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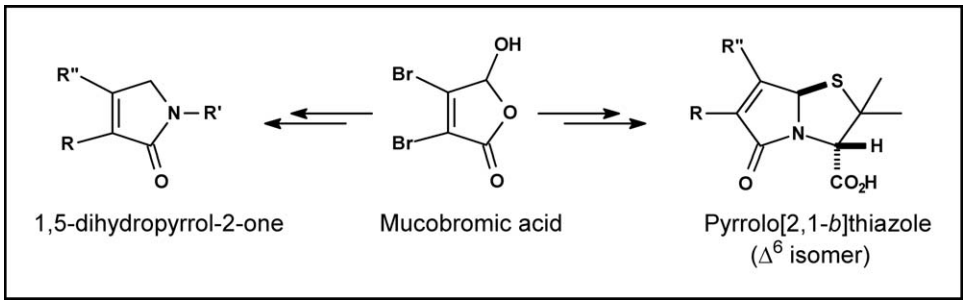

A modular synthesis of selectively-substituted pyrrolo[2,1-*b*]thiazoles (Δ^6 isomeric form) has been implemented, involving a distinctive bicyclization reaction of a mucobromic acid derivative followed by a Suzuki-Miyaura coupling. A novel process of Δ^6 to Δ^7 isomerization of the pyrrolothiazole structure was uncovered that appears to involve a 1,4-addition-1,2-elimination mechanism. Preparation of 1,5-dihydropyrrol-2-one structures, selectively substituted at the 3- and 4-positions, was also achieved using the mucobromic acid synthon in a reductive amination process.

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INTRODUCTION

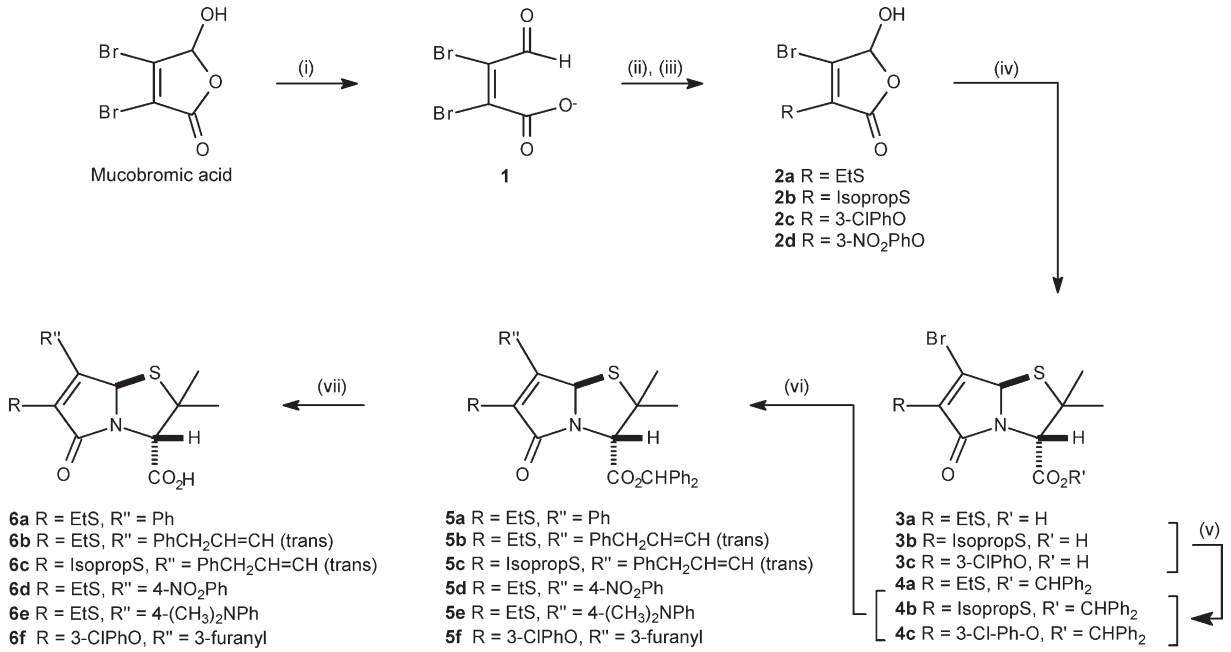
Pyrrolo[2,1-*b*]thiazole and 1,5-dihydropyrrol-2-one structures are important synthetic targets given the range of biological and other properties that they show [1,2]. As part of our research on development of serine protease inhibitors a modular synthesis of the above structures was required that allowed for ready variation of the substituent groups R, R′, and R″. Herein we report on a modular synthesis based on mucobromic acid, which is a cheap multifunctional building block [3–5].

RESULTS AND DISCUSSION

The first step in the modular synthesis (Scheme 1) was introduction of substituent R via a 1,4-addition-elimination reaction on the anionic ring-opened form of mucobromic acid. Thiols and phenols are suitable for this reaction as the corresponding thiolate and phenoxide nucleophiles are readily formed in aqueous base [6] here ethyl and isopropyl mercaptan as well as 3-chloro and 3-nitrophenol were used. Formation of the pyrrolo[2,1-*b*]thiazole structure was achieved by a bicyclization reaction of the muco derivative with D-penicillamine. This type of reaction was first reported by Wasserman et al. [7] and was later exploited by Moore and Arnold, who verified by X-ray crystallography that a single stereoisomer of the bicyclic product was formed. [8] The bicyclic structure **3** was converted to its benzhydryl ester **4** to facilitate its purification and for optimal formation of the subsequent Suzuki-Miyaura products **5a–f**. The R′ substituents (aryl, heteroaryl, and alkenyl groups) were introduced by a Suzuki-Miyaura coupling [9] using commercially available boronic acids or boronic acid pinacol esters.

A mechanism for the bicyclization with D-penicillamine is given in Scheme 2 together with data (this work) on the relative thermodynamic stability of the diastereomeric products **B** and **B′**: the stereochemical outcome appears to be controlled by an unfavorable endocyclic interaction between the 3-carboxyl group and the γ-lactam carbonyl that occurs in **B′** but not in **B**. The facile formation of structure type **B**, involving H_2O as a leaving group in a weakly acidic aqueous medium at ambient temperature, attests to the strong thermodynamic driving force for cyclization of structure type **A**. During the synthetic work, it was found that the bicyclization reaction did not proceed well where the halogen of muco structure **2** was replaced by nonelectron-withdrawing groups. The reaction rate and yield of the bicyclization was much lower (27–32%) when cysteine was used in place of penicillamine [10]. This difference may be as a result of a faster thiazolidine ring formation step with penicillamine due to a gem-dimethyl effect

Scheme 1. (i) KOH_{aq}, (ii) RSH or ArOH, KOH_{aq}, (iii) HCl_{aq}, (iv) D-penicillamine, EtOH/H_2O 1:1, HOAc (1.2 equiv.), (v) Diphenyldiazomethane, (vi) Suzuki-Miyaura coupling, (vii) $AlCl_3$ in CH_2Cl_2/$EtNO_2$, −80°C, 1 h.

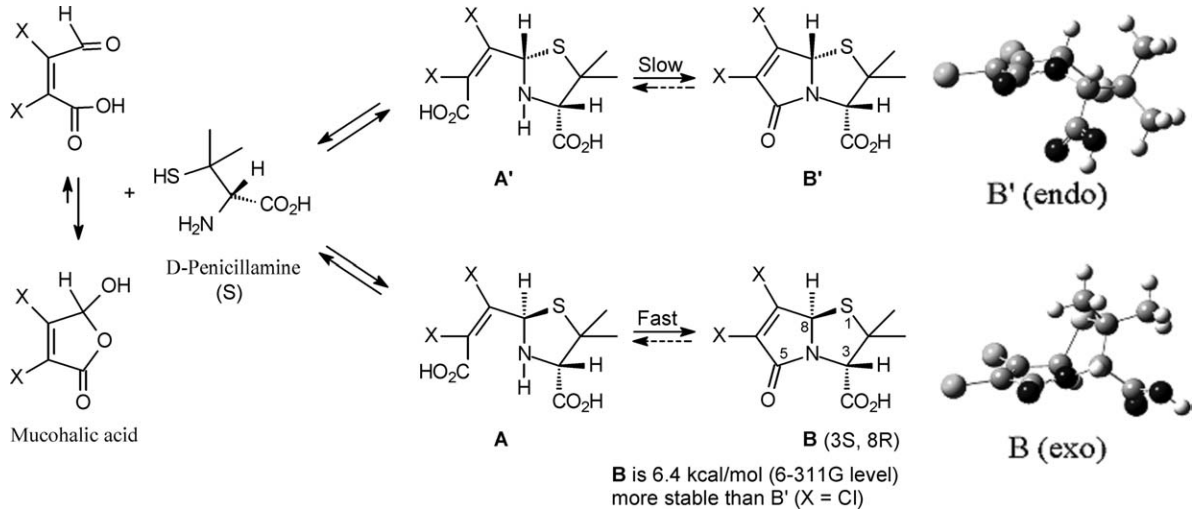


[11], making the bicyclization path dominant over competing side reactions.

