 1H), 5.79 (br s, 1H), 5.37 (dd, J = 13.0, 3.0 Hz, 1H), 3.84 (s, 3H), 3.11 (dd, J = 17.3, 13.0 Hz, 1H), 2.79 (dd, J = 17.3, 3.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.1, 164.3, 163.3, 160.0, 130.2, 127.7, 114.2, 103.2, 96.7, 95.4, 79.0, 55.4, 43.1. **HRMS** (FAB) *m/z*: calculated for $C_{16}H_{15}O_5$ $[M+H]^+$: 287.0919, found 287.0921.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge on the ACS Publications website.

Scheme S1 and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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