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Metal-Free, One-Pot Cascade Annulation of 2-Pyrones in Water for the Synthesis of Peptidomimetics

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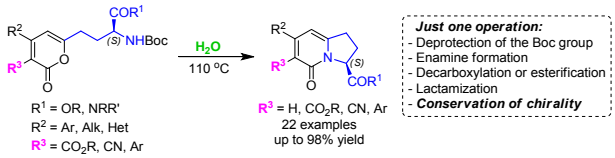


ABSTRACT: A one-pot, metal-free, double cyclization for the synthesis of bicyclic 2-pyridones as peptidomimetics was developed. In this process, the transformation of 2-pyrones bearing a tethered, homochiral α-amino acid started with removal of the *N*-Boc protective group under acidic or neutral conditions at elevated temperature, followed by several key transformations, including cyclic enamine formation, decarboxylation or esterification, isomerization and lactamization, to furnish bicyclic 2-pyridones in up to 98% yield with retention of the chirality at the α-carbon of the amino acid portion of the molecule. Exploration of the substrate scope revealed some selectivity between the decarboxylation and esterification pathways under thermal acidic conditions, while performing the reaction in boiling water yielded the decarboxylation products exclusively.

INTRODUCTION

The significance of natural and synthetic molecules containing 2-pyridone as a central structural scaffold and their broad applications in many fields has inspired chemists to develop novel synthetic methods for these compounds for various purposes. Several research groups have

developed fused, polycyclic 2-pyridones and related compounds as pharmaceutical lead peptidomimetics for the development of new drugs, as shown in Figure 1.[1,2] Some previous synthetic methods for accessing these types of peptidomimetics include the first total synthesis of **A58365A** by Danishefsky's group using the aza-[3+3] cycloaddition of vinylogous urethane and α-methyleneglutaric anhydride as a key step (Scheme 1a).[2a] The rhodium-catalyzed 1,3-dipolar cycloaddition of diazo compounds and dipolarophiles was originally developed by Padwa's group and later utilized by Zhang's and Haffner's groups for the synthesis of various analogs (Scheme 1b).[2a,d] Clive's methodology involved an enyne radical cyclization, followed by spiro rearrangement to construct a bicyclic core (Scheme 1c).[2a] In the Almqvist approach, the intermolecular cyclocondensation between *in situ*-generated acyl-ketenes and preformed cyclic imines was employed for the synthesis of multi-fused-ring 2-pyridones and several related compounds (Scheme 1d).[2c] Gembus's group applied a hydroxyl-*L*-lysine derivative as a starting material for double cyclization, followed by dehydration to prepare bicyclic pyrazinones (Scheme 1e).[2d] An approach involving multistep transformations from commercially available 2-hydroxy-6-methyl nicotinonitrile and another involving the anodic amide oxidation of pyrrolidines, followed by several transformations were reported by Dragovich's and Moeller's groups, respectively.[2a,b]

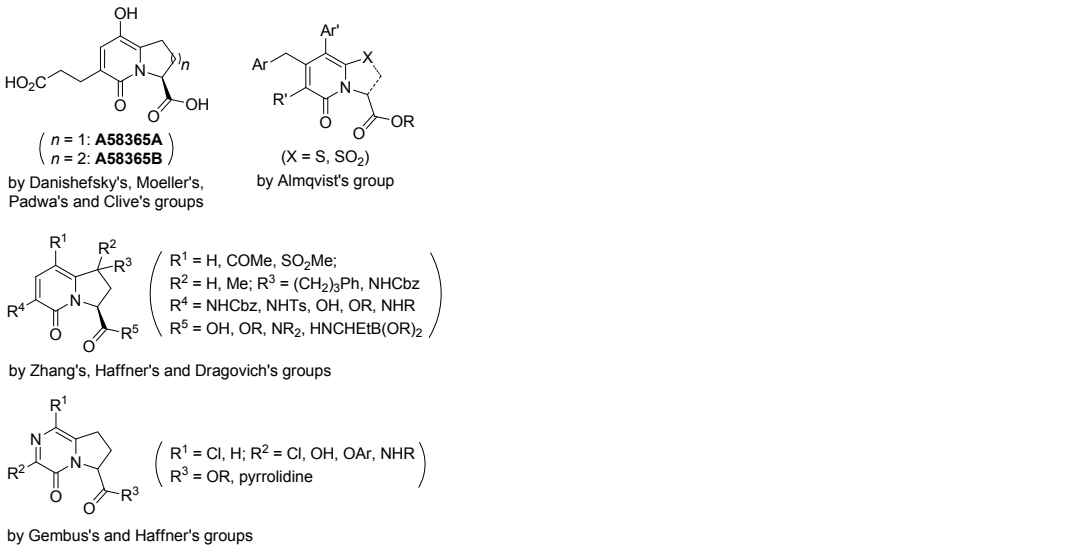
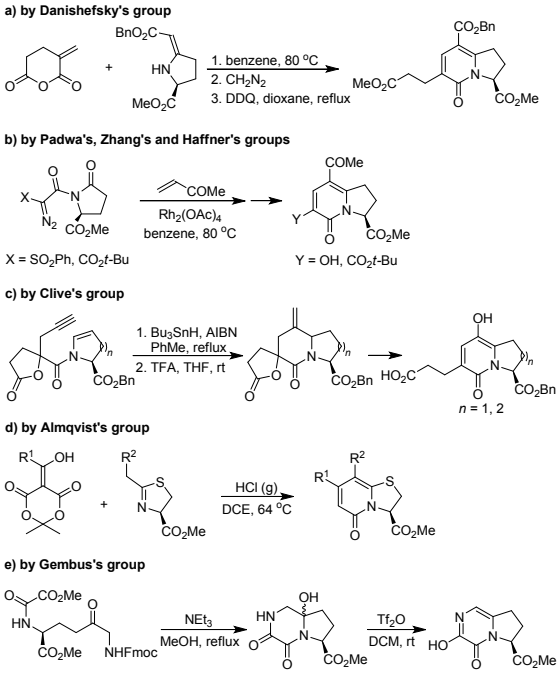


Figure 1. Examples of biologically active 2-pyridones with peptidomimetic cores developed by various groups.

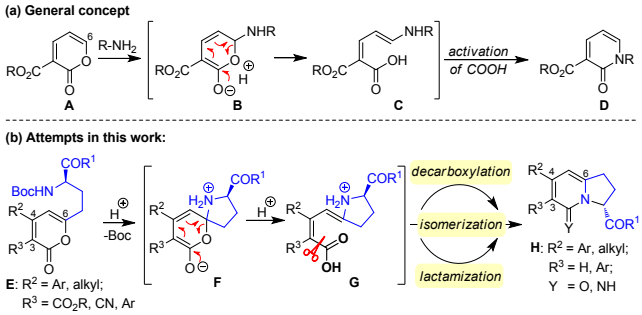
Scheme 1. Examples of Methodologies for the Construction of Bicyclic 2-Pyridone Cores



2-Pyrones are well-known versatile molecules for preparing a variety of heterocyclic systems due to the diversity of chemical reactions, including substitution, addition, photochemistry, and ring transformation, in which they participate.[3] In general, in reactions with 2-pyrones under defined conditions, various substrates can be converted into reactive intermediates in which decarboxylation occurs after addition, cyclization, or other rearrangements, leading to several useful scaffolds. The use of a 2-pyrone core to synthesize 2-pyridone systems via C-6 addition with the appropriate *N*-nucleophile, followed by ring opening and ring reclosure sequences, has been reported.[4] These processes require only mild reaction conditions, including low temperature (<60 °C), for carboxylic activation to avoid the extrusion of CO_2 from intermediate B, Scheme 2a.[4b,c] To the best of our knowledge, there have been no reported examples of intramolecular nucleophilic additions of 2-pyrones for the synthesis of 2-pyridones, although the analogous intermolecular reactions have been well documented.[4] Therefore, inspired by the successful development of 2-pyridones as peptidomimetics and our previously reported one-pot method of preparing bicyclic 2-pyridones under basic conditions at

elevated temperature,[5] herein we expanded this concept to access bicyclic 2-pyridones with chiral centers from the corresponding 2-pyrones in a facile manner, based on the intramolecular reaction, Scheme 2b. We envisaged that this process would involve several key steps, including *N*-Boc deprotection, intramolecular nucleophilic addition to the cyclic enamine, decarboxylation, isomerization and lactamization, to furnish the final products.

Scheme 2. General Concept and Novel Approach for the Conversion of 2-Pyrones to Bicyclic 2-Pyridones



RESULTS AND DISCUSSION

Our initial investigations involved the reaction of chiral 3-alkoxy carbonyl 2-pyrone **4a**. This compound was readily prepared from commercially available methyl *N*-Boc-(*L*)-pyroglutamate (**1a**) and phenylacetylene (**2a**) in the presence of lithium hexamethyldisilazane (LHMDS), which afforded the corresponding internal ynone **3a** in 85% yield. The thermal 1,4-addition of **3a** to dimethyl malonate in the presence of substoichiometric NaH in tetrahydrofuran (THF) furnished the desired 2-pyrone **4a** in good yield (up to 85%, Scheme 3).

Scheme 3. Synthetic Pathway to 2-Pyrones Bearing a Tethered, Homochiral α-Amino Acid

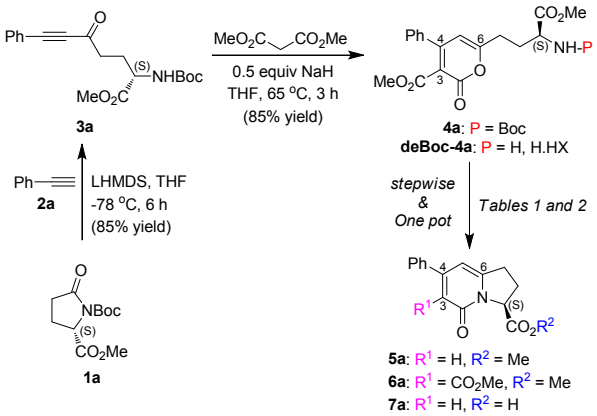


Table 1. Optimization conditions for the stepwise transformation of **4a** to bicyclic 2-pyridones.[a]

Entry	Condition		Yield (%)[b]	
	Step 1:	Step 2:	**5a**	**6a**
1	TMSCl (3 equiv), MeOH, 55 °C, 1.5 h	EDCI, *cat.* DMAP, DMF, rt, 14 h	6	18
2		SiO_2, DCM, rt, 3 h	41	14
3		MS 4 Å, DMAP, MeOH, 60 °C, 2 h	20	7
4		MS 4 Å, DCM, rt, 2 h	25	6
5		K_2CO_3, MeOH, rt, 3 h	41	14
6		K_2CO_3, MeOH, 60 °C, 1 h	52	5
7		b-Al_2O_3[c], DCM, rt, 3 h	40	14
8		n-Al_2O_3[d], DCM, rt, 3 h	26	22
9		Toluene, 150 °C, 1 h[e]	81	4
10	TFA (3 equiv), DCM, RT, 4 h	Toluene, 150 °C, 1 h[e]	92	0[g]
11	85 wt.% aq.H_3PO_4 (20 equiv), THF, RT, 5 h	-	nr[f]	
12	TBAF (10 equiv), THF, 70 °C, 2 h	-	0[g]	
13	NaO^{t}Bu (4 equiv), THF, H_2O (1 equiv), 70 °C, 4 h	-	0[g]	

[a] Reaction was conducted in a round-bottom flask using **4a** (0.22 mmol) in the indicated anhydrous solvents, except MeOH. [b] Isolated yield. [c] Basic. [d] Neutral. [e] Reaction was conducted in a pressurized tube. [f] nr = no reaction. [g] None of product **5a** or **6a** was observed.

Optimization of the Reaction Conditions. To demonstrate the overall transformation efficiency of 2-pyrone **4a** to various 2-pyridones, both stepwise and one-pot synthetic procedures were examined (Tables 1 and 2). Several strategies, including the use of acids, bases, and thermolytically neutral conditions for the deprotection of the *tert*-butyl carbamate (*N*-Boc) group, have been reported.[6] Based on our previous experience, the Boc group of amino moieties in **4a** was removed by employing the *in situ* generation of HCl from trimethyl chlorosilane (TMSCl) in MeOH;[5] after that, the volatile materials were removed *in vacuo* by a rotary evaporator. Then, the double cyclization of **deBoc-4a**[7] was examined under various conditions (Table 1). According to previously reported conditions for the intermolecular reaction,[4b] employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 4-dimethylaminopyridine (DMAP) as a carboxyl-activating agent gave **6a** as the major product, as expected, in a slightly lower yield (18%), and the decarboxylation product **5a** was also detected even when the reaction was conducted at room temperature (Table 1, entry 1). When testing other quenching methods, treating a solution of **deBoc-4a** in DCM with SiO_2 at room

temperature produced **5a** as the major product in 41% yield along with **6a** in 14%. These results suggested that **deBoc-4a** could be converted into intermediates **F** and **G** (Scheme 2b) and then transformed into the cyclized products under mild acidic conditions with SiO_2, albeit in moderate yield (Table 1, entry 2). When the reaction was performed in the presence of a base, such as DMAP, K_2CO_3, or b-Al_2O_3 (Table 1, entries 3, 5–7), or under neutral conditions with molecular sieves (MS 4 Å) and n-Al_2O_3 (Table 1, entries 4 and 8), in all cases, the desired product **5a** was obtained as the major product (up to 52% yield, Table 1, entry 6), while **6a** was still generated in significant amounts (up to 24% yield, Table 1, entry 8). Although the unexpected formation of **6a**, which could be obtained under almost neutral conditions without coupling reagents, was quite interesting, these results did not indicate an improvement in the overall efficiency of this process. In general, the rate of decarboxylation is strongly solvent dependent, and the use of nonpolar aprotic solvents facilitates decarboxylation. Thus, we next performed the reaction of **deBoc-4a** in toluene at 150 °C for 1 h, and under these conditions, **5a** was obtained in high yield and selectivity (Table 1, entry 9). However, **6a** was still detected under these conditions. Employment of trifluoroacetic acid (TFA)[6a] in DCM for *N*-Boc removal (Table 1, entry 10) gave **5a** as the sole product in 92% yield, which was a higher yield than that obtained using TMSCl in MeOH (Table 1, entry 9), regardless of the cyclization method. None of the products were observed when a milder acid, aqueous phosphoric acid (85 wt.%) in an excess amount,[6b] was employed at room temperature (Table 1, entry 11). In addition, the highly activated *N*-Boc group could be cleaved under basic conditions.[6c] The use of a mild base, tetra-*n*-butylammonium fluoride (TBAF)[6c] in an excess amount, in refluxing THF gave no desired product, and only complex mixtures of unidentifiable byproducts were observed (Table 1, entry 12). When the reaction was performed using a stronger base, NaO*t*Bu[6c] in refluxing THF and 1 equiv of water, nonchemoselective products from the aqueous acid extraction that contained carboxylic acid derivatives, including **7a**, were observed (Table 1, entry 13).