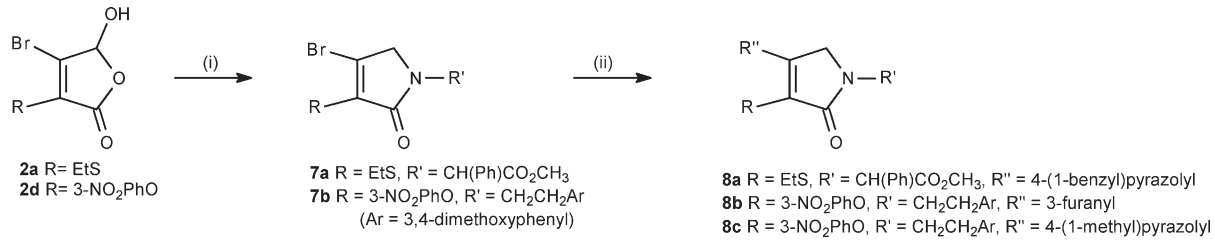
Muco synthons **2a** and **2d** were also used to prepare a set of 1,5-dihydropyrrol-2-ones (**8a–c**, Scheme 3) by reductive amination followed by Suzuki-Miyaura coupling. (R)-phenylglycine methyl ester was used for the preparation of **7a** and 2-(3,4-dimethoxyphenyl)ethylamine was used for **8b** and **8c**. This reaction occurs via imine formation with the neutral ring-opened form of the mucoderivative, which is present in very low equilibrium concentration with the ring-closed form [5]. Hydride addition to the imine leads directly to cyclization—here again the facile ring closure, involving water as a leaving group in a weakly acidic medium at ambient temperature, indicates the strong thermodynamic driving force for the formation of the unsaturated γ-lactam unit. In the reductive amination step with **2a,** a small amount of the desbromo reduction product was formed, which was removed prior to the coupling step.

Isomerisation of Δ^6 to the Δ^7 isomer. In previous work, we had found that, in at least one case, the Δ^7 isomer was thermodynamically more stable than the Δ^6 isomer. Thus, in the rearrangement reaction of a modified penicillin with MeOH/Et_3N (Scheme 4), the

Scheme 2. Mechanism of the bicyclization reaction between D-penicillamine and a mucohalic acid.

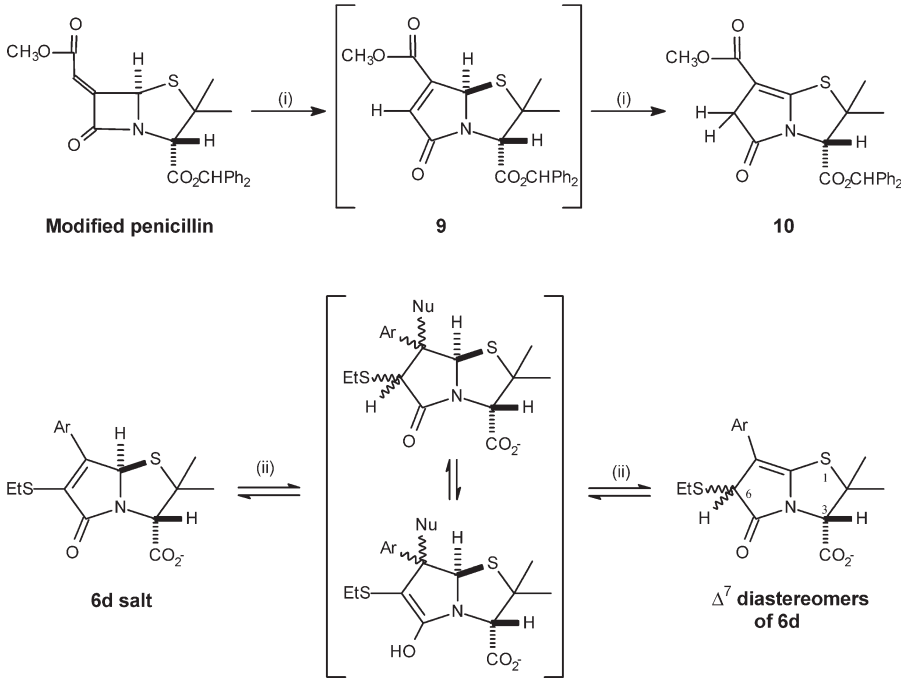


Scheme 3. (i) Reductive amination; (ii) Suzuki-Miyaura coupling



quantitatively isolated product was the Δ^7 pyrrolothiazole **10**, which must have been derived from the initially-formed Δ^6 isomer **9** [12]. The most likely isomerization mechanism under those reaction conditions is via deprotonation of the bridgehead hydrogen H-8. This process was found to lack general applicability. In this work, an alternative isomerization process was uncovered with the carboxylate salt of **6d**. The ^{1}H NMR spectrum of **6d** in D_2O buffer (50 m*M* phosphate, pH 7.2) containing 10% DMSO-d6 indicated the presence of ~1% each of two structures, which were not present in the free acid **6d** in $CDCl_3$. Unexpectedly, the ^{1}H NMR spectrum (D_2O) of the solids recovered after freeze-drying showed the presence of ~10% of each of the new structures with the remainder being, largely, unreacted **6d**. Indeed, the material recovered after freeze-drying twice from phosphate buffer/10%DMSO contained ~30% of each of the new structures (Fig. 1); this value rose to 41% when phosphate buffer/20% DMSO was used. Two further freeze-drying cycles from H_2O to maximize removal of DMSO did not alter the composition, however, on standing for several days at 4°C the solid material—a DMSO solvate by its ^{1}H NMR spectrum—was found to contain, largely, the Δ^7 isomers but no **6d**. The new structures did not correspond to the γ-lactam ring-opened form of **6d**. In previous work, we had shown that a signature of such ring-opened structures is the significant upfield shift of the resonance of a gem-dimethyl group [12], which was absent here, and in addition, **6d** was found to remain unchanged after 20 h at 21°C in D_2O buffer (50 m*M* phosphate, pH 7.2). The new resonances were consistent with two Δ^7 diastereomers (6-R and 6-S epimers) derived from the **6d** salt: two new sets of resonances were clearly observed for the aromatic hydrogens and for H-3, and the new resonances for the methylene hydrogens of the ethylsulfanyl unit at

Scheme 4. Mechanisms of Δ^6 to Δ^7 isomerization of selected pyrrolo-thiazole structures. Top route: Deprotonation of bridgehead hydrogen H-8: (i) CH_3OH/NEt_3; Lower route: 1,4 addition-1,2 elimination, (ii) aqueous phosphate buffer/20% DMSO (with freeze-drying), Ar = *p*-nitrophenyl, Nu = nucleophile-cum-leaving group.



