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An annulation method for the synthesis of alkyl-substituted 6-carbomethoxy-2-pyridones

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Dedicated to Professor Larry E. Overman, an inspiring mentor

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ABSTRACT

A protocol for the synthesis of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones was devised. Key steps include a Mannich reaction, acylation of a tosylamine, and a $PPh_3/TiCl_4$-promoted intramolecular Reformatsky-type reaction with a thioester as the electrophile. The latter process typically afforded a vinylogous thiocarbamate via elimination of water rather than the Dieckmann-type product which would have resulted from elimination of the thiol. However, the Dieckmann-type ketone product was obtained in one instance. Subsequent elimination of the tosyl group and desulfurization completed the pyridone synthesis.

1. Introduction

The 2-pyridone ring system is a component of several architecturally interesting biologically active natural products.[1] As a result, numerous annulation methods have been designed for its construction.[2,3] In this regard, we were attracted to the structure of lyconadin A (**1**, Fig. 1), a *Lycopodium* alkaloid with a unique pentacyclic skeleton that contains a 2-pyridone moiety. Lyconadin A was isolated by Kobayashi and co-workers from the club moss *Lycopodium complanatum*, and it was demonstrated to possess modest anticancer activity.[4] Recently, the Smith[5] and Sarpong[6] groups reported total syntheses of (+)-**1** and (±)-**1**, respectively.

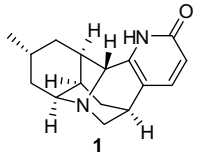

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Figure 1. Lyconadin A (**1**).

We have developed a cascade reaction initiated by a 7-*exo* acyl radical cyclization which constructs two carbocyclic rings and two stereocenters in a highly selective fashion.[7] This method shows promise for preparing the bicyclo[5.4.0]undecane ring system imbedded within the framework of **1**. Accordingly, we turned our attention to designing a total synthesis of **1** that incorporates the radical cascade process. To streamline the route, we desired to install the pyridone moiety at an early stage. Thus, we required a method for preparing a pyridone system with an alkyl group at C-5 and a carboxy group at C-6. Herein, we detail our efforts to synthesize such a compound, which have culminated in the discovery of a new protocol for pyridone annulation.

2. Results and discussion

In 1990, Kozikowski and co-workers developed a 2-pyridone synthesis which entailed a three-component coupling of ammonia, methyl propiolate, and a ketone (Scheme 1).[8] The simplicity of the procedure and the fact that it produces 5,6-disubstituted 2-pyridones were appealing. Unfortunately, its utility is restricted to symmetrical ketones and ketones which can only form a single enamine.[9] It occurred to us that α-keto esters, which fit in the latter category, would provide 6-carboxy-substituted 2-pyridones if subjected to the Kozikowski pyridone annulation.

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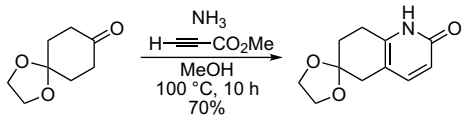
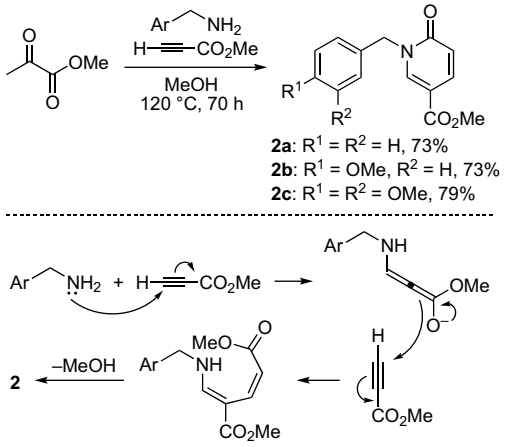


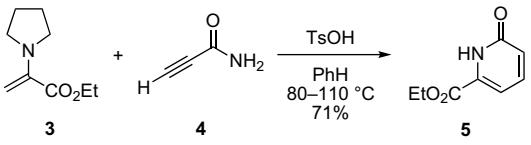
Scheme 1. Kozikowski pyridone annulation.

To probe the viability of this idea, we employed methyl pyruvate as the ketone component in this annulation. Reactions with ammonia failed to give any pyridone products, so we next examined benzylamines as ammonia surrogates. In these cases, we were able to obtain pyridones **2a–c** (Scheme 2). However, inspection of the NMR spectra revealed that the carbomethoxy groups were located on C-5 rather than C-6 in these adducts. A plausible mechanism for the formation of **2a–c** is depicted in Scheme 2 and involves Michael addition of the amine to methyl propiolate followed by a second Michael addition of the intermediate allenolate to another molecule of methyl propiolate. Lactamization then provides the 2-pyridone. Apparently, the α-keto ester was not participating in the annulation. This supposition was tested by conducting the reaction in ethanol with ethyl pyruvate as the α-keto ester. As expected, pyridone **2a** bearing a carbomethoxy group was obtained, and none of the corresponding ethyl ester was observed.



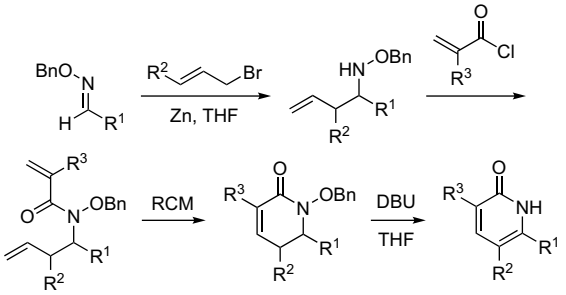
Scheme 2. Attempted Kozikowski pyridone annulation with methyl pyruvate. Yields are based on consumed methyl propiolate.

