On the origin of the thiopyrone CTP-431 "unexpectedly" isolated from the marine sponge *Cacospongia mycofijiensis*

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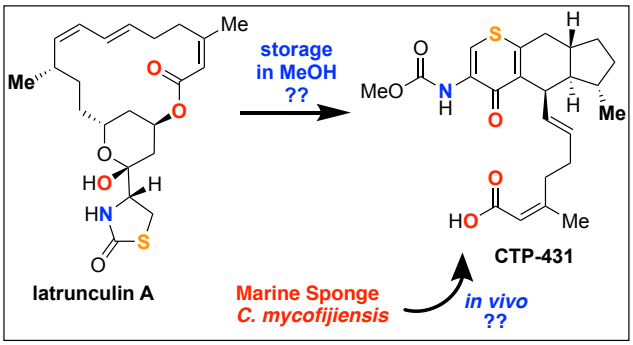

ABSTRACT

An intriguing hypothesis that latrunculin A, a well-known natural product, might have undergone transformation into the unprecedented thiopyrone CTP-431 upon long-term storage in methanol is advanced. Thus opening of the hemiacetal of latrunculin A, followed by E1CB elimination, and dehydration would give a polyene that could undergo intramolecular Diels-Alder reaction, followed by methanolysis of the thiazolidinone ring and ring closure by intramolecular thiol addition to an enone. Experimental evidence that the novel thiazolidinone to thiopyrone rearrangement can occur is presented.

The marine sponge *Cacospongia mycofijiensis*, found in the ocean surrounding Fiji, is a source of several polyketide natural products with interesting biological properties,[1] including the tubulin binding macrolide fijianolide B (also known as laulimalide),[2,3] the HIF1 signal inhibitor

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mycothiazole,[4,5] and the macrolide latrunculins (Figure 1).[6] The thiazolidinone-containing latruculins are of mixed polyketide synthesis (PKS) and non-ribosomal peptide synthesis (NRPS) origin, and latrunculin A **1** disrupts microfilament assembly to such an extent that it is the most widely used chemical tool to study actin binding.

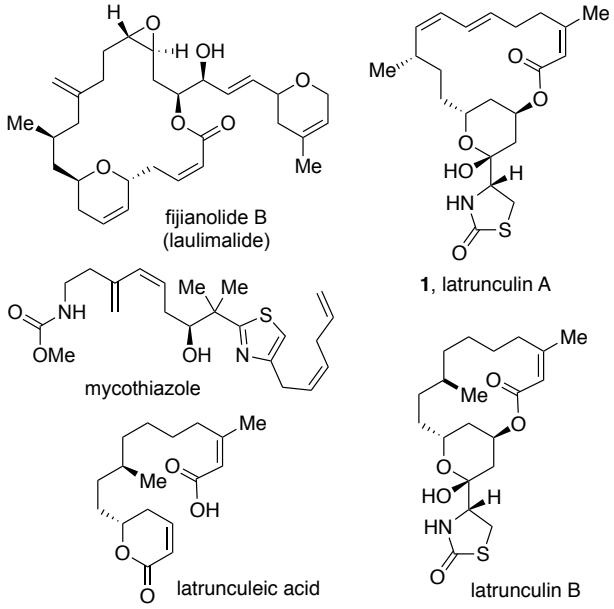
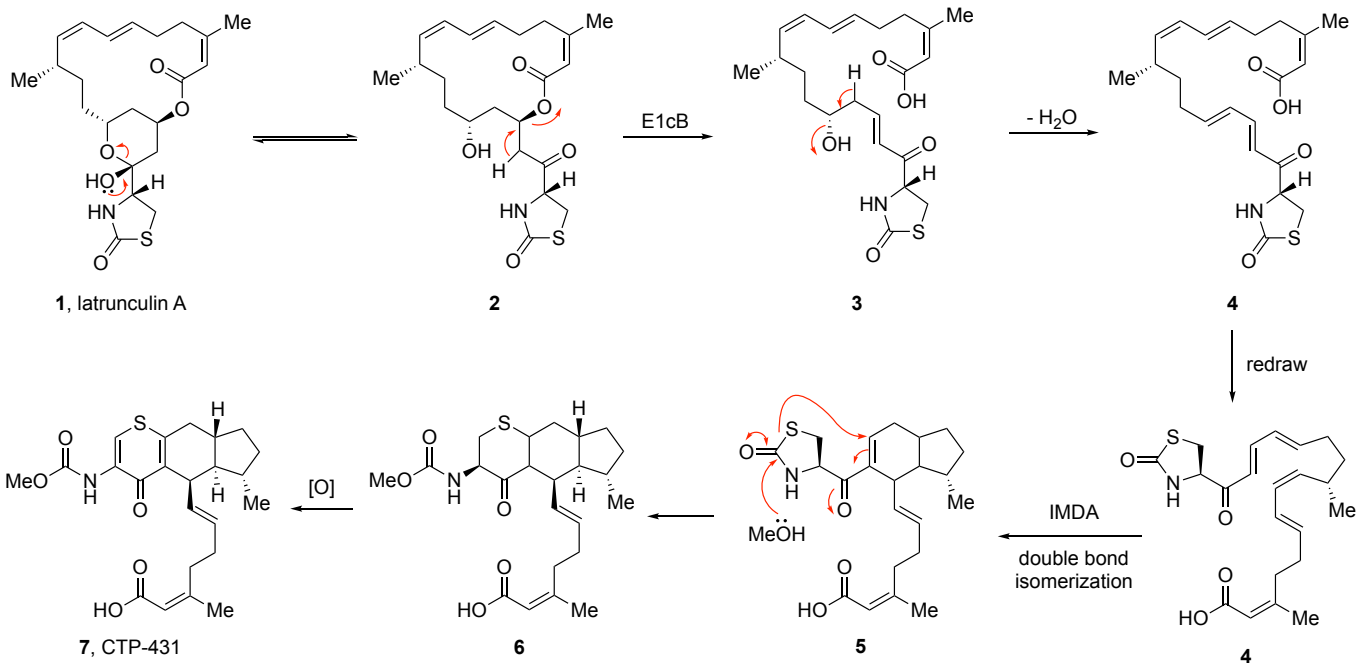