Table 2. Optimization conditions for the one-pot transformation of 4a to the corresponding bicyclic 2-pyridones.[a]

Entry	Additive (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]			
					4a	**5a**	**6a**	**7a**
1	TMSCl (10)	MeOH	100	1	-	37	17	-
2	TMSCl (10)	MeOH	150	1	-	76	5	-
3	TMSOTf (1.2)	Toluene	150	0.5	-	85	-	-
4	TFA (3)	Toluene	150	1	-	81	-	15
5	TFA (3)	Toluene	80	2	35	62	-	Trace[c]
6	*p*-TsOH.H_2O (1.2)	Toluene	150	1	-	83	-	12
7	85 wt.% aq. H_3PO_4 (20)	Toluene	80	10	-	91	-	-
8	Amberlyst-15 (2)	Toluene	100	40	-	93	-	Trace[c]
9	Amberlyst-15 (2)	DCE	100	20	-	92	-	Trace[c]
10	Amberlyst-15 (2)	THF	100	20	-	75	-	12
11	Amberlyst-15 (2)	MeCN	100	7	-	95	-	Trace[c]
12	Amberlyst-15 (2)	MeOH	100	2	-	61	35	-
13	Amberlyst-15 (2)	MeCN-H_2O (1:1)	100	2	-	-	-	87(91)[d]
14	Dowex-50WX4 (2)	MeCN	100	2	-	12	-	52
15	Amberlite-IR120H (2)	MeCN	100	2	-	18		60
16	-	H_2O	110	24	25	72	-	-
17	-	H_2O	150	4	-	95	-	-
18	-	MeOH	150	10	85	12	-	-
19	-	Ethylene glycol (EG)	150	10	67	20	-	-
20	-	H_2O-EG (1:1)	110	14	-	96	-	-
21	-	H_2O-EG (1:1)	150	1.33	-	98(96)[d]	-	-
22	-	H_2O-EG (1:1)[e]	150	0.67	-	98(95)[d]	-	-
23	-	H_2O-EG (1:1)[e]	110	3.5	-	97(95)[d]	-	-
24[f]	-	H_2O-EG (1:1)[e]	110	4(5)[g]	-	95(96)[g]	-	-

[a] Reaction was conducted in a pressurized tube using **4a** (0.22 mmol) in the indicated solvents (1-3 mL). [b] Isolated yield. [c] **7a** was observed in trace amounts, as detected by ^{1}H NMR, and was difficult to purify. [d] Using **4a** (1.1 mmol). [e] Concentration was diluted 5-fold. [f] Using a conventional round-bottom flask. [g] Using **4a** (11 mmol).

On the basis of the screening results in Table 1, the reaction works well under thermal acid treatment for the deprotection-cyclization strategy. Thus, a one-pot process was explored (Table 2). When **4a** was reacted in a pressurized tube in the presence of acidic MeOH at temperatures of 100 and 150 °C, significantly improved yields and selectivities were clearly observed (Table 2, entries 1 and 2). At higher temperatures, a better chemical yield (up to 81%) and combined yield with a ratio of 15:1 were achieved (Table 2, entry 2). Fortunately, no racemization of **5a** and **6a** occurred, which was proven by HPLC with a chiral column (ee > 99% for **5a** and **6a**), even when the reaction was conducted at high temperatures in polar solvents in the presence of excess acid.

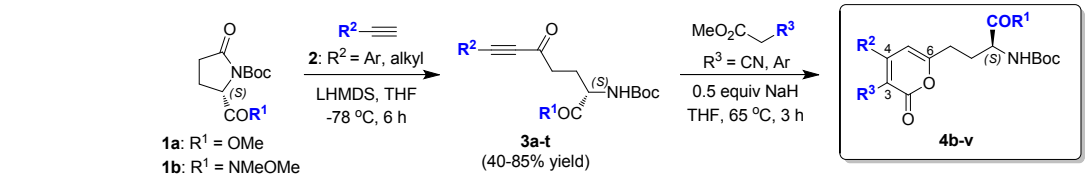
Selectivity for products **5a** and **6a** could be improved by avoiding the esterification between solvent MeOH and the intermediates. Thus, various acids for a one-pot synthesis were screened under different conditions. Employing a Lewis acid, such as TMSOTf, [6d] in a stoichiometric amount (1.2 equiv) at 150 °C for 0.5 h effectively facilitated this reaction to give **5a** in good yield (85%), while **6a** was not observed (Table 2, entry 3). However, a one-pot process using the strong organic acid TFA in excess (3 equiv) at 150 °C for 1 h gave the desired product **5a** and the hydrolysis product **7a** in a ratio of 5.4:1 with an excellent combined yield (96%); these products could be easily separated by acid-base extractions (Table 2, entry 4). Decreasing the reaction temperature to 80 °C with a longer reaction time (2 h) resulted in an incomplete reaction, and **7a** was still detectable (Table 2, entry 5). A similar result was obtained when *p*-TsOH·H_2O[6e] was employed in stoichiometric amounts (Table 2, entry 6). Interestingly, the use of a mild inorganic acid H_3PO_4 (aqueous, 85 wt.%), even in excess (20 equiv) at 80 °C with a longer reaction time (10 h), gave **5a** in excellent yield (91%) without **7a** (Table 2, entry 7). In general, the use of solid-supported reagents provides a practical and efficient synthetic method. Thus, we turned our attention to solid-supported sulfonic acids (Table 2, entries 8–15). Amberlyst-15 (hydrogen form)[6f] serves functions analogous to those of *p*-TsOH. Because of the physical resistance and swelling properties of Amberlyst-15,[8] all reactions employing this solid-supported reagent were carried out in various solvents at 100 °C. Using 2 equiv of Amberlyst-15, one-pot deprotection and cyclization took place completely in toluene, dichloroethane (DCE), THF, MeCN, and MeOH at different reaction rates (Table 2, entries 8–12). The reaction was very slow in toluene, DCM, and THF at 100 °C, ranging from 20 h to 40 h (Table 2, entries 8–10), but in MeCN, complete consumption of **4a** occurred in a shorter reaction time (7 h), providing **5a** in excellent yield (95%, Table 2, entry 11). Employment of Amberlyst-15 in a polar protic solvent, such as MeOH, at 100 °C gave similar results to those for use of TMSCl in MeOH but with a slightly higher combined yield (96%) and an easier operation (Table 2, entry

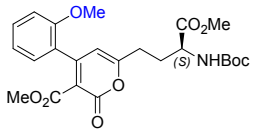
12). Although Amberlyst-15 (<2% moisture) was dried under vacuum prior to application in anhydrous solvents, a trace amount of **7a** was still detected (Table 2, entries 8–11). These results suggest that water is crucial. When the reaction was performed in a solvent mixture of MeCN and water (1:1), complete hydrolysis of the ester to the carboxylic acid **7a** was observed as a single product in excellent yield (Table 2, entry 13). Other solid-supported sulfonic acids, such as Dowex-50WX4 and Amberlite-IR120H,[6g] which contain high levels of moisture (>50%), did not work well, and **7a** was obtained as a major product in 52% and 60% yields, respectively (Table 2, entries 14 and 15). Removal of the *N*-Boc group using water at elevated temperature has been previously reported.[6h] The reaction of **4a** in water without any additives did not proceed to completion at 110 °C even after 1 day, affording **5a** in 72% yield and recovering **4a** in 25% yield (Table 2, entry 16). Increasing the reaction temperature to 150 °C could potentially drive the reaction to completion within 4 h to give **5a** in excellent yield (95%, Table 2, entry 17). Surprisingly, the reaction of **5a** in wet solvents, such as MeOH and EG, at 150 °C for 10 h also afforded product **5a**, even at low levels of conversion (up to 20%, Table 2, entries 18 and 19). The effects of the cosolvent, concentration and pressure could enhance the solubility of **4a** and reaction rate in water. Employing EG as a green cosolvent[9] reduced the reaction time from 4 h to 1.33 h at 150 °C (Table 2, entries 17 and 21) and from >24 h to 14 h at 110 °C (Table 2, entries 16 and 20). Interestingly, when the concentration of the reactant was diluted 5-fold, the reaction went to completion at 150 °C in 0.67 h and at 110 °C in 3.5 h (Table 2, entries 22 and 23). Decreasing the pressure of the reaction by changing the reaction apparatus from a pressurized tube to a conventional round-bottom flask equipped with a condenser had no significant effect on the reaction rate (Table 2, entry 24). Increasing the scale of **4a** (up to 5 g, 11 mmol) required a longer reaction time (5 h) at 110 °C to furnish the desired product **5a** in 96% yield (Table 2, entry 24). In summary, all reactions carried out in water at elevated temperature (110–150 °C)

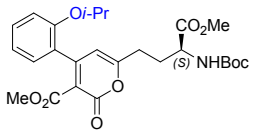
for defined times produced **5a** exclusively in excellent yields (95–98%, Table 2, entries 17 and 20–24).

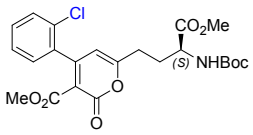
Scope of Substrates. Having established a simple method for the thermal double cyclization reaction to synthesize bicyclic 2-pyridones, a number of substrates **4** bearing different electronic and steric variations at C-4, different functional group compatibilities at C-3 of the 2-pyrone cores, and a tethered homochiral α-amino acid were prepared using the abovementioned procedure. The isolated yields of **4b-v** are shown in Scheme 4. In general, pyrones **4** could be prepared in moderate to excellent yields (53–91%), except for **4u**, which was synthesized in low yield (32%). With respect to the stability of both the starting materials **4** and products **5** and **6**, the results of our investigation of the generality and selectivity obtained with condition A (TMSCl in MeOH at 150 °C) and condition B (EG/water at 110 °C) in the one-pot synthesis of peptidomimetics are summarized in Scheme 5.

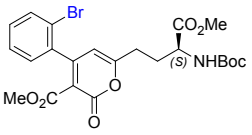
Scheme 4. Scope of Substrates **4**

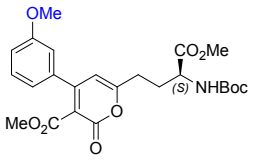


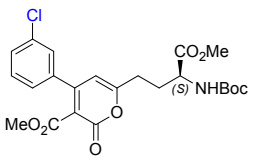

4b (73%)

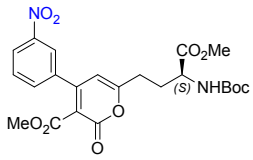

4c (80%)

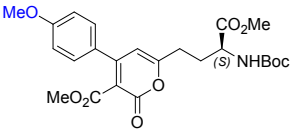

4d (53%)

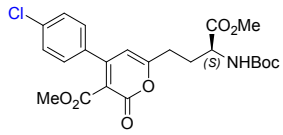

4e (54%)

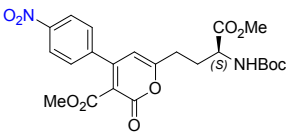

4f (72%)

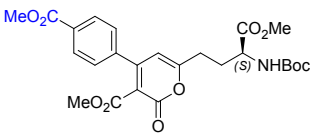

4g (81%)

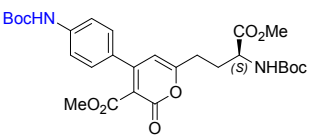

4h (90%)

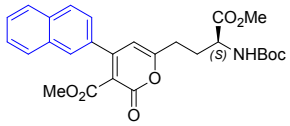

4i (75%)

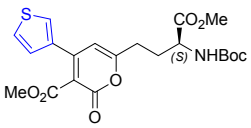

4j (84%)

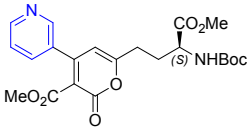

4k (88%)

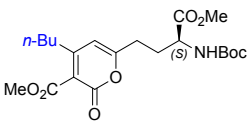

4l (83%)

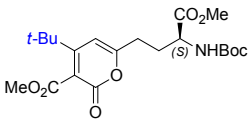

4m (91%)

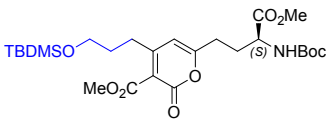

4n (83%)

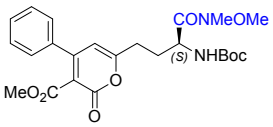

4o (75%)

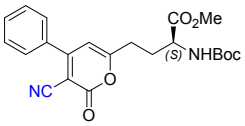

4p (64%)

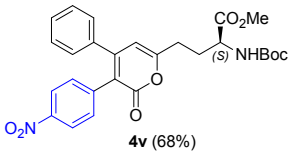

4q (80%)


4r (85%)