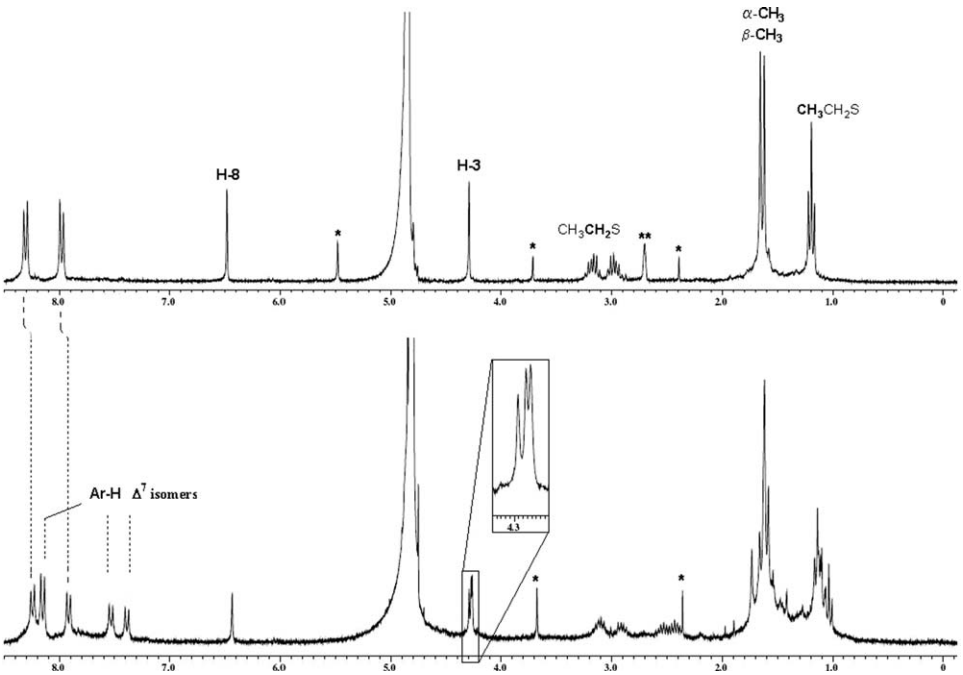


Figure 1. Top: ^{1}H NMR spectrum of the *p*-nitrophenyl derivative **6d** in D_2O phosphate buffer/10%DMSO-d6. Bottom: ^{1}H NMR spectrum in D_2O of the material recovered after two stages of freeze-drying from phosphate buffer/10% DMSO showing ~30% of each of the Δ^7 isomers. * = solvent impurities, ** = DMSO-d6. Note that a small displacement of chemical shift values is observed between D_2O buffer/10% DMSO-d6 and pure D_2O as solvent.

2.45 ppm were characteristic of those of a dialkyl sulfide such as diethyl sulfide. The initial observation in the D_2O buffer system showed a diminution in the intensity of the H-8 resonance of **6d** without the obvious appearance of a new peak indicating deuterium incorporation in the new structures. High-resolution mass

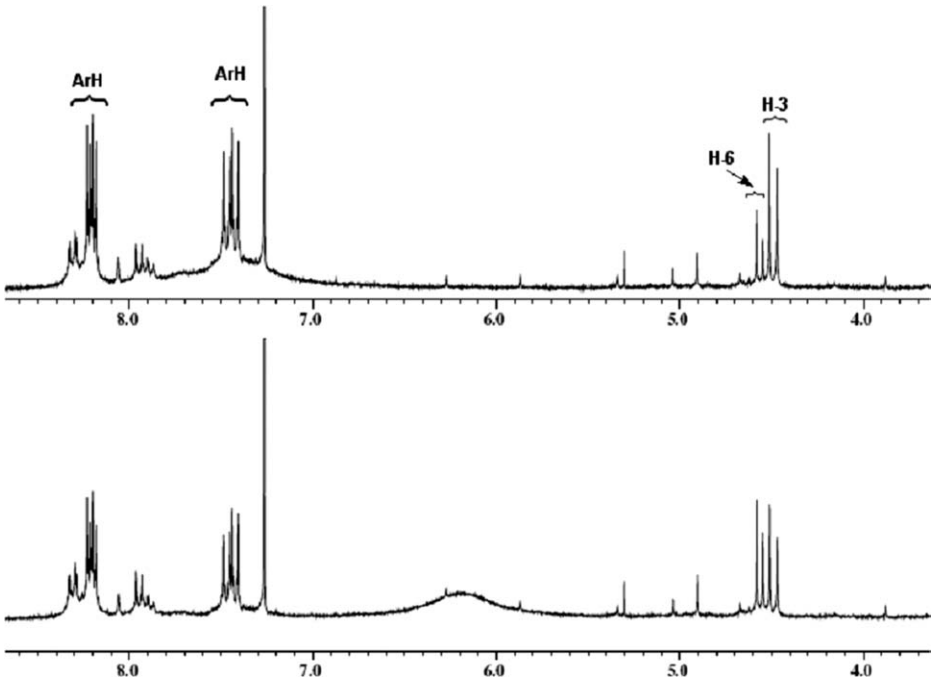


Figure 2. A portion of the ^{1}H NMR spectrum in $CDCl_3$ of the recovered free acids (crude) of each Δ^7 isomer of **6d**. (Bottom): before exchange with D_2O; (Top): after partial exchange with D_2O.

spectral analysis of this sample gave peaks at 393.0573 and at 394.0641, which correspond respectively, to the molecular weights of the Δ^6 isomer (calcd. 393.0579) and of the Δ^7 isomer containing one deuterium (calcd. 394.0642). The crude free acids of the Δ^7 isomers were recovered from an acidified aqueous solution (pH 3.5) of the solids by extraction with dichloromethane. The ^{1}H NMR spectrum (Fig. 2) of these clearly showed singlets, ~40:60, respectively, for each H-3 at 4.47 and 4.51, and at 4.55 and 4.58 ppm for each H-6; these latter hydrogens were characterized by being exchanged for deuterium on addition of D_2O. The enhancing effect of divalent sulfur on the kinetic acidity of α-hydrogens is well established [13].

The most likely mechanism of isomerization is via 1,4-addition-1,2-elimination as shown in Scheme 4, with phosphate dianion as the nucleophile-cum-leaving group. For an example of a reaction where phosphate di-anion has been shown to act as a nucleophile-cum-leaving group see [14]. The finding that a similar isomerization occurred with the phenyl derivative **6a** but not with the *N*,*N*-dimethyl derivative **6e** supports a 1,4 addition step. In the freeze-drying process water is removed faster than DMSO so that the frozen solution becomes enriched in DMSO, which may enhance the activity of the buffer nucleophiles [15] this may also be the case with the solid DMSO solvate. Isomerization of the earlier-stage synthon **3a** was unsuccessful under these conditions.

CONCLUSIONS

A concise modular synthesis of selectively-substituted pyrrolo[2,1-*b*]thiazoles (Δ^6 isomeric form) has been implemented, involving a distinctive bicyclization step with a mucobromic acid derivative. A novel process of Δ^6 to Δ^7 isomerization of these pyrrolothiazoles was uncovered that appears to involve a 1,4-addition-1,2-elimination mechanism, which is accelerated by repeated freeze-drying from a phosphate buffer/DMSO mixture. The synthesis of related monocyclic 3,4-disubstituted 1,5-dihydropyrrol-2-ones was also elaborated by reductive amination of the mucobromic acid derivative.

EXPERIMENTAL

1,4-Addition-elimination–general procedure. To a solution of mucobromic acid (1.00 g, 3.88 mmol) in water (4 mL) containing potassium hydroxide (256 mg, 4.56 mmol) was added the required alkyl mercaptan (5.82 mmol), or substituted phenol (4.27 mmol), in water (3.5 mL) containing potassium hydroxide (392 mg, 5.82 mmol). The mixture was allowed to stir at room temperature for 3 h. The pH was lowered to <2 using 1*M* HCl and extracted with dichloromethane (2 × 10 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to leave a brown (**2a** and **2b**) or orange (**2c**) to bright orange (**2d**) oil.

4-Bromo-3-ethylsulfanyl-5-hydroxy-5*H*-furan-2-one (2a). 568 mg, 2.38 mmol, 61%; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7 0.42 Hz, C**H$_3$**—CH_2), 3.23 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H$_{2A}$**S (diastereotopic)) overlapping with 3.29 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H$_{2B}$**S (diastereotopic)), 5.97 (s, 1H, **H**-5); ^{13}C NMR (67.5 MHz, $CDCl_3$, DEPT) δ15.49 (**C**$H_3$$CH_2$S), 25.01 ($CH_3$**C**$H_2$), 97.70 (**C**H(OH)O), 131.11, 139.27 (**C**-3, **C**-4), 166.53 (**C**=O); ESI-HRMS for $C_6H_7O_3SBr$: $[M - H]^-$ calcd: 236.9221, found: 236.9256 and 238.9241. This material was used directly in the bicyclization reaction (see below) without further purification.