Since α-keto esters were unreactive in the Kozikowski pyridone annulation, we decided to employ a preformed enamine derived from an α-keto ester instead. After some experimentation, we found that annulation of pyrrolidine enamine **3** and propiolamide (**4**) proceeded in the presence of toluenesulfonic acid, affording 2-pyridone **5** (Scheme 3). However, the reaction did not occur with homologues of enamine **3** that would lead to C-5 substituted pyridones. Apparently, the increased steric hindrance of these substrates prevented the reaction. Thus, the modified Kozikowski pyridone annulation was unsuitable for construction of 5-alkyl-6-carboxypyridones.



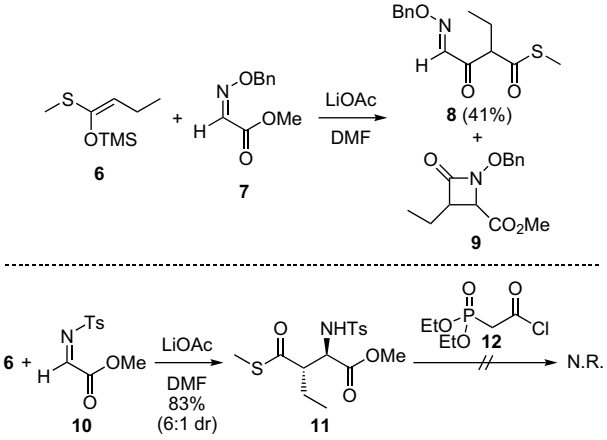
Scheme 3. Modified Kozikowski pyridone annulation.

At this point, we became aware of a novel pyridone annulation strategy developed by Donohoe and co-workers.[10] This process is summarized in Scheme 4 and uses ring-closing metathesis to form a dihydropyridone. Subsequent elimination generates the pyridone ring. We were intrigued by this approach, as it was demonstrated to provide a wide variety of substituted pyridones including 5-alkyl-6-carboxypyridones. However, ring-closing metathesis would not be a viable cyclization method in our case, as the substrate required for the total synthesis of lyconadin A would possess additional double bonds appended to the C-5 alkyl group (i.e., R^2 position in Scheme 4) for use in the key radical cascade reaction.[7] Therefore, we resolved to develop a pyridone annulation method based on the Donohoe strategy that would employ a different reaction in the cyclization step.



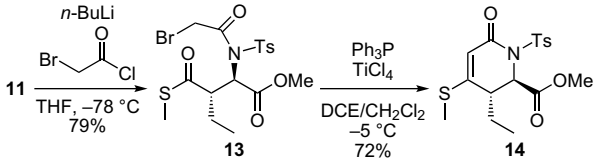
Scheme 4. Donohoe pyridone annulation.

We reasoned that an intramolecular Horner–Wadsworth–Emmons reaction could be substituted for the ring-closing metathesis step. We envisioned employing a thioester as an aldehyde surrogate, so we attempted the Mannich reaction of silyl ketene thioacetal **6** and oxime ether **7** (Scheme 5). Lewis acid promoted Mannich reactions only returned starting material, and a lithium acetate-catalyzed protocol[11] delivered Claisen adduct **8** as the major product in modest yield. Additionally, β-lactam **9** was identified as a minor product of this reaction. Fortunately, when tosylimine **10** was substituted for oxime ether **7**, Mannich adduct **11** was obtained in good yield as a ca. 6:1 mixture of diastereomers. The major isomer was assumed to possess the *anti* configuration in accordance with the acyclic transition state proposed by Mukaiyama and co-workers for the Mannich reaction.[11] Although the isomers could be separated, in practice the mixture was carried forward since both stereocenters would be destroyed later in the synthesis. Unfortunately, we were unable to acylate the nitrogen atom of **11** with acid chloride **12** or related reagents that would allow us to pursue the intramolecular Horner–Wadsworth–Emmons reaction. Apparently, the tosylamine is not nucleophilic enough to react with inductively deactivated acid chlorides such as **12**.



Scheme 5. Attempted synthesis of Horner–Wadsworth–Emmons cyclization substrate.

This setback prompted us to examine an intramolecular Reformatsky reaction as a substitute for the Horner–Wadsworth–Emmons cyclization. To this end, acylation of **11** with bromoacetyl chloride was successful, affording α-bromo tosylamide **13** in good yield (Scheme 6). However, we were unable to selectively reduce the thioester moiety in **13**, as exposure to Raney Ni[12] or Lindlar catalyst/Et_3SiH[13] led to preferential reduction of the bromide. Similar results were obtained with the chlorinated analogue of **13**.

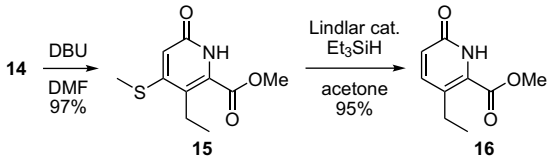


Scheme 6. Intramolecular Reformatsky-type condensation.

To the best of our knowledge, Reformatsky reactions utilizing thioesters as acyl electrophiles are unknown.[14] However, published examples of Reformatsky reactions with species such as *N*-acyloxazolidinones,[15] *N*-acyl pyrazoles,[16] and lactones[17] encouraged us to directly attempt the cyclization of **13**. SmI_2 is typically employed in intramolecular Reformatsky reactions,[14a,18] but treatment of **13** with this reagent merely resulted in debromination. Then, we discovered the work of Hashimoto and co-workers regarding reductive Claisen-type condensations of α-bromothioesters. These researchers discovered that the combination of PPh_3 and $TiCl_4$ promotes the formation of enolates from α-bromothioesters. These species then undergo both self-condensations and crossed-Claisen-type reactions, affording various types of β-ketothioester adducts.[19] Fortunately, application of the Hashimoto protocol to substrate **13** resulted in facile cyclization. Interestingly, vinylogous thiocarbamate **14** was generated rather than the corresponding Dieckmann-type product. The reaction was quite moisture-sensitive, as debrominated starting material predominated when anhydrous conditions were not employed.