Figure 1. Marine natural products from the sponge *Cacospongia mycofijiensis.*

In the course of their seminal studies on the biology and chemistry of metabolites extracted from *C. mycofijiensis*, in 2008 the Crews laboratory reported the "unexpected" isolation of a new compound, CTP-431 **7**, containing an unprecedented thiopyrone ring fused to a hydrindane, the structure being confirmed by X-ray crystallographic analysis.[1] Although Crews *et al*. proposed a logical biogenesis involving a PKS-NRPS derived linear precursor that could cyclize to both latrunculin A and CTP-431, our attention was caught by the unusual provenance of CTP-431. It was isolated from a crude sponge extract that had been stored in methanol at 4 °C for 19 years, and in which the expected compound latrunculin A was found to be entirely absent. This absence, coupled with the similarity in carbon backbones of latrunculin A and CTP-431 and the complete absence of other thiopyrones from the natural world, invite the intriguing hypothesis that latrunculin A might have undergone transformation into CTP-431 upon long-term storage in methanol. The likely

product of methanolysis of the thiazolidinone ring would be a methyl carbamate resembling the one found in CTP-431, providing support for our hypothesis.

We therefore propose that a possible mechanism (Scheme 1) for this interconversion would proceed from the hemiacetal of latrunculin A **1** to its open-chain isomer **2**, followed by E1CB elimination of the lactone and subsequent dehydration of alcohol **3** to give polyene **4**; the structures of congeners such as latrunculeic acid (Figure 1) provide some evidence that this carboxylate elimination can occur readily.[7] Intramolecular Diels-Alder (IMDA) reaction of **4**, followed by isomerization of the double bond to restore conjugation, would give the hydrindane **5**. Methanolysis of the thiazolidinone would lead to rapid 6-*endo*-trig conjugate addition of the thiol to give thiopyranone **6**, and autoxidation of the tricyclic system would give the final product, CTP-431 **7** (Scheme 1).

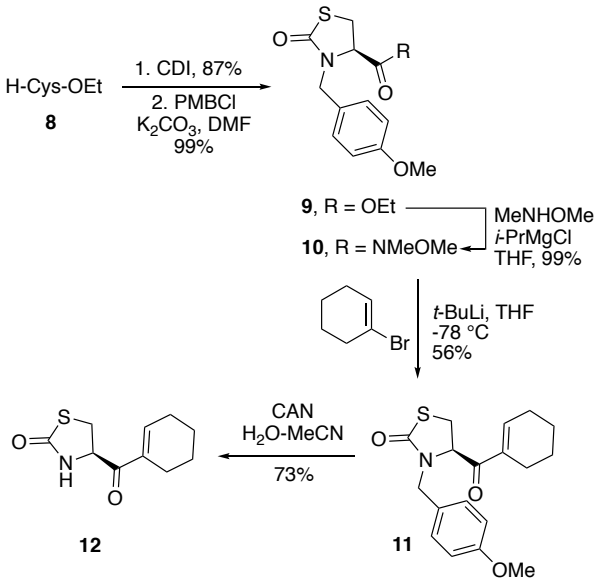


Scheme 1. Proposed conversion of latrunculin A into CTP-131.

The fascinating possibility of such an extended sequence of spontaneous reactions occurring over a prolonged period prompted us to embark upon a model study to investigate the feasibility of such a transformation. There are two pivotal steps in the proposed sequence of events outlined in Scheme 1, the IMDA reaction of triene **4** to give, after double bond isomerization, hydrindane **5**, and the

subsequent methanolysis of the thiazolidinone ring followed by reclosure by intramolecular thiol addition to the enone (**5** to **6**, Scheme 1). Of these, the former is well precedented with several examples of IMDA reactions of trienes leading to hydrindane derivatives, including many with a similar substitution pattern on diene and dienophile fragments,[8-12] although the conditions usually required to effect IMDA reactions vary from those used to store the natural sample. Nevertheless, we took the view that such an IMDA step was feasible, and thus our experimental focus was on the key thiazolidinone ring-opening step.