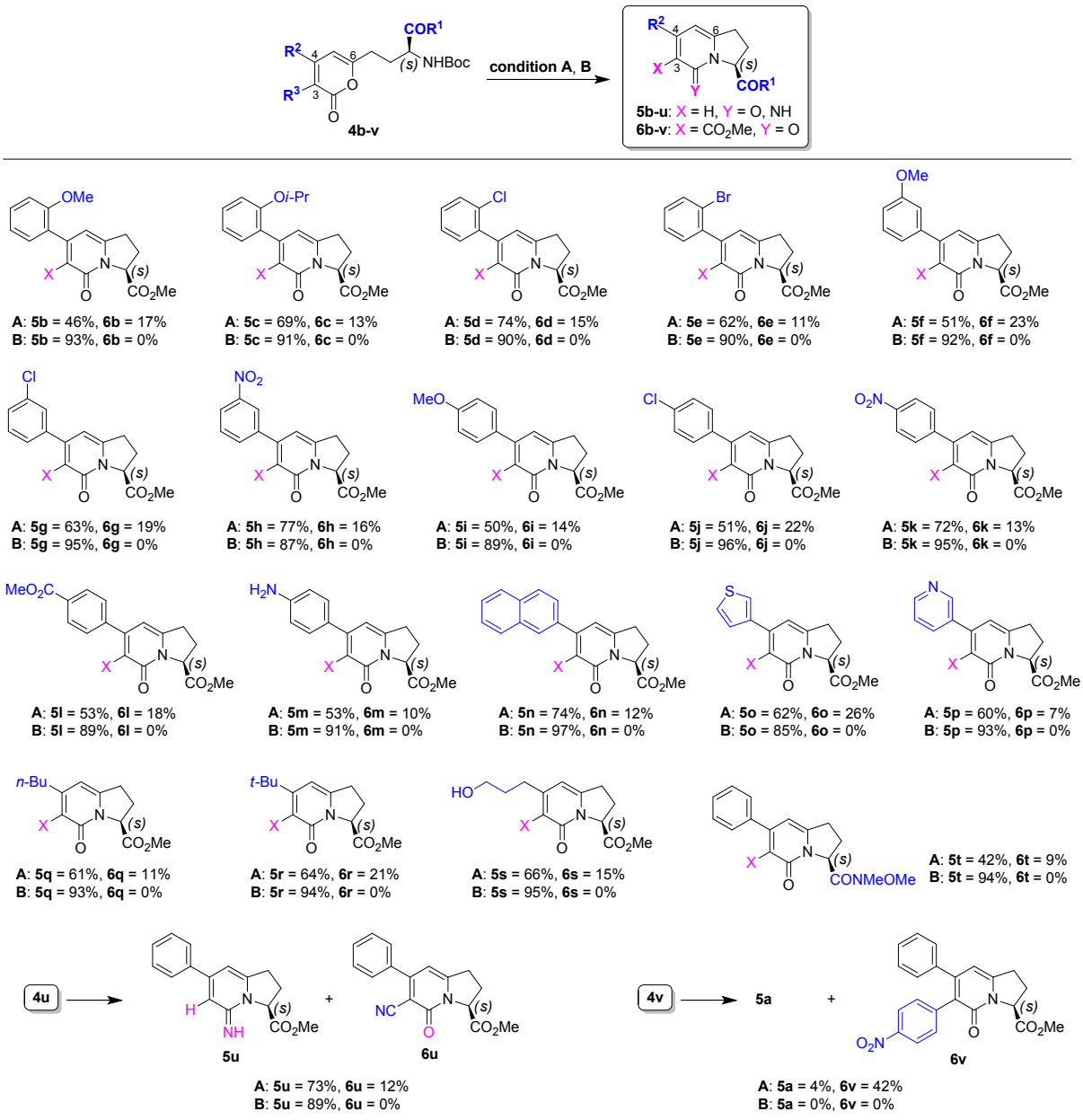

4s (81%)


4t (86%)


4u (32%)


4v (68%)

Scheme 5. Scope of Reactions using Substrates with Variations at the C3/4-Position and Various Functional Group Compatibilities[a]



[a] Condition A: TMSCl in MeOH at 150 °C, except for **4t** (100 °C for 1 h); Condition B: EG/water (1:1) at 110 °C for 4 h (**4b-k** and **4n**), 3.5 h (**4l**, **4o** and **4t**), 1.5 h (**4m** and **4p**), or 2 h (**4q-s** and **4u**) or at 150 °C for 3 h (**4v**).

Employment of condition A: In most cases, heating TMSCl in MeOH at 150 °C for 1 h preferentially generated the decarboxylation products **5** in moderate to excellent combined yields (46–93%), as shown in Scheme 5. When R^2 was an aryl group bearing electron-donating or electron-withdrawing groups at the *ortho*-, *meta*- or *para*-positions, the decarboxylation products

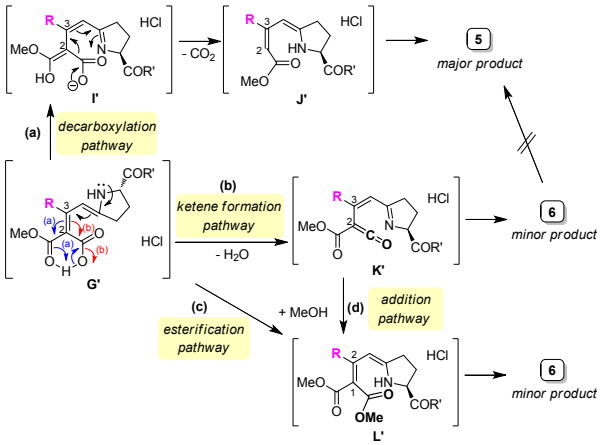
(**5b–m**) were formed in competition with the esterification products (**6b–m**) in ratios of 2.2–5.6:1. In the case of a bulkier electron-donating group, such as *ortho*-O^{i}PrAr in 4c, the combined yield and selectivity of the decarboxylation product (**5c**) was higher than that achieved with *ortho*-OMeAr (**5b**). The presence of a Cl-Ar group at the *ortho*- or *meta*-positions in **4d** and **4g** resulted in higher combined yields and product selectivity (**5d/6d** and **5g/6g**) than the presence of an OMe-directing group in **4b**. An *ortho*-Br group in **4e** was well tolerated, and the substrate gave the desired products 5e/6e in good yield and selectivity (5.6:1, 73% combined yield). The inductive effect of an NO_2 moiety at the *meta*-position in **4h** did not significantly enhance the reactivity of the C=O group toward decarboxylation over esterification compared to the effect of the neutral aromatic ring in **4a**, despite slightly improving the total chemical yield (4.8:1, 93% combined yield). Having strong electron-withdrawing substituents, NO_2 and NH_3^+, at the *para*-position, such as in **4k** and **4m**, favored the decarboxylation step and afforded the cyclization products **5k/6k** and **5m/6m** in 85% and 63% combined yields in ratios of 5.5:1 and 5.3:1, respectively, while **4l**, bearing a moderately electron-withdrawing group (*p*-CO_2MeAr), also resulted in a good yield with moderate selectivity (3:1, 72% combined yield). The presence of a naphthyl group in **4n** resulted in good product selectivity and a good combined yield (6.2:1, 86%). Heteroaromatic 2-pyrones bearing 3-thienyl (**4o**) and 3-pyridinyl (**4p**) moieties were also tolerated in this reaction, furnishing the desired products in moderate to good overall yields (88 and 67%, respectively), and the decarboxylation-to-esterification selectivity observed with 3-pyridinyl **4p** was higher by 8.6-fold. The reactions of 2-pyrones bearing long alkyl chains (**4q** and **4s**) and steric *t*-Bu groups (**4r**) also proceeded smoothly and gave both cyclization products (**5q/6q**, **5r/6r** and **5s/6s**) in moderate to good combined yields (72%, 85%, and 81%, respectively) in ratios of 3.0–5.5:1. Other 2-pyrone derivatives **4**, including the Weinreb amide 2-pyrone **4t**, cyano 2-pyrone **4u**, and 3,4-diaryl 2-pyrone **4v**, were also explored. In the case of the Weinreb amide 2-pyrone **4t**, the amide was sensitive to the acidic conditions and was

converted to methyl ester products. Fortunately, lowering the reaction temperature to 100 °C increased the combined yield (89%) and improved the **5t/6t** ratio (3.5:1). In the case of the 2-pyrone bearing a cyano group at C-3 (**4u**), the decarboxylation product, amidine **5u**, was obtained in good yield (73%) and selectivity (6:1). Notably, the ethyl derivative of 2-pyridone **6u** was selectively synthesized in good yield using our previously developed methodology, but **5u** was not observed.[5] We also demonstrated that these conditions were suitable for the preparation of 3,4-diaryl 2-pyridones. When **4v** was employed, the esterification product **6v** was obtained in a higher yield than that previously reported for a nonchiral version.[5] Surprisingly, **5a** was obtained, presumably from the loss of the nitroaryl group instead of CO_2.[10]

Employment of condition B: In general, performing a one-pot transformation in water at 110 °C produced exclusively the decarboxylation products **5b–u** in very good to excellent yields (85–97%), as shown in Scheme 5. The electronic nature of the substituent at C-4 only slightly affected the reaction rates and yields. When R^2 is an aryl group with substituents such as –Oalkyl (**4b**, **4c**, **4f**, and **4i**), –Cl or –Br (**4d**, **4e**, **4g**, and **4j**), and $–NO_2$ (**4h** and **4k**) at the *ortho*-, *meta*- or *para*-positions, the reaction rate was lower than that with **4a**, and the reaction was completed in 4 h to give the corresponding compounds **5** in very good to excellent yields (87–96%). The less soluble naphthyl group in **4n** resulted in a slow reaction rate and required a longer reaction time (4 h) for complete transformation to afford **5n** in excellent yield (97%). The introduction of weakly polar groups, such as aryl ester (**4l**) and 3-thienyl (**4o**), at R^2 did not significantly improve the water solubility, and the reaction was completed in 3.5 h to give **5l** and **5o** in very good yields (89% and 85%, respectively). When R^2 possessed polar functional groups that enhanced the water solubility, such as amine (**4m**) and pyridinyl (**4p**) groups, the reaction rates were faster than that with **4a**, and the reactions were complete within 1.5 h to give **5m** and **5p** in excellent yields (91% and 93%, respectively). Similarly, when R^2 was a small alkyl group (**4q** and **4r**), the reaction was completed within 2 h to give **5q** and **5r** in excellent yields (93% and

94%, respectively). Surprisingly, the reaction of pyrone possessing a long alkyl chain with an OTBS group (**4s**) in boiling water for 2 h unexpectedly afforded the corresponding alcohol (**5s**) in excellent yield (95%); the deprotection of OTBS under these conditions has not been previously reported. For pyrone with a weakly polar group at R^1, such as the Weinreb amide 2-pyrone **4t**, the reaction rate in boiling water was equal to that of **4a**, and the reaction was complete within 3.5 h to give **5t** in 94% yield. Other 2-pyrone derivatives **4**, including cyano 2-pyrone **4u** and 3,4-diaryl 2-pyrone **4v**, gave different results from those of condition A. In the case of the 2-pyrone bearing a cyano group at C-3 (**4u**), amidine **5u** was obtained as a single product, without **6u**, in very good yield (89%), after heating at 110 °C for 2 h. Due to the hydrophobicity of 3,4-diaryl 2-pyrone **4v**, a longer reaction time (3 h), higher temperature (150 °C), and cosolvent (EG or MeOH) were required to increase the solubility of **4v** in water and the acidity of the reaction. Although the reaction went to complete conversion, these conditions did not afford any 2-pyridone products. These results demonstrate that an alcohol could not trap the carboxyl intermediate **G** as a more stable ester via the esterification pathway (Scheme 2). Therefore, condition B was unsuitable for the preparation of 3,4-diaryl 2-pyridones.

Scheme 6. Proposed Transformations of **4a-t** to **5/6a-t** using Condition A



The proposed mechanisms for the formation of products **5** and **6** using condition A are depicted in Scheme 6. The driving force of the reaction was the nitrogen-facilitated

delocalization of electrons to active carboxylic derivatives of **G′** via (a) a decarboxylation pathway or (b) a ketene formation pathway to generate intermediates **J′** or **K′**, respectively. The formation of a detectable amount of **6** allowed us to determine the role of the alcoholic media in the reaction system. We envisaged that this product was generated via the direct intramolecular cycloaddition of the ketene intermediate **K′**, the esterification of intermediate **G′** (pathway c), or the nucleophilic addition of intermediate **K′** (pathway d) with an alcohol, and these intermediates could then undergo rotatory isomerization and ring closure to generate the corresponding 2-pyridone **6**. To implement these, **4a** was reacted in acidic EtOH instead of MeOH. Analysis of the crude reaction mixtures by GC/MS revealed high conversion to the esterification products **8a** and **10a** at 150 °C. Further studies were carried out to confirm the stability of **6** under the optimal conditions using **6a** and **6p** as representatives. No transformations of **6a/6p** to **5a/5p** were observed when **6a/6p** were subjected to the optimal conditions. Prolonged heating of **4a** for 4 h afforded **5a/6a** in a ratio of 13:1 and 72% combined yield. These results suggest that **5** could not be generated from **6** under condition A.

CONCLUSION

We have developed a facile and efficient one-pot method for synthesizing bicyclic 2-pyridones bearing a chiral center as a peptidomimetic core. Unlike other approaches, which normally employed Lewis acid/base- or metal-mediated cyclizations, our strategy provided mild condition and required no special treatment for multi-chemical transformations, including Boc deprotection, cyclic enamine formation, decarboxylation or esterification, isomerization, and lactamization, to furnish the bicyclic 2-pyridones in a one-pot process. An exploration of the substrate scope revealed some selectivity between the decarboxylation and esterification pathways under thermal acidic conditions using TMSCl in MeOH (condition A), while performing the reaction without any additional reagents in boiling water exclusively yielded the

decarboxylation products (condition B). Observation of CO_2Me group at C_3 in **6** would stem from the use of alcohol in acidic condition at high temperature for carboxylic activation to avoid the extrusion of CO_2 from intermediate B. In general, all substrates **4**, except pyrone with alkyl-OTBS **4s**, were tolerated under the applied conditions. The deprotection of OTBS group to the corresponding alcohol **5s** in boiling water has not been previously reported. The reaction in boiling water was particularly well suited for almost all substrates, except 3,4-diaryl 2-pyrone **4v**, and provided the desired products **5** in better yields than those produced by the other tested solvents. The addition of EG as a cosolvent improved the aqueous solubility of the pyrone **4** and significantly reduced the reaction time. Both conditions gave products with retention of the chirality at the α-carbon of the amino acid portion of the molecule.

EXPERIMENTAL SECTION

General Information:

Unless otherwise noted, all commercial-grade reagents and substrates **1a** and **2** were ordered from Sigma Aldrich, Fluka, Merck, TCI, and ACRŌS Organics. These chemicals were used without further purification. Substrate **1b** was prepared according to the literature. Solid-supported sulfonic acids, Amberlyst-15, Dowex-50WX4 and Amberlite-IR120H were dried under vacuum at room temperature before use. Anhydrous solvents were purified by a solvent purification system. MeOH and EG were used without further purification. Column chromatography was carried out using silica gel. Preparative thin-layer chromatography (PTLC) was carried out on a glass plate precoated with 0.25 mm of silica gel 60 F_{254}. Flash column chromatography was performed on 230-400 mesh silica gel. ^{1}H NMR spectra were recorded on a 300 MHz NMR spectrometer. Chemical shifts (δ values) for ^{1}H NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane (δ = 0.00 ppm) as an internal reference, and the coupling constants (*J* values) are in Hz. ^{13}C spectra were recorded on a 75 MHz NMR

spectrometer with complete proton decoupling. Infrared (IR) spectra were obtained using the universal attenuated total reflectance (UATR) technique and are reported in wavenumbers (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed using a time-of-flight (TOF) instrument. Optical rotations were recorded on a polarimeter. Melting points (mp) were determined and are reported without correction. HPLC analysis was performed on a chiral column with a UV/VIS detector.