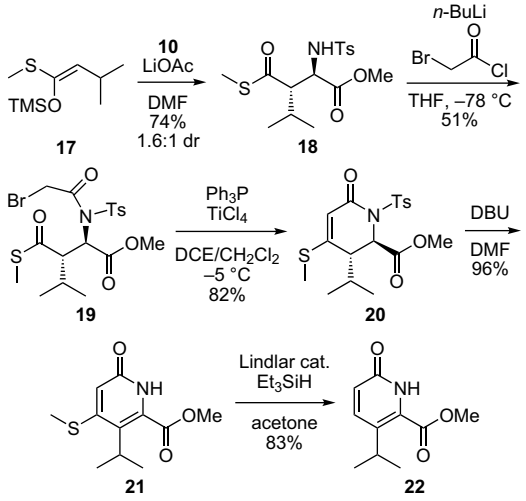
Conversion of compound **14** into the desired 2-pyridone required elimination of the tosyl group and desulfurization. In principle, these two steps could be conducted in either order. In practice, attempts to cleave the vinyl sulfide from dihydropyridone **14** were unsuccessful. The use of $NiCl_2/NaBH_4$[20]and Raney Ni[21] resulted in over-reduction to the saturated derivative, whereas Ni-containing complex reducing agents (NiCRA's and NiCRA-bpy)[22] promoted elimination to the pyridone but not desulfurization. Moreover, the vinyl sulfide moiety of **14** was quite resistant to acidic or basic hydrolysis; instead, the methyl ester group was hydrolyzed preferentially.

Due to the problems encountered in the desulfurization of **14**, we decided to conduct the elimination step first. Thus, treatment of **14** with DBU afforded pyridone **15** in excellent yield (Scheme 7). Although Raney Ni caused over-reduction of **15**, the combination of Lindlar catalyst and Et_3SiH[13] selectively cleaved the vinyl sulfide without reducing the pyridone. We were pleased to find that the desired pyridone **16** could be obtained in 95% yield by this method.



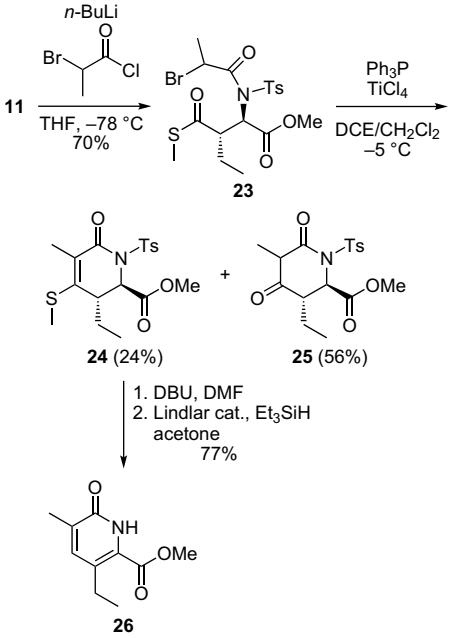
Scheme 7. Synthesis of pyridone **16**.

With a route to the desired 5-alkyl-6-carbomethoxy-2-pyridone nucleus secured, we briefly explored the scope of the annulation method. We found that C-5 alkyl groups larger than ethyl are tolerated, as shown in Scheme 8. Interestingly, the Mannich reaction between silyl ketene thioacetal **17** and tosylimine **10** was less selective (1.6:1 *anti*/*syn*) than the corresponding reaction between **6** and **10** (Scheme 5). As both diastereomers converge to the same pyridone, the lack of selectivity is inconsequential. Acylation of the diastereomeric mixture of tosylamines **18** was sluggish and lower yielding compared to the acylation of **11**; it is likely that optimization of this transformation would lead to an improved result. Fortunately, cyclization, elimination, and desulfurization each proceeded smoothly, affording isopropyl-substituted pyridone **22** in good yield from intermediate **19**.



Scheme 8. Synthesis of isopropyl-substituted pyridone **22**.

Moreover, a 3,5-dialkyl-substituted pyridone can be fashioned via this protocol, as outlined in Scheme 9. Acylation of **11** with 2-bromopropanoyl chloride provided tosylamide **23**. Then, in contrast to previous results, cyclization of **23** afforded a separable 1:2.4 mixture



Scheme 9. Synthesis of dialkyl-substituted pyridone **26**.

of vinyl sulfide **24** and ketone **25** in 80% overall yield. Apparently, the presence of a substituent on the enolate intermediate alters the product distribution of the cyclization. Vinyl sulfide **24** was processed in analogous fashion to sulfides **14** and **20**, delivering 3,5-dialkyl-substituted pyridone **26**. In principle, it should also be possible to convert **25** into **26** via a sequence of ketone reduction, mesylation (or halogenation) of the resultant alcohol, and bis-elimination.

3. Conclusion

Prompted by the structure of the alkaloid lyconadin A, we devised a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones. Our protocol was inspired by the metathesis-based pyridone synthesis of Donohoe and co-workers.[10] The annulation substrate is prepared via a Mannich reaction followed by acylation of the resulting tosylamine. Cyclization is accomplished by means of an intramolecular Reformatsky-type reaction employing a thioester as an acyl electrophile.[19] Typically, vinylogous thiocarbamates (i.e., **14**, **20**, and **24**) were the products of this cyclization, but in one case the Dieckmann-type product (**25**) was also obtained. Elimination of the tosyl group and desulfurization complete the pyridone synthesis. We believe that this new synthetic strategy will have utility in the synthesis of complex molecules, and attempts to apply our method to the total synthesis of lyconadin A are in progress.