The ring opening of thiazolidinones is reported to occur under aqueous alkaline conditions, followed by decarboxylation to give cysteamine derivatives.[13,14] The present case necessitates a methanolysis initiated ring-rearrangement reaction of the thiazolidinone to a tetrahydrothiopyranone, and therefore as a model for the CTP-431 system, we selected the cyclohexenyl ketone **12**. The synthesis began with the cyclization of cysteine ethyl ester **8** using CDI, followed by protection of the nitrogen with a 4-methoxybenzyl (PMB) group to give the thiazolidinone **9**. Conversion into the cyclohexenyl ketone **11** was effected *via* the known Weinreb amide **10**,[15] using 1-bromocyclohexene and *t*-BuLi. The PMB group was removed oxidatively using cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile to give the thiazolidinone ring-rearrangement precursor **12** (Scheme 2). The structures of both thiazolidinones **11** and **12** were confirmed by X-ray crystallography (Figure 2).



Scheme 2. Synthesis of model thiazolidinone enone **12**.

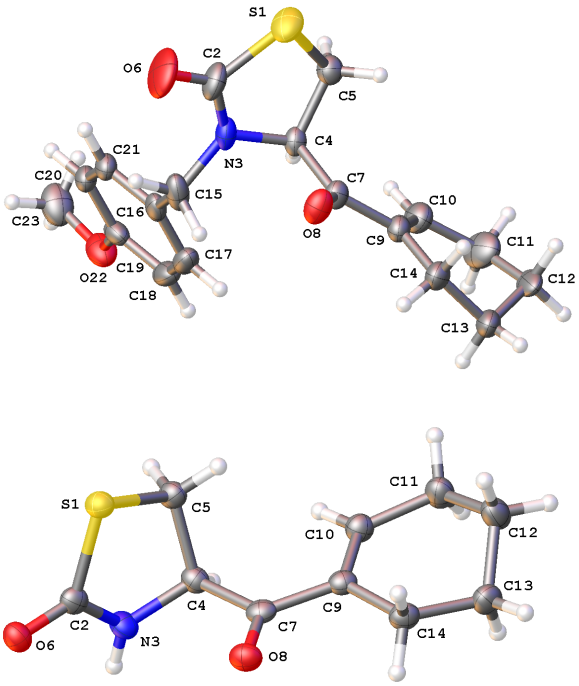
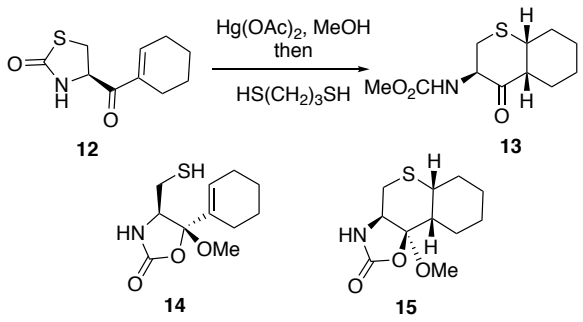


Figure 2. X-Ray crystal structures of thiazolidinones **11** (CCDC 1840513) and **12** (CCDC 1840514).

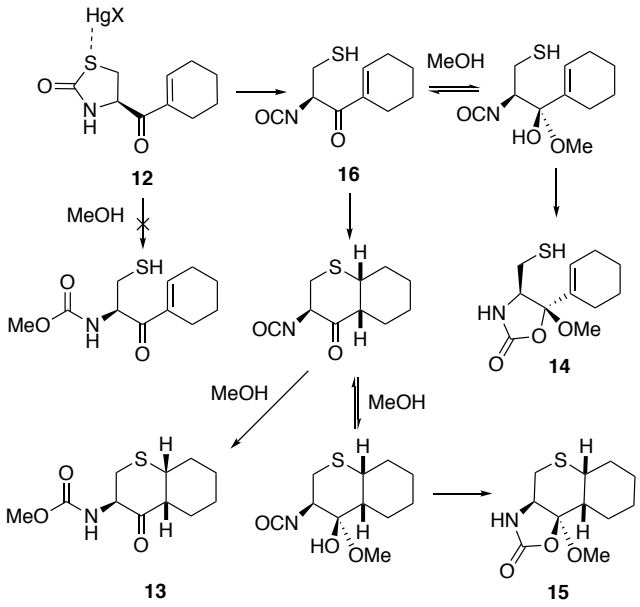
According to our initial hypothesis, the ring rearrangement requires the attack of methanol on the thiazolidinone carbonyl, followed by elimination and conjugate addition of the thiol to the enone functionality via a 6-*endo*-trig process, a known but rare process.[16-18] Although the ring opening of