Preparation of 1b. This compound was synthesized according to the literature method.[11] To a two-neck round-bottom flask containing a suspension of (*S*)-(-)-2-pyrrolidone 5-carboxylic acid (2.00 g, 15.5 mmol, 1.0 equiv) in DCM (70 mL) under an argon atmosphere was added dropwise *N*,*N'*-diisopropylethylamine (DIPEA, 6.0 mL, 34.4 mmol, 2.2 equiv). The mixture was cooled on an ice-bath, *N*,*N'*-diisopropylcarbodiimide (DIC, 2.7 mL, 17.2 mmol, 1.1 equiv) was added, and the reaction was stirred for 30 min. Then, *N*,*O*-dimethylhydroxyl amine hydrochloride (3.02 g, 31.0 mmol, 2.0 equiv) was directly added, followed by stirring at room temperature for an additional 2 days. The volatile material was concentrated to half its volume, and the mixture was cooled at -18 °C overnight. The urea byproduct was removed by filtration through a celite pad, and the filtrate was concentrated under reduced pressure. The crude product was dissolved in DCM (30 mL), and a solution of Boc_2O (3.38 g, 15.5 mmol) in DCM (10 mL), triethylamine (2.2 mL, 15.8 mmol), and DMAP (300 mg, 2.5 mmol) was added. The reaction was stirred at room temperature for 14 h, quenched with 10% citric acid (20 mL), and extracted with DCM (2 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel (hexane/EtOAc = 4:1 to 1:4) to afford **1b** as yellow oil (4.23 g, 72% yield).

*tert-Butyl (S)-2-(methoxy(methyl)carbamoyl)-5-oxopyrrolidine-1-carboxylate (**1b**).*

$[\alpha]_D^{28}$ -11 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 2979, 1786, 1754, 1714, 1673, 1458, 1305, 1253, 1150, 1022, 997, 843, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (dd, *J* = 9.3, 2.5 Hz, 1H), 3.79 (s, 3H), 3.24 (s, 3H), 2.72–2.57 (m, 1H), 2.45 (ddd, *J* = 17.3, 9.3, 3.0 Hz, 1H), 2.38–2.22 (m, 1H), 1.95 (ddt, *J* = 9.8, 5.4, 2.7 Hz, 1H), 1.91 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 173.8, 171.4, 149.4, 82.9, 61.3, 56.7, 32.3, 30.9, 27.8, 21.2; HRMS (ESI-TOF) calcd for $C_{12}H_{20}N_2Na_1O_5$ $(M+Na)^+$ 295.1264, found 295.1265.

General Procedure for the Synthesis of Internal Ynones 3a–t. Lithium hexamethyldisilazane (LHMDS, 1 M in THF, 6.2 mL, 6.2 mmol, 1.5 equiv) was added dropwise to a two-neck round-bottom flask containing a solution of alkyne **2** (6.2 mmol, 1.5 equiv) in THF (5 mL) under an argon atmosphere at -78 °C and stirred for 1 h. Then, a solution of the lactam **1** (4.1 mmol, 1.0 equiv) in THF (5 mL) was added dropwise, and the mixture was stirred for an additional 6 h. The reaction was quenched with sat. NH_4Cl (10 mL), gradually warmed to room temperature, and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using hexane and EtOAc as eluents to afford compound **3**.[12]

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-5-oxo-7-phenyl-6-heptynoate (**3a**)*. Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 10:1), the product **3a** was obtained as a brown solid (1.20 g, 85% yield), mp 52.7–53.5 °C; $[\alpha]_D^{27}$ +13.3 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3366, 2978, 2200, 1742, 1713, 1674, 1444, 1367, 1248, 1159, 1054, 760, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 2H), 7.50–7.31 (m, 3H), 5.29 (d, *J* = 7.9 Hz, 1H), 4.42–4.28 (m, 1H), 3.76 (s, 3H), 2.91–2.69 (m, 2H), 2.36–2.20 (m, 1H), 2.11–1.97 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.9, 172.4, 155.2, 132.9, 130.6, 128.5, 119.6, 91.1, 87.4, 79.8, 52.6, 52.2,

41.2, 28.1, 26.5; HRMS (ESI-TOF) calcd for $C_{19}H_{23}N_1Na_1O_5$ $(M+Na)^+$ 368.1474, found 368.1472. These spectroscopic data were identical to those reported previously.[12a]

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(2-methoxyphenyl)-5-oxo-6-heptynoate (**3b**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3b** was obtained as yellow oil (1.31 g, 85% yield), $[\alpha]_D^{29}$ +12.8 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3373, 2977, 2196, 1712, 1667, 1596, 1491, 1366, 1247, 1161, 1022, 852, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.37 (m, 2H), 6.98–6.88 (m, 2H), 5.38 (d, *J* = 8.1 Hz, 1H), 4.42–4.29 (m, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 2.92–2.68 (m, 2H), 2.38–2.20 (m, 1H), 2.19–2.04 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.9, 172.4, 161.2, 155.1, 134.6, 132.4, 120.3, 110.6, 108.6, 91.3, 88.7, 79.6, 55.5, 52.6, 52.4, 41.2, 27.9, 26.4; HRMS (ESI-TOF) calcd for $C_{20}H_{25}N_1Na_1O_6$ $(M+Na)^+$ 398.1580, found 398.1577.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(2-isopropoxyphenyl)-5-oxo-6-heptynoate (**3c**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 4:1), the product **3c** was obtained as brown oil (1.39 g, 84% yield), $[\alpha]_D^{26}$ +37.1 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3367, 2978, 2195, 1739, 1715, 1667, 1486, 1366, 1273, 1161, 1051, 950, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.37 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H), 6.94–6.87 (m, 2H), 5.16 (d, *J* = 7.4 Hz, 1H), 4.67–4.55 (m, 1H), 4.40–4.28 (m, 1H), 3.74 (s, 3H), 2.87–2.68 (m, 2H), 2.35–2.20 (m, 1H), 2.17–2.00 (m, 1H), 1.43 (s, 9H), 1.38 (d, *J* = 6.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 186.2, 172.5, 160.2, 155.2, 135.0, 132.3, 120.4, 113.8, 110.3, 91.4, 89.6, 79.9, 71.5, 52.8, 52.3, 41.4, 28.2, 26.8, 21.9; HRMS (ESI-TOF) calcd for $C_{22}H_{29}N_1Na_1O_6$ $(M+Na)^+$ 426.1893, found 426.1888.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(2-chlorophenyl)-5-oxo-6-heptynoate (**3d**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 4:1), the product **3d** was obtained as brown oil (872 mg, 56%

yield), $[\alpha]_D^{26}$ +17.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3368, 2978, 2204, 1739, 1712, 1674, 1503, 1366, 1247, 1159, 1050, 757, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.48–7.36 (m, 2H), 7.28 (ddd, *J* = 7.5, 7.4, 1.6 Hz, 1H), 5.33 (d, *J* = 7.4 Hz, 1H), 4.44–4.30 (m, 1H), 3.76 (s, 3H), 2.95–2.72 (m, 2H), 2.40–2.25 (m, 1H), 2.22–2.00 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.8, 172.4, 155.2, 137.3, 134.6, 131.7, 129.5, 126.7, 119.9, 91.3, 87.4, 79.9, 52.6, 52.3, 41.4, 28.1, 26.7; HRMS (ESI-TOF) calcd for $C_{19}H_{22}Cl_1N_1Na_1O_5$ $(M+Na)^+$ 402.1084, found 402.1089.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(2-bromophenyl)-5-oxo-6-heptynoate (**3e**)*.

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 4:1), the product **3e** was obtained as brown oil (1.01 g, 58% yield), $[\alpha]_D^{26}$ +19.6 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3368, 2978, 2204, 1739, 1710, 1673, 1468, 1366, 1246, 1160, 1026, 757, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66–7.55 (m, 2H), 7.37–7.27 (m, 2H), 5.33 (d, *J* = 8.4 Hz, 1H), 4.43–4.30 (m, 1H), 3.76 (s, 3H), 2.95–2.75 (m, 2H), 2.40–2.25 (m, 1H), 2.23–2.00 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.7, 172.3, 155.1, 134.6, 132.5, 131.7, 127.1, 126.5, 122.0, 90.5, 88.9, 79.7, 52.5, 52.2, 41.3, 28.0, 26.5; HRMS (ESI-TOF) calcd for $C_{19}H_{22}Br_1N_1Na_1O_5$ $(M+Na)^+$ 446.0579, found 446.0586.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(3-methoxyphenyl)-5-oxo-6-heptynoate (**3f**)*.

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3f** was obtained as brown oil (1.26 g, 82% yield), $[\alpha]_D^{28}$ +12.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3368, 2976, 2192, 1739, 1715, 1670, 1489, 1366, 1207, 1162, 1045, 783, 684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.00 (ddd, *J* = 8.3, 7.8, 1.7 Hz, 1H), 5.46 (d, *J* = 8.2 Hz, 1H), 4.43–4.30 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.92–2.70 (m, 2H), 2.38–2.20 (m, 1H), 2.14–1.97 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.7, 172.3,

159.0, 155.1, 129.4, 125.1, 120.3, 117.2, 90.7, 86.9, 79.5, 54.9, 52.4, 52.0, 41.0, 27.9, 26.1; HRMS (ESI-TOF) calcd for $C_{20}H_{25}N_1Na_1O_6$ $(M+Na)^+$ 398.1580, found 398.1581.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(3-chlorophenyl)-5-oxo-6-heptynoate (**3g**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3g** was obtained as brown oil (965 mg, 62% yield), $[\alpha]_D^{26}$ +17.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3375,2978, 2006, 1744, 1713, 1676, 1503, 1367, 1249, 1163, 1056, 788, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.54 (m, 1H), 7.48–7.41 (m, 2H), 7.34 (d, *J* = 7.7 Hz, 1H), 5.20 (d, *J* = 7.4 Hz, 1H), 4.44–4.30 (m, 1H), 3.77 (s, 3H), 2.91–2.69 (m, 2H), 2.35–2.22 (m, 1H), 2.13–1.96 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.7, 172.5, 155.3, 134.5, 132.6, 130.99, 130.96, 129.8, 121.4, 89.0, 87.9, 80.0, 52.6, 52.4, 41.3, 28.2, 26.6; HRMS (ESI-TOF) calcd for $C_{19}H_{22}Cl_1N_1Na_1O_5$ $(M+Na)^+$ 402.1084, found 402.1089.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(3-nitrophenyl)-5-oxo-6-heptynoate (**3h**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 10:1), the product **3h** was obtained as brown solid (736 mg, 46% yield), mp 69.5–71.1 °C; $[\alpha]_D^{28}$ +11.7 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3393, 2978, 2208, 1740, 1711, 1675, 1532, 1352, 1252, 1161, 1053, 734, 672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 1.7, 1.7 Hz, 1H), 8.33 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1H), 7.91 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.66 (dd, *J* = 8.3, 7.8 Hz, 1H), 5.37 (d, *J* = 8.1 Hz, 1H), 4.47–4.32 (m, 1H), 3.79 (s, 3H), 3.00–2.77 (m, 2H), 2.40–2.25 (m, 1H), 2.15–2.00 (m, 1H), 1.46 (s, 9H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.3, 172.3, 155.2, 147.8, 138.2, 129.7, 127.3, 125.0, 121.4, 88.3, 86.9, 79.7, 52.4, 52.2, 41.1, 28.0, 26.2; HRMS (ESI-TOF) calcd for $C_{19}H_{22}N_2Na_1O_7$ $(M+Na)^+$ 413.1325, found 413.1330.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(4-methoxyphenyl)-5-oxo-6-heptynoate (**3i**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3i** was obtained as yellow solid (1.12 g, 73% yield), mp 63.5–65.1 °C; $[\alpha]_D^{27}$ +105.8 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3367, 2979, 2191, 1739, 1715, 1602, 1441, 1366, 1251, 1162, 1026, 834, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.43 (d, *J* = 8.2 Hz, 1H), 4.42–4.30 (m, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 2.90–2.68 (m, 2H), 2.35–2.20 (m, 1H), 2.13–1.98 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.7, 172.3, 161.4, 155.1, 134.8, 114.1, 111.1, 92.2, 87.1, 79.5, 55.0, 52.5, 52.0, 40.9, 27.9, 26.3; HRMS (ESI-TOF) calcd for $C_{20}H_{25}N_1Na_1O_6$ $(M+Na)^+$ 398.1580, found 398.1587.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(4-chlorophenyl)-5-oxo-6-heptynoate (**3j**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3j** was obtained as a brown solid (1.29 g, 83% yield), mp 93.5–96.4 °C; $[\alpha]_D^{27}$ +6.5 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3367, 2978, 2202, 1711, 1674, 1489, 1366, 1248, 1160, 1089, 1014, 830, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 5.33 (d, *J* = 8.3 Hz, 1H), 4.43–4.30 (m, 1H), 3.76 (s, 3H), 2.92–2.69 (m, 2H), 2.38–2.20 (m, 1H), 2.14–1.97 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.6, 172.3, 155.2, 136.9, 134.0, 128.9, 118.0, 89.5, 88.0, 79.7, 52.5, 52.2, 41.1, 28.0, 26.3; HRMS (ESI-TOF) calcd for $C_{19}H_{22}Cl_1N_1Na_1O_5$ $(M+Na)^+$ 402.1084, found 402.1088.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(4-nitrophenyl)-5-oxo-6-heptynoate (**3k**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3k** was obtained as brown oil (881 mg, 55% yield), $[\alpha]_D^{27}$ +5.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3385, 2978, 2208, 1739, 1710, 1676, 1521, 1344, 1268, 1161, 1052, 857, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 2H),

7.76 (d, J = 8.7 Hz, 2H), 5.28 (d, J = 7.7 Hz, 1H), 4.45–4.30 (m, 1H), 3.78 (s, 3H), 2.96–2.75 (m, 2H), 2.40–2.23 (m, 1H), 2.13–1.98 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.4, 172.3, 155.2, 148.4, 133.5, 126.3, 123.6, 90.2, 87.1, 79.9, 52.5, 52.3, 41.2, 28.1, 26.4; HRMS (ESI-TOF) calcd for $C_{19}H_{22}N_2Na_1O_7$ $(M+Na)^+$ 413.1325, found 413.1338.

