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Gold(I)-catalyzed, one-pot, oxidative formation of 2,4-disubstituted thiazoles: Application to the synthesis of a pateamine-related macrodiolide

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ABSTRACT

Thiazoles are important heterocyclic motifs in many target molecules. Extension of a reported gold(I)-catalyzed oxidative coupling of alkynes and thioamides to the synthesis of functionalized thiazole-containing products is presented, including the compatibility of this reaction with ester, protected hydroxyl, alkene and thioether groups. The utility of this one-pot process is demonstrated in the preparation of the thiazole-containing macrodiolide of a simplified analogue of pateamine A.

1. Introduction

The thiazole heteroaromatic motif is considered to be a privileged scaffold in drug discovery and is present in many drugs on the market and in clinical trials [1–4]. The thiazole ring offers electrophilic and nucleophilic sites, providing ligand points for bioreceptors, with additional electronic effects provided by substituents [5]. 2,4-Disubstituted thiazole-containing natural products exhibit remarkably diverse biological activities, displaying anticancer, antibacterial, antifungal, anti-inflammatory, anthelmintic and antihypertensive properties [6–11]. Preparation of thiazoles is most commonly achieved through Hantzsch-type couplings between thioamides and α-haloketones [12–17], although other methods are employed [18]. (−)-Pateamine A (PatA, **1**, Fig. 1) is a 2,4-disubstituted thiazole-containing macrodiolide natural product [7,19,20] with exquisite potency and an unusual mode of action [21–23]. PatA displays anti-cancer, immunosuppressive, anti-cachectic and anti-viral activity [7,20,24–29]. These effects are mediated by binding of PatA to the eukaryotic initiation factor eIF4A, causing inhibition of protein translation [21,22]. A simplified analogue, (−)-DMDA-PatA (**2**), possesses a similar bioactivity profile [30–33].

Previous synthetic endeavours in the pateamine A system have mostly involved modified Hantzsch couplings to form the thiazole ring [20,30,34–36], while an alternative strategy used sequential organometallic couplings of 2,4-dibromothiazole to incorporate the pre-assembled heterocycle into the macrocycle [31,37]. Our long-standing interest in PatA [21,38] has led us to investigate analogues that may be more synthetically tractable. We have previously reported the synthesis of simplified triazole analogue **3** (Fig. 2), which was 10,000-fold less active towards cancer cells compared to PatA [39]. In seeking to prepare a simplified pateamine analogue with the thiazole motif reinstated, e.g. **4**, various

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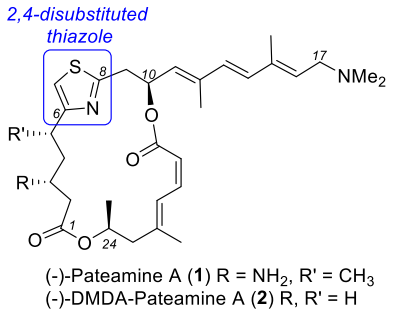


Fig. 1. Structures of (−)-pateamine A (**1**) and (−)-DMDA-pateamine A (**2**).

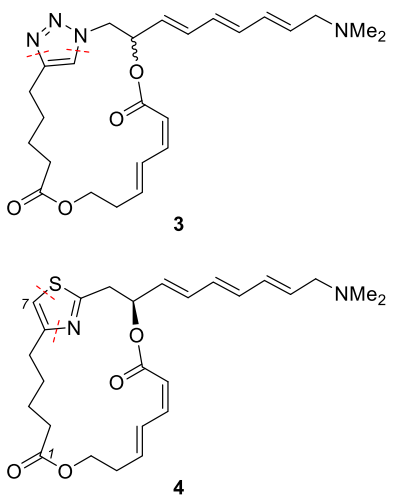


Fig. 2. Structures of simplified triazole analogue (±)-**3** [39] and proposed thiazole variant **4**, with the retrosynthetic disconnections for the heterocyclic motifs shown in red.

synthetic strategies were considered. Ideally, construction of the thiazole ring would be a major connection point for efficiency purposes and would capitalize on the modularity of our previous triazole analogue synthesis, which featured an alkyne-azide cycloaddition process (disconnection points shown in Fig. 2) [39]. A reported gold(I)-catalyzed, oxidative, one-pot coupling of alkynes with thioamides to afford 2,4-disubstituted thioamides seemed to capture these goals [40,41]. Mechanistically, this gold(I)-catalyzed coupling of alkynes with thioamides is related to a Hantzsch reaction in that an α-keto mesylate, formed by oxidation of the alkyne (via a gold carbene), undergoes cyclization with the thioamide. The one-pot nature of this multistep reaction sequence [42] enables a telescoped synthesis of thiazoles from readily available alkyne and thioamide precursors.

In the context of targeting PatA analogue **4**, the alkyne fragment of our previous triazole route, **5** [39], could be directly incorporated into this one-pot thiazole synthesis, while various C8—C11 thioamide fragments **6**, containing suitable functionalities for forming the macrocycle and attaching the sidechain **7**, were envisaged for construction of the PatA structure (Scheme 1). Formation of the macrocycle was anticipated to involve the alkyne-thioamide coupling between **5** and **6**, followed by base-induced eliminative ring opening of the δ-valerolactone moiety [39,43] to afford a *Z,E*-dienoic acid and, finally, macrolactonization. Attachment of a fully assembled sidechain is a feature of our intended synthetic approach and is envisaged to involve an olefination between C11 of fragment **6** (or the complete macrolactone) and C12 of fragment **7**. Julia-Kocienski coupling of sulfone **6a** (PT = phenyltetrazolyl) with aldehyde **7a** (which might contain a suitable precursor to the *N,N*-dimethylamine moiety) or a Wittig-type olefination between an aldehyde **6b** and a phosphorus ylide **7b** or phosphonate **7c** would attach the sidechain to the C8—C11 fragment. Equivalent reactions between the sidechain **7** and the preconstructed macrodiolide containing the corresponding functional motifs at C11 would facilitate a streamlined approach. In the case of a macrodiolide appended with a C11 aldehyde derived from **6b** or **6c**, stepwise construction of the sidechain could be achieved via an established method [31,35—37], providing a backup approach.

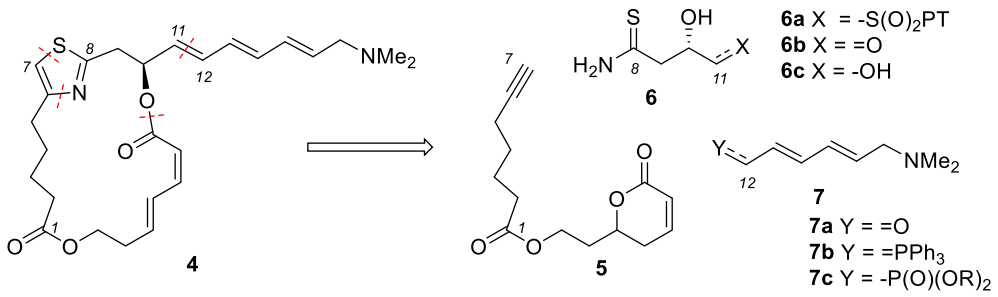
2. Results and discussion

In applying the one-pot, gold(I)-catalyzed, oxidative coupling of alkynes with thioamides to the synthesis of PatA analogues, we were conscious that the initial studies of this chemistry had explored relatively simple substrates [40,41]. Some functional group compatibility had been demonstrated, with chloroalkane, protected alcohols, phthalimido, alkene and (hetero)aromatic moieties present in the products, which were obtained in reasonable to high yields. For the preparation of PatA analogues, several functional groups would be present in the alkyne and thioamide substrates, including some not present in the original studies.

Our studies began with simple substrates, specifically 1-octyne (**8**) and propanethioamide (**9**), so as to test the reaction parameters in our setting. In Zhang's optimized method [40], methanesulfonic acid (MsOH) and 8-methylquinoline-*N*-oxide (**11**) are added slowly to a DCM solution of the alkyne and the gold(I) catalyst, Mor-DalPhosAuOMs (**12**). A keto-mesylate forms in situ and is then heated with the thioamide in a sealed tube. Following this method, using as substrates **8** and **9**, the product 2-ethyl-4-hexylthiazole (**10**) was obtained in 49% isolated yield (Table 1, entry 1). While this was a pleasing initial result, efforts were made to optimize the reaction and enhance the yield to levels consistent with those reported in the earlier work [40]. Using a fresh bottle of high purity MsOH caused a distinct improvement in yield (62%) (Entry 2), which was attributed to the presence of less water than in our original bottle, given that MsOH is hygroscopic and gold carbenes are sensitive to hydrolysis. Alternative halogenated solvents, 1,2-dichloroethane (DCE) and chlorobenzene, were detrimental to the result (Entries 3 and 4), fitting with previous observations [41], and were not investigated further.

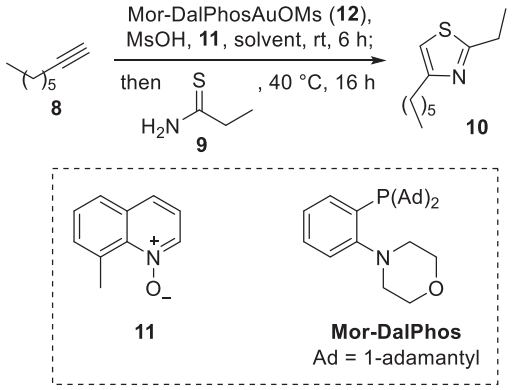
Next, ethyl ester-containing alkyne **14**, representing the C1—C7 fragment of simplified PatA analogue **4**, was prepared by esterification of commercially available 6-heptynoic acid (**13**). The gold(I)-catalyzed coupling of the ester-functionalized alkyne **14** with propanethioamide (**9**) proceeded smoothly and afforded the product **15** cleanly and in a reasonable yield (53%) (Table 2, entry 1). In an effort to improve the yield and facilitate the method, the modification of Wu and co-workers was investigated, whereby the benzeneaminium mesylate salt **16** was used in place of MsOH, circumventing the need for slow addition of the reagents by syringe pump and elevated temperatures [41]. However, in our hands, the modification gave poorer results than the original (Entry 2). An attempt to combine these methods, by slow addition of a solution of the mesylate salt, was detrimental (Entry 3). In a further effort to optimize the reaction, the impact of varying the conditions of the first step, formation of the keto-sulfonate intermediate, was studied (see Supporting Information for details) but no additional benefit was found.

With satisfactory results obtained from an ester-containing alkyne substrate, attention turned to the compatibility of functionalized thioamides. Initially, the phenyltetrazolyl thioether **17**



Scheme 1. Retrosynthetic analysis of simplified thiazole analogue **4** of PatA.

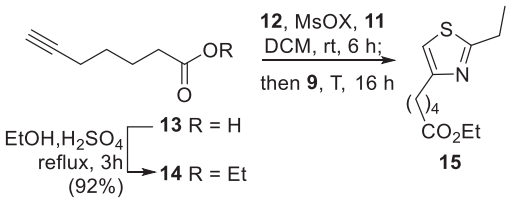
Table 1
Gold(I)-catalyzed coupling of 1-octyne (**8**) and propanethioamide (**9**) to afford 2-ethyl-4-hexylthiazole (**10**):[a] solvent screening.