4-Bromo-5-hydroxy-3-isopropylsulfanyl-5*H*-furan-2-one (2b). (754 mg, 2.98 mmol, 50%); ^{1}H NMR (270 MHz, $CDCl_3$) δ1.32 (d, 6H, J = 6.93 Hz (C**H$_3$**)$_2$CHS, diastereotopic methyl groups with coincident chemical shifts), 4.22 (sept, 1H, J = 6.68 Hz, (CH_3)$_2$C**H**S), 6.00 (s, 1H **H**-5); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 23.59, 23.96 ((**C**H_3)$_2$CHS (diastereotopic methyl groups)), 35.82 ((CH_3)$_2$**C**HS), 97.82 (**C**H(OH)O), 131.43, 141.27 (**C**-3, **C**-4), 166.83 (**C**=O); EI-HRMS for $C_7H_9O_3SBr$: $[M]^+$ calcd: 251.9459, found: 251.9456 and 253.9453. This material was used directly in the bicyclization reaction (see below) without further purification.

4-Bromo-3-(3-chlorophenoxy)-5*H*-furan-2-one (2c). Purification by silica gel column chromatography using 1:1 dichloromethane/hexane containing 5% acetic acid, followed by washing with water to remove acetic acid, gave **2c** as a colorless gum (590 mg, 1.93 mmol, 50%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.10 (s, 1H, **H**-5), 6.96 (ddd, 1H, J = 8.18, 2.47, 0.99 Hz, Ar**H**), 7.07 (app t, 1H, J = 2.23 Hz, Ar**H**), 7.17 (ddd, 1H, J = 7.92, 1.98, 0.99 Hz, Ar**H**), 7.28 (t, 1H, J = 8.16 Hz, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 96.24 (**C**H(OH)O), 115.93, 118.15, 123.02 (**C**-3/**C**-4), 125.07, 130.42, 134.90 (**C**-3/**C**-4), 142.34, 154.26 (Ar**C**), 164.52 (**C**=O); ESI-HRMS for $C_{10}H_6O_4BrCl$: $[M + Na]^+$ calcd: 326.9036, found: 326.9046 and 328.9040.

4-Bromo-3-(3-nitrophenoxy)-5*H*-furan-2-one (2d). Purification by silica gel column chromatography using 1:1 dichloromethane/hexane containing 5% acetic acid, followed by washing with water to remove acetic acid, gave **2d** as a pale yellow gum (637 mg, 2.02 mmol, 52%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.17 (s, 1H, **H**-5), 7.44 (ddd, 1H, J = 8.16, 2.47, 1.24 Hz, Ar**H**), 7.56 (t, 1H, J = 8.16 Hz, Ar**H**), 7.88 (app t, 1H, J = 1.98 Hz, Ar**H**), 8.05 (ddd, 1H, J = 8.16, 1.98, 0.99 Hz, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 96.26 (**C**H(OH)O), 112.75, 119.81, 124.0, 124.54 (**C**-3/**C**-4), 130.63, 142.36 (**C**-3/**C**-4), 148.87, 154.39 (Ar**C**), 163.61 (**C**=O); ESI-HRMS for $C_{10}H_6O_6Br$: $[M + H]^+$ calcd: 337.9276, found: 337.9290 and 339.9274.

Bicyclization–general procedure. To a solution of D-penicillamine (315 mg, 2.11 mmol) and sodium chloride (144 mg) in water (3 mL) containing acetic acid (144 μL, 2.52 mmol) was added a solution of the required muco derivative **2a-2c** (1.92 mmol) in ethanol (3 mL). The mixture was stirred at room temperature overnight and was then extracted with dichloromethane (10 mL). The organic layer was dried, filtered and concentrated by rotary evaporation to yield the free acid as a yellow solid.

(3S,7aR)-7-Bromo-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*] thiazole-3-carboxylic acid (3a). A yellow solid (459 mg, 1.31 mmol, 68%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.42 Hz, C**H$_3$**CH_2S), 1.59 (s, 3H, α-C**H$_3$**), 1.62 (s, 3H, β-C**H$_3$**), 3.14 (dq, 1H, J = 13.5, 7.42 Hz,

$CH_3C\mathbf{H_{2A}}S$ (diastereotopic)) overlapping with 3.25 (dq, 1H, J = 13.5, 7.42 Hz, $CH_3C\mathbf{H_{2B}}S$ (diastereotopic)), 4.66 (s, 1H, **H**-3), 5.87 (s, 1H, **H**-8). This material was converted into its benzhydryl ester (see below) without further purification.

(3S,7aR)-7-Bromo-6-isopropylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo [2,1-*b*]thiazole-3-carboxylic acid (3b). A yellow solid (458 mg, 1.25 mmol, 65%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.30 (d, 3H, J = 6.68 Hz, $(C\mathbf{H_{3A}})_2$CHS (diastereotopic)) overlapping with 1.31 (d, 3H, J = 6.68 Hz, $(C\mathbf{H_{3B}})_2$CHS (diastereotopic)), 1.58 (s, 3H, α-C$\mathbf{H_3}$), 1.62 (s, 3H, β-C$\mathbf{H_3}$), 4.09 (sept, 1H, J = 6.68 Hz, $(CH_3)_2C\mathbf{H}$S), 4.68 (s, 1H, **H**-3), 5.90 (s, 1H, **H**-8). This material was converted into its benzhydryl ester (see below) without further purification.

(3S,7aR)-7-Bromo-6-(3-chlorophenoxy)-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid (3c). A pale yellow oil (611 mg, 1.46 mmol, 76%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.66 (s, 6H, α-C$\mathbf{H_3}$, β-C$\mathbf{H_3}$), 4.62 (s, 1H, **H**-3), 5.96 (s, 1H, **H**-8), 6.93 (ddd, 1H, J = 7.92, 2.47, 0.99 Hz, **H**ArCl), 7.05 (app t, 1H, J = 2.24 Hz, **H**ArCl), 7.11 (ddd, 1H, J = 7.92, 2.47, 0.99 Hz, **H**ArCl), 7.25 (t, 1H, J = 7.92 Hz, **H**ArCl). This material was converted into its benzhydryl ester (see below) without further purification.

Benzyhydryl ester formation–general procedure. To the required pyrrolothiazole acid **3a-3c** in dichloromethane at room temperature was added dropwise a solution of diphenyldiazomethane (∼0.65*M*) in dichloromethane (prepared by oxidation of benzophenone hydrazone with activated MnO_2) until a pale pink color persisted and the evolution of nitrogen gas was no longer observable (2–3 h). The solution was concentrated by rotary evaporation to yield a yellow solid, which was purified by silica gel column chromatography as indicated below.

(3S,7aR)-7-Bromo-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*] thiazole-3-carboxylic acid benzhydryl ester (4a). Purification using 3:1 dichloromethane/hexane gave **4a** as a pale yellow solid (438 mg, 0.84 mmol, 49%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 3H, α-C$\mathbf{H_3}$), 1.29 (t, J = 7.42 Hz, 3H, C$\mathbf{H_3}CH_2$S), 1.50 (s, 3H, β-C$\mathbf{H_3}$), 3.13 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}$S (diastereotopic)) overlapping with 3.25 (dq, 1H, J = 13.50, 7.72 Hz, $CH_3C\mathbf{H_{2B}}$S (diastereotopic)), 4.79 (s, 1H, **H**-3), 5.89 (s, 1H, **H**-8), 6.98 (s, 1H, C**H**$(Ph)_2$), 7.26–7.39 (m, 10H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ15.62 (**C**H_3CH_2S), 25.03 (α-**C**H_3), 26.11 (CH_3**C**H_2S), 32.13 (β-**C**H_3), 60.70, 68.76, 72.26 (**C**-2, **C**-3, **C**-8), 78.48 (**C**$H(Ph)_2$), 126.92, 127.73, 128.12, 128.39, 128.55, 128.59, 132.58, 138.97, 139.05, 139.09 (Ar**C**, **C**-6, **C**-7), 167.49, 169.53 (2× **C**=O); ESI-HRMS for $C_{24}H_{24}NO_3Br$: [M + Na]$^+$ calcd: 540.0283, found: 540.0291 and 542.0333.