*Methyl (S)-4-[6-((tert-butoxycarbonyl)amino)-7-methoxy-3,7-dioxo-1-heptynyl]benzoate (**3l**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3l** was obtained as a pale yellow solid (1.36 g, 82% yield), mp 73.3–75.5 °C; $[\alpha]_D^{27}$ +23.6 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3376, 2954, 2204, 1715, 1674, 1507, 1436, 1366, 1273, 1162, 1095, 769, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 5.24 (d, J = 7.3 Hz, 1H), 4.43–4.30 (m, 1H), 3.94 (s, 3H), 3.77 (s, 3H), 2.93–2.60 (m, 2H), 2.37–2.20 (m, 1H), 2.13–1.95 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.6, 172.3, 165.7, 155.2, 132.5, 131.5, 129.4, 124.0, 89.0, 88.9, 79.7, 52.5, 52.1, 41.2, 28.0, 26.2; HRMS (ESI-TOF) calcd for $C_{21}H_{25}N_1Na_1O_7$ $(M+Na)^+$ 426.1529, found 426.1523.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-[4-(tert-butoxycarbonyl)amino]phenyl-5-oxo-6-heptynoate (**3m**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 7:3), the product **3m** was obtained as a yellow solid (756 mg, 40% yield), mp 125.8–127.9 °C; $[\alpha]_D^{28}$ +11.3 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3357, 2979, 2191, 1698, 1585, 1518, 1367, 1314, 1229, 1151, 1049, 839, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 9.2 Hz, 2H), 7.45 (d, J = 9.2 Hz, 2H), 5.28 (d, J = 8.1 Hz, 1H), 4.42–4.30 (m, 1H), 3.76 (s, 3H), 2.89–2.67 (m, 2H), 2.35–2.20 (m, 1H), 2.15–1.97 (m, 1H), 1.52 (s, 9H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 186.1, 172.5, 155.3, 152.2, 141.2, 134.2, 117.9, 113.0, 92.4, 87.4, 81.0, 80.0, 52.7, 52.3, 41.1, 28.1, 28.1, 26.5; HRMS (ESI-TOF) calcd for $C_{24}H_{32}N_2Na_1O_7$ $(M+Na)^+$ 483.2107, found 483.2119.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-7-(2-naphthalenyl)-5-oxo-6-heptynoate (**3n**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 5:1), the product **3n** was obtained as brown oil (1.20 g, 74% yield), $[\alpha]_D^{26}$ +24.7 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3365, 2977, 2195, 1739, 1711, 1668, 1501, 1436, 1366, 1161, 1051, 817, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 1.0 Hz, 1H), 7.87–7.80 (m, 3H), 7.60–7.49 (m, 3H), 5.18 (d, *J* = 7.5 Hz, 1H), 4.45–4.33 (m, 1H), 3.77 (s, 3H), 2.95–2.70 (m, 2H), 2.38–2.23 (m, 1H), 2.15–2.00 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 186.1, 172.6, 155.4, 134.4, 133.9, 132.6, 128.4, 128.3, 128.2, 128.0, 127.8, 127.0, 116.9, 91.8, 87.7, 80.1, 52.8, 52.4, 41.4, 28.2, 26.7; HRMS (ESI-TOF) calcd for $C_{23}H_{25}N_1Na_1O_5$ $(M+Na)^+$ 418.1630, found 418.1639.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-5-oxo-7-(3-thioenyl)-6-heptynoate (**3o**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3o** was obtained as a brown solid (720 mg, 50% yield), mp 60.0–62.1 °C; $[\alpha]_D^{28}$ +4.3 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3372, 2978, 2193, 1739, 1709, 1667, 1505, 1365, 1248, 1160, 1053, 787, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.35 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.22 (dd, *J* = 5.1, 1.2 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 4.43–4.29 (m, 1H), 3.76 (s, 3H), 2.90–2.68 (m, 2H), 2.33–2.20 (m, 1H), 2.13–1.95 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.9, 172.4, 155.2, 1433.9, 130.0, 126.1, 118.8, 87.6, 86.5, 79.8, 52.6, 52.2, 41.0, 28.1, 26.4; HRMS (ESI-TOF) calcd for $C_{17}H_{21}N_1Na_1O_5S$ $(M+Na)^+$ 374.1038, found 374.1041.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-5-oxo-7-(3-pyridinyl)-6-heptynoate (**3p**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3p** was obtained as brown oil (596 mg, 42% yield), $[\alpha]_D^{28}$ +12.5 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3363, 2977, 2205, 1743, 1709, 1674, 1514,

1366, 1249, 1159, 1024, 808, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 2.1, 0.9 Hz, 1H), 8.67 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.87 (ddd, *J* = 7.9, 2.1, 1.7 Hz, 1H), 7.35 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 5.15 (d, *J* = 7.3 Hz, 1H), 4.42–4.30 (m, 1H), 3.77 (s, 3H), 2.95–2.71 (m, 2H), 2.36–2.20 (m, 1H), 2.11–1.96 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 185.6, 172.5, 155.3, 153.3, 150.8, 139.9, 123.2, 117.2, 99.0, 87.1, 80.2, 52.7, 52.5, 41.3, 28.3, 26.5; HRMS (ESI-TOF) calcd for $C_{18}H_{22}N_2Na_1O_5$ $(M+Na)^+$ 369.1426, found 369.1428.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-5-oxo-6-undecynoate (**3q**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 4:1), the product **3q** was obtained as brown oil (614 mg, 46% yield), $[\alpha]_D^{27}$ +18.2 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3367, 2959, 2211, 1715, 1674, 1502, 1437, 1366, 1247, 1160, 1050, 870, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (d, *J* = 6.9 Hz, 1H), 4.36–4.22 (m, 1H), 3.75 (s, 3H), 2.77–2.53 (m, 2H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.27–2.10 (m, 1H), 2.05–1.87 (m, 1H), 1.63–1.48 (m, 2H), 1.50–1.35 (m, 12H), 0.93 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 186.1, 172.4, 155.2, 94.8, 80.4, 79.7, 52.6, 52.1, 41.2, 29.4, 28.0, 26.3, 21.7, 18.4, 13.2; HRMS (ESI-TOF) calcd for $C_{17}H_{27}N_1Na_1O_5$ $(M+Na)^+$ 348.1787, found 348.1795.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-8,8-dimethyl-5-oxo-6-nonynoate (**3r**).*

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 4:1), the product **3r** was obtained as yellow oil (601 mg, 45% yield), $[\alpha]_D^{27}$ +23.4 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3367, 2974, 2213, 1715, 1674, 1501, 1456, 1366, 1262, 1162, 1053, 867, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (d, *J* = 7.1 Hz, 1H), 4.37–4.24 (m, 1H), 3.75 (s, 3H), 2.77–2.52 (m, 2H), 2.27–2.11 (m, 1H), 2.06–1.89 (m, 1H), 1.45 (s, 9H), 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 186.1, 172.3, 155.1, 101.6, 79.5, 78.7, 52.5, 52.0, 41.1, 29.7, 27.9, 26.2; HRMS (ESI-TOF) calcd for $C_{17}H_{27}N_1Na_1O_5$ $(M+Na)^+$ 348.1787, found 348.1797.

*Methyl (S)-2-[(tert-butoxycarbonyl)amino]-10-[(tert-butyldimethylsilyl)oxy]-5-oxo-6-decynoate (**3s**)*.

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 4:1), the product **3s** was obtained as brown oil (1.18 g, 65% yield), $[\alpha]_D^{29}$ +16.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3367, 2954, 2212, 1716, 1676, 1501, 1366, 1251, 1162, 1103, 834, 776, 662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (d, *J* = 7.4 H, 1H), 4.30–4.19 (m, 1H), 3.71 (s, 3H), 3.65 (t, *J* = 5.8 Hz, 2H), 2.63–2.50 (m, 2H), 2.43 (t, *J* = 7.1 H, 2H), 2.22–2.08 (m, 1H), 2.00–1.85 (m, 1H), 1.41 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 186.1, 172.5, 155.2, 94.6, 80.5, 79.9, 61.1, 52.7, 52.3, 41.3, 30.6, 28.2, 26.5, 25.8, 18.2, 15.3, -5.5; HRMS (ESI-TOF) calcd for $C_{22}H_{39}N_1Na_1O_6Si$ $(M+Na)^+$ 464.2444, found 464.2442.

*tert-Butyl (S)-1-[methoxy(methyl)amino]-1,5-dioxo-7-phenyl-6-heptyn-2-yl-carbamate (**3t**)*.

Following the general procedure for the synthesis of internal ynones and purification by column chromatography (hexane/EtOAc = 3:1), the product **3t** was obtained as yellow oil (845 mg, 55% yield), $[\alpha]_D^{27}$ –1.5 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3326, 2976, 2201, 1709, 1665, 1489, 1366, 1248, 1164, 1049, 992, 758, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.54 (m, 2H), 7.51–7.34 (m, 3H), 5.33 (m, 1H), 4.82–4.65 (m, 1H), 3.79 (s, 3H), 3.23 (s, 3H), 2.90–2.70 (m, 2H), 2.27–2.10 (m, 1H), 2.09–1.87 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 186.1, 172.1, 155.3, 132.8, 130.5, 128.4, 119.6, 90.6, 87.4, 79.4, 61.4, 49.5, 41.0, 31.9, 28.1, 26.5; HRMS (ESI-TOF) calcd for $C_{20}H_{26}N_2Na_1O_5$ $(M+Na)^+$ 397.1739, found 397.1742.

General Procedure for the Synthesis of 2-Pyrones 4a–v. To a two-neck round-bottom flask containing a suspension of sodium hydride (20 mg, 60% in oil, 0.5 mmol, 0.5 equiv) in THF (0.2 mL) under an argon atmosphere was added dropwise a solution of dimethyl malonate (159 mg, 1.20 mmol, 1.2 equiv) in THF (1.7 mL) at room temperature, and the resulting mixture was stirred for 5 min. Then, a solution of the ynone **3a–t** (1.00 mmol, 1.0 equiv) in THF (1.7 mL)

was added, and the reaction was refluxed at 65 °C for 3 h. The reaction was cooled to room temperature, quenched with sat. NH_4Cl (10 mL), and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography on silica gel using hexane and EtOAc as eluents to afford the 2-pyrones **4a–t**. Compounds **4u** and **4v** were synthesized according to the general procedure using **3u** or **3v** (1.00 mmol) with ethyl cyanoacetate (136 mg, 1.2 mmol, 1.2 equiv) or ethyl 4-nitrophenylacetate (251 mg, 1.2 mmol, 1.2 equiv), respectively.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-2-oxo-4-phenyl-2H-pyran-3-carboxylate (**4a**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4a** was obtained as yellow oil (1.09 g, 85% yield), $[\alpha]_D^{27}$ +32.5 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3366, 2977, 1708, 1637, 1545, 1435, 1367, 1249, 1159, 1033, 817, 766, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.35 (m, 5H), 6.21 (s, 1H), 5.19 (d, *J* = 7.8 Hz, 1H), 4.45–4.30 (m, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 2.75–2.58 (m, 2H), 2.35–2.20 (m, 1H), 2.10–1.95 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.2, 164.4, 159.7, 155.2, 154.9, 135.7, 130.2, 128.7, 127.0, 116.0, 105.8, 80.1, 52.4, 30.0, 29.7, 28.1; HRMS (ESI-TOF) calcd for $C_{23}H_{28}N_1O_8$ $(M+H)^+$ 446.1815, found 446.1807.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(2-methoxyphenyl)-2-oxo-2H-pyran-3-carboxylate (**4b**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4b** was obtained as yellow oil (347 mg, 73% yield), $[\alpha]_D^{28}$ +41.2 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3369, 2951, 1712, 1637, 1541, 1494, 1435, 1366, 1251, 1161, 1023, 756, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.20 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.00 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.95 (d, *J* = 8.3

Hz, 1H), 6.15 (s, 1H), 5.21 (d, *J* = 7.8 Hz, 1H), 4.40–4.29 (m, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H), 2.70–2.50 (m, 2H), 2.33–2.18 (m, 1H), 2.08–1.90 (m, 1H), 1.43 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 164.9, 163.8, 159.7, 155.7, 155.2, 154.1, 131.3, 128.7, 120.7, 116.6, 110.9, 107.1, 80.0, 55.3, 52.6, 52.4, 52.0, 29.9, 29.8, 28.1; HRMS (ESI-TOF) calcd for $C_{24}H_{29}N_1Na_1O_9$ $(M+Na)^+$ 498.1740, found 498.1745.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(2-iso-propoxy phenyl)-2-oxo-2H-pyran-3-carboxylate (**4c**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4c** was obtained as yellow oil (403 mg, 80% yield), $[\alpha]_D^{27}$ +32.6 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3363, 2979, 1737, 1712, 1638, 1489, 1451, 1366, 1248, 1161, 1023, 734, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.31 (m, 1H), 7.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.00–6.90 (m, 2H), 6.18 (s, 1H), 5.30 (d, *J* = 8.2 Hz, 1H), 4.61–4.48 (m, 1H), 4.45–4.30 (m, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 2.72–2.55 (m, 2H), 2.34–2.18 (m, 1H), 2.10–1.94 (m, 1H) , 1.43 (s, 9H) , 1.29 (d, *J* = 6.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.1, 164.6, 163.3, 159.6, 155.1, 154.7, 154.0, 130.9, 128.7, 126.3, 120.4, 116.5, 114.0, 107.1, 79.8, 71.0, 52.5, 52.3, 51.8, 29.7, 29.7, 28.0, 21.6; HRMS (ESI^+) calcd for $C_{26}H_{33}N_1Na_1O_9$ $(M+Na)^+$ 526.2053, found 526.2066.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(2-chlorophenyl)-2-oxo-2H-pyran-3-carboxylate (**4d**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4d** was obtained as yellow oil (254 mg, 53% yield), $[\alpha]_D^{27}$ +23.1 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3368, 2978, 1713, 1637, 1542, 1435, 1366, 1249, 1160, 1104, 1021, 760, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.41–7.28 (m, 2H), 7.21 (dd, *J* = 7.4, 1.9 Hz, 1H), 6.09 (s, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 4.40–4.29 (m, 1H), 3.76 (s, 3H), 3.60 (s, 3H), 2.74–2.58 (m, 2H), 2.47–2.20 (m, 1H), 2.12–1.95