Entry	Solvent	Yield (%)[b]
1	DCM	49
2[c]	DCM	62
3[c]	DCE	18
4[c]	PhCl	54

[a] Reaction details: Alkyne **8** (1.0 eq) and **12** (5 mol%) were stirred in the anhydrous chlorinated solvent for 15 min. A solution of 8-methylquinoline-*N*-oxide (**11**) (1.3 eq) and methanesulfonic acid (1.2 eq) in the same solvent was added over 5 h to the alkyne solution via a syringe pump. After a further 1 h, a solution of thioamide **9** (1.2 eq) in solvent was added and the reaction heated at 40 °C for 16 h.
[b] Isolated yield after silica gel chromatography.
[c] A new bottle of high purity (99%) MsOH from Acros Organics was used.

Table 2
Gold(I)-catalyzed coupling of ethyl hept-6-ynoate (**14**) and propanethioamide (**9**) to afford ester-functionalized thiazole (**15**):[a] investigation of mesylate source.

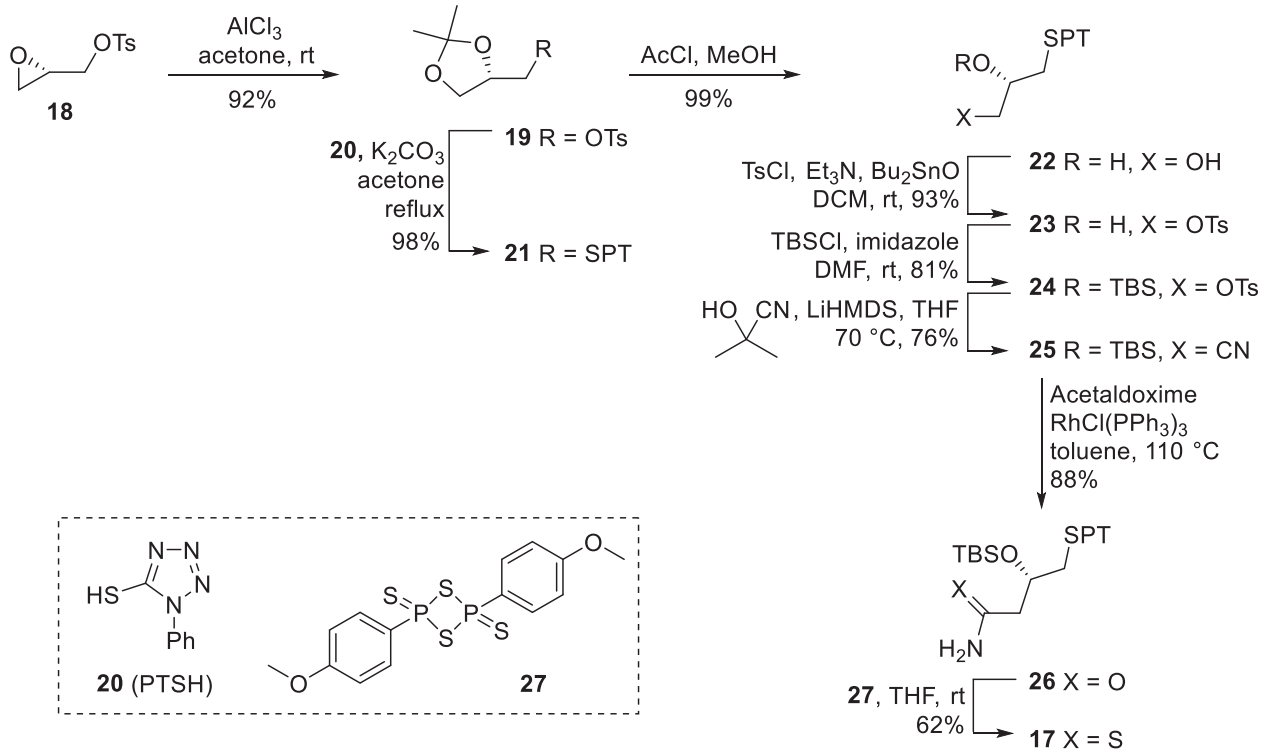


Entry	Mesylate Source	Slow Addition	T[b]	Yield (%)[c]
1	MsOH (1.2)	Yes	40 °C	53
2[d]	**16** (1.2)	No	rt	27
3[d]	**16** (1.2)	Yes	40 °C	3

[a] Reaction details: A DCM solution of alkyne **14** (1.0 eq) and **12** (5 mol%) was treated with 8-methylquinoline-*N*-oxide (**11**) (1.2–1.3 eq) and the mesylate source (1.2 eq), either as a solution by syringe pump over 5 h or directly as solids. After a total of 6 h, thioamide **9** (1.2 eq) was added and the reaction conducted at the noted temperature for 16 h.
[b] Reaction temperature after addition of **9**.
[c] Isolated yield of thiazole **15** after silica gel chromatography.
[d] *N*,*N*-Dimethylbenzeneaminium mesylate salt ($PhNMe_2H^+$ ^-OMs, **16**) was prepared from *N*,*N*-dimethylaniline and methanesulfonic acid.

was explored as a fragment representing **6a** for a Julia-Kocienski approach to sidechain attachment. To this end, thioamide **17** was prepared from (2*S*)-(+)-glycidyl tosylate (**18**) (Scheme 2). Transformation of the enantiopure (*S*)-epoxide **18** into acetonide **19** was achieved in high yield with acetone and a Lewis acid catalyst, $AlCl_3$ [44]. Substitution of tosylate **19** by 1-phenyl-1*H*-tetrazole-5-thiol (PTSH, **20**) afforded thioether **21**, and acetonide deprotection with acetyl chloride in methanol provided diol **22** in nearly quantitative yield over three steps. Selective tosylation of the primary alcohol was achieved using TsCl, triethylamine and catalytic dibutyltin oxide [45]. Mosher ester analysis of the resulting chiral alcohol **23** confirmed that the major enantiomer had the *S*-configuration but indicated that a small amount of racemization had occurred, most likely in the transformation of epoxide **18** to acetonide **19**, with the resulting ee being 92% (see Supporting Information for details). Protection of the secondary alcohol **23** as silyl ether **24** was followed by substitution of the tosylate by cyanide to afford nitrile **25**. Initial attempts using potassium cyanide produced **25** in modest yields (see Supporting Information for an example). After considerable experimentation, reaction of tosylate **24** with lithium cyanide, generated in situ by treatment of acetone cyanohydrin with lithium bis(trimethylsilyl)amide (LiHMDS), was determined to be the preferred route to nitrile **25** because of the better yields, improved handling and lower toxicity of acetone cyanohydrin compared with cyanide salts [46]. Conversion of nitrile **25** into thioamide **17** was initially attempted by direct one-pot thiolation methods [47,48], but these were abandoned in favour of a more conventional approach via the amide **26**. Thus, transformation of nitrile **25** into the amido sulfide **26** employed acetaldoxime and Wilkinson's catalyst [49]. Finally, conversion of amide **26** into thioamide **17** was achieved satisfactorily using Lawesson's reagent (**27**) [50,51].

Gratifying, the gold(I)-catalyzed alkyne-thioamide coupling between **14** and **17** proceeded smoothly and afforded product **28** in 61% yield using just a 1 mol% loading of the gold catalyst (Scheme 3). In order to explore the Julia-Kocienski olefination on this model of the macrodiolide, thioether **28** was oxidized to the sulfone **29**. While *m*CPBA led to over-oxidation and produced the thiazole *S*-oxide, not the desired sulfone **29** (see Supporting Information), hydrogen peroxide and catalytic ammonium heptamolybdate afforded the desired sulfone **29** in a satisfactory yield. With the protected thiazole-containing sulfone **29** in hand, focus turned to attachment of the PatA sidechain in order to test the proposed methodology. A concern with the Julia-Kocienski method for sidechain attachment was the potential for β-oxygen-substituted sulfonyl anions to undergo elimination under the basic reaction

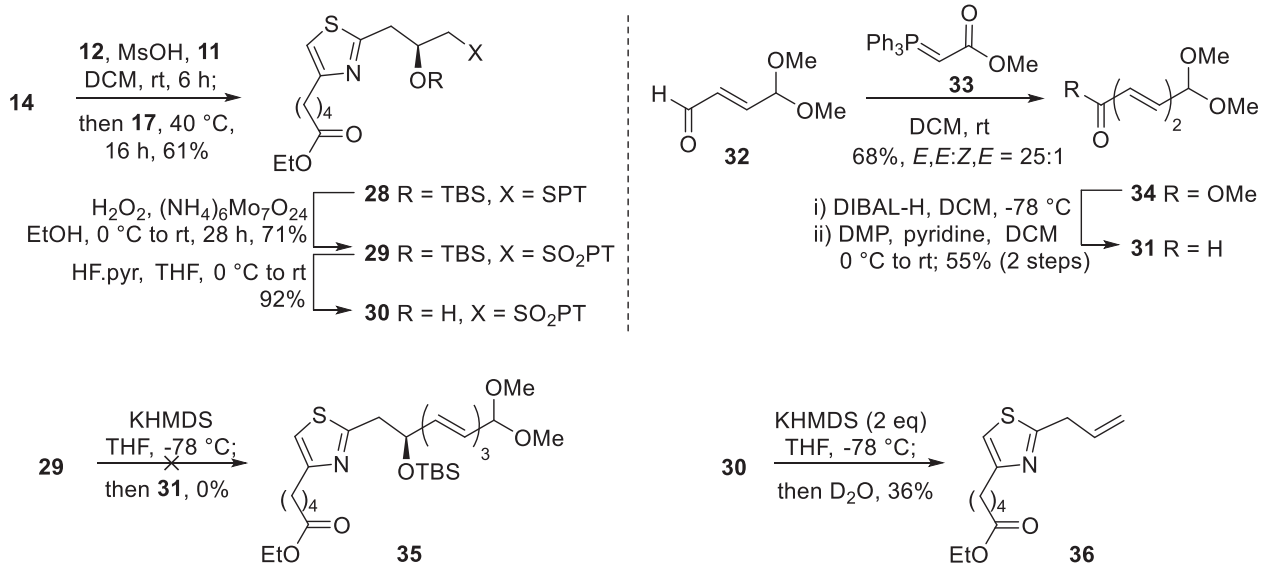


Scheme 2. Synthesis of thioamide **17** from (2*S*)-(+)-glycidyl tosylate (**18**).

conditions. This was deemed to be most risky with the macrodiolide ester group [52] in place and less likely with a silyl-protected or free hydroxyl group. Therefore, β-silyloxysulfone **29** and its desilylated derivative, β-hydroxysulfone **30**, were selected to explore the Julia-Kocienski reaction for attachment of the sidechain.