(3S,7aR)-7-Bromo-6-isopropylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo [2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (4b). Purification using 3:1 dichloromethane/hexane gave **4b** as a yellowish solid (488 mg, 0.92 mmol, 33%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (s, 3H, α-C$\mathbf{H_3}$) overlapping with 1.28 (d, 3H, J = 6.93 Hz, $(C\mathbf{H_{3A}})_2$CHS (diastereotopic)) overlapping with 1.30 (d, 3H, J = 6.93 Hz, $(C\mathbf{H_{3B}})_2$CHS (diastereotopic)), 1.49 (s, 3H, β-C$\mathbf{H_3}$), 4.13 (sept, 1H, J = 6.80 Hz, $(CH_3)_2C\mathbf{H}$S), 4.81 (s, 1H, **H**-3), 5.92 (s, 1H, **H**-8), 6.98 (s, 1H, C**H**$(Ph)_2$), 7.30–7.37 (m, 10H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 23.19, 24.27 ($(CH_3)_2$CHS (diastereotopic methyl groups)), 26.10 (α-**C**H_3), 32.22 ($(CH_3)_2$**C**H), 35.63 (β-**C**H_3), 60.71, 68.77, 72.32 (**C**-2, **C**-3, **C**-8), 78.47 (**C**H-Ar_2), 126.92, 127.69, 128.11, 128.38, 128.54, 128.58, 132.90, 139.05, 139.09, 140.92 (Ar**C**, **C**-6, **C**-7), 167.48, 169.67 (2× **C**=O); ESI-HRMS for $C_{25}H_{26}NO_3S_2Br$: [M + H]$^+$ calcd: 532.0616, found: 532.0595 and 534.0617.

(3S,7aR)-7-Bromo-6-(3-chlorophenoxy)-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (4c). Purification using 1:1 dichloromethane/hexane gave **4c** as a pale yellow solid (535 mg, 0.92 mmol, 63%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 3H, α-C$\mathbf{H_3}$), 1.53 (s, 3H, β-C$\mathbf{H_3}$), 4.76 (s, 1H, **H**-3), 5.95 (s, 1H, **H**-8), 6.92 (dd, 1H, J = 8.16, 2.47 Hz, **H**ArCl), 6.98 (s, 1H, C**H**Ph_2), 7.05 (app t, 1H, J = 2.23 Hz, **H**ArCl), 7.11 (dd, 1H, J = 8.16, 2.23 Hz, **H**ArCl), 7.25 (t, 1H, J = 8.16 Hz, **H**ArCl), 7.29–7.38 (m, 10H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 26.23 (α-**C**H_3), 32.06 (β-**C**H_3), 60.80, 68.39, 69.10 (**C**-2, **C**-3, **C**-8), 78.68 (**C**HPh_2), 115.32, 117.79, 122.42, 124.49, 126.94, 127.77, 128.19, 128.47, 128.60, 128.65, 130.38, 135.06, 139.97, 139.03, 144.31, 155.33 (Ar**C**, **C**-6, **C**-7), 165.92, 167.33 (2× **C**=O); ESI-HRMS for $C_{28}H_{23}NO_4SClBr$: [M + Na]$^+$ calcd: 606.0117, found: 606.0129 and 608.0104.

Reductive Amination–General Procedure. (R)-(4-Bromo-3-ethylsulfanyl-2-oxo-2,5-dihydropyrrol-1-yl)-phenylacetic acid methyl ester (7a). To a stirred solution of **2a** (412 mg, 1.72 mmol) and phenyl glycine methyl ester hydrochloride (416 mg, 2.06 mmol) in chloroform (5 mL) was gradually added sodium triacetoxyborohydride (547 mg, 2.58 mmol). The solution color lightened during addition from dark to pale yellow. After stirring for 10 min at room temperature the mixture was diluted with chloroform (10 mL) and washed twice with DIW (10 mL). The organic extracts were combined, dried, filtered, and concentrated by rotary evaporation to leave a yellow solid. Purification by silica gel column chromatography using 1:1 hexane/ethylacetate gave **7a** as a pale yellow glassy solid (238 mg, 0.643 mmol, 35%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (t, J = 7.42 Hz, 3H, (C$\mathbf{H_3}CH_2$S), 3.15 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}$S(diastereotopic)) overlapping with 3.21 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2B}}$S(diastereotopic)), 3.58 (d, J = 18.80 Hz, 1H, **H**-5_A), 3.79 (s, 3H, OC$\mathbf{H_3}$), 4.44 (d, J = 18.80 Hz, 1H, **H**-5_B), 6.06 (s, 1H, C**H**C(O)), 7.23–7.44 (m, 5H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.47 (**C**H_3CH_2S), 25.22 (CH_3**C**H_2S), 52.58, 54.08, 57.82 (**C**-5, O**C**H_3, N**C**H(Ph)), 128.47, 129.01, 129.23, 131.56, 133.57, 134.63, 140.52 (Ar**C**, **C**-3, **C**-4), 167.13, 170.47 (2× **C**=O); ESI-HRMS for $C_{15}H_{16}BrNO_3S$: [M + H]$^+$ calcd: 370.0113, found: 370.0103 and 372.0041.

(R)-(3-Ethylsulfanyl-2-oxo-2,5-dihydropyrrol-1-yl)-phenylacetic acid methyl ester (desbromo structure). An off-white solid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.42 Hz, C$\mathbf{H_3}CH_2$S), 2.89 (q, 2H, J = 7.42 Hz, $CH_3C\mathbf{H_2}$S (diastereotopic methylene hydrogens with coincident chemical shifts), 3.51 (dd, 1H, J = 19.55, 2.47 Hz, **H**-5_A), 3.77 (s, 3H, OC$\mathbf{H_3}$), 4.35 (dd, 1H, J = 19.55, 2.47 Hz, **H**-5_B), 6.12 (s, 1H, C**H**C(O)), 6.51 (t, 1H, J = 2.47, **H**-4), 7.20–7.39 (m, 5H, Ar**H**); ESI-HRMS for $C_{15}H_{17}NO_3S$: [M]$^+$ calcd: 291.0929, found: 291.0927.

4-Bromo-3-(3-nitrophenoxy)-1-phenethyl-1,5-dihydropyrrol-2-one (7b). Prepared as for **7a** but using **2d** with 2-(3,4-dimethoxyphenyl)ethylamine hydrochloride, in dichloroethane with a 12 h reaction time; purification by silica gel column chromatography using ethylacetate/hexane 1:1 then 3:1 gave **7b** as a yellow oil (239 mg, 0.516 mmol, 30%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.89 (t, 2H, J = 7.17 Hz, $NCH_2C\mathbf{H_2}$), 3.71 (t, 2H, J = 7.17 Hz, $NC\mathbf{H_2}CH_2$), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H,

OCH_3), 3.91 (s, 2H, C**H**$_2$NC(O)), 6.73–6.86 (m, 3H, **H**Ar(-$OCH_3)_2$), 7.305 (ddd, 1H, J = 8.16, 2.47, 0.99 Hz, **H**ArNO_2), 7.50 (t, 1H, J = 8.16 Hz, **H**ArNO_2), 7.80 (app t, 1H, J = 2.47 Hz, **H**ArNO_2), 7.98 (ddd, 1H, J = 8.16, 2.23, 0.99 Hz, **H**ArNO_2); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 34.12 (NCH_2**C**H_2), 44.56, 52.98 (N**C**H_2CH_2, **C**H_2NC(O); 55.90 (2 × O**C**H_3), 111.43, 111.64, 117.71, 114.89, 118.58, 120.61, 123.21, 130.20, 130.38, 144.72, 147.92, 148.95, 149.14, 155.67 (Ar**C**, **C**-3, **C**-4), 162.97 (**C**=O); ESI-HRMS for $C_{20}H_{19}N_2O_6Br$: [M + H]$^+$ calcd: 463.0505, found: 463.0490 and 465.0471.