(m, 1H), 1.43 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 164.9, 164.1, 159.1, 155.2, 154.9, 135.1, 131.2, 130.6, 129.9, 128.6, 126.9, 117.1, 106.3, 80.2, 52.6, 52.5, 52.4, 30.1, 29.9, 28.2; HRMS (ESI-TOF) calcd for $C_{23}H_{26}Cl_1N_1Na_1O_8$ $(M+Na)^+$ 502.1245, found 502.1258.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(2-bromophenyl)-2-oxo-2H-pyran-3-carboxylate (**4e**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4e** was obtained as yellow oil (283 mg, 54% yield), $[\alpha]_D^{27}$ +8.7 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3371, 2977, 1712, 1636, 1542, 1435, 1365, 1248, 1259, 1103, 1019, 760, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.62 (m, 1H), 7.40–7.33 (m, 1H), 7.31–7.24 (m, 1H), 7.21–7.16 (m, 1H), 6.06 (s, 1H), 5.12 (br s, 1H), 4.40 (br s, 1H), 3.76 (s, 3H), 3.59 (s, 3H), 2.71–2.58 (m, 2H), 2.35–2.20 (m, 1H), 2.10–1.95 (m, 1H), 1.43 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 164.9, 164.0, 159.2, 156.4, 155.2, 137.2, 133.1, 130.6, 128.6, 127.4, 120.4, 117.0, 106.4, 80.3, 52.7, 52.6, 52.4, 30.1, 29.9, 28.2; HRMS (ESI-TOF) calcd for $C_{23}H_{26}Br_1N_1Na_1O_8$ $(M+Na)^+$ 546.0739, found 546.0728.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(3-methoxyphenyl)-2-oxo-2H-pyran-3-carboxylate (**4f**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4f** was obtained as yellow oil (343 mg, 72% yield), $[\alpha]_D^{26}$ +36.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3372, 2972, 1737, 1708, 1637, 1548, 1434, 1365, 1241, 1161, 1026, 781, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.0, 7.9 Hz, 1H), 6.93–6.83 (m, 3H), 6.14 (s, 1H), 5.22 (d, *J* = 8.4 Hz, 1H), 4.35–4.20 (m, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.61 (s, 3H), 2.65–2.50 (m, 2H), 2.28–2.14 (m, 1H), 2.05–1.87 (m, 1H), 1.35 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.2, 164.3, 159.6, 155.2, 154.7, 136.9, 129.9, 119.3, 116.0, 115.9, 112.4, 105.7, 80.0, 55.2, 52.42, 52.37, 29.9, 29.7, 28.0; HRMS (ESI-TOF) calcd for $C_{24}H_{29}N_1Na_1O_9$ $(M+Na)^+$ 498.1740, found 498.1750.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(3-chlorophenyl)-2-oxo-2H-pyran-3-carboxylate (**4g**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4g** was obtained as yellow oil (388 mg, 81% yield), $[\alpha]_D^{28}$ +11.7 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3371, 2954, 1737, 1710, 1638, 1546, 1435, 1366, 1249, 1161, 1027, 786 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.34 (m, 3H), 7.30–7.26 (m, 1H), 6.17 (s, 1H), 5.14 (d, *J* = 7.6 Hz, 1H), 4.44–4.30 (m, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.75–2.57 (m, 2H), 2.36–2.22 (m, 1H), 2.07–1.94 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.3, 165.0, 164.9, 159.5, 155.3, 153.5, 137.5, 135.0, 130.3, 130.2, 127.3, 125.4, 116.6, 105.5, 80.4, 52.7, 52.6, 52.5, 30.1, 30.0, 28.2; HRMS (ESI-TOF) calcd for $C_{23}H_{26}Cl_1N_1Na_1O_8$ $(M+Na)^+$ 502.1245, found 502.1242.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(3-nitrophenyl)-2-oxo-2H-pyran-3-carboxylate (**4h**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4h** was obtained as a yellow solid (441 mg, 90% yield), mp 51.8–53.0 °C; $[\alpha]_D^{27}$ +14.5 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3378, 2978, 1710, 1638, 1530, 1436, 1349, 1253, 1208, 1161, 1028, 816, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37–8.26 (m, 2H), 7.82–7.75 (m, 1H), 7.69 (dd, *J* = 8.1, 7.9 Hz, 1H), 6.29 (s, 1H), 5.34 (d, *J* = 8.4 Hz, 1H), 4.45–4.30 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.82–2.65 (m, 2H), 2.40–2.25 (m, 1H), 2.15–1.97 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.1, 165.6, 162.4, 159.0, 155.2, 152.5, 148.1, 137.2, 133.0, 130.0, 124.6, 122.1, 116.7, 105.1, 80.0, 52.6, 52.4, 52.3, 30.0, 29.6, 28.0; HRMS (ESI-TOF) calcd for $C_{23}H_{26}N_2Na_1O_{10}$ $(M+Na)^+$ 513.1485, found 513.1479.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(4-methoxyphenyl)-2-oxo-2H-pyran-3-carboxylate (**4i**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4i** was obtained as a yellow solid (357 mg, 75% yield), mp 59.1–61.5 °C; $[\alpha]_D^{26}$ +27.4 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3371, 2977, 1708, 1606, 1512, 1435, 1366, 1250, 1161, 1028, 832, 734, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.22 (s, 1H), 5.25 (d, *J* = 8.2 Hz, 1H), 4.45–4.30 (m, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 2.73–2.57 (m, 2H), 2.35–2.20 (m, 1H), 2.10–1.95 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.7, 164.0, 161.3, 159.9, 155.2, 154.3, 128.9, 127.7, 114.9, 114.2, 105.7, 80.1, 55.3, 52.4, 52.4, 30.0, 29.8, 28.1; HRMS (ESI-TOF) calcd for $C_{24}H_{29}N_1Na_1O_9$ $(M+Na)^+$ 498.1740, found 498.1734.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(4-chlorophenyl)-2-oxo-2H-pyran-3-carboxylate (**4j**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4j** was obtained as a yellow solid (403 mg, 84% yield), mp 60.2–62.1 °C, $[\alpha]_D^{26}$ +19.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3371, 2978, 1709, 1637, 1544, 1493, 1366, 1250, 1160, 1090, 1025, 828, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 6.18 (s, 1H), 5.21 (d, *J* = 8.0 Hz, 1H), 4.45–4.30 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.75–2.58 (m, 2H), 2.36–2.20 (m, 1H), 2.10–1.94 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.0, 164.7, 159.5, 155.3, 153.7, 136.5, 134.1, 129.1, 128.5, 116.2, 105.5, 80.2, 52.6, 52.5, 52.5, 30.0, 29.8, 28.2; HRMS (ESI-TOF) calcd for $C_{23}H_{26}Cl_1N_1Na_1O_8$ $(M+Na)^+$ 502.1245, found 502.1238.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(4-nitrophenyl)-2-oxo-2H-pyran-3-carboxylate (**4k**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:2), the product **4k** was obtained as a yellow solid (432 mg, 88% yield), mp 70.5–72.1 °C; $[\alpha]_D^{26}$ +27.8 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3374, 2972, 1711,

1638, 1548, 1521, 1435, 1347, 1255, 1160, 1024, 844, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 6.20 (s, 1H), 5.22 (d, *J* = 8.2 Hz, 1H), 4.45–4.30 (m, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 2.80–2.60 (m, 2H), 2.48–2.23 (m, 1H), 2.10–1.95 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.6, 164.4, 158.9, 155.3, 153.0, 148.6, 142.1, 128.3, 123.9, 116.8, 105.2, 80.3, 52.8, 52.6, 52.4, 30.1, 29.8, 28.2; HRMS (ESI-TOF) calcd for $C_{23}H_{26}N_2Na_1O_{10}$ $(M+Na)^+$ 513.1485, found 513.1469.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-[(4-methoxycarbonyl) phenyl]-2-oxo-2H-pyran-3-carboxylate (**4l**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4l** was obtained as a yellow solid (418 mg, 83% yield), mp 63.8–65.0 °C; $[\alpha]_D^{27}$ +17.5 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3373, 2954, 1712, 1637, 1508, 1435, 1366, 1277, 1161, 1101, 1025, 772, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 6.23 (s, 1H), 5.33 (d, *J* = 8.7 Hz, 1H), 4.44–4.30 (m, 1H), 3.95 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 2.80–2.60 (m, 2H), 2.37–2.23 (m, 1H), 2.15–1.96 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.1, 165.9, 165.0, 164.7, 159.2, 154.0, 140.0, 131.4, 129.8, 127.1, 116.4, 105.3, 80.0, 52.4, 52.4, 52.2, 30.0, 29.6, 28.0; HRMS (ESI-TOF) calcd for $C_{25}H_{29}N_1Na_1O_{10}$ $(M+Na)^+$ 526.1689, found 526.1698.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-[(4-(tert-butoxycarbonyl)amino)phenyl]-2-oxo-2H-pyran-3-carboxylate (**4m**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 7:3), the product **4m** was obtained as a yellow solid (511 mg, 91% yield), mp 130.1–132.3 °C; $[\alpha]_D^{26}$ +21.2 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3334, 2977, 1699, 1590, 1519, 1366, 1319, 1233, 1153, 1052, 1024, 827, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.23 (s, 1H), 5.35 (d, *J* = 8.2 Hz, 1H), 4.45–4.28 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.74–2.56 (m, 2H), 2.35–2.18 (m, 1H), 2.13–1.95 (m,

1H), 1.51 (s, 9H), 1.44 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.6, 164.0, 159.9, 155.2, 154.2, 152.4, 140.9, 129.2, 128.1, 128.1, 114.9, 105.6, 80.8, 80.0, 52.4, 52.4, 29.9, 29.6, 28.1; HRMS (ESI-TOF) calcd for $C_{28}H_{36}N_2Na_1O_{10}$ $(M+Na)^+$ 583.2268, found 583.2263.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(2-naphthalenyl)-2-oxo-2H-pyran-3-carboxylate (**4n**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4n** was obtained as a yellow solid (412 mg, 83% yield), mp 67.5–69.2 °C; $[\alpha]_D^{27}$ +27.8 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3373, 2979, 1737, 1709, 1637, 1545, 1435, 1366, 1264, 1161, 1028, 821, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96–7.82 (m, 4H), 7.61–7.50 (m, 2H), 7.46 (dd, *J* = 8.6, 1.5 Hz, 1H), 6.33 (s, 1H), 5.30 (d, *J* = 8.9 Hz, 1H), 4.46–4.33 (m, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 2.76–2.58 (m, 2H), 2.38–2.21 (m, 1H), 2.12–1.96 (m, 1H), 1.44 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.3, 164.4, 159.7, 155.2, 154.9, 133.6, 132.9, 132.7, 128.6, 127.4, 127.6, 127.5, 127.3, 126.9, 123.9, 116.0, 105.9, 80.0, 52.4, 52.4, 30.0, 29.7, 28.1; HRMS (ESI-TOF) calcd for $C_{27}H_{29}N_1Na_1O_8$ $(M+Na)^+$ 518.1791, found 518.1790.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-2-oxo-4-(3-thioenyl)-2H-pyran-3-carboxylate (**4o**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4o** was obtained as a yellow solid (339 mg, 75% yield), mp 59.0–61.8 °C; $[\alpha]_D^{26}$ +26.4 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max}3370, 3105, 2978, 1734, 1703, 1639, 1553, 1435, 1366, 1249, 1160, 1028, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.43 (dd, *J* = 5.1, 2.9 Hz, 1H), 7.19 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.32 (s, 1H), 5.37 (d, *J* = 8.4 Hz, 1H), 4.45–4.30 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.71–2.55 (m, 2H), 2.33–2.18 (m, 1H), 2.09–1.95 (m, 1H), 1.44 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.1, 165.6, 163.9, 159.9, 155.2, 147.7, 135.7, 127.3, 127.1, 126.2, 114.6, 105.0, 79.9, 52.6,

52.4, 52.3, 29.8, 29.5, 28.0; HRMS (ESI-TOF) calcd for $C_{21}H_{25}N_1Na_1O_8S$ $(M+Na)^+$ 474.1199, found 474.1193.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-2-oxo-4-(3-pyridinyl)-2H-pyran-3-carboxylate (**4p**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 2:3), the product **4p** was obtained as yellow oil (286 mg, 64% yield), $[\alpha]_D^{27}$ +19.4 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3373, 2978, 1709, 1638, 1545, 1435, 1366, 1258, 1161, 1102, 1026, 818, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.65 (d, *J* = 1.8 Hz, 1H), 7.75 (m, 1H), 7.41 (ddd, *J* = 7.9, 4.9, 0.7 Hz, 1H), 6.21 (s, 1H), 5.32 (d, *J* = 8.1 Hz, 1H), 4.45–4.28 (m, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 2.78–2.59 (m, 2H), 2.48–2.20 (m, 1H), 2.10–1.95 (m, 1H), 1.44 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.4, 164.6, 159.1, 155.3, 152.0, 151.0, 147.6, 134.6, 131.8, 123.3, 116.7, 105.4, 80.2, 52.6, 52.5, 52.4, 30.1, 29.8, 28.1; HRMS (ESI-TOF) calcd for $C_{22}H_{26}N_2Na_1O_8$ $(M+Na)^+$ 469.1587, found 469.1576.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-butyl-2-oxo-2H-pyran-3-carboxylate (**4q**)*.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4q** was obtained as yellow oil (341 mg, 80% yield), $[\alpha]_D^{26}$ +33.3 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3369, 2957, 1712, 1642, 1559, 1515, 1435, 1366, 1255, 1162, 1048, 816, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (s, 1H), 5.32 (d, *J* = 8.3 Hz, 1H), 4.39–4.27 (m, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 2.68–2.55 (m, 2H), 2.47 (t, *J* = 7.7 Hz, 2H), 2.30–2.15 (m, 1H), 2.05–1.93 (m, 1H), 1.62–1.49 (m, 2H), 1.45 (s, 9H), 1.44–1.30 (m, 2H), 0.93 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.1, 164.9, 164.2, 159.4, 155.1, 115.9, 105.6, 79.7, 52.4, 52.19, 52.17, 33.1, 30.7, 29.7, 29.4, 27.9, 22.2, 13.4; HRMS (ESI-TOF) calcd for $C_{21}H_{31}N_1Na_1O_8$ $(M+Na)^+$ 448.1947, found 448.1952.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-(tert-butyl)-2-oxo-2H-pyran-3-carboxylate (**4r**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4r** was obtained as a white solid (362 mg, 85% yield), mp 52.8–55.6 °C; $[\alpha]_D^{26}$ +18.3 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3371, 2976, 1738, 1706, 1643, 1506, 1435, 1366, 1255, 1162, 1047, 815, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 1H), 5.26 (d, *J* = 8.3 Hz, 1H), 4.40–4.27 (m, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 2.63–2.52 (m, 2H), 2.30–2.15 (m, 1H), 2.05–1.87 (m, 1H), 1.45 (s, 9H), 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.3, 166.9, 162.3, 161.9, 161.2, 155.2, 116.5, 107.6, 103.5, 80.0, 52.5, 52.5, 52.4, 36.4, 31.40, 29.8, 29.0, 28.1; HRMS (ESI-TOF) calcd for $C_{21}H_{31}N_1Na_1O_8$ $(M+Na)^+$ 448.1947, found 448.1952.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutyl]-4-[(tert-butyldimethylsilyl)oxy]-2-oxo-2H-pyran-3-carboxylate (**4s**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4s** was obtained as yellow oil (438 mg, 81% yield), $[\alpha]_D^{27}$ +23.8 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3369, 2954, 2855, 1715, 1643, 1562, 1435, 1366, 1252, 1162, 1046, 835, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.12 (d, *J* = 7.1 Hz, 1H), 4.40–4.28 (m, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.64 (t, *J* = 5.9 Hz, 2H), 2.67–2.48 (m, 4H), 2.30–2.15 (m, 1H), 2.04–1.87 (m, 1H), 1.87–1.70 (m, 1H), 1.45 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.2, 165.0, 164.3, 159.8, 159.5, 155.2, 116.1, 105.9, 80.0, 61.9, 52.5, 52.4, 52.3, 31.9, 30.4, 29.8, 28.1, 25.7, 18.1, -5.6; HRMS (ESI-TOF) calcd for $C_{26}H_{43}N_1Na_1O_9Si$ $(M+Na)^+$ 564.2605, found 564.2611.