4. Experimental

4.1. General

Benzene, dimethylformamide, methylene chloride, and tetrahydrofuran were dried by passage through a solvent drying system containing cylinders of activated alumina. 1,2-Dichloroethane was dried over activated 4 Å molecular sieves. Flash chromatography was carried out using 60–230 mesh silica gel. ^{1}H NMR spectra were acquired on 500 MHz spectrometers with chloroform (7.27 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were acquired on spectrometers operating at 125 MHz with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

4.2. Methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate (2a)

To a solution of methyl pyruvate (17.5 μL, 19.4 mg, 0.190 mmol) and methyl propiolate (32.0 μL, 32.2 mg, 0.383 mmol) in MeOH (0.6 mL) was added benzylamine (41.5 μL, 40.7 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc in hexanes elution) afforded **2a** (33.9 mg, 0.139 mmol, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (d, J=3.0 Hz, 1H), 7.84 (dd, J=9.2, 2.8 Hz, 1H), 7.38–7.32 (m, 5H), 6.58 (d, J=9.5 Hz, 1H), 5.17 (s, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 162.7, 142.9, 138.7, 135.7, 129.3 (2C), 128.6, 128.4 (2C), 120.3, 110.2, 52.9, 52.3; IR (film) ν_{max} 2951, 1719, 1666, 1612, 1542, 1496, 1446, 1300, 1151 cm^{-1}; HRMS (ESI) m/z 266.07975 (MNa^+, $C_{14}H_{13}NO_3Na^+$ requires 266.07876).

4.3. Methyl 1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (2b)

To a solution of methyl pyruvate (17.5 μL, 19.4 mg, 0.190 mmol) and methyl propiolate (31.8 μL, 31.9 mg, 0.380 mmol) in MeOH (0.6 mL) was added p-methoxybenzylamine (49.3 μL, 52.1 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc in hexanes elution) afforded **2b** (38.0 mg, 0.139 mmol, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (d, J=2.5 Hz, 1H), 7.81 (dd, J=9.8, 2.8 Hz, 1H), 7.29 (d, J=9.0 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 6.56 (d, J=9.5 Hz, 1H), 5.09 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 162.7, 159.9, 142.7, 138.6, 130.1 (2C), 127.8, 120.2, 114.6 (2C), 110.1, 55.5, 52.5, 52.3; IR (film) ν_{max} 2953, 2838, 1716, 1612, 1544, 1515, 1396, 1297, 1114 cm^{-1}; HRMS (ESI) m/z 274.10674 (MH^+, $C_{15}H_{15}NO_4H^+$ requires 274.10738).

4.4. Methyl 1-(3,4-dimethoxybenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (2c)

To a solution of methyl pyruvate (17.5 μL, 19.4 mg, 0.190 mmol) and methyl propiolate (31.8 μL, 31.9 mg, 0.380 mmol) in MeOH (0.6 mL) was added 3,4-dimethoxybenzylamine (56.4 μL, 63.5 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc in hexanes elution) afforded **2c** (45.4 mg, 0.150 mmol, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (d, J=2.5 Hz, 1H), 7.83 (dd, J=10.0, 2.5 Hz, 1H), 6.91–6.89 (m, 2H), 6.84 (d, J=7.5 Hz, 1H), 6.58 (d, J=9.5 Hz, 1H), 5.10 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 162.8, 149.6, 149.5, 142.6, 138.7, 128.2, 121.2, 120.2, 111.9, 111.5, 110.2, 56.22, 56.16, 52.7, 52.3; IR (film) ν_{max} 1718, 1667, 1517, 1446, 1301, 1263, 1239 cm^{-1}; HRMS (ESI) m/z 304.11635 (MH^+, $C_{16}H_{17}NO_5H^+$ requires 304.11795).

4.5. Ethyl 6-oxo-1,6-dihydropyridine-2-carboxylate (5)

A mixture of ethyl pyruvate (21 μL, 22 mg, 0.19 mmol), 4 Å MS (66.2 mg), pyrrolidine (19.5 μL, 16.9 mg, 0.238 mmol) and anhydrous benzene (2.0 mL) was refluxed at 80 °C for 5 h. The mixture was allowed to cool to rt and was then filtered under Ar. The solution of crude enamine was placed in a sealable tube and treated with propiolamide[23] (33 mg, 0.48 mmol) followed by p-TsOH (36 mg, 0.21 mmol). The vessel was sealed, and the resulting mixture was stirred at 80 °C for 48 h, then at 110 °C for 12 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (SiO_2, 4% MeOH in EtOAc elution), affording **5** (22.5 mg, 0.135 mmol, 71%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.73 (br s, 1H), 7.46 (dd, J=9.2, 6.8 Hz, 1H), 6.98 (dd, J=7.0, 1.0 Hz, 1H), 6.81 (dd, J=9.5, 1.0 Hz, 1H), 4.42 (q, J=7.0 Hz, 2H), 1.41 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 160.1, 140.0, 133.9, 127.3, 109.4, 63.1, 14.4; IR (film) ν_{max} 2979, 1726, 1661, 1610, 1472, 1349, 1284, 1164, 1022 cm^{-1}; HRMS (ESI) m/z 190.04838 (MNa^+, $C_8H_9NO_3Na^+$ requires 190.04746).