Suzuki-Miyaura Coupling–general Procedure. To a solution of the required benzhydryl ester **4a–4c**, or the muco derivatives **7a** and **7b**, (0.498 mmol) in degassed 1:1 toluene/water (4 mL each) was added the required boronic acid (0.747 mmol), cesium fluoride (151 mg, 0.996 mmol), $PdCl_2(PPh_3)_2$ (8.74 mg, 0.01245 mmol), and benzyldimethylhexadecyl ammonium chloride (4.93 mg, 0.01245 mmol). The mixture was heated to reflux under N_2 for 2–48 h during which time the color changed from yellow-brown to either pink or brown; reaction progress was monitored by ^{1}H NMR spectroscopy. The mixture was allowed to cool to room temperature, quenched with 0.5*M* HCl (50 mL) and diluted with toluene (20 mL) and separated. The aqueous layer was re-extracted with toluene (20 mL), the organic extracts were combined, washed with DIW (30 mL), dried, filtered, and concentrated by rotary evaporation to yield a red orange gel, which was purified by silica gel column chromatography as indicated below.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-phenyl-2,3,5,7a-tetrahydro pyrrolo [2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5a). The reaction time is 2.5 h; purification using 3:1 dichloromethane/hexane gave **5a** as a pale yellow solid (121 mg, 0.235 mmol, 47%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S), 1.32 (s, 3H, α-C**H**$_3$), 1.54 (s, 3H, β-C**H**$_3$), 3.12 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)), 3.28 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 4.83 (s, 1H, **H**-3), 6.30 (s, 1H, **H**-8), 7.01 (s, 1H, C**H**(Ar)$_2$), 7.25–7.48 (m, 13H, Ar**H**), 7.70–7.80 (m, 2H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.39 (**C**H_3CH_2S), 26.11, 26.44 (α-**C**H_3, CH_3**C**H_2S), 31.82 (β-**C**H_3), 61.12, 67.94, 68.81 (**C**-2, **C**-3, **C**-8), 78.40 (**C**HPh$_2$), 126.95, 127.82, 128.09, 128.20, 128.38, 128.58, 128.60, 128.65, 130.02, 131.80, 139.23, 139.30, 154.19 (Ar**C**, **C**-6, **C**-7), 168.02, 172.07 (2 × **C**=O); ESI-HRMS for $C_{30}H_{29}NO_3S_2$: [M + H]$^{+1}$ calcd: 516.1667, found: 516.1660.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-((E)-3-phenylpropenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5b). Three h reaction time; purification using 1:1 hexane/ethyl acetate gave **5b** as a pale yellow solid (144 mg, 0.259 mmol, 65%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S) overlapping with 1.26 (s, 3H, α-C**H**$_3$), 1.50 (s, 3H, β-C**H**$_3$), 3.00 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)) overlapping with 3.11 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 3.58 (d, 2H, J = 6.93 Hz, ArC**H**$_2$CH = CH), 4.70 (s, 1H, **H**-3), 5.89 (s, 1H, **H**-8), 6.14 (dt, 1H, J = 16.08, 6.93 Hz, $ArCH_2$C**H**=CH—), 6.69 (d, 1H, J = 15.83 Hz, $ArCH_2$CH=C**H**—), 6.96 (s, 1H, C**H**(Ph)$_2$), 7.16–7.36 (m, 15H, Ar**H**); ESI-HRMS for $C_{33}H_{33}NO_3S_2$: [M + H]$^{+1}$ calcd: 556.1980, found: 556.1969.

(3S,7aR)-6-Isopropylsulfanyl-2,2-dimethyl-5-oxo-7-((Z)-3-phenylpropenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5c). The reaction time is 2.5 h; purification using 3:1 dichloromethane/hexane gave **5c** as a yellow solid (317 mg, 0.556 mmol, 60%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (d, 3H, J = 6.80 Hz, (C**H**$_{3A}$)$_2$CHS(diastereotopic) overlapping with 1.25 (s, 3H, α-C**H**$_3$) overlapping with 1.27 (d, 3H, J = 6.80 Hz (C**H**$_{3B}$)$_2$CHS (diastereotopic)), 1.49 (s, 3H, β-C**H**$_3$), 3.57 (d, 2H, J = 6.93 Hz, ArC**H**$_2$CH=CH), 3.88 (sept, 1H, J = 6.68 Hz, $(CH_3)_2$C**H**S), 4.73 (s, 1H, **H**-3), 5.93 (s, 1H, **H**-8), 6.15 (dt, 1H, J = 15.83, 7.17 Hz, $ArCH_2$C**H**=CH), 6.72 (d, 1H, J = 15.83 Hz, $ArCH_2$CH=C**H**), 6.96 (s, 1H, C**H**(Ph)$_2$), 7.15–7.38 (m, 15H, Ar**H**); ESI-HRMS for $C_{34}H_{35}NO_3S_2$: [M + H]$^{+1}$ calcd: 570.2137, found: 570.2133.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-7-(4-nitrophenyl)-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5d). Twenty-four h reaction time; purification using 3:1 dichloromethane/hexane gave **5d** as a yellow glassy solid (125 mg, 0.223 mmol, 40%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S), 1.33 (s, 3H, α-C**H**$_3$), 1.56 (s, 3H, β-C**H**$_3$), 3.23 (dq, 1H, J = 13.50, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)), 3.41 (dq, 1H, J = 13.50, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 4.81 (s, 1H, **H**-3), 6.30 (s, 1H, **H**-8), 7.02 (s, 1H, C**H**(Ph)$_2$), 7.28–7.39 (m, 10H, Ar**H**), 7.86 (d, 2H, J = 8.91 Hz, **H**ArNO_2), 8.29 (d, 2H, J = 8.91 Hz, **H**ArNO_2); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.54 (**C**H_3CH_2S), 26.03, 26.42 (CH_3**C**H_2S, α-**C**H_3), 31.73 (β-**C**H_3), 61.64, 67.90, 68.47 (**C**-2, **C**-3, **C**-8), 78.58 (**C**H(Ph)$_2$), 123.82, 126.90, 127.81, 128.16, 128.47, 128.59, 128.62, 128.84, 131.56, 137.78, 139.06, 139.11, 147.73, 149.86 (Ar**C**, **C**-6, **C**-7), 167.72, 170.83 (2 × **C**=O); ESI-HRMS for $C_{30}H_{28}N_2O_5S_2$: [M − H]$^-$ calcd: 559.1361, found: 559.1378.

(3S,7aR)-7-(4-Dimethylaminophenyl)-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a-tetrahydro-pyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5e). Two h reaction time; purification using 3:1 hexane/ethyl acetate gave **5e** as an orange-red glassy solid (312 mg, 0.559 mmol, 67%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.42 Hz, C**H**$_3$CH$_2$S), 1.31 (s, 3H, α-C**H**$_3$), 1.51 (s, 3H, β-C**H**$_3$), 3.03 (s, 6H, N(C**H**$_3$)$_2$ overlapping with 3.04 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2A}$S (diastereotopic)), 3.17 (dq, 1H, J = 13.5, 7.42 Hz, CH_3C**H**$_{2B}$S (diastereotopic)), 4.83 (s, 1H, **H**-3), 6.28 (s, 1H, **H**-8), 6.70 (d, 2H, J = 9.15 Hz, $N(CH_3)_2$Ar**H**), 7.00 (s, 1H, C**H**(Ph)$_2$), 7.29–7.42 (m, 10H, Ar**H**), 7.81 (d, 2H, J = 9.15 Hz, $N(CH_3)_2$Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.25 (**C**H_3CH_2S), 26.41, 26.64 (CH_3**C**H_2S, α-**C**H_3), 32.08 (β-**C**H_3), 39.99 (N(**C**H_3)$_2$, 60.57, 67.89, 68.89 (**C**-2, **C**-3, **C**-8), 78.20 (**C**H(Ph)$_2$), 111.32 (**C**-7), 119.26, 120.06, 126.94, 127.76, 127.92, 128.39, 128.52, 128.55, 129.90, 139.30, 139.37, 151.31, 156.43 (Ar**C**, **C**-6, **C**-7), 168.25, 173.22 (2× **C**=O); ESI-HRMS for $C_{32}H_{34}N_2O_3S_2$: [M − H]$^-$ calcd: 557.1933, found: 557.1906.