In preparing the sidechain fragment **7**, it was expected that either a dimethylamino group, as in the natural product, or an ester terminus, as adopted in our earlier synthesis [39], was unlikely to be compatible with macrolactone formation. Therefore, acetal **31**, representing a temporarily protected aldehyde as a precursor to the amine, was sought. This was prepared by extension of aldehyde **32** [39] using Wittig methodology. Ideally, a one-step preparation of dienal **31** would be achieved by reaction of **32** with (triphenylphosphoranylidine)acetaldehyde. However, availability of this ylide was problematic at the time and so we resorted to a three-step sequence via the ester **34** using the stabilized ylide **33** and redox chemistry.

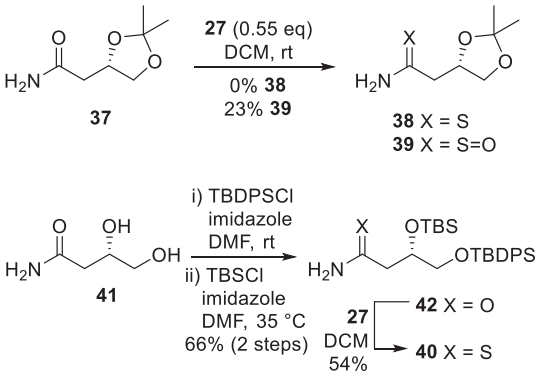
Unfortunately, the attempted Julia-Kocienski coupling of β-silyloxysulfone **29** with aldehyde **31** failed to produce the desired triene **35**. Instead, an array of unidentified by-products was formed, potentially including elimination products.



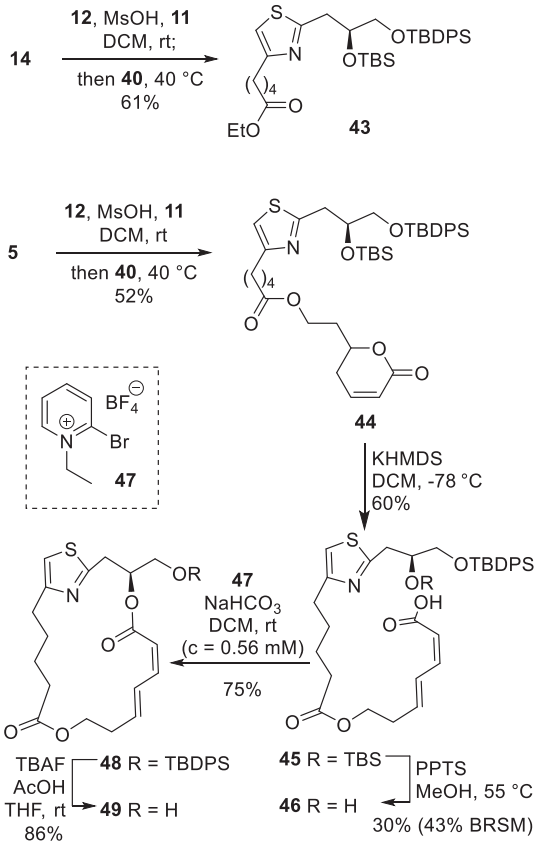
Scheme 3. Gold(I)-catalyzed coupling of ethyl hept-6-ynoate (**14**) and functionalized thioamide **17**, and attempted Julia-Kocienski reaction with assembled sidechain **31**.

In the hope that β-hydroxysulfone **30** would have reduced potential for elimination of the C10 oxygen, and to help identify possible reaction products, it was subjected to deprotonation and quenching with D_2O. To our disappointment, only alkene **36** was identified in the product mixture, presumably arising from a Smiles rearrangement of the deprotonated substrate. Given the apparent incompatibility in this system between the Julia-Kocienski conditions and a β-oxygen substituent, we decided to change strategy, and proceed via C11-oxygenated intermediates, ultimately allowing generation of an aldehyde terminus to the macrodiolide. This would enable either adoption of the established stepwise sidechain extension methodology [31,35–37], or attachment of a complete sidechain via a reversed-direction Julia-Kocienski or Wittig coupling. To this end, diol **6c** (see Scheme 1) was sought in protected form as the C8–C11 thioamide fragment. The known [53] acetonide-protected amide **37** was treated with Lawesson's reagent, but to our surprise the isolated product was the *S*-oxide **39** and not the thioamide **38**, as determined by NMR and MS analysis (*m/z* 192.0685; calculated for $C_7H_{14}NO_3S^+$ $[M+H]^+$ 192.0689) (Scheme 4). This is most likely the result of oxidation of the desired product **38** by atmospheric oxygen during the work up and purification processes. Critcher and Pattenden reported preparation and reaction of thioamide **38** in their preliminary synthetic studies towards PatA [54], so the observed instability in our hands is not necessarily an insurmountable obstacle. Nonetheless, it was deemed desirable to generate a thioamide that was less susceptible to oxidation. Therefore, various protecting groups for the diol were investigated with a view to increasing the air stability of the thioamide by tuning its steric environment, while considering orthogonality for sequential deprotection (see Supporting Information for details). Eventually, the differentially doubly silylated thioamide **40** was found to be sufficiently stable for isolation and characterization, although the orthogonality profile of the silyl protecting groups was not ideal. Thioamide **40** was prepared from commercially available diol **41** by selective silylation at the primary hydroxyl with TBDPSCl and then at the secondary hydroxyl with TBSCl to afford amide **42**, and finally treatment with Lawesson's reagent (**27**).

Thioamide **40** engaged in the key gold(I)-catalyzed coupling with alkyne **14** to afford thiazole **43** in an encouraging yield (Scheme 5). Reassuringly, the gold(I)-catalyzed reaction of thioamide **40** with the lactone-containing alkyne **5** proceeded similarly and delivered thiazole **44** in 52% yield (57% BRSM), representing the entire carbon skeleton of the macrocycle in the simplified PatA analogue **4**. Ring opening of the lactone was performed through a base-induced elimination [43], as featured in our synthesis of the triazole analogue [39]. However, TBAF, employed previously as the base [39,43,55], was unsuitable due to the necessity of retaining the



Scheme 4. Preparation of thioamides **38** and **40** and *S*-oxide **39**.



Scheme 5. Gold(I)-catalyzed couplings of thioamide **40** with ethyl hept-6-ynoate (**14**) or lactone-containing alkyne **5** to afford thiazoles **43** and **44**, and macrodiolide formation.

TBDPS protecting group on the primary alcohol, so KHMDS was used instead and smoothly afforded the *Z,E*-dienoic acid **45**. Selective removal of the TBS protecting group on the secondary alcohol while retaining the *Z,E*-dienoic acid was challenging. Ultimately, the chosen method involved treatment of the *Z,E*-dienoic acid **45** with PPTS at elevated temperature, which produced seco acid **46**, albeit in a modest yield and accompanied by several highly polar by-products. The alternative order of deprotection and lactone ring opening was also investigated but was less satisfactory (see Supporting Information for details).

Macrocyclization was achieved through a modified Mukaiyama protocol following the conditions reported by Zhuo and Fürstner in their syntheses of PatA and DMDA-PatA [31,37]. Specifically, seco acid **46** was treated with the Mukaiyama reagent **47** under high dilution conditions to afford **48** in 75% yield. The $^1H-^1H$ NMR coupling constants of the alkenes in compound **48** were consistent with previously reported characterisation data of related *Z,E*-diene-containing macrolactones and no other geometric isomers were observed by NMR analysis [31,37]. Subsequent desilylation of compound **48** with buffered TBAF provided alcohol **49**, the macrodiolide moiety of the target PatA analogue **4**. Alcohol **49** is a simplified equivalent of intermediates in Pattenden's and Fürstner's syntheses of PatA and DMDA-PatA, respectively, and is poised for oxidation and sidechain attachment, either with a fully-assembled sidechain or via the established stepwise construction [31,35–37]. These studies are on-going and will be reported in due course.

In summary, the utility and compatibility of a one-pot, gold(I)-catalyzed, oxidative alkyne-thioamide coupling [40,41] have been demonstrated and culminated in the preparation of the

macrodiolide of a simplified analogue of pateamine A. Its application as a major strategic connection in a setting with multiple functionality types highlights future opportunities for this gold(I)-catalyzed coupling of alkyne and thioamide building blocks in the preparation of complex thiazole-containing molecules.

3. Experimental

2-Ethyl-4-hexylthiazole (10). To a solution of Mor-DalPhosAuOMs (**12**) (17 mg, 0.023 mmol, 0.05 equiv.) in deoxygenated anhydrous DCM (0.9 mL) was added 1-octyne (**8**) (70 mg, 0.45 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature under argon atmosphere for 15 min. Then a solution of 8-methylquinoline *N*-oxide (**11**) (94 mg, 0.59 mmol, 1.3 equiv.) and methanesulfonic acid (35 μL, 0.54 mmol, 1.2 equiv.) in deoxygenated anhydrous DCM (0.9 mL) was added to the reaction mixture via a syringe pump under argon atmosphere over 5 h. Upon completion, the reaction mixture was further stirred for 1 h before adding propanethioamide (**9**) (48 mg, 0.54 mmol, 1.2 equiv.) in anhydrous DCM (0.5 mL) dropwise. The resulting mixture was stirred at 40 °C in a sealed vial for 16 h before concentration under reduced pressure. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 10:1) to provide the title compound **10** (78 mg, 62%) as a yellow oil. $\mathbf{R_f}$: 0.47 (pet. ether/EtOAc = 5:1). δ **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.69 (s, 1H), 3.00 (q, J = 7.6 Hz, 2H), 2.72 (t, J = 7.3 Hz, 2H), 1.72–1.65 (m, 2H), 1.36 (t, J = 7.6 Hz, 3H), 1.40–1.27 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.2, 157.2, 111.3, 31.62, 31.58, 29.2, 29.0, 26.9, 22.6, 14.3, 14.0. **FTIR** (thin film) ν 2956, 2925, 2855, 1522, 1457, 1376, 1320, 1260, 1182, 1131, 1096, 1049, 970, 829, 804, 726 cm^{-1}. **HRMS** (ESI): Calculated for $C_{11}H_{20}NS^+$ $[M+H]^+$ 198.1311; found 198.1317.

Ethyl hept-6-ynoate (14). To an oven-dried 20 mL round-bottomed flask outfitted with a stir bar, a condenser, a gas inlet adapter and a rubber septum, absolute ethanol (5.0 mL), hept-6-ynoic acid (**13**) (99.7 mg, 0.790 mmol) and concentrated H_2SO_4 (1 drop) were added sequentially. The mixture was refluxed for 3 h before cooling to room temperature and the solvent removed under reduced pressure. The crude product was diluted with diethyl ether (50 mL), washed with saturated $NaHCO_3$ (5 mL) and water (5 mL). The organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was then purified by flash silica gel chromatography (pet. ether/Et_2O = 10/1) to afford the title compound **14** (112 mg, 92%) as a colourless oil. $\mathbf{R_f}$: 0.43 (pet. ether/EtOAc = 5:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.32 (t, J = 7.4 Hz, 2H), 2.21 (td, J = 7.0, 2.6 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.79–1.71 (m, 2H), 1.60–1.53 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4, 84.0, 68.6, 60.3, 33.8, 27.9, 24.0, 18.1, 14.3. These characterization data match those reported in the literature [56,57].