4.6. *S*-Methyl 4-(benzyloxyimino)-2-ethyl-3-oxobutanethioate (8)

n-BuLi (1.6 M in hexane, 567 μL, 0.907 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (198 μL, 153 mg, 0.950 mmol) in anhydrous THF (2.0 mL) at −5 °C under Ar. The resulting mixture was stirred at −5 °C for 30 min, cooled to −78 °C, and treated with a solution of *S*-methyl butanethioate (101 μL, 97.5 mg, 0.825 mmol) in anhydrous THF (590 μL). The mixture was then stirred at −78 °C for 30 min, treated with TMSCl (121 μL, 104 mg, 0.953 mmol), stirred at −78 °C for 1 h, allowed to warm to rt, and stirred at rt for 15 min. The solvent was removed in vacuo, the residue was suspended in hexane, and crude silyl ketene thioacetal **6** was obtained by filtration. Compound **6** was then dissolved in anhydrous DMF (650 μL), and this solution was added

to a stirred solution of LiOAc (3.9 mg, 0.059 mmol) in anhydrous DMF (880 μL) at rt under Ar. Next, a solution of methyl 2-(benzyloxyimino)acetate (**7**, 113.8 mg, 0.589 mmol) in anhydrous DMF (650 μL) was added to the mixture, and it was stirred at rt under Ar for 6 h. The reaction was quenched by the addition of satd aq NH_4Cl (0.2 mL), and the mixture was extracted with EtOAc (3×1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc in hexanes elution) afforded **8** (67.4 mg, 0.241 mmol, 41%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (s, 1H), 7.40–7.36 (m, 5H), 5.31 (s, 2H), 4.47 (t, J=7.2 Hz, 1H), 2.28 (s, 3H), 1.99–1.92 (m, 2H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.5, 192.3, 147.6, 142.8, 136.2, 129.0 (2C), 128.8 (2C), 78.6, 63.0, 23.0, 19.5, 12.1; IR (film) ν_{max} 2968, 2932, 1748, 1705, 1678, 1583, 1367, 1340, 1269, 1181, 1009 cm^{-1}; HRMS (ESI) m/z 280.10158 (MH^+, $C_{14}H_{17}NO_3SH^+$ requires 280.10019). Additionally, an undetermined amount of β-lactam **9** (identified by HRMS) could be obtained contaminated with recovered **7**.

4.7. Methyl 2-(4-methylphenylsulfonamido)-3-(methylthiocarbonyl)pentanoate (11)

n-BuLi (1.6 M in hexane, 690 μL, 1.1 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (240 μL, 186 mg, 1.15 mmol) in anhydrous THF (4.3 mL) at −5 °C under Ar. The resulting mixture was stirred at −5 °C for 30 min, cooled to −78 °C, and treated with a solution of *S*-methyl butanethioate (120 μL, 118 mg, 0.998 mmol) in anhydrous THF (810 μL). The mixture was then stirred at −78 °C for 30 min, treated with TMSCl (146 μL, 125 mg, 1.15 mmol), stirred at −78 °C for 1 h, allowed to warm to rt, and stirred at rt for 15 min. The solvent was removed in vacuo, the residue was suspended in hexane, and crude silyl ketene thioacetal **6** was obtained by filtration. Compound **6** was then dissolved in anhydrous DMF (1.0 mL), and this solution was added to a stirred solution of LiOAc (4.2 mg, 0.0643 mmol) in anhydrous DMF (0.84 mL) at rt under Ar. Next, a solution of methyl 2-(tosylimino)-acetate (**10**, 156 mg, 0.647 mmol) in anhydrous DMF (1.0 mL) was added to the mixture, and the resulting mixture was stirred at rt under Ar for 6 h. The reaction was quenched by the addition of satd aq NH_4Cl (0.2 mL), and the mixture was extracted with EtOAc (3×1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc in hexanes elution) afforded **11** (193 mg, 0.537 mmol, 83%) as a white solid that was a 6:1 mixture of diastereomers favoring the *anti* isomer (data for major isomer): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J=8.5 Hz, 2H), 7.28 (d, J=9.0 Hz, 2H), 5.56 (d, J=11.0 Hz, 1H), 4.15 (dd, J=10.2, 4.8 Hz, 1H), 3.46 (s, 3H), 3.00–2.96 (m, 1H), 2.41 (s, 3H), 2.25 (s, 3H), 1.89–1.80 (m, 1H), 1.72–1.63 (m, 1H), 0.98 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.2, 170.7, 143.8, 137.4, 129.7 (2C), 127.5 (2C), 56.8, 56.5, 52.8, 23.0, 21.8, 12.0, 11.8; IR (film) ν_{max} 3279, 2966, 1744, 1674, 1598, 1435, 1385, 1165 cm^{-1}; HRMS (ESI) m/z 360.09427 (MH^+, $C_{15}H_{21}NO_5S_2H^+$ requires 360.09339).

4.8. Methyl 2-(2-bromo-*N*-tosylacetamido)-3-(methylthiocarbonyl)pentanoate (13)

A solution of **11** (100 mg, 0.278 mmol) in anhydrous THF (3.0 mL) at −78 °C under Ar was treated with *n*-BuLi (1.6 M in hexane, 180 μL, 0.289 mmol), stirred at −78 °C for 10 min and at rt for 5 min, then recooled to −78 °C. Bromoacetyl chloride (25.5 μL, 48.8 mg, 0.310 mmol) was added, and the resulting mixture was stirred at −78 °C under Ar for 30 min, warmed to rt, and stirred for 12 h. The reaction was quenched by the addition of satd aq NH_4Cl (0.5 mL), and the mixture was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (0.5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 8% EtOAc in hexanes elution) afforded **13** (106 mg, 0.221 mmol, 79%) as a colorless oil that was a 6:1 mixture of diastereomers favoring the *anti* isomer (data for major isomer): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, J=8.5 Hz, 2H), 7.42 (d, J=8.5 Hz, 2H), 5.46 (d, J=10.0 Hz, 1H), 4.56 (d, J=13.0 Hz, 1H), 4.18 (d, J=13.5 Hz, 1H), 3.56 (s, 3H), 3.54–3.51 (m, 1H), 2.49 (s, 3H), 2.39 (s, 3H), 1.60–1.54 (m, 2H), 0.99 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.9, 168.7, 166.5, 146.4, 135.2, 130.3 (2C), 128.8 (2C), 62.5, 53.7, 52.8, 29.2, 23.7, 22.0, 12.1, 11.8; IR (film) ν_{max} 2958, 1747, 1682, 1596, 1436, 1369, 1023 cm^{-1}; HRMS (ESI) m/z 501.99658 (MNa^+, $C_{17}H_{22}NO_6BrS_2Na^+$ requires 501.99641).