thiazolidinones is known under aqueous conditions (*vide supra*), alcoholysis reactions are rare. Mellor *et al.* have reported the conversion of 4-vinyl thiazolidinones to methyl carbamates using potassium hydroxide in methanol,[19] but these conditions gave no identifiable products in the case of our cyclohexenyl derivative **12**. The use of sodium or potassium methoxide in methanol at various temperatures similarly led only to decomposition of the starting material. With basic conditions having failed and Brønsted acids such as TsOH giving no reaction at all, a variety of metal salts were employed as Lewis acid catalysts (see Table S1, Supporting Information), in the hope that coordination to the sulfur atom might increase the reactivity of the thiazolidinone towards methanol. Silver(I) acetate, lead(II) chloride, gold(I) chloride, zinc(II) chloride and scandium(III) triflate all gave no reaction, while other silver salts such as $AgBF_4$ and $AgPF_6$ resulted in decomposition of the thiazolidinone **12**. An attempt to use mercury(II) acetate in methanol at room temperature gave no isolable product, but when these conditions were followed by addition of excess 1,3-propanedithiol to sequester the mercury away from the thiol, the products **13**, **14** and **15** were isolated in 7%, 12% and 51% yield respectively (Scheme 3). While we were pleased to identify the desired product of the thiol conjugate addition reaction **13**, it was in a disappointing yield, with most of the material converted to the side-products **14** and **15**. The stereochemistry of **14** was suggested by NOESY spectroscopy, but is inconsequential since compound **14** represents a dead end in our proposed reaction pathway (Scheme 4). Attempts to improve on this result using other mercury sources proved fruitless, but the use of a less polar solvent mixture – 19:1 toluene:methanol – disfavoured the hemiacetal formation, giving none of the side-product **14** and a slightly improved yield (12%) of the desired product **13**. Applying the1,3-propanedithiol work-up to reactions with other metal catalysts did not improve the outcomes of those reactions, and attempts to convert the cyclic carbamate **15** into the methyl carbamate **13** under acidic or basic conditions were unsuccessful.

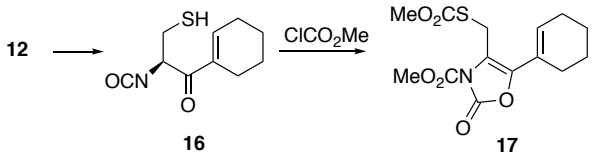


Scheme 3. Ring opening rearrangement of thiazolidinone **12** into thiopyranone derivatives.

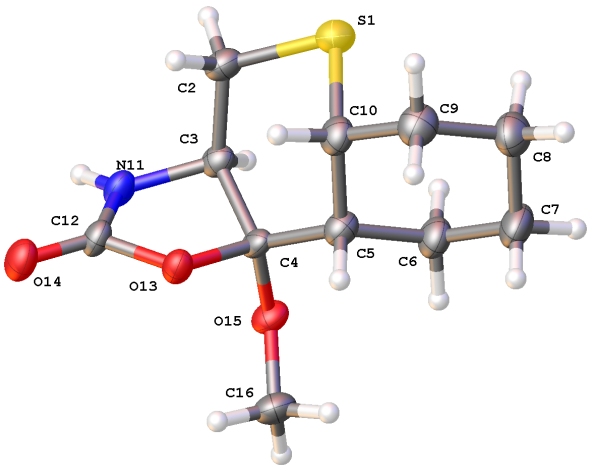
The formation of the major product **15**, identified by X-ray crystallography (Figure 3), initially suggested the possibility that the thiazolidinone had undergone attack not by methanol, but by the hemiacetal of the pendant ketone. However, the fact that conjugate addition had also occurred indicated that the thiol must have been liberated while the enone functionality was still intact, leading us to propose instead that an elimination reaction occurs first, producing a thiol and an isocyanate **16** (Scheme 4); the thiol is rapidly trapped by the enone, and the ketone oxygen is well placed to undergo reaction with the isocyanate as its hemiacetal. Further support for this mechanism came from the failed ring-rearrangement of the PMB-protected thiazolidinone **11** under the same reaction conditions. When the hydrolysis was carried out under aqueous conditions, followed by treatment of the product with an excess of methyl chloroformate, the intermediate thiol **16** was trapped, the isocyanate intercepted by the ketone oxygen in its enol form to give, after further reaction at nitrogen with methyl chloroformate, the adduct **17** (Scheme 5), the structure of which was also confirmed by X-ray crystallography (Figure 3).



Scheme 4. Proposed mechanism for ring opening rearrangement of thiazolidinone **12** into thiopyranone derivatives.



Scheme 5. Interception of thiol intermediate **16** with methyl chloroformate.