Ethyl 5-(2-ethylthiazol-4-yl)pentanoate (15). To a solution of Mor-DalPhosAuOMs (**12**) (27.5 mg, 0.0364 mmol, 0.05 equiv.) in deoxygenated anhydrous DCM (1.4 mL) was added alkyne **14** (111 mg, 0.718 mmol, 1.0 equiv.). The resulting mixture was stirred at room temperature under argon atmosphere for 15 min. Then a solution of 8-methylquinoline *N*-oxide (**11**) (148 mg, 0.929 mmol, 1.30 equiv.) and methanesulfonic acid (56 μL, 0.86 mmol, 1.2 equiv.) in deoxygenated anhydrous DCM (1.4 mL) was added to the reaction mixture via a syringe pump under argon atmosphere over 5 h. The reaction mixture was further stirred for 1 h before adding propanethioamide (**9**) (74 mg, 0.83 mmol, 1.16 equiv.) in anhydrous DCM (0.8 mL). The resulting mixture was stirred at 40 °C in a sealed vial for 16 h before concentration under reduced pressure. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 5:1) to provide the title compound **15** (90.8 mg, 53%) as a yellow oil. $\mathbf{R_f}$: 0.39 (pet. ether/EtOAc = 5:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.73 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.00 (q, J = 7.6 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 1.78–1.66 (m, 4H), 1.37 (t, J = 7.6 Hz, 3H, H-10), 1.25 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7, 172.4, 156.5, 111.8, 60.3, 34.2, 31.3, 28.7, 27.0, 24.6, 14.33, 14.27. **FTIR** (thin film) ν 2975, 2935, 2870, 1731, 1522, 1458, 1373, 1350, 1313, 1254, 1178, 1140, 1096, 1029, 968, 938, 859, 791, 735 cm^{-1}. **HRMS** (ESI): Calculated for $C_{12}H_{20}NO_2S^+$ $[M+H]^+$ 242.1209; found 242.1212.

(*S*)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (19). To a solution of (2*S*)-(+)-glycidyl tosylate (**18**) (3.18 g, 13.9 mmol, 1 equiv.) in dry acetone (14 mL) was added aluminium chloride (58.0 mg, 0.435 mmol, 0.03 equiv.), and the solution was stirred at room temperature for 1 h. The reaction mixture was then cooled to 2 °C and saturated $NaHCO_3$ aqueous solution (30 mL) was added slowly. The resulting mixture was then extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were then dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 5:1) to provide the title compound **19** (7.00 g, 92%) as a colorless oil. $\mathbf{R_f}$: 0.50 (pet. ether/EtOAc = 2:1). **Melting point**: 69–72 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.83–7.78 (m, 2H), 7.40–7.33 (m, 2H), 4.30–4.24 (m, 1H), 4.06–4.00 (m, 2H), 3.97 (dd, J = 10.1, 6.2 Hz, 1H), 3.77 (dd, J = 8.8, 5.1 Hz, 1H), 2.45 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 145.1, 132.6, 129.9, 128.0, 110.1, 72.9, 69.5, 66.2, 26.7, 25.2, 21.7. **FTIR** (thin film) ν 2987, 1598, 1495, 1455, 1359, 1257, 1213, 1189, 1175, 1095, 1054, 974, 788, 664, 554 cm^{-1}. **HRMS** (ESI): Calculated for $C_{13}H_{19}O_5S^+$ $[M+H]^+$ 287.0948; found 287.0951. $[\alpha]_D^{20}$ +3.0 (c = 1.00, EtOH) (lit [58]. $[\alpha]_D^{20}$ +4.5 (c 1.00 EtOH)). These characterization data match those reported in the literature [58].

(*S*)-5-(((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)thio)-1-phenyl-1*H*-tetrazole (21). To a solution of tosylate **19** (8.15 g, 28.5 mmol, 1 equiv.) and 1-phenyl-1*H*-tetrazole-5-thiol (**20**) (15.66 g, 87.87 mmol, 3.1 equiv.) in acetone (250 mL) was added K_2CO_3 (19.7 g, 0.142 mmol, 5.0 equiv.) at room temperature. The reaction mixture was refluxed for 16 h and then evaporated to remove solvent under vacuum. The residue was partitioned between ethyl acetate and water. The aqueous phase was extracted with diethyl ether (4 × 100 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and then concentrated under reduced pressure. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 5:1) to provide the title compound **21** (8.14 g, 98%). $\mathbf{R_f}$: 0.48 (pet. ether/EtOAc = 2:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.62–7.49 (m, 5H), 4.61–4.51 (m, 1H), 4.20–4.13 (m, 1H), 3.81 (dd, J = 8.6, 5.6 Hz, 1H), 3.67 (dd, J = 13.6, 4.5 Hz, 1H), 3.51 (dd, J = 13.5, 7.1 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.9 (C-7), 133.5, 130.1, 129.8, 123.7, 110.0, 73.7, 68.3, 36.6, 26.8, 25.2. **FTIR** (thin film) ν 2981, 2933, 2883, 1596, 1501, 1460, 1389, 1377, 1366, 1280, 1245, 1213, 1190, 1175, 1150, 1090, 1081, 1073, 1051, 1015, 1000, 976, 960, 918, 869, 818, 785, 766, 736, 710, 694, 685, 555, 510, 462, 447 cm^{-1}. **HRMS** (ESI): Calculated for $C_{13}H_{17}N_4O_2S^+$ $[M+H]^+$ 293.1067; found 293.1070. $[\alpha]_D^{25}$ −360 (c = 0.375, DCM).

(*S*)-3-((1-Phenyl-1H-tetrazol-5-yl)thio)propane-1,2-diol (22). To a solution of acetonide **21** (5.12 g, 17.5 mmol, 1.0 equiv.) in methanol (67 mL) was added acetyl chloride (0.37 mL, 5.3 mmol, 0.3 equiv.) at 2 °C. Then the reaction mixture was stirred at room temperature for 24 h. Then the reaction mixture was evaporated under reduced vacuum and the residue was purified by a short silica plug (pet. ether/EtOAc = 1:2) to provide the title compound **22** (4.40 g, 99%) as a colourless oil. $\mathbf{R_f}$: 0.13 (pet. ether/EtOAc = 1:2).**^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.65–7.52 (m, 5H), 4.16–4.07 (m, 1H), 3.81–3.68 (m, 2H), 3.60 (dd, J = 14.5, 5.6 Hz, 1H), 3.47 (dd, J = 14.5, 6.1 Hz, 1H), 3.27 (d, J = 6.1 Hz, 1H, OH), 3.01 (t,

$J = 6.5$ Hz, 1H, OH)·**^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.0, 130.5, 129.9, 123.9, 71.1, 63.9, 35.9. **FTIR** (thin film) ν 3432, 3396, 3069, 2935, 2882, 1596, 1499, 1461, 1410, 1388, 1318, 1284, 1243, 1176, 1093, 1074, 1038, 1016, 761, 694, 549 cm^{-1}. **HRMS** (ESI): Calculated for $C_{10}H_{13}N_4O_2S^+$ $[M+H]^+$ 253.0754; found 253.0756. $[\alpha]_D^{23}$ +3.7 ($c = 1.16$, $CHCl_3$).

(*S*)-2-Hydroxy-3-((1-phenyl-1*H*-tetrazol-5-yl)thio)propyl 4-methylbenzenesulfonate (23). To a solution of diol **22** (4.53 g, 17.9 mmol, 1.0 equiv.) in anhydrous DCM (150 mL) were added dibutyltin oxide (0.918 g, 3.59 mmol, 0.2 equiv.) at room temperature. The resulting mixture was stirred at room temperature for 1 h. Triethylamine (2.50 mL, 17.9 mmol, 1.0 equiv.) was added dropwise to the reaction mixture. Then 4-toluenesulfonyl chloride (3.50 g, 17.9 mmol, 1.0 equiv.) in anhydrous DCM (50 mL) was added to the reaction mixture by a syringe pump over 1 h. The reaction mixture was stirred for 8 h. The reaction was added water (35 mL) and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 2:1) to provide the title compound **23** (6.76 g, 93%) as a foamy gel. **R_f**: 0.63 (pet. ether/EtOAc = 1:2). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.84–7.78 (m, 2H), 7.62–7.53 (m, 5H), 7.36 (d, $J = 8.0$ Hz, 2H), 4.36–4.29 (m, 1H), 4.14 (dd, $J = 5.4$, 1.9 Hz, 2H), 3.59 (dd, $J = 14.6$, 3.6 Hz, 1H), 3.44 (dd, $J = 14.6$, 7.0 Hz, 1H), 2.45 (s, 3H)·**^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.4, 145.3, 133.3, 132.3, 130.4, 130.0, 129.9, 128.0, 123.8, 71.1, 68.6, 36.1, 21.7. **FTIR** (thin film) ν 3255, 3065, 2922, 1595, 1501, 1448, 1418, 1384, 1331, 1289, 1213, 1172, 1121, 1089, 1064, 1033, 1010, 816, 762, 712, 681, 608, 567 cm^{-1}. **HRMS** (ESI): Calculated for $C_{17}H_{19}N_4O_4S_2^+$ $[M+H]^+$ 407.0842; found 407.0839. $[\alpha]_D^{23}$ −46 ($c = 0.385$, DCM).