4.9. Methyl 3-ethyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (14)

A solution of **13** (28.1 mg, 0.0585 mmol) in anhydrous 1,2-dichloroethane (810 μL) at −20 °C under Ar was treated with $TiCl_4$ (1.0 M in CH_2Cl_2, 87 μL, 0.087 mmol) followed by a solution of PPh_3 (22 mg, 0.0839 mmol) in anhydrous CH_2Cl_2 (270 μL). The resultant mixture was stirred at −5 °C under Ar for 16 h. The reaction was quenched by the addition of H_2O (100 μL), and the layers were separated. The aqueous layer was extracted with EtOAc (3×1 mL), and the combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 15% EtOAc in hexanes elution) afforded **14** (16.2 mg, 0.0422 mmol, 72%) as a colorless oil that was a 6:1 mixture of diastereomers favoring the *anti* isomer (data for major isomer): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 5.46 (d, J=2.5 Hz, 1H), 5.39 (d, J=5.0 Hz, 1H), 3.59 (s, 3H), 3.17–3.13 (m, 1H), 2.43 (s, 3H), 2.24 (s, 3H), 2.14–2.09 (m, 1H), 1.69–1.63 (m, 1H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 161.7, 161.0, 145.0, 135.8, 129.6 (2C), 129.3 (2C), 112.6, 58.5, 52.7, 45.2, 21.9, 21.1, 14.9, 12.4; IR (film) ν_{max} 2924, 2853, 1747, 1682, 1532, 1260, 1167, 1087 cm^{-1}; HRMS (ESI) m/z 406.07600 (MNa^+, $C_{17}H_{21}NO_5S_2Na^+$ requires 406.07534).

4.10. Methyl 3-ethyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (15)

A solution of **14** (33 mg, 0.086 mmol) in DMF (3.0 mL) at rt was treated with DBU (193 μL, 197 mg, 1.29 mmol). The resulting mixture was stirred at rt for 6 h, treated with H_2O (0.5 mL) and satd aq NH_4Cl (0.5 mL), and extracted with EtOAc (3×1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3% MeOH in CH_2Cl_2 elution) afforded **15** (19 mg, 0.084 mmol, 97%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.50 (br s, 1H), 6.41 (s, 1H), 3.97 (s, 3H), 2.93 (q, J=7.3 Hz, 2H), 2.43 (s, 3H), 1.18 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.8, 160.0, 157.9, 128.3, 126.3, 117.2, 53.5, 21.3, 15.0, 14.2; IR (film) ν_{max} 2965, 2930, 1739, 1641, 1527, 1423, 1343, 1280, 1229, 1109, 1055, 927 cm^{-1}; HRMS (ESI) m/z 228.06996 (MH^+, $C_{10}H_{13}NO_3SH^+$ requires 228.06889).

4.11. Methyl 3-ethyl-6-oxo-1,6-dihydropyridine-2-carboxylate (16)

To a vigorously stirred mixture of **15** (20.6 mg, 0.0906 mmol) and Lindlar catalyst (606.6 mg) in acetone (4.0 mL) at rt under Ar was added Et_3SiH (214.5 μL, 156 mg, 1.34 mmol) dropwise. The resulting mixture was stirred at rt for 4 h, filtered through a plug of Celite (washed with 7×3.5 mL acetone), and concentrated in vacuo. Flash chromatography (SiO_2, 4% MeOH in CH_2Cl_2 elution) afforded **16** (15.6 mg, 0.0861 mmol, 95%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.51 (br s, 1H), 7.34 (d, J=9.0 Hz, 1H), 6.76 (d, J=9.5 Hz, 1H), 3.97 (s, 3H), 2.84 (q, J=7.5 Hz, 2H), 1.18 (t, J=7.5 Hz, 3H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 161.9, 161.4, 144.6, 128.9, 128.1, 127.3, 53.4, 25.0, 15.2; IR (film) ν_{max} 2968, 1736, 1662, 1605, 1437, 1324, 1282, 1234, 1099 cm^{-1}; HRMS (ESI) *m*/*z* 182.08252 (MH^+, $C_9H_{11}NO_3H^+$ requires 182.08117).