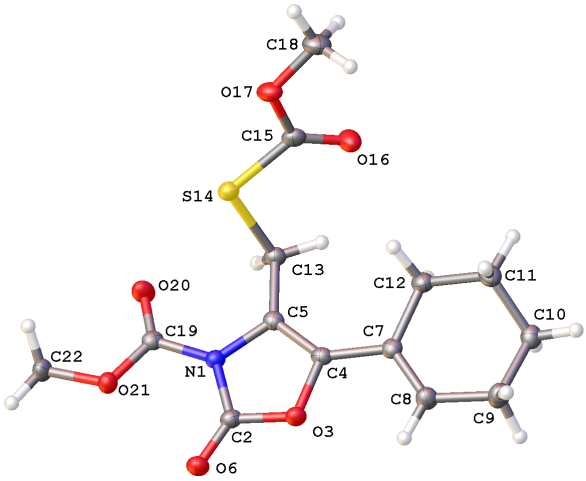


Figure 3. X-Ray crystal structures of oxazolidinones **15** (CCDC 1840516) and **17** (CCDC 1840515).

In summary, we have investigated some of the key steps required for the conversion of latrunculin A **1** to its congener CTP-431 **7** and demonstrated experimentally that the critical ring rearrangement sequence of the thiazolidinone to the corresponding tetrahydrothiopyranone is viable. Although the conditions required for both this key step and the proposed IMDA reaction vary significantly from those used to store the natural sample, given the crude nature of the sponge extract it is impossible to discount the possibility of some form of catalysis in the latter case. Hence we believe that these are feasible steps along the pathway from latrunculin A to CTP-431, and we hope that this will stimulate further work on the origins of this remarkable natural, or possibly unnatural, product.

EXPERIMENTAL SECTION

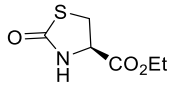
General experimental details

Commercially available reagents were used throughout without purification unless otherwise stated. All anhydrous solvents were used as supplied, except tetrahydrofuran and dichloromethane that were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless otherwise stated, and all glassware was flame-dried before use. Light petroleum refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether.

Analytical thin layer chromatography was carried out on aluminum-backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm and/or by chemical staining. Flash chromatography was carried out using silica gel, with the eluent specified.

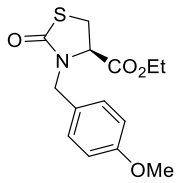
Infrared spectra were recorded using an FT-IR spectrometer over the range 4000–600 cm^{-1}. NMR spectra were recorded at 400 or 500 MHz (1H frequency, 100 or 125 MHz 13C frequency). Chemical shifts are quoted in parts per million (ppm), and are referenced to residual H in the deuterated solvent as the internal standard. Coupling constants, *J*, are quoted in Hz. In the 13C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from the DEPT spectra. Mass spectra were recorded on a time-of-flight (TOF) mass spectrometer using electrospray ionization (ESI).

Ethyl (*R*)-2-oxothiazolidine-4-carboxylate



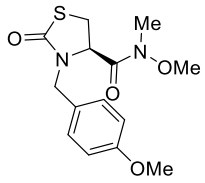
1,1-Carbonyldiimidazole (8.11 g, 50 mmol) was added in portions over 5 min to a stirred suspension of (*L*)-cysteine ethyl ester hydrochloride (9.28 g, 50 mmol) in THF (150 mL). The mixture was stirred at room temperature for 16 h, filtered through a pad of Celite® and washed with THF (150 mL). The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with light petroleum and ethyl acetate (1:1) to give the *title compound* as a colorless oil (6.39 g, 87%); $[\alpha]_D^{25}$ -58.1 (*c* 3.14, $CHCl_3$) (lit.,[20] $[\alpha]_D^{20}$ -51.8 (*c* 3.14, $CHCl_3$) ; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_6H_9NO_3SNa$ 198.0195; found 198.0202; ν_{max} (thin film)/cm^{-1} 3299 (br), 2984, 2940, 2907, 2873, 1742, 1686, 1206, 1025; δ_H (400 MHz; $CDCl_3$) 6.31 (1 H, br s), 4.43 (1 H, ddd, *J* 8.0, 5.2, 0.8), 4.28 (2 H, q, *J* 6.8), 3.71 (1 H, dd, *J* 11.2, 8.0), 3.63 (1 H, dd, *J* 11.2, 5.2), 1.32 (3 H, t, *J* 6.8); δ_C (100 MHz, $CDCl_3$) 174.4, 169.8, 62.4 (CH_2), 55.9 (CH), 31.7 (CH_2), 14.1 (Me).