*Methyl (S)-6-[3-((tert-butoxycarbonyl)amino)-4-[methoxy(methyl)amino]-4-oxobutyl]-2-oxo-4-phenyl-2H-pyran-3-carboxylate (**4t**).*

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 4:1), the product **4t** was obtained as a yellow solid (408 mg, 86% yield), mp 57.5–59.9 °C; $[\alpha]_D^{27}$ –40.1 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3324, 2977, 1737, 1709, 1661, 1547, 1365, 1250, 1164, 1022, 993, 734, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.35 (m, 5H), 6.25 (s, 1H), 5.37 (d, *J* = 8.6 Hz, 1H), 4.79–4.65 (m, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 3.20 (s, 3H), 2.77–2.58 (m, 2H), 2.26–2.10 (m, 1H), 1.97–1.80 (m, 1H), 1.43 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.9, 165.3, 164.8, 159.8, 155.4, 155.0, 135.8, 130.2, 128.8, 127.1, 115.8, 105.8, 79.8, 61.5, 52.4, 49.5, 32.0, 29.92, 29.89, 28.2; HRMS (ESI-TOF) calcd for $C_{24}H_{30}N_2Na_1O_8$ $(M+Na)^+$ 497.1900, found 497.1905.

Methyl (S)-2-[(tert-butoxycarbonyl)amino]-4-(3-cyano-2-oxo-4-phenyl-2H-pyran-6-yl)butanoate ***(4u)***.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4u** was obtained as yellow oil (132 mg, 32% yield), $[\alpha]_D^{28}$ –1.7 (*c* 0.4, $CHCl_3$); IR (UATR) ν_{max} 3368, 2978, 2227, 1735, 1711, 1629, 1526, 1367, 1249, 1217, 1162, 1051, 850, 764, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.2 Hz, 2H), 7.65–7.51 (m, 3H), 6.40 (s, 1H), 5.15 (d, *J* = 7.8 Hz, 1H), 4.45–4.34 (m, 1H), 3.79 (s, 3H), 2.82–2.64 (m, 2H), 2.40–2.24 (m, 1H), 2.10–1.97 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.1, 167.8, 163.7, 159.4, 155.4, 133.8, 132.2, 129.3, 128.1, 114.2, 105.9, 95.8, 80.5, 52.7, 52.3, 30.6, 30.0, 28.3; HRMS (ESI-TOF) calcd for $C_{22}H_{24}N_2Na_1O_6$ $(M+Na)^+$ 435.1532, found 435.1540.

Methyl (S)-2-[(tert-butoxycarbonyl)amino]-4-[3-(4-nitrophenyl)-2-oxo-4-phenyl-2H-pyran-6-yl] butanoate ***(4v)***.

Following the general procedure for the synthesis of 2-pyrones and purification by column chromatography (hexane/EtOAc = 3:1), the product **4v** was obtained as a brown solid (346 mg, 68% yield), mp 78.6–80.9 °C; $[\alpha]_D^{28}$ +9.5 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3367, 2978, 1709,

1638, 1517, 1344, 1247, 1161, 1051, 852, 768, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.32–7.21 (m, 3H), 7.12–7.05 (m, 2H), 6.28 (s, 1H), 5.22 (d, *J* = 7.9 Hz, 1H), 4.48–4.35 (m, 1H), 3.77 (s, 3H), 2.78–2.61 (m, 2H), 2.40–2.28 (m, 1H), 2.13–1.99 (m, 1H), 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.3, 163.1, 162.2, 155.3, 154.1, 146.8, 140.9, 136.4, 131.9, 129.7, 128.6, 128.5, 123.0, 120.1, 107.1, 80.2, 52.5, 30.0, 29.9, 28.2; HRMS (ESI-TOF) calcd for $C_{27}H_{28}N_2Na_1O_8$ $(M+Na)^+$ 531.1743, found 531.1756.

Optimization conditions for the stepwise transformation of 4a to bicyclic 2-pyridones (Table 1).

Step 1. Preparation of **de-Boc 4a**: A solution of 2-pyrone **4a** (1.00 g, 2.2 mmol) in MeOH (30 mL) was added trimethyl chlorosilane (TMSCl, 1.0 mL, 7.9 mmol, 3.5 equiv) and the mixture was stirred at 55 °C for 1.5 h. Then, the volatile organic materials were removed under reduced pressure to afford **de-Boc 4a** as a brown solid (841 mg, quantitative yield). This compound was analyzed by spectroscopic techniques to confirm the stability of 2-pyrone core under the employing conditions before using in the next step without further purification.

*(S)-1-Methoxy-4-[3-(methoxycarbonyl)-2-oxo-4-phenyl-2H-pyran-6-yl]-1-oxobutan-2-ammonium chloride (**de-Boc 4a**).*

mp 87.6–90.5 °C, $[\alpha]_D^{27}$ +9.9 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 3397, 2953, 1739, 1712, 1646, 1547, 1436, 1355, 1250, 1208, 1104, 1034, 818, 768, 734, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (br s, 2H), 7.42–7.36 (m, 5H), 6.47 (s, 1H), 4.36–4.30 (m, 1H), 3.70 (s, 3H), 3.63 (s, 3H), 3.04–2.83 (m, 2H), 2.52–2.45 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.3, 165.3, 163.5, 160.0, 155.1, 135.5, 130.3, 128.8, 127.1, 115.9, 106.6, 53.3, 52.4, 52.3, 29.4, 27.1; HRMS (ESI-TOF) calcd for $C_{18}H_{20}N_1O_6$ $(M+H)^+$ 346.1285, found 346.1292.

Step 2. Examinations for the one-pot transformation of **deBoc-4a** to the corresponding bicyclic 2-pyridones:

General procedure: A solution of **de-Boc 4a** (84.0 mg, 0.22 mmol) in solvents was treated with reagents and conditions as shown in Table 1. Then, the reaction was quenched using method A–C. Crude products were purified by preparative thin layer chromatography (EtOAc/DCM = 4:1). Method A: The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 20 mL). The organic part was washed successively with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Method B: The solution part was collected by filtration through a paper pad and the pad was successively washed with 10% MeOH in DCM. The filtrate was concentrated under reduced pressure. Method C: The solvent was removed under reduced pressure.

Entry 1: A solution of **de-Boc 4a** in DMF (3 mL) was stirred at 0 °C for 7 h. Then, the mixture was treated with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI, 56.0 mg, 0.26 mmol, 1.2 equiv) and 4-dimethylaminopyridine (DMAP, 9.1 mg, 0.06 mmol, 0.3 equiv) at 0 °C and stirred at room temperature for 14 h. The reaction was quenched using method A to afford **5a** (3.4 mg, 6% yield) and **6a** (13.0 mg, 18% yield).

Entry 2: A solution of **de-Boc 4a** in DCM (10 mL) was treated with silica gel (neutral type, 3.0 g) and the mixture was stirred at room temperature for 3 h. The reaction was quenched using method B to afford **5a** (24.4 mg, 41% yield) and **6a** (10.0 mg, 14% yield).

Entry 3: A solution of **de-Boc 4a** in MeOH (10 mL) was treated with DMAP (9.1 mg, 0.06 mmol) and molecular sieves (4Å, 3.0 g) and the mixture was stirred at 60 °C for 2 h. The reaction was quenched using method B to afford **5a** (11.9 mg, 20% yield) and **6a** (5.1 mg, 7% yield).

Entry 4: A solution of **de-Boc 4a** in DCM (10 mL) was treated with molecular sieves (4Å, 3.0 g) and the mixture was stirred at room temperature for 3 h. The reaction was quenched using method B to afford **5a** (15.0 mg, 25% yield) and **6a** (4.1 mg, 6% yield).

Entries 5 and 6: A solution of **de-Boc 4a** in MeOH (3 mL) was treated with K_2CO_3 (61.9 mg, 0.44 mmol) and the mixture was stirred at room temperature for 3 h (entry 5) or 60 °C for 1 h

(entry 6). The reaction was quenched using method A to afford **5a** and **6a** as shown in Table 2: entry 5: **5a** 24.5 mg, 41% and **6a** 9.9 mg, 14% yields; entry 6: **5a** 31.0 mg, 52% and **6a** 3.4 mg, 5% yields.

Entries 7 and 8: A solution of **de-Boc 4a** in DCM (10 mL) was treated with b-Al_2O_3 (entry 7), or n-Al_2O_3 (entry 8) (3.0 g) and the mixture was stirred at room temperature for 3 h. The reaction was quenched using method B to afford **5a** and **6a** as shown in Table 2; entry 7: **5a** 23.9 mg, 40% and **6a** 10.0 mg, 14% yields; entry 8: **5a** 15.5 mg, 26% and **6a** 15.9 mg, 22% yields.

Entry 9: In a pressurized tube, a solution of **de-Boc 4a** in dry toluene (3 mL) was stirred at 150 °C for 1 h. The reaction was quenched using method C to afford **5a** (48.0 mg, 81% yield) and **6a** (2.7 mg, 4% yield).

Entry 10: Following the experimental procedure of optimization conditions for the stepwise transformation of **4a** (Table 1, step 1). A solution of 2-pyrone **4a** (100 mg, 0.22 mmol) in DCM (1 mL) was added trifluoroacetic acid (TFA, 0.05 mL, 0.66 mmol, 3.0 equiv) and the mixture was stirred at room temperature for 4 h to give **de-Boc 4a** as a brown solid (105 mg, quantitative yield). Following the experimental procedure of optimization conditions for the stepwise transformation of **4a** (Table 1, entry 9), the product **5a** was obtained as yellow oil (54.6 mg, 92% yield).

Optimization conditions for the one-pot transformation of 4a to the corresponding bicyclic 2-pyridones (Table 2):

General procedure: In a pressurized tube, a solution of 2-pyrone **4a** (100 mg, 0.22 mmol) in solvents was treated with reagents and conditions as shown in Table 2. Then, the reaction was quenched and purified using method A–C.

Method A: The volatile organic materials were removed under reduced pressure. Crude products were purified by preparative thin layer chromatography (EtOAc/DCM = 4:1, entries 1 and 2) or flash column chromatography on silica gel (EtOAc for entry 3).

Method B: The reaction was quenched with water (5 mL) and extracted with 30% *i*-PrOH in DCM (2 x 20 mL). The organic part was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude products were purified by flash column chromatography on silica gel (EtOAc/MeOH= 9:1 for entries 4 and 6, or EtOAc for entries 5, 7, 16, 17 and 20–23).

Method C: The solution part was collected by filtration through a paper pad and the pad was successively washed with 10% MeOH in DCM. The filtrate was removed under reduced pressure. Crude products were purified by flash column chromatography on silica gel (EtOAc for entries 8, 9, and 11, or EtOAc/MeOH = 9:1 for entries 10, 14 and 15), preparative thin layer chromatography (EtOAc/DCM = 4:1, entry 12), or crystallization (EtOH, entry 13).

Entries 1 and 2: A solution of 2-pyrone **4a** in MeOH (3 mL) was added trimethyl chlorosilane (TMSCl, 0.3 mL, 2.4 mmol, 11 equiv) and the mixture was stirred at 100 °C (entry 1) or 150 °C (entry 2) for 1 h. The reaction was quenched and purified using method A to afford **5a** and **6a** as show in Table 2; entry 1: **5a** 22.0 mg, 37% and **6a** 12.3 mg, 17% yields; entry 2: **5a** 45.0 mg, 76% and **6a** 3.7 mg, 5% yields. The retention of the chirality of **5a** and **6a** in a thermal acid environment was investigated using HPLC analysis.

Entry 3: A solution of 2-pyrone **4a** in dry toluene (3 mL) was added trimethylsilyl trifluoromethanesulfonate (TMSOTf, 99% purity, 0.05 mL, 0.27 mmol, 1.2 equiv) and the mixture was stirred at 150 °C for 30 min. The reaction was quenched and purified using method A to afford **5a** (50.1 mg, 85% yield).

Entry 4: A solution of 2-pyrone **4a** in dry toluene (3 mL) was added trifluoroacetic acid (TFA, 0.05 mL, 0.66 mmol, 3.0 equiv) and the mixture was stirred at 150 °C for 1 h. The reaction was quenched and purified using method B to afford **5a** (48.0 mg, 81% yield) and **7a** (8.2 mg, 15% yield).

Entry 5: A solution of 2-pyrone **4a** in dry toluene (3 mL) was added trifluoroacetic acid (TFA, 0.05 mL, 0.66 mmol, 3.0 equiv) and the mixture was stirred at 80 °C for 2 h. The reaction was

quenched and purified using method B to afford **4a** (35.2 mg, 35% yield) and **5a** (36.9 mg, 62% yields). Compound **7a** was observed in a trace amount by ^{1}H-NMR analysis.

Entry 6: A solution of 2-pyrone **4a** in dry toluene (3 mL) was added *p*-toluenesulfonic acid monohydrate (*p*-TsOH.H_2O, 99% purity, 51 mg, 0.27 mmol, 1.2 equiv) and the mixture was stirred at 150 °C for 1 h. The reaction was quenched and purified using method B to afford **5a (**49.0 mg, 83% yield) and **7a** (6.8 mg, 12% yield).

Entry 7: A solution of 2-pyrone **4a** in dry toluene (3 mL) was added aqueous phosphoric acid (aq.H_3PO_4, 85 wt%, 0.26 mL, 4.4 mmol, 20 equiv) and the mixture was stirred at 80 °C for 10 h. The reaction was quenched and purified using method B to afford **5a** (54.1 mg, 91% yield).