(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-((1-phenyl-1*H*-tetrazol-5-yl)thio)propyl 4-methylbenzene-sulfonate (24). To a solution of tosylate **23** (2.86 g, 7.04 mmol, 1.0 equiv.), imidazole (2.88 g, 42.2 mmol, 6.0 equiv.) and 4-dimethylaminopyridine (91.4 mg, 0.704 mmol, 0.1 equiv.) in anhydrous DMF (30 mL) was added *tert*-butyldimethylsilyl chloride (3.18 g, 21.1 mmol, 3.0 equiv.). The reaction mixture was stirred at room temperature for 16 h. Then the reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (3 × 50 mL). The combined aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 5:1) to provide the title compound **24** (2.96 g, 81%) as a white crystal. **R_f**: 0.50 (pet. ether/EtOAc = 2:1). **Melting point**: 122–123 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.81–7.75 (m, 2H), 7.61–7.51 (m, 5H), 7.32 (d, $J = 8.0$ Hz, 2H), 4.32 (quin, $J = 5.2$ Hz, 1H), 4.09–4.02 (m, 2H), 3.53 (dd, $J = 13.7$, 5.5 Hz, 2H), 3.45 (dd, $J = 13.7$, 6.0 Hz, 2H), 2.43 (s, 3H), 0.81 (s, 9H), 0.023 (s, 3H), 0.018 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.8, 145.1, 133.2, 132.5, 130.3, 129.91, 129.86, 128.0, 71.2, 68.2, 36.6, 25.6, 21.7, 17.9, −4.77, −4.85. **FTIR** (solid) ν 2951, 2929, 2890, 2855, 1597, 1500, 1473, 1460, 1446, 1423, 1397, 1358, 1307, 1294, 1277, 1255, 1189, 1172, 1110, 1090, 1041, 1017, 997, 976, 929, 865, 841, 824, 809, 778, 764, 738, 692, 666, 609, 573, 553, 489, 469 cm^{-1}. **HRMS** (ESI): Calculated for $C_{23}H_{33}N_4O_4S_2Si^+$ $[M+H]^+$ 521.1707; found 521.1706. $[\alpha]_D^{18}$ +276 ($c = 0.25$, DCM).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-((1-phenyl-1*H*-tetrazol-5-yl)thio)butanenitrile (25). To a solution of LiHMDS (1.52 mL, 1.0 M in THF, 1.52 mmol, 4.0 equiv.) in anhydrous THF (2.0 mL) was added acetone cyanohydrin (145 μL, 1.60 mmol, 4.2 equiv.). The mixture was then stirred at room temperature for 1 h. Silyl ether **24** (193 mg, 0.370 mmol, 1.0 equiv.) in anhydrous THF (3.0 mL) was added to the resulting mixture and then the reaction mixture was heated at reflux for 20 h under argon atmosphere. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was extracted by ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 4:1) to provide the title compound **25** (106 mg, 76%) as a white solid.**R_f**: 0.45 (pet. ether/EtOAc = 3:1). **Melting point**: 108–109 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.62–7.53 (m, 5H), 4.51–4.45 (m, 1H), 3.60 (dd, $J = 13.9$, 5.7 Hz, 1H), 3.48 (dd, $J = 13.9$, 6.0 Hz, 1H), 2.71 (dd, $J = 4.9$, 1.3 Hz, 2H), 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.6, 133.4, 130.4, 130.0, 123.8, 116.7, 66.5, 38.8, 25.6, 25.5, 17.9, −4.6, −4.8. **FTIR** (thin film) ν 2954, 2929, 2887, 2856, 1597, 1499, 1471, 1463, 1411, 1388, 1363, 1279, 1251, 1099, 1075, 1014, 938, 838, 806, 779, 760, 712, 687, 665, 552 cm^{-1}. **HRMS** (ESI): Calculated for $C_{17}H_{26}N_5OSSi^+$ $[M+H]^+$ 376.1622; found 376.1627. $[\alpha]_D^{18}$ +93.3 ($c = 0.15$, DCM).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-((1-phenyl-1*H*-tetrazol-5-yl)thio)butanamide (26). To a 20 mL vial were added nitrile **25** (0.927 g, 2.47 mmol, 1.0 equiv.), freshly prepared acetaldoxime (0.729 g, 12.4 mmol, 5.0 equiv.), $RhCl(PPh_3)_3$ (0.026 g, 0.28 μmol, 0.01 equiv.) and anhydrous toluene (8 mL). The reaction mixture was vigorously stirred at 110 °C under argon atmosphere in the sealed vial for 22 h. Then solvent was removed under vacuum. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 1:1) to provide the title compound **26** (855 mg, 88%) as a white solid. **R_f**: 0.11 (pet. ether/EtOAc = 1:1). **Melting point**: 78–79 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.62–7.51 (m, 5H), 6.26 (br. s, 1H, N–H), 5.48 (br. s, 1H, N–H), 4.54 (quin, $J = 5.5$ Hz, 1H), 3.64 (dd, $J = 13.7$, 5.5 Hz, 1H), 3.52 (dd, $J = 13.7$, 6.2 Hz, 1H), 2.63 (dd, $J = 14.9$, 5.2 Hz, 1H), 2.54 (dd, $J = 14.9$, 5.4 Hz, 1H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.1, 154.2, 133.5, 130.3, 129.9, 123.8, 67.7, 42.5, 39.1, 25.7, 18.0, −4.6, −4.8. **FTIR** (solid) ν 3389, 3339, 3197, 2954, 2929, 2887, 2856, 1673, 1615, 1598, 1499, 1471, 1463, 1407, 1389, 1362, 1335, 1251, 1162, 1090, 1015, 955, 838, 811, 779, 761, 694, 667, 573, 557 cm^{-1}. **HRMS** (ESI): Calculated for $C_{17}H_{28}N_5O_2SSi^+$ $[M+H]^+$ 394.1727; found 394.1726. $[\alpha]_D^{23}$ +165 ($c = 1.65$, DCM).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-((1-phenyl-1*H*-tetrazol-5-yl)thio)butanethioamide (17). To a solution of amide **26** (299 mg, 0.760 mmol, 1.0 equiv.) in anhydrous THF (15 mL) was added Lawesson's reagent (215 mg, 0.533 mmol, 0.7 equiv.). The reaction mixture was stirred at room temperature for 30 min. Saturated aqueous $NaHCO_3$ solution (10 mL) was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 3:1) to provide the title compound **17** (192 mg, 62%) as a yellow oil. **R_f**: 0.4 (pet. ether/EtOAc = 1:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.16 (br.s, 1H), 7.62–7.52 (m, 5H), 7.49 (br.s, 1H), 4.61–4.56 (m, 1H), 3.67 (dd, $J = 13.9$, 4.8 Hz, 1H, H-1), 3.49 (dd, $J = 13.9$, 6.5 Hz, 1H), 3.13 (ddd, $J = 14.4$, 4.6, 1.0 Hz, 1H), 3.07 (dd, $J = 14.5$, 5.4 Hz, 1H), 0.89 (s, 9H), 0.165 (s, 3H), 0.162 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 205.8, 154.4, 133.4, 130.3, 129.9, 123.8, 69.7, 50.8, 38.5, 25.8, 17.9, −4.6, −4.8. **FTIR** (thin film) ν 3307, 3182, 2953, 2928, 2885, 2855, 1620, 1597, 1499, 1461, 1408, 1388, 1361, 1333, 1316, 1279, 1250, 1209, 1146, 1088, 1014, 939, 917, 836, 809, 778, 730, 692, 663, 552, 465 cm^{-1}. **HRMS** (ESI): Calculated for $C_{17}H_{28}N_5OS_2Si^+$ $[M+H]^+$ 410.1499; found 410.1479. $[\alpha]_D^{18}$ −317 ($c = 0.23$, DCM).

Ethyl (*S*)-5-(2-(2-((*tert*-butyldimethylsilyl)oxy)-3-((1-phenyl-1*H*-tetrazol-5-yl)thio)propyl)thiazol-4-yl)pentanoate (28). To a solution of Mor-DalPhosAuOMs (**12**) (35 mg, 0.047 mmol, 0.11 equiv.) in deoxygenated anhydrous DCM (2.40 mL) was added alkyne **14** (137 mg, 0.889 mmol, 2.1 equiv.). The resulting mixture

was stirred at room temperature for 15 min. Then a solution of 8-methylquinoline *N*-oxide (**11**) (185 mg, 1.16 mmol, 2.73 equiv.) and methanesulfonic acid (74.0 μL, 1.14 mmol, 2.68 equiv.) in deoxygenated anhydrous DCM (2.40 mL) was added to the reaction mixture via a syringe pump over 5 h under argon atmosphere. Upon completion, the reaction mixture was further stirred for 1 h before adding thioamide **17** (174 mg, 0.425 mmol, 1.0 equiv.) in anhydrous DCM (2.40 mL). The resulting mixture was stirred at 40 °C in a sealed vial for 20 h under argon atmosphere before concentration under reduced pressure. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 4:1) to provide the title compound **28** (148 mg, 61%) as a yellow oil. $\mathbf{R_f}$: 0.33 (pet. ether/EtOAc = 3:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.61–7.52 (m, 5H), 6.77 (s, 1H), 4.55 (quin, *J* = 5.6 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 13.4, 5.1 Hz, 1H), 3.51 (dd, *J* = 13.4, 6.0 Hz, 1H), 3.27 (d, *J* = 5.3 Hz, 2H), 2.74 (t, *J* = 7.1 Hz, 2H), 2.32 (t, *J* = 7.0 Hz, 2H), 1.76–1.64 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.83 (s, 9H), 0.06 (s, 3H), −0.10 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.6, 165.1, 156.7, 154.3, 133.6, 130.1, 129.8, 123.8, 113.1, 69.8, 60.2, 39.8, 39.3, 34.1, 31.1, 28.7, 25.7, 24.6, 18.0, 14.2, −4.7, −5.0. **FTIR** (thin film) *ν* 3104, 3068, 3050, 2950, 2918, 1732, 1534, 1462, 1426, 1407, 1275, 1190 cm^{-1}. **HRMS** (ESI): Calculated for $C_{26}H_{40}N_5O_3S_2Si^+$ $[M+H]^+$ 562.2336; found 562.2344. $[\alpha]_D^{21}$ −4.5 (*c* = 0.56, $CHCl_3$).

Ethyl (*S*)-5-(2-(2-((*tert*-butyldimethylsilyl)oxy)-3-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)propyl)-thiazol-4-yl)pentanoate (29). To a solution of thioether **28** (120 mg, 0.214 mmol, 1.0 equiv.) in EtOH (5 mL) was added the prepared oxidant solution of $(NH_4)_6Mo_7O_{24}$ (135 mg, 0.109 mmol, 0.50 equiv.) in H_2O_2 (0.70 mL, 30% w/w in water, 6.3 mmol, 30 equiv.), and the yellow reaction mixture was stirred for 38 h at room temperature. Saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added slowly then ethanol solvent was removed by evaporation under vacuum. The residual aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (pet. ether/EtOAc = 3:1) to afford the title compound **29** (89 mg, 71%) as a colourless oil. $\mathbf{R_f}$: 0.22 (pet. ether/EtOAc = 3:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.69–7.64 (m, 2H), 7.64–7.56 (m, 3H), 6.80 (s, 1H), 4.87–4.81 (m, 1H), 4.14 (dd, *J* = 10.9, 4.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.01 (dd, *J* = 14.9, 6.4 Hz, 1H), 3.34 (d, *J* = 5.7 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.77–1.63 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.6, 163.5, 157.1, 154.1, 133.1, 131.4, 129.7, 125.2, 113.3, 66.4, 61.4, 60.2, 40.7, 34.1, 31.1, 28.6, 25.7, 24.5, 17.8, 14.3, −4.8, −4.9. **FTIR** (thin film) *ν* 3111, 3072, 2930, 2857, 1730, 1595, 1521, 1498, 1463, 1420, 1343, 1299, 1255, 1154, 1122 cm^{-1}. **HRMS** (ESI): Calculated for $C_{26}H_{40}N_5O_5S_2Si^+$ $[M+H]^+$ 594.2235; found 594.2242. $[\alpha]_D^{18}$ −41.2 (*c* = 0.17, DCM).