4.12. Methyl 4-methyl 2-(4-methylphenylsulfonamido)-3-(methylthiocarbonyl)pentanoate (18)

Following the procedure detailed for the synthesis of **11**, but using *n*-BuLi (1.6 M in hexane, 3.40 mL, 5.5 mmol), 1,1,1,3,3,3-hexamethyldisilazane (1.20 mL, 930 mg, 5.75 mmol), anhydrous THF (12 mL), *S*-methyl 3-methylbutanethioate (661.2 mg, 5.00 mmol), anhydrous THF (3.5 mL), TMSCl (750 μL, 625 mg, 5.75 mmol), anhydrous DMF (4.5 mL), LiOAc (66.0 mg, 1.00 mmol), **10** (1.207 g, 5.00 mmol), and anhydrous DMF (3.5 mL) afforded **18** (1.382 g, 3.70 mmol, 74%) as a white solid that was a 1.6:1 mixture of diastereomers favoring the *anti* isomer. The isomers could be separated for characterization purposes. For *anti*-**18**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, *J*=8.5 Hz, 2H), 7.28 (d, *J*=8.5 Hz, 2H), 5.42 (d, *J*=9.0 Hz, 1H), 4.16 (dd, *J*=8.8, 5.8 Hz, 1H), 3.48 (s, 3H), 2.71 (dd, *J*=8.0, 6.0 Hz, 1H), 2.40 (s, 3H), 2.25 (s, 3H), 2.24–2.18 (m, 1H), 1.03 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.5, 170.5, 144.1, 136.7, 129.9 (2C), 127.6 (2C), 64.6, 55.5, 52.8, 28.0, 21.8, 21.1, 20.0, 12.2; IR (film) ν_{max} 3279, 2957, 1741, 1674, 1455, 1432, 1339, 1312, 1200, 1164, 1093 cm^{-1}; HRMS (ESI) *m*/*z* 374.10872 (MH^+, $C_{16}H_{23}NO_5S_2H^+$ requires 374.10904).

For *syn*-**18**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=7.5 Hz, 2H), 5.62 (d, *J*=10.5 Hz, 1H), 4.27 (dd, *J*=10.5, 4.0 Hz, 1H), 3.40 (s, 3H), 2.64 (dd, *J*=9.5, 4.0 Hz, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 2.22–2.16 (m, 1H), 0.98 (d, *J*=7.0 Hz, 3H), 0.94 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.1, 170.5, 143.7, 137.5, 129.7 (2C), 127.4 (2C), 61.6, 55.9, 52.6, 28.1, 21.7, 20.9, 19.9, 12.1; IR (film) ν_{max} 3342, 2965, 1745, 1670, 1342, 1168, 1143, 1093 cm^{-1}; HRMS (ESI) *m*/*z* 374.10852 (MH^+, $C_{16}H_{23}NO_5S_2H^+$ requires 374.10904).

4.13. Methyl 2-(2-bromo-*N*-tosylacetamido)-4-methyl-3-(methylthiocarbonyl)pentanoate (19)

Following the procedure detailed for the synthesis of **13**, but using **18** (448.2 mg, 1.20 mmol), anhydrous THF (3.0 mL), *n*-BuLi (1.6 M in hexane, 1.1 mL, 1.8 mmol), and bromoacetyl chloride (400 μL, 756 mg, 4.80 mmol) afforded **19** (304.8 mg, 0.616 mmol, 51%) as a colorless oil that was a 1.6:1 mixture of diastereomers: ^1H NMR ($CDCl_3$, 500 MHz, data for major isomer) δ 7.97 (d, *J*=7.0 Hz, 2H), 7.39 (d, *J*=8.5 Hz, 2H), 5.34 (d, *J*=7.0 Hz, 1H), 4.53 (d, *J*=14.5 Hz, 1H), 4.06 (d, *J*=13.5 Hz, 1H), 3.59 (s, 3H), 3.56–3.51 (m, 1H), 2.47 (s, 3H), 2.36 (s, 3H), 2.28–2.17 (m, 1H), 1.05 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.5 Hz, 3H); HRMS (ESI) *m*/*z* 494.03259 (MH^+, $C_{18}H_{24}BrNO_6S_2H^+$ requires 494.03012).

4.14. Methyl 3-isopropyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (20)

Following the procedure detailed for the synthesis of **14**, but using **19** (19.7 mg, 0.0398 mmol), anhydrous 1,2-dichloroethane (540 μL), $TiCl_4$ (1.0 M in CH_2Cl_2, 61 μL, 0.061 mmol), PPh_3 (16 mg, 0.061 mmol), and anhydrous CH_2Cl_2 (180 μL) afforded **20** (13 mg, 0.033 mmol, 82%) as a colorless oil that was a ca. 3:1 mixture of diastereomers: ^1H NMR ($CDCl_3$, 500 MHz, data for major isomer) δ 8.00 (d, *J*=8.5 Hz, 2H), 7.32 (d, *J*=9.0 Hz, 2H), 5.43 (s, 1H), 5.41 (d, *J*=2.0 Hz, 1H), 3.68 (s, 3H), 2.73 (dd, *J*=7.0, 2.0 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H), 2.07–2.00 (m, 1H), 1.14 (d, *J*=7.0 Hz, 3H), 1.13 (d, *J*=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, data for major isomer) δ 170.6, 161.3, 160.2, 145.0, 132.4, 130.0 (2C), 129.1 (2C), 112.2, 58.8, 53.2, 49.7, 31.5, 21.9, 21.3, 20.3, 15.0; IR (film) ν_{max} 2961, 1749, 1683, 1352, 1167 cm^{-1}; HRMS (ESI) *m*/*z* 398.10827 (MH^+, $C_{18}H_{23}NO_5S_2H^+$ requires 398.10904).

4.15. Methyl 3-isopropyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (21)

Following the procedure detailed for the synthesis of **15**, but using **20** (26 mg, 0.065 mmol), DMF (2.2 mL), and DBU (147 μL, 149 mg, 0.981 mmol) afforded **21** (15.2 mg, 0.063 mmol, 96%) as a colorless film: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.80 (br s, 1H), 6.38 (s, 1H), 3.96 (s, 3H), 2.43 (s, 3H), 2.06–1.99 (m, 1H), 1.35 (d, *J*=7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.7, 173.0, 159.8, 139.0, 130.2, 116.4, 53.5, 28.2, 20.6 (2C), 15.7; IR (film) ν_{max} 2925, 1737, 1650, 1461 cm^{-1}; HRMS (ESI) *m*/*z* 242.08599 (MH^+, $C_{11}H_{15}NO_3SH^+$ requires 242.08454).