Ethyl (*R*)-3-(4-methoxybenzyl)-2-oxothiazolidine-4-carboxylate 9



Potassium carbonate (5.52 g, 40 mmol), sodium iodide (0.45 g, 3 mmol) and 4-methoxybenzyl chloride (2.35 g, 15 mmol) were added sequentially to a stirred solution of the above ester (1.75 g, 10 mmol) in DMF (25 mL). The resulting mixture was stirred at room temperature for 16 h, diluted with water (75 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography eluting with light petroleum and ethyl acetate (4:1 then 3:1) gave the *title compound* as a colorless oil (2.94 g, 99%); $[\alpha]_D^{30}$ -66.8 (*c* 1.30, EtOH) (lit.,[20] $[\alpha]_D^{20}$ -96.7 (*c* 1.3, EtOH) ; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{17}NO_4SNa$ 318.0770; found 318.0757; δ_H (400 MHz; $CDCl_3$) 7.17 (2 H, d, *J* 8.6), 6.87 (2 H, d, *J* 8.6), 5.09 (1 H, d, *J* 14.8), 4.25 (2 H, q, *J* 7.0), 4.13 (1 H, dd, *J* 8.6, 3.2), 4.00 (1 H, d, *J* 14.8), 3.81 (3 H, s), 3.48 (1 H, dd, *J* 11.4, 8.6), 3.34 (1 H, dd, *J* 11.4, 3.2), 1.31 (3 H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 171.5, 169.9, 159.4, 129.8 (CH), 127.6, 114.2 (CH), 62.2 (CH_2), 59.3 (CH), 55.3 (Me), 47.3 (CH_2), 29.0 (CH_2), 14.2 (Me).

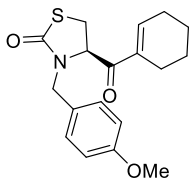
(*R*)-*N*-Methoxy-3-(4-methoxybenzyl)-*N*-methyl-2-oxothiazolidine-4-carboxamide 10



A solution of isopropylmagnesium chloride (0.99 M in THF; 12.2 mL, 12.0 mmol) was added dropwise to a suspension of N,O-dimethylhydroxylamine hydrochloride (0.585 g, 6.0 mmol) and ester **9** (1.18 g, 4.0 mmol) in THF (40 mL) at -20 °C. The resulting mixture was stirred at -20 °C for 30 min, then quenched with saturated ammonium chloride solution (10 mL) followed by ethyl acetate (20 mL) and water (50 mL). The aqueous phase was extracted with ethyl acetate (4 x 20 mL), and the combined organic phases were washed with brine (25 mL)

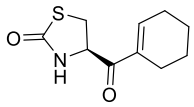
then dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with light petroleum and ethyl acetate (1:1) gave the *title compound* as a colorless oil (1.23 g, 99%); $[\alpha]_D^{25}$ -63.8 (*c* 1.00, CH_2Cl_2); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{19}N_2O_4S$ 311.1060; found 311.1055; ν_{max} (thin film)/cm^{-1} 3002, 2939, 1682, 1612, 1514, 1259, 1176, 732; δ_H (400 MHz; $CDCl_3$) 7.16 (2 H, d, *J* 8.4), 6.86 (2 H, d, *J* 8.4), 5.13 (1 H, d, *J* 14.6), 4.40 (1 H, dd, *J* 8.6, 4.8), 3.84 (1 H, d, *J* 14.6), 3.79 (3 H, s), 3.46 (1 H, dd, *J* 11.2, 8.6), 3.38 (3 H, s), 3.21 (3 H, s), 3.15 (1 H, dd, *J* 11.2, 4.8); δ_C (100 MHz, $CDCl_3$) 172.3, 169.1, 159.4, 130.0 (CH), 127.6, 114.1 (CH), 61.2 (Me), 57.4 (CH), 55.3 (Me), 46.9 (CH_2), 32.5 (Me), 28.0 (CH_2). NMR data matches those described in the literature.[15]

(*R*)-4-(Cyclohex-1-ene-1-carbonyl)-3-(4-methoxybenzyl)thiazolidin-2-one 11



tert-Butyllithium (1.35 M in pentane; 14.8 mL, 20 mmol) was added dropwise to a solution of 1-bromocyclohexene[21] (3.61 g, 22 mmol) in THF (150 mL) at -78 °C. After 15 min at -78 °C, a solution of Weinreb amide **10** (3.10 g, 10 mmol) in THF (50 mL) was added. The mixture was stirred at -78 °C for 1 h, quenched with saturated ammonium chloride solution (50 mL), warmed to room temperature and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with light petroleum and ethyl acetate (3:1 then 2:1) gave the *title compound* as a colorless solid (1.85 g, 56%); mp 212-214 °C; $[\alpha]_D^{24}$ -13.7 (c 0.45, $CHCl_3$); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{21}NO_3SNa$ 354.1134; found 354.1137; ν_{max} (ATR)/cm^{-1} 3002, 2927, 1733, 1673, 1661; δ_H (400 MHz; $CDCl_3$) 7.11 (2 H, d, *J* 8.5), 6.86 (2 H, d, *J* 8.5), 6.67 (1 H, td, *J* 4.1, 2.1), 5.12 (1 H, d, *J* 14.8), 4.81 (1 H, dd, *J* 9.2, 4.8), 3.82 (3 H, s), 3.70 (1 H, d, *J* 14.8), 3.47 (1 H, dd, *J* 11.2, 9.2), 3.12 (1 H, dd, *J* 11.2, 4.8), 2.40-2.13 (4 H, m), 1.70-1.62 (4 H, m); δ_C (100 MHz, $CDCl_3$) 194.8, 172.1, 159.3, 141.9 (CH), 137.2, 129.9 (CH), 127.8, 114.2 (CH), 59.2 (CH), 55.2 (Me), 47.1 (CH_2), 29.2 (CH_2), 26.3 (CH_2), 23.3 (CH_2), 21.6 (CH_2), 21.3 (CH_2).