Ethyl (*S*)-5-(2-(2-hydroxy-3-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)propyl)thiazol-4-yl)pentanoate (30). To a solution of sulfone **29** (31.7 mg, 0.0534 mmol, 1.0 equiv.) in anhydrous THF (0.1 mL) was added a solution of HF-pyridine (135 μL, 5.15 mmol, 99 equiv.) in anhydrous THF (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred for 2 days at room temperature and 2.0 mL saturated $NaHCO_3$ aqueous solution was added. Then the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (pet. ether/EtOAc = 2:1) to afford the title compound **30** (23.2 mg, 92%) as a colourless oil. $\mathbf{R_f}$: 0.44 (pet. ether/EtOAc = 1:1). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.72–7.55 (m, 5H), 6.81 (s, 1H), 4.78–4.70 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.95 (dd, *J* = 15.0, 8.7 Hz, 1H), 3.78 (dd, *J* = 15.0, 3.2 Hz, 1H), 3.28 (dd, *J* = 15.7, 3.8 Hz, 1H), 3.18 (dd, *J* = 15.7, 7.3 Hz, 1H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.1 Hz, 2H), 1.76–1.62 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 173.6, 164.8, 156.9, 154.0, 133.0, 131.5, 129.5, 125.6, 112.9, 65.5, 61.2, 60.3, 37.9, 34.0, 30.9, 28.4, 24.4, 14.2. **FTIR** (thin film) *ν* 3397, 3105, 2937, 2864, 1769, 1728, 1694, 1595, 1523, 1498, 1461, 1434, 1348, 1311, 1280, 1246, 1176, 1152, 1112, 1076, 1032, 1018, 979, 926, 885, 844, 831, 803, 764, 725, 689, 633, 581, 536, 489, 450 cm^{-1}. **HRMS** (ESI): Calculated for $C_{20}H_{26}N_5O_5S_2^+$ $[M+H]^+$ 480.1370; found 480.1376. $[\alpha]_D^{20}$ +7.5 (*c* = 0.99, $CHCl_3$).

Methyl (2*E*,4*E*)-6,6-dimethoxyhexa-2,4-dienoate (34). To a solution of known aldehyde **32** [39] (3.03 g, 23 mmol, 1.0 equiv.) in anhydrous DCM (20 mL) was added methyl (triphenylphosphoranylidene)-acetate (**33**) (8.00 g, 23.9 mmol, 1.04 equiv.). Then the reaction mixture was stirred at room temperature under argon atmosphere for 16 h. Solvent was evaporated and the crude material was then purified by flash silica gel chromatography (pet. ether/EtOAc/Et_3N = 10:1:0.1) to afford the title compound **34** (2.95 g, 68%) as a yellow oil. $\mathbf{R_f}$: 0.47 (pet. ether/EtOAc = 4:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28 (ddd, *J* = 15.4, 11.2, 0.4 Hz, 1H), 6.48 (dddd, *J* = 15.5, 11.2, 1.2, 0.7 Hz, 1H), 6.00 (dd, *J* = 15.5, 4.3 Hz, 1H), 5.96 (dd, *J* = 15.4, 0.4 Hz, 1H), 4.91 (dd, *J* = 4.3, 1.2 Hz, 1H), 3.75 (s, 3H), 3.33 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.1, 143.2, 137.6, 131.0, 122.7, 101.3, 52.7, 51.7. **FTIR** (thin film) *ν* 2951, 2832, 1719, 1651, 1619, 1436, 1359, 1313, 1267, 1234, 1190, 1174, 1126, 1051, 1002, 956, 911, 875, 723 cm^{-1}. **HRMS** (ESI): Calculated for $C_8H_{11}O_3^+$ $[M-OCH_3]^+$ 155.0703; found 155.0699.

(2*E*,4*E*)-6,6-Dimethoxyhexa-2,4-dienal (31). To a solution of methyl ester **34** (1.62 g, 8.70 mmol, 1.0 equiv.) in anhydrous DCM (87 mL) was added a solution of diisobutylaluminium hydride (31.0 mL, 1.0 M in cyclohexane, 31.0 mmol, 3.56 equiv.) slowly at −78 °C. The reaction mixture was stirred at −78 °C for 6 h and then quenched by addition of saturated aqueous potassium sodium tartrate (80 mL). The resulting mixture was stirred at room temperature for 2 h and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (pet. ether/EtOAc/Et_3N = 2:1:0.02) to afford the primary alcohol intermediate (0.97 g, 71%) as a yellow oil. $\mathbf{R_f}$: 0.38 (pet. ether/EtOAc = 2:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.37 (dd, *J* = 15.2, 10.7, 1H), 6.28 (ddt, *J* = 15.4, 10.5, 1.6 Hz, 1H), 5.92 (dt, *J* = 15.1, 5.7 Hz, 1H), 5.64 (dd, *J* = 15.3, 4.8 Hz, 1H), 4.84 (d, *J* = 4.8 Hz, 1H), 4.21 (t, *J* = 5.6 Hz, 2H), 3.32 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 134.0, 132.9, 129.9, 129.4, 102.4, 63.2, 52.6. **FTIR** (thin film) *ν* 3394, 2991, 2936, 1830, 1663, 1629, 1447, 1350, 1298, 1190, 1128, 1072, 1045, 990, 952, 905, 849, 586, 487 cm^{-1}. **HRMS** (ESI): Calculated for $C_7H_{11}O_2^+$ $[M-OCH_3]^+$ 127.0754; found 127.0750.

To a solution of the intermediate alcohol (0.21 g, 1.3 mmol, 1.0 equiv.) in wet DCM (17 mL) was added, sequentially, pyridine (0.36 mL, 4.5 mmol, 3.5 equiv.) and Dess-Martin periodinane (0.75 g, 1.76 mmol, 1.3 equiv.) at 2 °C. Then the reaction mixture was stirred at 2–4 °C for 2 h. The reaction mixture was diluted with Et_2O (15 mL) and added a mixture of saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ ($Na_2S_2O_3$/$NaHCO_3$ = 1:1, 15 mL). The resulting mixture was stirred vigorously for 30 min and then the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (pet. ether/Et_2O/Et_3N = 4:1:0.04) to afford the title compound **31** (0.159 g, 76%) as a yellow oil. $\mathbf{R_f}$: 0.11 (pet. ether/EtOAc = 9:1). **^{1}H NMR** (500 MHz, C_6D_6): δ 9.30 (d, *J* = 7.8 Hz, 1H), 6.34–6.25 (m, 1H), 6.25–6.17 (m, 1H), 5.88 (ddd, *J* = 14.9, 7.8, 2.8 Hz, 1H), 5.71 (dt, *J* = 15.2, 4.6 Hz, 1H),

4.64 (d, $J = 4.3$ Hz, 1H), 3.07 (d, $J = 1.4$ Hz, 6H). **^{13}C NMR** (125 MHz, C_6D_6): δ 192.5, 149.2, 139.3, 133.3, 131.2, 101.3, 52.2. **FTIR** (thin film) ν 2937, 2830, 1680, 1647, 1602, 1445, 1350, 1188, 1155, 1130, 1103, 1049, 1012, 989, 954, 909, 866, 565, 536 cm^{-1}. **HRMS** (ESI): Calculated for $C_7H_8O_2^+$ [M-OCH_3]$^+$ 125.0597; found 125.0590.

Ethyl 5-(2-allylthiazol-4-yl)pentanoate (36). To a solution of β-hydroxysulfone **30** (6.8 mg, 0.014 mmol, 1.0 equiv.) in anhydrous THF (0.5 mL) at −78 °C was added KHMDS (51 μL, 0.5 M in toluene, 0.026 mmol, 1.8 equiv.) under argon. Then the reaction mixture was stirred at −78 °C for 30 min. Deuterium oxide (20 μL) was added to the reaction mixture at −78 °C and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched with 1 mL saturated aqueous NH_4Cl solution and then extracted with ethyl acetate (3 × 5 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (pet. ether/EtOAc = 3:1) to afford the eliminated by-product **36** (1.3 mg, 36%) as a colourless oil. **R_f**: 0.50 (pet. ether/EtOAc = 2:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.04 (ddt, $J = 16.9, 10.0, 6.8$ Hz, 1H), 5.30−5.17 (m, 2H), 4.12 (q, $J = 7.2$ Hz, 2H), 3.74 (dt, $J = 6.9, 1.4$ Hz, 1H), 2.77 (t, $J = 7.1$ Hz, 2H), 2.33 (t, $J = 7.2$ Hz, 2H), 1.78−1.65 (m, 4H), 1.25 (t, $J = 7.0$ Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7, 168.7, 156.9, 134.0, 118.2, 112.6, 60.3, 37.8, 34.1, 31.2, 29.7 (grease peak), 28.7, 24.6, 14.3. **FTIR** (thin film) ν 2918, 2850, 1731, 1639, 1522, 1461, 1374, 1350, 1299, 1231, 1178, 1136, 1094, 1027, 920, 864, 795, 734, 584, 553 cm^{-1}. **HRMS** (ESI): Calculated for $C_{13}H_{20}NO_2S^+$ [M+H]$^+$ 254.1209; found 254.1212.