(3S,7aR)-6-(3-Chlorophenoxy)-7-furan-3-yl-2,2-dimethyl-5-oxo-2,3,5,7a-tetra hydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid benzhydryl ester (5f). Three h reaction time; purification using 3:1 hexane/ethylacetate gave **5f** as a yellow oil (116 mg, 0.199 mmol, 40%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.34 (s, 3H, α-C**H**$_3$), 1.58 (s, 3H, β-C**H**$_3$), 4.72 (s, 1H, **H**-3), 6.11 (s, 1H, **H**-8), 6.62 (d, 1H, J = 1.73 Hz, furanyl), 6.93 (ddd, 1H, J = 8.16, 2.47, 0.99 Hz, **H**ArCl), 6.99 (s, 1H, C**H**Ph$_2$), 7.04–7.09 (m, 2H, **H**ArCl), 7.22 (t, 1H, J = 8.16 Hz, **H**ArCl), 7.27–7.40 (m, 10H, Ar**H**), 7.45 (d, 1H, J = 1.73 Hz, furanyl), 7.74 (s, 1H, furanyl); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 26.43 (α-**C**H_3), 31.79 (β-**C**H_3), 61.30, 64.97, 67.44 (**C**-2, **C**-3, **C**-8), 78.52 (**C**H(Ph)$_2$), 108.58, 114.37, 116.84, 123.81, 126.94, 127.80, 128.14, 128.43, 128.58, 128.63, 135.04, 135.17, 138.51, 139.08, 139.17, 156.18 (Ar**C**, **C**-

furanyl, **C**-6, **C**-7), 167.79, 167.83 (2 × **C**=O); ESI-HRMS for $C_{32}H_{26}NO_5SCl$: $[M + Na]^+$ calcd: 594.1118, found: 594.1133.

[4-(1-Benzyl-1*H*-pyrazol-4-yl)-3-ethylsulfanyl-2-oxo-2,5-dihydropyrrol-1-yl]-phenylacetic acid methyl ester (8a). Forty-eight h reaction time using the boronic acid pinacol ester with **7a**; purification using 1:1 hexane/ethylacetate gave **8a** as a brown oil (129 mg, 0.288 mmol, 45%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, J = 7.42 Hz, 3H, C**H$_3$**CH$_2$S), 3.08 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2A}$**S (diastereotopic)) overlapping with 3.16 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2B}$**S (diastereotopic)), 3.74 (d, 1H, J = 18.06 Hz, **H**-5$_A$), 3.79 (s, 3H, OC**H$_3$**), 4.61 (d, J = 18.31 Hz, 1H, **H**-5$_B$), 5.31 (s, 2H, PhC**H$_2$**N), 6.18 (s, 1H, C**H**C(O)), 7.15–7.41 (m, 10H, Ar**H**), 7.86 (s, 1H, C=C**H**—N), 8.05 (s, 1H, C—C**H**=N); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.46 (**C**H$_3$CH$_2$S), 26.29 (CH$_3$**C**H$_2$S), 49.31, 52.41, 56.25, 57.68 (**C**-5, O**C**H$_3$, (Ph)**C**H$_2$N) (**C**HC(O)), 115.62, 120.95 (**C**=**C**), 127.54, 127.75, 128.24, 128.41, 128.68, 128.85, 128.96, 129.09, 129.18, 134.27, 135.71, 138.42, 145.52 (Ar**C**, **C**-3, **C**-4, N=**C**), 170.08, 170.89 (2 × **C**=O); ESI-HRMS for $C_{25}H_{25}N_3O_3S$: $[M - H]^-$ calcd: 448.1695, found: 448.1692.

4-Furan-3-yl-3-(3-nitrophenoxy)-1-phenethyl-1,5-dihydropyrrol-2-one (8b). Three h reaction time using the boronic acid with **7b**; purification using 1:3 hexane/ethylacetate gave **8b** as a pale yellow solid (135 mg, 0.30 mmol, 60%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.92 (t, 2H, J = 7.42 Hz, NCH$_2$C**H$_2$**), 3.75 (t, 2H, J = 7.42 Hz, NC**H$_2$**CH$_2$), 3.85 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 3.90 (s, 3H, NC**H$_3$**), 4.08 (s, 2H, C**H$_2$**NC(O)), 6.56 (d, 1H, J = 1.98 Hz, furanyl), 6.76–6.85 (m, 3H, **H**Ar(OCH$_3$)$_2$), 7.315 (ddd, 1H, J = 8.41, 2.27, 0.74 Hz, **H**ArNO$_2$), 7.44 (d, 1H, J = 1.98 Hz, furanyl), 7.49 (t, 1H, J = 8.41 Hz, **H**ArNO$_2$), 7.70 (s, 1H, furanyl), 7.81 (app t, 1H, J = 2.47 Hz, **H**ArNO$_2$), 7.95 (ddd, 1H, J = 8.41, 2.23, 0.74 Hz, **H**ArNO$_2$); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 34.23 (NCH$_2$**C**H$_2$), 44.48, 48.59 (N**C**H$_2$CH$_2$, **C**H$_2$NC(O); 55.88 (2 x O**C**H$_3$), 108.13, 111.07, 111.34, 111.69, 116.28, 118.06, 120.62, 122.60, 127.83, 130.25, 130.72, 139.28, 141.49, 144.18, 147.77, 149.05, 156.39 (Ar**C**, **C**-furanyl, **C**-3, **C**-4), 164.87 (**C**=O); ESI-HRMS for $C_{24}H_{22}N_2O_7$: $[M + H]^+$ calcd: 451.1505, found: 451.1501.

4-(1-Methyl-1*H*-pyrazol-4-yl)-3-(3-nitrophenoxy)-1-phenethyl-1,5-dihydropyrrol-2-one (8c). Twenty-four h reaction time using the boronic acid pinacol ester with **7b**; purification using ethylacetate then methanol gave **8c** as a pale yellow oil (173 mg, 0.373 mmol, 75%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.92 (t, 2H, J = 7.17 Hz, NCH$_2$C**H$_2$**), 3.74 (t, 2H, J = 7.17 Hz, NC**H$_2$**CH$_2$), 3.85 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 3.90 (s, 3H, NCH$_3$), 4.09 (s, 2H, C**H$_2$**NC(O)), 6.76–6.84 (m, 3H, **H**Ar(OCH$_3$)$_2$), 7.31 (ddd, 1H, J = 8.41, 2.27, 0.74 Hz, **H**ArNO$_2$), 7.49 (t, 1H, J = 8.41 Hz, **H**ArNO$_2$), 7.59 (s, 1H, pyrazole), 7.60 (s, 1H, pyrazole), 7.81 (app t, 1H, J = 2.47 Hz, **H**ArNO$_2$), 7.95 ((ddd, 1H, J = 8.16, 2.23, 0.74 Hz, **H**ArNO$_2$); ESI-HRMS for $C_{24}H_{24}N_4O_6$: $[M + H]^+$ calcd: 465.1774, found: 465.1785.