(*R*)-4-(Cyclohex-1-ene-1-carbonyl)thiazolidin-2-one 12



A solution of ammonium cerium nitrate (5.82 g, 10.62 mmol) in water (18 mL) was added to a solution of thiazolidinone **11** in acetonitrile (35 mL). The resulting mixture was stirred at room temperature for 20 min, diluted with saturated sodium thiosulfate solution (15 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Column chromatography eluting with light petroleum and ethyl acetate (3:1 then 1:1) gave the *title compound* as a colorless solid (0.545 g, 73%); mp 166-168 °C; $[\alpha]_D^{24}$ -25.8 (c 0.6, $CHCl_3$); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{13}NO_2SNa$ 234.0559; found 234.0559; ν_{max} (ATR)/cm^{-1} 3181, 3073, 2931, 2856, 1669, 1653, 1203, 1194; δ_H (400 MHz; $CDCl_3$) 6.91 (1 H, dd, *J* 3.8, 2.1), 6.12 (1 H, br s), 5.08 (1 H, ddd, *J* 8.4, 7.1, 0.8), 3.67 (1 H, dd, *J* 11.1, 8.4), 3.51 (1 H, dd, *J* 11.1, 7.1), 2.44-2.13 (4 H, m), 1.76-1.63 (4 H, m); δ_C (100 MHz, $CDCl_3$) 194.9, 175.5, 142.9 (CH), 136.8, 57.7 (CH), 32.4 (CH_2), 26.3 (CH_2), 23.3 (CH_2), 21.6 (CH_2), 21.3 (CH_2).

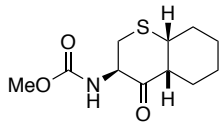
Ring rearrangement

Method 1: Mercury(II) acetate (0.382 g, 1.2 mmol) was added to a solution of **11** (0.084 g, 0.4 mmol) in methanol (8 mL). The resulting suspension was stirred at room temperature for 15 min, and then 1,3-propanedithiol (0.361 mL, 3.6 mmol) was added. The suspension was stirred for a further 1 h, filtered and concentrated *in vacuo*. Column chromatography eluting with ethyl acetate and light petroleum (1:4) gave compound **13** (0.07 g, 7%) followed by compound **14** (0.012 g, 12%) followed by compound **15** (0.049 g, 51%).

Method 2: Mercury(II) acetate (0.382 g, 1.2 mmol) was added to a solution of **11** (0.084 g, 0.4 mmol) in toluene (7.6 mL) and methanol (0.4 mL). The resulting suspension was stirred at room

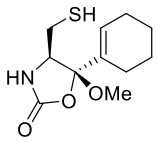
temperature for 15 min, and then 1,3-propanedithiol (0.361 mL, 3.6 mmol) was added. The suspension was stirred for a further 45 min, filtered and concentrated *in vacuo*. Column chromatography eluting with ethyl acetate and light petroleum (1:4) gave compound **13** (0.012 g, 12%) followed by compound **15** (0.031 g, 32%);

Methyl ((3*R*,4a*S*,8a*S*)-4-oxooctahydro-2H-thiochromen-3-yl)carbamate 13



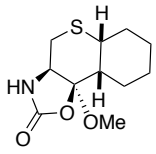
Colorless oil; $[\alpha]_D^{24}$ 8.1 (c 0.2, $CHCl_3$); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{17}NO_3SNa$ 266.0821; found 266.0812; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 1711, 1500; δ_H (400 MHz; $CDCl_3$) 5.99 (1 H, br s), 4.53 (1 H, dt, *J* 11.7, 5.6), 3.70 (3 H, s), 3.35 (1 H, dd, *J* 13.7, 5.6), 3.19-3.14 (2 H, m), 2.89 (1 H, dd, *J* 13.7, 11.7), 1.89-1.82 (2 H, m), 2.25 (1 H, dddd, *J* 13.7, 5.3, 3.4, 2.0), 1.58-1.52 (3 H, m), 1.43-1.34 (2 H, m); δ_C (100 MHz, $CDCl_3$) 205.7, 156.2, 60.6 (CH), 52.3 (Me + CH), 46.1 (CH), 32.1 (CH_2), 31.0 (CH_2), 27.1 (CH_2), 26.7 (CH_2), 20.9 (CH_2).