(*S*)-(1-Amino-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylidene)-λ^4-sulfanone (39). Lawesson's reagent (**27**) (freshly re-purified by washing with DCM and Et_2O, 37 mg, 0.090 mmol, 0.55 equiv.) was added to a solution of amide **37** (26 mg, 0.16 mmol, 1.0 equiv.) in anhydrous DCM. The reaction mixture was stirred vigorously under argon atmosphere at room temperature for 12 h. Saturated aqueous $NaHCO_3$ solution (3 mL) was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude material was purified by silica flash chromatography (pet. Ether/EtOAc = 2:1) to afford the thioamide *S*-oxide **39** as a yellow oil (7.2 mg, 23%). **R_f**: 0.43 (pet. Ether/EtOAc = 1:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.77 (br. s, 1H, N−H), 7.54 (br. s, 1H, N−H), 4.46 (dtd, $J = 8.5, 6.5, 3.3$ Hz, 1H), 4.14 (dd, $J = 8.4, 6.1$ Hz, 1H), 3.65 (dd, $J = 8.4, 6.7$ Hz, 1H), 3.04 (ddd, $J = 15.3, 3.3, 1.0$ Hz, 1H), 2.91 (dd, $J = 15.3, 8.4$ Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 206.1, 109.9, 73.8, 68.6, 48.8, 27.0, 25.5. **FTIR** (solid) ν 3312, 3188, 2984, 2933, 1654, 1636, 1629, 1438, 1420, 1381, 1372, 1324, 1249, 1214, 1152, 1106, 1060, 965,929, 884, 832, 512 cm^{-1}. **HRMS** (ESI): Calculated for $C_7H_{14}NO_3S^+$ [M + H]$^+$ 192.0689; found 192.0685. $[\alpha]_D^{22}$ −67.5 ($c = 0.215$, DCM).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy)butanamide (42). Imidazole (400 mg, 5.87 mmol, 1.55 equiv.) and *tert*-butyldiphenylchlorosilane (1.04 mL, 4.00 mmol, 1.05 equiv.) were added to a solution of amide **41** (0.40 g, 3.8 mmol, 1.0 equiv.) in 3.8 mL anhydrous DMF. The reaction mixture was stirred at room temperature for 24 h, and the reaction was quenched with distilled water (5 mL). Then DMF and water was removed at 60 °C by oil pump. The residue was then purified by flash silica chromatography (pet. ether/EtOAc = 1:2) to afford (*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxybutanamide as a colourless oil (911 mg, 67%). **R_f**: 0.23 (pet. Ether/EtOAc = 1:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.67−7.60 (m, 4H), 7.47−7.36 (m, 6H), 6.21 (br. s, 1H, N−H), 5.72 (br. s, 1H,N−H), 4.16−4.05 (m, 1H), 3.66 (dd, $J = 10.2, 4.6$ Hz, 1H), 3.60 (dd, $J = 10.2, 6.6$ Hz, 1H), 3.26 (br. s, O−H), 2.42−2.37 (m, 2H), 1.07 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.2, 135.4, 132.81, 132.79, 129.946, 129.938, 127.8, 68.8, 67.0, 38.8, 26.8, 19.2. **FTIR** (thin film) ν 3338, 3202, 2956, 2930, 2857, 1663, 1617, 1589, 1472, 1462, 1427, 1391, 1361, 1111, 1070, 1007, 998, 823, 803, 740, 700, 621, 613, 504, 489 cm^{-1}. **HRMS** (ESI): Calculated for $C_{20}H_{28}NO_3Si^+$ [M + H]$^+$ 358.1833; found 358.1838. $[\alpha]_D^{25}$ −24.4 ($c = 0.41$, DCM). Imidazole (5.44 g, 79.3 mmol, 6.0 equiv.) and *tert*-butyldimethylsilyl chloride (5.97 g, 39.6 mmol, 3.0 equiv.) were added to a solution of the TBDPS-protected intermediate (911 mg, 2.55 mmol, 1.0 equiv.) in 50 mL anhydrous DMF. The reaction mixture was stirred at 30−35 °C for 14 days under nitrogen atmosphere. Then reaction mixture was quenched by addition of 50 mL ice-water. Then DMF and water was removed at 60 °C by oil pump. The residue was re-dissolved in ethyl acetate (200 mL) and washed with distilled water (3 × 50 mL). The combined aqueous phase was then extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered, and then concentrated by rotary evaporation. The crude material was purified by flash silica chromatography (pet. ether/EtOAc = 2:1) to afford the title compound **42** as a colorless oil (6.12 g, 98%). **R_f**: 0.30 (pet. Ether/EtOAc = 2:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68−7.62 (m, 4H), 7.46−7.34 (m, 6H), 6.11 (br. s, 1H, N−H), 5.29 (br. s, 1H,N−H), 4.15−4.05 (m, 1H), 3.63 (dd, $J = 10.2, 4.8$ Hz, 1H), 3.54 (dd, $J = 10.1, 7.0$ Hz, 1H), 2.66 (dd, $J = 14.8, 4.1$ Hz, 1H), 2.42 (dd, $J = 14.8, 6.3$ Hz, 1H), 1.04 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), −0.06 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): 173.4 (C-1), 135.6, 135.5, 133.2, 133.1, 129.8, 129.7, 127.74, 127.73, 70.2 (C-3), 66.9 (C-4), 41.0 (C-2), 26.8, 25.7, 19.2, 17.9, −4.7, −5.1. **FTIR** (thin film) ν 3327, 3190, 3072, 2954, 2929, 2890, 2857, 1670, 1612, 1590, 1472, 1463, 1427, 1390, 1361, 1253, 1189, 1110, 1075, 999, 983, 964, 939, 824, 804, 777, 739, 700, 665, 613, 504, 490 cm^{-1}. **HRMS** (ESI): Calculated for $C_{26}H_{42}NO_3Si_2^+$ [M + H]$^+$ 472.2698; found 472.2704. $[\alpha]_D^{25}$ +71.7 ($c = 0.35$, DCM).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy)butanethioamide (40). Lawesson's reagent (1.54 g, 3.82 mmol, 0.6 equiv.) was added to a solution of amide **42** (3.06 g, 6.36 mmol, 1.0 equiv.) in anhydrous deoxygenated DCM (63 mL) under argon atmosphere. The reaction mixture was stirred vigorously at room temperature for 20 min. Upon completion, the reaction mixture was directly loaded onto a short silica plug and purified using DCM as eluent rapidly. The fractions were immediately collected and evaporated at 10 °C under vacuum to afford the title compound **40** as a yellow oil (1.71 g, 54%). **R_f**: 0.37 (DCM). **Note**: A tendency of **40** towards air oxidation was observed: upon purification, the product should be stored in the freezer at −20 °C under argon atmosphere. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.76 (br. s, 1H, N−H), 7.69−7.63 (m, 4H), 7.46−7.36 (m, 7H), 4.14−4.08 (m, 1H, H-3), 3.64 (dd, $J = 10.3, 4.7$ Hz, 1H, H-4a), 3.58 (dd, $J = 10.4, 6.8$ Hz, 1H, H-4b), 3.11 (dd, $J = 14.4, 4.1$ Hz, 1H, H-2a), 3.00 (dd, $J = 14.4, 6.0$ Hz, 1H, H-2b), 1.06 (s, 9H), 0.83 (s, 9H), 0.04 (s, 3H), −0.06 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 207.7 (C-1), 135.6, 135.5, 133.1, 132.9, 129.81, 129.77, 127.77, 127.74, 72.3 (C-3), 66.4 (C-4), 49.7 (C-2), 26.8, 25.8, 19.2, 17.9, −4.7, −5.0. **FTIR** (thin film) ν 3290, 3169, 3071, 2954, 2929, 2887, 2856, 1618, 1471, 1462, 1427, 1406, 1390, 1361, 1325, 1255, 1188, 1111, 1071, 998, 939, 834, 823, 803, 778, 739, 701, 690, 665, 622, 613, 505, 492 cm^{-1}. **HRMS** (ESI):. Calculated for $C_{26}H_{42}NO_2SSi_2^+$ [M + H]$^+$ 488.2469; found 488.2463. $[\alpha]_D^{25}$ −97.8 ($c = 0.92$, DCM).

Ethyl (*S*)-5-(2-(2-((*tert*-butyldimethylsilyl)oxy)-3-((*tert*-butyldiphenylsilyl)oxy)propyl)thiazol-4-yl)pentanoate (43). To a solution of Mor-DalPhosAuOMs (**12**) (2.9 mg, 0.0039 mmol, 0.1 equiv.) in anhydrous deoxygenated DCM (0.2 mL) was added alkyne **14** (12 mg, 0.074 mmol, 2.1 equiv.). The resulting mixture was stirred at room temperature under argon atmosphere for 15 min. Then a solution of 8-methylquinoline *N*-oxide (**11**) (17.0 mg, 0.106 mmol, 2.74 equiv.) and methanesulfonic acid (5.5 μL, 0.085 mmol, 2.52 equiv.) in degassed anhydrous DCM (0.2 mL) was

added to the reaction mixture via a syringe pump under argon atmosphere over 5 h. Upon completion, the reaction mixture was further stirred for 1 h before a solution of thioamide **40** (11.9 mg, 0.024 mmol, 1.0 eq) in deoxygenated anhydrous DCM (0.8 mL) adding. The resulting mixture was stirred at 45 °C (oil bath temperature) in a sealed vial under argon atmosphere for 12 h before concentration under reduced pressure. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 10:1) to provide the title compound **43** (9.5 mg, 61%) as a colourless oil. **R_f**: 0.60 (pet. ether/EtOAc = 5:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.69–7.62 (m, 4H), 7.45–7.34 (m, 6H), 6.74 (s, 1H), 4.18–4.11 (m, overlapped, 3H), 3.63 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.54 (dd, *J* = 10.2, 6.7 Hz, 1H), 3.39 (dd, *J* = 14.5, 4.0 Hz, 1H), 3.11 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.33 (t, *J* = 7.0 Hz, 2H), 1.77–1.66 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.76 (s, 9H), −0.15 (s, 3H), −0.25 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.7, 167.1, 156.4, 135.62, 135.59, 133.30, 129.67, 129.65, 127.684, 127.678, 112.5, 72.8, 67.4, 60.3, 38.6, 34.2, 31.2, 28.8, 26.9, 25.8, 24.6, 19.2, 18.0, 14.3, −4.8, −5.3. **FTIR** (thin film) *ν* 2954, 2929, 2857, 1735, 1472, 1462, 1428, 1254, 1186, 1112, 1075, 836, 824, 805, 777, 740, 702, 690, 505, 493 cm^{-1}. **HRMS** (ESI): Calculated for $C_{35}H_{54}NO_4SSi_2^+$ $[M+H]^+$ 640.3307; found 640.3296. $[\alpha]_D^{26}$ −111.1 (*c* = 0.45, DCM).

2-(6-Oxo-3,6-dihydro-2*H*-pyran-2-yl)ethyl 5-(2-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3-((*tert*-butyldiphenylsilyl)oxy)propyl) thiazol-4-yl)pentanoate (44). To a solution of Mor-DalPhosAuOMs (**12**) (26.0 mg, 0.0344 mmol, 0.01 equiv.) in anhydrous deoxygenated DCM (7.0 mL) was added alkyne **5** (862 mg, 3.44 mmol, 1.03 equiv.). The resulting mixture was stirred at room temperature under argon atmosphere for 30 min. Then a solution of 8-methylquinoline *N*-oxide (**11**) (712 mg, 4.47 mmol, 1.34 equiv.) and methanesulfonic acid (268 μL, 4.13 mmol, 1.24 equiv.) in degassed anhydrous DCM (6.9 mL) was added to the reaction mixture via a syringe pump under argon atmosphere over 9 h. Upon completion, the reaction mixture was further stirred for 1 h before a solution of thioamide **40** (1.63 g, 3.34 mmol, 1.0 equiv.) in deoxygenated anhydrous deoxygenated DCM (22 mL) was added. The resulting mixture was stirred at 45 °C (oil bath temperature) in a sealed vial for 72 h under argon atmosphere before concentration under reduced pressure. The crude material was purified by silica gel flash chromatography (pet. ether/EtOAc = 3:2) to provide the title compound **44** (1.31 g, 52%, BRSM 57%) as a yellow oil. **R_f**: 0.52 (pet. ether/EtOAc = 1:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.69–7.62 (m, 4H), 7.46–7.33 (m, 6H), 6.94–6.82 (m, 1H), 6.75 (s, 1H), 6.04 (dt, *J* = 9.9, 1.7 Hz, 1H), 4.61–4.50 (m, 1H), 4.35–4.22 (m, 2H), 4.17–4.09 (m, 1H), 3.63 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.53 (dd, *J* = 10.2, 6.7 Hz, 1H), 3.39 (dd, *J* = 14.5, 3.9 Hz, 1H), 3.11 (dd, *J* = 14.6, 7.8 Hz, 1H), 2.75 (t, *J* = 7.1 Hz, 2H), 2.43–2.31 (m, 2H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.16–2.09 (m, 1H), 2.04–1.95 (m, 1H), 1.78–1.64 (m, 4H), 1.05 (s, 9H), 0.76 (s, 9H), −0.15 (s, 3H), −0.25 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4, 167.2, 163.9, 156.3, 144.73, 144.72, 135.59, 135.56, 133.4, 133.3, 129.65, 129.63, 127.66, 127.65, 121.5, 112.6, 74.7, 72.7, 67.3, 59.8, 38.6, 34.02, 33.97, 31.2, 29.4 28.7, 26.8, 25.7, 24.5, 19.2, 17.9, −4.8, −5.3. **FTIR** (thin film) *ν* 2953, 2929, 2856, 1731, 1472, 1462, 1428, 1389, 1361, 1248 cm^{-1}. **HRMS** (ESI): Calculated for $C_{40}H_{58}NO_6SSi_2^+$ $[M+H]^+$ 736.3518; found 736.3494. $[\alpha]_D^{25}$ −14.3 (*c* = 1.05, DCM).