Benzhydryl removal–general procedure. The required benzhydryl ester (0.6748 mmol) was dissolved in dichloromethane (15 mL) and cooled under nitrogen to −84°C (liquid N_2/ethylacetate slurry). A solution of aluminum trichloride (222 mg, 1.664 mmol) in nitroethane (1.39 mL) was added in one portion to the cooled pyrrolothiazole solution at which point the solution changed color from pale to intense yellow. The reaction mixture was allowed to stir at −84°C for 1 h at which point ethyl acetate (70 mL) and 5% sodium carbonate (45 mL) were added successively while maintaining the temperature at −84°C. The reaction mixture was allowed to warm to room temperature at which point the aqueous layer was separated and filtered through celite before being extracted with ethyl acetate (20 mL). The aqueous portion was layered with ethyl acetate (30 mL) and the pH lowered to 2.2 using 1*M* HCl. The organic extract was separated and the aqueous portion extracted with a further portion of ethyl acetate (30 mL). The organic extracts were combined, dried, filtered, and concentrated by reduced pressure to yield a solid, which was further dried under vacuum.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-phenyl-2,3,5,7a-tetrahydro pyrrolo[2,1-*b*] thiazole-3-carboxylic acid (6a). A pale yellow solid (166 mg, 0.475 mmol, 70%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.42 Hz, C**H$_3$**CH$_2$S), 1.65 (s, 3H, α-CH$_3$), 1.70 (s, 3H, β-CH$_3$), 3.11 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2A}$**S (diastereotopic)) overlapping with 3.24 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2B}$**S (diastereotopic)), 4.66 (s, 1H, **H**-3), 6.27 (s, 1H, **H**-8), 7.42–7.47 ((m, 3H, Ar**H**)), 7.73–7.76 (m, 2H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.30 (**C**H$_3$CH$_2$S), 26.28, 26.80 (α-**C**H$_3$, CH$_3$**C**H$_2$S), 30.79 (β-**C**H$_3$), 60.73, 68.00, 68.82 (**C**-2, **C**-3, **C**-8), 127.03, 128.24, 128.66, 130 0.18, 131.53 (Ar**C**, **C**-7) 154.31 (**C**-6), 172.36, 172.76 (2 × **C**=O); ESI-HRMS for $C_{17}H_{19}NO_3S_2$: $[M - H]^-$ calcd: 348.0728, found: 348.0733.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-5-oxo-7-((Z)-3-phenyl-propenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6b). A pale yellow solid (27.2 mg, 0.0698 mmol, 27%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.42 Hz, C**H$_3$**CH$_2$S), 1.60 (s, 3H, α-C**H$_3$**), 1.62 (s, 3H, β-C**H$_3$**), 2.99 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2A}$**S (diastereotopic)) overlapping with 3.07 (dq, 1H, J = 13.50, 7.42 Hz, CH$_3$C**H$_{2B}$**S (diastereotopic), 3.58 (d, 2H, J = 6.93 Hz, PhC**H$_2$**CH=CH—), 4.52 (s, 1H, **H**-3), 5.85 (s, 1H, **H**-8), 6.21 (dt, 1H, J = 16.08, 6.93 Hz, PhCH$_2$C**H**=CH), 6.70 (d, 1H, J = 16.08 Hz, PhCH$_2$CH=C**H**), 7.18–7.44 (m, 5H, Ar**H**); ESI-HRMS for $C_{20}H_{23}NO_3S_2$: $[M - H]^-$ calcd: 388.1041, found: 388.1039.

(3S,7aR)-6-Isopropylsulfanyl-2,2-dimethyl-5-oxo-7-((Z)-3-phenyl-propenyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6c). A pale yellow solid (44 mg, 0.109 mmol, 19%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.24 (d, 3H, J = 6.68 Hz, (C**H$_{3A}$**)$_2$CHS (diastereotopic)) overlapping with 1.26 (d, 3H, J = 6.68Hz, (C**H$_{3B}$**)$_2$CHS (diastereotopic)), 1.59 (s, 3H, α-C**H$_3$**), 1.62 (s, 3H, β-C**H$_3$**), 3.58 (d, 2H, J = 6.93 Hz, Ph-C**H$_2$**CH=CH), 3.82 (sept, 1H, J = 6.68 Hz, (CH$_3$)$_2$C**H**S), 4.53 (s, 1H, **H**-3), 5.87 (s, 1H, **H**-8), 6.22 (dt, 1H, J = 7.17, 16.08 Hz, Ph-CH$_2$C**H**=CH), 6.72 (d, 1H, J = 15.83 Hz, Ph-CH$_2$CH=C**H**), 7.17–7.36 (m, 5H, Ar**H**); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 23.21, 24.06, (**C**H$_3$)$_2$CHS (diastereotopic methyl groups)), 26.64, 30.81, 36.77 (α-**C**H$_3$, β-**C**H$_3$, (CH$_3$)$_2$**C**HS), 39.70 (Ar**C**H$_2$C=C), 60.51, 66.74, 67.52 (**C**-2, **C**-3, **C**-8), 123.03 (ArCH$_2$**C**H=CH), 126.44, 126.61, 128.58, 128.68, 138.35, 139.20 (Ar**C**, **C**-7, ArCH$_2$CH=**C**H), 157.64 (**C**-6), 171.97, 173.18 (2 × **C**=O); ESI-HRMS for $C_{21}H_{25}NO_3S_2$: $[M - H]^-$ calcd: 402.1198, found: 402.1190.

(3S,7aR)-6-Ethylsulfanyl-2,2-dimethyl-7-(4-nitrophenyl)-5oxo-2,3,5,7a-tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6d). An orange solid (48.7 mg, 0.123 mmol, 55%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.42 Hz, C**H$_3$**CH$_2$S),

1.66 (s, 3H, α-CH_3), 1.71 (s, 3H, β-CH_3), 3.24 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}S$ (diastereotopic)), 3.38 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2B}}S$ (diastereotopic)), 4.67 (s, 1H, **H**-3), 6.27 (s, 1H, **H**-8), 7.89 (d, 2H, J = 9.15 Hz, **H**ArNO_2), 8.31 (d, 2H, J = 9.15 Hz, **H**ArNO_2); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.51 ($\mathbf{C}H_3CH_2S$), 26.14, 26.73 (α-$\mathbf{C}H_3$, $CH_3\mathbf{C}H_2S$), 30.86 (β-$\mathbf{C}H_3$), 61.13, 67.92, 68.46 (**C**-2, **C**-3, **C**-8), 123.86, 128.91, 131.71, 137.57, 147.85, 149.79 (Ar**C**, **C**-6, **C**-7), 171.43, 171.88 (2 × **C**=O); ESI-HRMS for $C_{17}H_{18}N_2O_5S_2$: $[M - H]^-$ calcd: 393.0579, found: 393.0591.

(3S,7aR)-7-(4-Dimethylaminophenyl)-6-ethylsulfanyl-2,2-dimethyl-5-oxo-2,3,5,7a -tetrahydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6e). An orange-red solid (122 mg, 0.311 mmol, 65%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.42 Hz, $C\mathbf{H_3}CH_2S$), 1.64 (s, 3H, α-$C\mathbf{H_3}$), 1.72 (s, 3H, β-$C\mathbf{H_3}$), 3.05 (s, 6H, $N(C\mathbf{H_3})_2$ overlapping with 3.04 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2A}}S$) overlapping with 3.14 (dq, 1H, J = 13.50, 7.42 Hz, $CH_3C\mathbf{H_{2B}}S$)), 4.57 (s, 1H, **H**-3), 6.20 (s, 1H, **H**-8), 6.72 (d, 2H, J = 8.91 Hz, $N(CH_3)_2Ar\mathbf{H}$), 7.86 (d, 2H, J = 8.91 Hz, $N(CH_3)_2Ar\mathbf{H}$); ^{13}C NMR (67.93 MHz, $CDCl_3$, DEPT) δ 15.21 ($\mathbf{C}H_3CH_2S$), 26.61, 26.86 (α-$\mathbf{C}H_3$, $CH_3\mathbf{C}H_2S$), 30.19 (β-$\mathbf{C}H_3$), 40.00 ($N(\mathbf{C}H_3)_2$, 59.89, 68.09, 68.58 (**C**-2, **C**-3, **C**-8), 111.34, 118.95, 120.02, 130.10, 151.51, 156.76 (Ar**C**, **C**-6, **C**-7), 170.82, 174.84 (2 × **C**=O); ESI-HRMS for $C_{19}H_{24}N_2O_3S_2$: $[M - H]^-$ calcd: 391.1150, found: 391.1135.

(3S,7aR)-6-(3-Chlorophenoxy)-7-furan-3-yl-2,2-dimethyl-5-oxo-2,3,5,7a-tetra hydropyrrolo[2,1-*b*]thiazole-3-carboxylic acid (6f). A pale yellow solid (64 mg, 0.154 mmol, 45%); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.66 (s, 3H, α-$C\mathbf{H_3}$), 1.70 (s, 3H, β-$C\mathbf{H_3}$), 4.56 (s, 1H, **H**-3), 6.08 (s, 1H, **H**-8), 6.65 (d, 1H, J = 1.98 Hz, furanyl), 6.94 (ddd, 1H, J = 8.16, 2.23, 0.74, **H**ArCl), 7.06–7.11 (m, 2H, **H**ArCl), 7.24 (t, 1H, J = 8.16 Hz, **H**ArCl), 7.48 (d, J = 1.98 Hz, furanyl), 7.78 (s, 1H, furanyl); ESI-HRMS for $C_{19}H_{16}NO_5SCl$: $[M - H]^-$ calcd: 404.0359, found: 404.0376.

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