4.16. Methyl 3-isopropyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (22)

Following the procedure detailed for the synthesis of **16**, but using **21** (10 mg, 0.041 mmol), Lindlar catalyst (300 mg), acetone (2.0 mL), and Et_3SiH (98 μL, 71 mg, 0.61 mmol) afforded **22** (6.7 mg, 0.034 mmol, 83%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.28 (br s, 1H), 7.54 (d, *J*=10.0 Hz, 1H), 6.80 (d, *J*=9.5 Hz, 1H), 3.97 (s, 3H), 2.06–1.96 (m, 1H), 1.19 (d, *J*=7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 159.4, 145.3, 131.2, 128.7, 127.2, 52.9, 27.2, 22.9 (2C); IR (film) ν_{max} 2973, 1696, 1668, 1378 cm^{-1}; HRMS (ESI) *m*/*z* 196.09627 (MH^+, $C_{10}H_{13}NO_3H^+$ requires 196.09682).

4.17. Methyl 2-(2-bromo-*N*-tosylpropanamido)-3-(methylthiocarbonyl)pentanoate (23)

Following the procedure detailed for the synthesis of **13**, but using **11** (584.5 mg, 1.63 mmol), anhydrous THF (8.0 mL), *n*-BuLi (1.6 M in hexane, 1.50 mL, 2.40 mmol), and 2-bromopropanoyl chloride (1.111 g, 6.50 mmol) afforded **23** (561 mg, 1.13 mmol, 70%) as a colorless oil that was a mixture of diastereomers at the bromo-bearing carbon: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 5.77–5.72 (m, 1H), 4.14–4.10 (m, 1H), 3.58 (s, 3H), 2.77–2.72 (m, 1H), 2.40 (s, 3H), 2.08 (s, 3H), 1.63–1.54 (m, 1H), 1.48–1.40 (m, 1H), 1.27–1.19 (m, 3H), 0.88–0.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.7, 175.7, 172.3, 143.3, 139.2, 129.6 (2C), 127.4 (2C), 60.6, 51.8, 50.4, 31.7, 23.7, 22.3, 21.7, 17.8, 14.0, 11.9; IR (film) ν_{max} 2960, 1738, 1435, 1336, 1161 cm^{-1}; HRMS (ESI) *m*/*z* 494.02870 (MH^+, $C_{18}H_{24}BrNO_6S_2H^+$ requires 494.03012).

4.18. Methyl 3-ethyl-5-methyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (24)

Following the procedure detailed for the synthesis of **14**, but using **23** (43 mg, 0.0870 mmol), anhydrous 1,2-dichloroethane (1.2 mL), $TiCl_4$ (1.0 M in CH_2Cl_2, 140 μL, 0.140 mmol), PPh_3 (34 mg, 0.13 mmol), and anhydrous CH_2Cl_2 (400 μL) afforded **24** (8.1 mg, 0.020 mmol, 24%) as a colorless film that was a ca. 1.1:1 mixture of diastereomers, and ketone **25** (18 mg, 0.049 mmol, 56%) as a colorless film. for **24**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77 and 7.74 (2d, *J*=8.5 Hz, 2H), 7.31–7.27 (m, 2H), 6.00 and 5.57 (2d, *J*=9.0 and 10.0 Hz, 1H), 3.65 and 3.66 (2s, 3H), 2.98–2.94 and 2.86–2.82 (2m, 1H), 2.43 and 2.42 (2s, 3H), 2.18 (s, 3H), 1.73–1.64 and 1.85–1.79 (2m, 1H), 1.57 (s, 3H), 1.53–1.46 and 1.43–1.38 (2m, 1H), 0.92 and 0.99 (2t, *J*=7.5 Hz, 3H); HRMS (ESI) *m*/*z* 398.10839 (MH^+, $C_{18}H_{23}NO_5S_2H^+$ requires 398.10904).

For **25**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, *J*=8.5 Hz, 2H), 7.33 (d, *J*=8.5 Hz, 2H), 5.45 (s, 1H), 3.80 (s, 3H), 3.16 (q, *J*=7.5 Hz, 1H), 2.73 (sextet, *J*=7.3 Hz, 1H), 2.47–2.40 (m, 1H), 2.44 (s, 3H), 2.36 (sextet, *J*=7.2 Hz, 1H), 1.38 (d, *J*=7.0 Hz, 3H), 1.12 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 169.5, 145.4, 135.4, 132.9, 129.7

(2C), 129.4 (2C), 61.3, 53.3, 42.0, 25.2, 21.9, 18.5, 14.6, 12.5; IR (film) ν_{max} 2931, 1749, 1708, 1359, 1171, 1087 cm^{-1}; HRMS (ESI) m/z 368.11745 (MH^+, $C_{17}H_{21}NO_6SH^+$ requires 368.11623).

4.19. Methyl 3-ethyl-5-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (26)

Following the procedure detailed for the synthesis of **15**, but using **24** (3.7 mg, 0.0093 mmol), DMF (1.1 mL), and DBU (71 μL, 72 mg, 0.47 mmol) afforded the vinyl sulfide intermediate, which was reduced according to the procedure detailed for the synthesis of **16**, but using Lindlar catalyst (230 mg), acetone (1.5 mL), and Et_3SiH (75 μL, 55 mg, 0.47 mmol), affording **26** (1.4 mg, 0.0072 mmol, 77%) as a white film: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.36 (br s, 1H), 7.20 (s, 1H), 3.95 (s, 3H), 2.82 (q, J=7.5 Hz, 2H), 2.21 (s, 3H), 1.18 (t, J=7.2 Hz, 3H); HRMS (ESI) m/z 218.06491 (MNa^+, $C_{10}H_{13}NO_3Na^+$ requires 218.07876).

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