(2*Z*,4*E*)-7-((5-(2-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-((*tert*-butyldiphenylsilyl)oxy)propyl)-thiazol-4-yl)pentanoyl) oxy)hepta-2,4-dienoic acid (45). Potassium bis(trimethylsilyl) amide solution (145 μL, 1.0 M in THF, 0.145 mmol, 1.3 equiv.) was added dropwise to a solution of thiazole **44** (82.2 mg, 0.112 mmol, 1.0 equiv.) in anhydrous THF (2.0 mL) at −78 °C. The reaction mixture was stirred at that temperature under argon atmosphere for 2 h. Aqueous sulfuric acid (193 μL, 2 vol%) was added to the reaction mixture dropwise at −78 °C, and then the resulting mixture was allowed to warm up to room temperature and stir at room temperature for 5 min. The mixture was then added ethyl acetate (6 mL) and saturated brine (2 mL). The aqueous phase was extracted by ethyl acetate (3 × 5 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered, and then concentrated by rotary evaporation. The crude material was purified by flash silica chromatography (pet. ether/EtOAc = 4:1) to afford the title compound **45** as a colourless oil (49.0 mg, 60%). **R_f**: 0.27 (pet. ether/EtOAc = 5:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4H), 7.45–7.35 (m, overlapped, 7H), 6.75 (s, 1H), 6.58 (t, *J* = 11.3 Hz, 1H), 6.04 (dt, *J* = 15.5, 6.4 Hz, 1H), 5.62 (d, *J* = 11.4 Hz, 1H), 4.20 (t, *J* = 5.7 Hz, 2H), 4.14(tt, *J* = 7.9, 4.2 Hz, 1H), 3.62 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.53 (dd, *J* = 10.2, 6.9 Hz, 1H), 3.47 (dd, *J* = 14.5, 3.9 Hz, 1H), 3.19 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.54–2.48 (m, 2H), 2.34 (t, *J* = 6.7 Hz, 2H), 1.75–1.68 (m, 4H), 1.05 (s, 9H), 0.75 (s, 9H), −0.17 (s, 3H), −0.25 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.5, 169.6, 168.1, 156.1, 144.6, 139.3, 135.59, 135.58, 133.4, 133.3, 129.65, 129.62, 129.2 (C-15), 127.67, 127.66, 117.3, 112.9, 72.6, 67.2, 62.4, 38.1, 34.2, 31.8, 30.7, 29.2, 26.8, 25.8, 24.6, 19.2, 17.9, −4.9, −5.4. **FTIR** (thin film) *ν* 3070, 3050, 2953, 2929, 2893, 2857, 1736, 1695, 1640, 1602, 1525, 1471, 1428, 1389, 1361, 1252 cm^{-1}. **HRMS** (ESI): Calculated for $C_{40}H_{58}NO_6SSi_2^+$ $[M+H]^+$ 736.3518; found 736.3519. $[\alpha]_D^{23}$ −13.7 (*c* = 0.99, DCM).

(2*Z*,4*E*)-7-((5-(2-((*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-hydroxypropyl)thiazol-4-yl)pentanoyl)oxy)hepta-2,4-dienoic acid (46). Pyridinium *p*-toluenesulfonate (156 mg, 0.621 mmol, 10.0 equiv.) was added to a solution of acid **45** (46 mg, 0.063 mmol, 1.0 equiv.) in MeOH (4.5 mL). The reaction mixture was stirred at 45–50 °C for 27 h. Upon completion, the reaction mixture was concentrated under reduced pressure and the residue was directly loaded onto a silica column and purified by flash chromatography using pet. ether/EtOAc = 2:1 as eluent to afford the title compound **46** as a colourless oil (11.9 mg, 30%, BRSM 43%). **R_f**: 0.56 (pet. ether/EtOAc = 1:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68–7.62 (m, 4H), 7.45–7.32 (m, overlapped, 7H), 6.79 (s, 1H), 6.59 (t, *J* = 11.4 Hz, 1H), 6.06 (dt, *J* = 15.1, 6.2 Hz, 1H), 5.59 (d, *J* = 11.4 Hz, 1H), 4.22 (t, *J* = 5.8 Hz, 2H), 4.15–4.07 (m, 1H), 3.72 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.67 (dd, *J* = 9.7, 5.3 Hz, 2H), 3.31 (dd, *J* = 15.6, 3.1 Hz, 1H), 3.20 (dd, *J* = 15.1, 8.7 Hz, 1H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.55–2.49 (m, 2H), 2.35 (t, *J* = 6.6 Hz, 2H), 1.76–1.63 (m, 4H), 1.07 (s, 9H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.6, 170.1, 167.7, 156.1, 145.4, 140.0, 135.52, 135.51, 133.10, 133.07, 129.76, 129.75, 129.1, 127.74, 127.72, 116.8, 112.8, 71.3, 66.8, 62.5, 36.3, 34.0, 31.9, 30.6, 28.8, 26.8, 24.4, 19.2. **FTIR** (thin film) *ν* 3391, 3069, 2929, 2857, 1733, 1640, 1602, 1525, 1461, 1428, 1389, 1361, 1185, 1112, 999, 964, 939, 859, 824, 741, 703, 614, 593, 506, 434, 418 cm^{-1}. **HRMS** (ESI): Calculated for $C_{34}H_{44}NO_6SSi^+$ $[M+H]^+$ 622.2653; found 622.2625. $[\alpha]_D^{24}$ −9.0 (*c* = 0.69, DCM).

(*S*,6*Z*,8*E*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4,12-dioxa-1(2,4)-thiazolacycloheptadecaphane-6,8-diene-5,13-dione (48). To a mixture of acid **46** (12.9 mg, 0.0203 mmol, 1.0 equiv.) and solid $NaHCO_3$ (419 mg, 4.99 mmol, 246 equiv.) in anhydrous DCM (36 mL) was added 2-bromo-1-ethyl-pyridinium tetrafluoroborate (**47**) (141 mg, 0.515 mmol, 24.6 equiv.). The reaction mixture was stirred in the dark under argon atmosphere at room temperature for 19 h. The reaction was quenched by addition of distilled water (3.9 mL). The aqueous phase was separated and extracted by ethyl acetate (4 × 8 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered, and then concentrated by rotary evaporation. The crude material was purified by flash silica chromatography (pet. ether/EtOAc = 2:1) to afford the title compound **48** as a colorless oil (9.4 mg, 75%). **R_f**: 0.73 (pet. ether/EtOAc = 1:1). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.70–7.64 (m, 4H), 7.45–7.36 (m, 6H), 7.19 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.73 (s, 1H), 6.46 (t, *J* = 11.4 Hz, 1H), 5.93 (ddd, *J* = 15.3, 8.9, 5.6 Hz, 1H), 5.51–5.47 (m, overlapped, 2H), 4.26 (td, *J* = 10.6, 10.1, 2.8 Hz, 1H), 4.22–4.18 (m, 1H), 3.84 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.79 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.33

(dd, J = 14.6, 2.7 Hz, 1H), 3.25 (dd, J = 14.7, 11.0 Hz, 1H), 2.76 (dt, J = 13.7, 6.3 Hz, 1H), 2.64 (dt, J = 15.0, 7.7 Hz, 1H), 2.52–2.45 (m, 1H), 2.44–2.36 (m, 1H), 2.29 (t, J = 7.6 Hz, 2H), 1.76 (dt, J = 14.5, 7.5 Hz, 1H), 1.66 (dt, J = 13.9, 6.8 Hz, 1H), 1.56–1.49 (m, 2H), 1.07 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 173.4, 165.8, 164.7, 156.6, 144.8, 140.1, 135.61, 135.56, 133.13, 133.10, 129.8, 129.5, 127.8, 127.7, 116.1, 113.1, 72.7, 65.3), 61.8, 35.2, 34.6, 32.6, 30.8, 28.2, 26.8, 24.1, 19.3. **FTIR** (thin film) ν 2954, 2931, 2858, 1723, 1640, 1602, 1523, 1472, 1461, 1428, 1388, 1361, 1260, 1228, 1173, 1114, 1091, 998, 964, 823, 742, 703, 615, 505 cm^{-1}. **HRMS** (ESI): Calculated for $C_{34}H_{42}NO_5SSi^+$ [M + H]$^+$ 604.2547; found 604.2519. $[\alpha]_D^{25}$ −32.5 (c = 0.07, DCM).

(*S*,6*Z*,8*E*)-3-(Hydroxymethyl)-4,12-dioxa-1(2,4)-thiazolacycloheptadecaphane-6,8-diene-5,13-dione (49). To a solution of macrocyclic compound **48** (35.7 mg, 0.0591 mmol, 1.0 equiv.) and acetic acid (16.4 μL, 0.286 mmol, 4.85 equiv.) in anhydrous THF (3.0 mL) was slowly added tetrabutylammonium fluoride (118 μL, 1.0 M in THF, 0.118 mmol, 2.0 equiv.) over 20 min at 0 °C. Then the reaction mixture was allowed to warm up to room temperature and stirred at room temperature for 17 h. The reaction mixture was then diluted with ethyl acetate (20 mL) and added saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous phase was separated and extracted by ethyl acetate (3 × 5 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered, and then concentrated by rotary evaporation. The crude material was purified by flash silica chromatography (pet. ether/EtOAc = 1:2) to afford the title compound **49** (18.5 mg, 86%) as a colourless oil. **R_f**: 0.25 (pet. ether/EtOAc = 1:2). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.17 (dd, J = 15.7, 11.7 Hz, 1H), 6.73 (s, 1H), 6.48 (t, J = 11.3 Hz, 1H), 5.95 (ddd, J = 15.0, 8.7, 5.6 Hz, 1H), 5.51 (d, J = 11.3 Hz, 1H), 5.49–5.44 (m, 1H), 4.30–4.25 (m, 1H), 4.20–4.15 (m, 1H), 3.86 (dd, J = 11.9, 4.0 Hz, 1H), 3.81 (dd, J = 11.9, 5.3 Hz, 1H), 3.30–3.26 (m, 2H), 2.78 (dt, J = 13.2, 6.3 Hz, 1H), 2.64 (dt, J = 14.8, 7.6 Hz, 1H), 2.53–2.37 (m, 2H), 2.28 (t, J = 7.6 Hz, 2H), 1.81–1.60 (m, 2H), 1.52–1.48 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4, 165.3, 164.9, 156.7, 145.3, 140.6, 129.2, 115.6, 113.2, 73.1, 64.4, 61.7, 34.7, 34.6, 32.5, 30.8, 28.2, 24.0. **FTIR** (thin film) ν 3355, 2923, 2854, 1719, 1639, 1602, 1524, 1458, 1420, 1380, 1260 cm^{-1}. **HRMS** (ESI): Calculated for $C_{18}H_{24}NO_5S^+$ [M + H]$^+$ 366.1370; found 366.1346. $[\alpha]_D^{25}$ −137 (c = 0.125, DCM).

Declaration of competing interest

The authors have no conflicting interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132109.

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