(4*R*,5*R*)-5-(Cyclohex-1-en-1-yl)-4-(mercaptomethyl)-5-methoxyoxazolidin-2-one 14



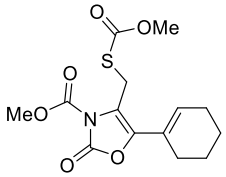
Colorless oil; $[\alpha]_D^{24}$ -6.1 (c 0.2, $CHCl_3$); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{17}NO_3SNa$ 266.0821; found 266.0820; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2929, 1768, 1291; δ_H (400 MHz; $CDCl_3$) 6.13 (1 H, dt, *J* 3.9, 2.1), 5.66 (1 H, br s), 3.70 (1 H, ddd, *J* 10.4, 3.6, 0.9), 3.29 (3 H, s), 2.87 (1 H, ddd, *J* 14.1, 7.3, 3.6), 2.75 (1 H, dt, *J* 14.1, 10.4), 2.19-2.09 (2 H, m), 2.02-1.85 (2 H, m), 1.75-1.60 (4 H, m), 1.45 (1 H, dd, *J* 10.4, 7.3); δ_C (100 MHz, $CDCl_3$) 156.2, 132.5, 127.8 (CH), 106.7, 63.7 (CH), 51.1 (Me), 25.3 (CH_2), 24.7 (CH_2), 23.5 (CH_2), 22.3 (CH_2), 21.9 (CH_2).

(3a*R*,5a*S*,9a*S*,9b*R*)-9b-Methoxyoctahydro-4H-thiochromeno[3,4-d]oxazol-2(3H)-one 15



Colorless solid, mp 81-83 °C; $[\alpha]_D^{24}$ 21.5 (c 1.0, $CHCl_3$); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{17}NO_3SNa$ 266.0821; found 266.0819; ν_{max} ($CHCl_3$)/cm^{-1} 3261, 3006, 2939, 1753, 1447, 1375; δ_H (400 MHz; $CDCl_3$) 5.43 (1 H, br s), 3.77 (1 H, dd, *J* 6.4, 4.8, 1.0), 3.44-3.40 (1 H, m), 3.41 (3 H, s), 3.14 (1 H, dd, *J* 14.3, 4.8), 2.62 (1 H, dd, *J* 14.3, 6.4), 2.40 (1 H, ddd, *J* 11.3, 8.1, 3.6), 11.92-1.84 (2 H, m), 1.70-1.66 (4 H, m), 1.55-1.51 (1 H, m), 1.33-1.29 (1 H, m); δ_C (100 MHz, $CDCl_3$) 157.1, 107.4, 54.9 (CH), 49.1 (Me), 40.5 (CH), 38.4 (CH), 31.5 (CH_2), 31.1 (CH_2), 25.4 (CH_2), 23.0 (CH_2), 20.6 (CH_2).

Methyl 5-(cyclohex-1-en-1-yl)-4-(((methoxycarbonyl)thio)methyl)-2-oxooxazole-3(2H)-carboxylate 17



Potassium hydroxide (0.224 g, 4.0 mmol) was added to a solution of thiazolidinone **11** (0.042 g, 0.20 mmol) in water (1 mL) and 1,4-dioxane (1 mL). The mixture was stirred at room temperature for 30 min, diluted with hydrochloric acid (6 M; 1 mL) and extracted with ethyl acetate (3 x 3 mL). The organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in THF (2 mL), and cooled to 0 °C, then triethylamine (0.04 mL, 0.24 mmol) and methyl chloroformate (0.08 mL, 1.0 mmol) were added sequentially. The mixture was stirred at room temperature for 5 min, diluted with hydrochloric acid (1 M; 2 mL) and extracted with ethyl acetate (5 mL). The organic phases was washed with hydrochloric acid (1 M; 3 x 1 mL) and brine (2 mL), dried (Na_2SO_4), filtered and concentrated. Column chromatography eluting with ethyl acetate and light petroleum (1:6 to 1:1) gave the *title compound* as a colorless solid (0.006 g, 9%); δ_H (400 MHz; $CDCl_3$) 6.23 (1 H, tt, *J* 3.8, 1.7), 4.34 (2 H, s), 4.02 (3 H, s), 3.85 (3 H, s), 2.36-2.31 (2 H,

m), 2.27-2.21 (2 H, m), 1.79-1.66 (4 H, m); δ_C (100 MHz, $CDCl_3$) 170.3, 150.1, 149.5, 140.5, 132.2 (CH), 124.3, 115.2, 54.8 (Me), 54.5 (Me), 26.3 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 22.0 (CH_2), 21.5 (CH_2).

ASSOCIATED CONTENT

Supporting Information

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

Table S1, copies of ^{1}H NMR and ^{13}C NMR spectra. (PDF), and X-ray crystallographic data for compounds **11**, **12**, **15** and **17** (CIF).

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Notes

The authors declare no competing financial interest.

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