Entries 8–13: A solution of 2-pyrone **4a** in the indicated solvent (2 mL) was added Amberlyst-15 hydrogen form, dry (4.7 meq/g by dry weight, 100 mg, 0.47 mmol, 2 equiv) and the mixture was stirred at 100 °C for the indicated time, 2-40 h. The reaction was quenched and purified using method C to afford **5a**, **6a** and **7a** as shown in Table 2; entry 8: **5a** 54.9 mg, 93% yield; entry 9: **5a** 54.5 mg, 92% yield, entry 10: **5a** 44.2 mg, 75% and **7a** 6.8 mg, 12% yields; entry 11: **5a** 56.4 mg, 95% yield; entry 12: **5a** 36.1 mg, 61% and **6a** 25.0 mg, 35% yields; entry 13: **7a** 49 mg, 87% yield. Entries 8, 9, and 11, compound **7a** was observed in a trace amount. Entry 13, using **4a** (500 mg, 1.1 mmol) and Amberlyst-15 hydrogen form (500 mg, 2.4 mmol, 2 equiv) in a solvent of MeCN/water (1:1, 10 mL) gave **7a** (255 mg, 91% yield), after purification of crude product by crystallization in EtOH.

Entries 14 and 15: A solution of 2-pyrone **4a** in MeCN (2 mL) was added Dowex-50WX4 (entry 14, 1.1 meq/g by wetted bed volume, 430 mg, 0.47 mmol, 2 equiv) or Amberlite-IR120H (entry 15, 4.4 meq/g by dry weight, 107 mg, 0.47 mmol, 2 equiv) and the mixture was stirred at 100 °C for 2 h. The reaction was quenched and purified using method C to afford **5a**, and **7a** as shown in Table 2; entry 14: **5a** 7.0 mg, 12% and **7a** 29.0 mg, 52% yields; entry 15: **5a** 10.7 mg, 18% and **7a** 33.8 mg, 60% yields.

Entries 16, 17, and 20–23: A solution of 2-pyrone **4a** in the indicated solvent (2 or 10 mL) was stirred at the indicated conditions, 110 °C or 150 °C for 40 min to 24 h. The reaction was quenched and purified using method B to afford the desired product **5a** in 72–98% yields, as shown in Table 2; entry 16: **4a** 25.1 mg, 25% and **5a** 42.7 mg, 72% yields; entry 17: **5a** 56.0 mg, 95% yield; entry 20: **5a** 56.9 mg, 96% yield; entry 21: **5a** 58.2 mg, 98% yield; entry 22: **5a** 58.0 mg, 98% yield; entry 23: **5a** 57.5 mg, 97% yield; entry 24: **5a** 56.1 mg, 95% yield. Entries 21–23, using **4a** (500 mg, 1.1 mmol) in a solution of EG/water (1:1, 10 mL or 50 mL) gave **5a** in 95–96% yields, as shown in Table 2; entry 21: **5a** 282 mg, 95% yield; entry 22: **5a** 285 mg, 96% yield; entry 23: **5a** 291 mg, 98% yield.

Entry 24: Scale up for the synthesis of 5a. In a 1000 mL round-bottom flask equipped with a condenser, 2-pyrone **4a** (5.00 g, 11 mmol) in a solution of EG/water (1:1, 500 mL) was heated by a heating mantle to 110 °C for 5 h, and the reaction was monitored by TLC. Then, the reaction was cooled to room temperature and extracted with 10% *i*-PrOH in DCM (3 x 100 mL). The combined organic layer was washed with water (100 mL) and dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure to give the crude products, which were purified by flash column chromatography on silica gel (EtOAc) to afford **5a** (2.85 g, 96% yield).

*Methyl (S)-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5a**).*

Following the experimental procedure of optimization conditions for the one-pot transformation of **4a** (Table 2, entry 2), the product **5a** was obtained as yellow oil (45.0 mg, 76% yield), $[\alpha]_D^{28}$ – 166.0 (*c* 1.0, $CHCl_3$); HPLC analysis (DAICEL Chiralpak IC-3 column, MeOH/water = 35:65, flow rate 0.5 mL/min, λ = 254 nm), t_R major = 31.22, t_R minor = 34.52, > 99% ee.

Following the experimental procedure of optimization conditions for the one-pot transformation of **4a** (Table 2, entry 23), the product **5a** was obtained as yellow oil (57.8 mg, 97% yield), $[\alpha]_D^{28}$ –169.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2954, 1744, 1655, 1588, 1435, 1370, 1206, 1181, 1044, 855, 765, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–7.50 (m, 2H), 7.47–7.45 (m, 3H), 6.59 (brs, 1H), 6.38 (d, *J* = 0.9 Hz, 1H), 5.14 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.79 (s, 3H), 3.31–3.25 (m, 1H), 3.25–3.03 (m, 1H), 2.51–2.44 (m, 1H), 2.39–2.25 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.5, 161.6, 153.3, 150.0, 137.9, 129.1, 128.7, 126.7, 114.1, 100.8, 60.9, 52.6, 30.4, 26.1; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_1O_3$ $(M+H)^+$ 270.1130, found 270.1134.

*Dimethyl (S)-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6a**).*

Following the experimental procedure of optimization conditions for the one-pot transformation of **4a** (Table 2, entry 2), the product **6a** was obtained as a yellow solid (3.7 mg, 5% yield), mp 67.1–68.9 °C; $[\alpha]_D^{29}$ –168.3 (*c* 1.0, $CHCl_3$); HPLC analysis (DAICEL Chiralpak IC-3 column, MeOH/water = 40:60, flow rate 0.5 mL/min, λ = 254 nm), t_R major = 14.77, t_R minor = 21.99, > 99% ee.

IR (UATR) ν_{max} 2952, 1729, 1645, 1595, 1530, 1436, 1377, 1260, 1207, 1172, 1106, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5H), 6.19 (s, 1H), 5.15 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 3.33–3.29 (m, 1H), 3.28–3.05 (m, 1H), 2.62–2.46 (m, 1H), 2.40–2.27 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.1, 166.7, 158.5, 153.1, 151.1, 138.0, 129.0, 128.5, 127.2, 120.7, 102.9, 61.5, 52.8, 52.0, 30.7, 26.0; HRMS (ESI-TOF) calcd for $C_{18}H_{18}N_1O_5$ $(M+H)^+$ 328.1185, found 328.1184;

*(S)-5-Oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3-carboxylic acid (**7a**).*

Following the experimental procedure of optimization conditions for the one-pot transformation of **4a** (Table 2, entry 13, using **4a** 500 mg) and purification by crystallization in EtOH, the product **7a** was obtained as a white solid (255.0 mg, 91% yield), mp 222.8–224.1 °C; $[\alpha]_D^{26}$ –117.4 (*c* 1.1, MeOH).

IR (UATR) ν_{max} 3446, 3057, 2969, 1722, 1646, 1548, 1443, 1346, 1215, 1163, 1025, 885, 771, 695 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.70–7.60 (m, 2H), 7.55–7.40 (m, 3H), 6.69 (s, 1H),

6.60 (s, 1H), 5.15 (d, J = 7.8 Hz, 1H), 3.32–3.20 (m, 2H), 2.73–2.55 (m, 1H), 2.45–2.30 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ 173.1, 164.0, 156.2, 153.2, 139.0, 130.7, 130.1, 128.0, 113.8, 103.3, 63.1, 31.4, 27.3; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N_1O_3$ $(M+H)^+$ 256.0968, found 256.0971.

General procedure for the synthesis of 5b–u and 6b–v.

Condition A: In a pressurized tube, trimethyl chlorosilane (TMSCl, 0.3 mL, 2.4 mmol, 11 equiv) was added to a solution of 2-pyrone **4** (0.22 mmol) in MeOH (3 mL), and the mixture was stirred at 150 °C for 1 h (except for **4t**, at 100 °C for 1 h). Then, the reaction was cooled to room temperature, and the volatile organic materials were removed under reduced pressure. The crude products were purified by PTLC using EtOAc and DCM or MeOH as eluents to give compounds **5** and **6**. Except in the reactions of 2-pyrones **4m** and **4u**, the reaction was quenched with sat. $NaHCO_3$ (10 mL) and extracted with DCM (2 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure to give the crude products.

Condition B: In a pressurized tube, 2-pyrone **4** (0.22 mmol) in a solution of EG/water (1:1, 2 mL) was heated at 110 °C for 3.5 h (**4a**, **4l**, **4o**, and **4t**), 4 h (**4b–k** and **4n**), 1.5 h (**4m** and **4p**), or 2 h (**4q–s** and **4u**) or at 150 °C for 3 h (**4v**). Then, the reaction was cooled to room temperature, diluted with water (10 mL), and extracted with 10% *i*-PrOH in DCM (2 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure to give the crude products, which were purified by flash column chromatography on silica gel using EtOAc as the eluent to give compound **5**.

*Methyl (S)-7-(2-methoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5b**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5b** was obtained as a brown solid (30.3 mg, 46% yield), mp 139.0–141.1 °C; $[\alpha]_D^{28}$ –125.6 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5b** was obtained as a brown solid (61.5 mg, 93% yield), mp 139.9–141.5 °C; $[\alpha]_D^{28}$ –126.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1744, 1656, 1578, 1435, 1368, 1250, 1180, 1021, 863, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 2H), 7.05–6.93 (m, 2H), 6.54 (s, 1H), 6.37 (s, 1H), 5.13 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.30–3.14 (m, 1H), 3.14–3.03 (m, 1H), 2.52–2.45 (m, 1H), 2.40–2.26 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.7, 161.7, 156.4, 151.7, 148.5, 130.2, 130.0, 127.7, 120.8, 117.1, 111.3, 103.7, 61.0, 55.5, 52.7, 30.4, 26.3; HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_1Na_1O_4$ $(M+Na)^+$ 322.1055, found 322.1050.

*Methyl (S)-7-(2-iso-propoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5c**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5c** was obtained as brown oil (49.5 mg, 69% yield), $[\alpha]_D^{27}$ –114.1 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5c** was obtained as brown oil (65.9 mg, 91% yield), $[\alpha]_D^{28}$ –115.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2976, 1746, 1657, 1590, 1522, 1452, 1370, 1247, 1205, 1122, 951, 854, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 2H), 7.02–6.93 (m, 2H), 6.54 (s, 1H), 6.40 (s, 1H), 5.14 (dd, *J* = 9.4, 3.2 Hz, 1H), 4.68–4.45 (m, 1H), 3.81 (s, 3H), 3.29–3.14 (m, 1H), 3.13–3.01 (m, 1H), 2.62–2.45 (m, 1H), 2.47–2.35 (m, 1H), 1.30 (d, *J* = 5.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.7, 161.7, 154.8, 152.1, 148.2, 130.2, 129.9, 128.9, 120.8, 116.9, 114.6, 103.8, 71.0, 61.0, 52.6, 30.3, 26.2, 21.9; HRMS (ESI-TOF) calcd for $C_{19}H_{21}N_1Na_1O_4$ $(M+Na)^+$ 350.1368, found 350.1357.

*Methyl (S)-7-(2-chlorophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5d**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5d** was obtained as a brown solid (49.2 mg, 74% yield), mp 75.2–77.0 °C; $[\alpha]_D^{26}$ –127.8 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5d** was obtained as a brown solid (60.0 mg, 90% yield), mp 75.5–76.8 °C; $[\alpha]_D^{28}$ –128.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2954, 1744, 1659, 1587, 1435, 1368, 1274, 1206, 1180, 1040, 857, 760, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59–7.42 (m, 1H), 7.38–7.28 (m, 3H), 6.43 (s, 1H), 6.25 (s, 1H), 5.17 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.83 (s, 3H), 3.32–3.28 (m, 1H), 3.28–3.05 (m, 1H), 2.65–2.48 (m, 1H), 2.40–2.27 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.6, 161.4, 152.2, 149.3, 137.9, 131.8, 130.3, 130.1, 129.7, 127.0, 117.7, 103.3, 61.2, 52.8, 30.5, 26.2; HRMS (ESI-TOF) calcd for $C_{16}H_{14}Cl_1N_1Na_1O_3$ $(M+Na)^+$ 326.0560, found 326.0546.

*Methyl (S)-7-(2-bromophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5e**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5e** was obtained as a brown solid (47.6 mg, 62% yield), mp 62.9–63.8 °C; $[\alpha]_D^{28}$ –102.4 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5e** was obtained as a brown solid (69.0 mg, 90% yield), mp 63.1–64.0 °C; $[\alpha]_D^{28}$ –102.6 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1743, 1658, 1594, 1523, 1434, 1369, 1267, 1207, 1180, 1108, 761, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.50–7.28 (m, 3H), 6.39 (s, 1H), 6.21 (s, 1H), 5.17 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.82 (s, 3H), 3.33–3.18 (m, 1H), 3.18–3.05 (m, 1H), 2.64–2.48 (m, 1H), 2.40–2.29 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.5, 161.3, 153.7, 149.3, 139.9, 133.2, 130.2, 130.1, 129.8, 127.5, 121.2, 117.5, 103.3, 61.1, 52.7, 30.5, 26.2; HRMS (ESI-TOF) calcd for $C_{16}H_{14}Br_1N_1Na_1O_3$ $(M+Na)^+$ 370.0055, found 370.0045.

*Methyl (S)-7-(3-methoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5f**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5f** was obtained as yellow oil (33.4 mg, 51% yield), $[\alpha]_D^{28}$ –120.9 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5f** was obtained as yellow oil (60.3 mg, 92% yield), $[\alpha]_D^{28}$ –122.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2928, 1745, 1659, 1593, 1434, 1367, 1271, 1178, 1043, 987, 852, 785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.14 (ddd, *J* = 7.9, 1.4, 0.8 Hz, 1H), 7.08 (dd, *J* = 2.3, 1.4 Hz, 1H), 6.96 (ddd, *J* = 7.9, 2.3, 0.8 Hz, 1H), 6.62 (brs, 1H), 6.38 (d, *J* = 1.1 Hz, 1H), 5.17 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.34–3.19 (m, 1H), 3.19–3.05 (m, 1H), 2.64–2.47 (m, 1H), 2.40–2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.6, 161.7, 159.9, 153.4, 150.0, 139.6, 129.9, 119.3, 114.9, 114.5, 112.4, 101.1, 61.1, 55.3, 52.8, 30.5, 26.3; HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_1Na_1O_4$ $(M+Na)^+$ 322.1055, found 322.1057.

*Methyl (S)-7-(3-chlorophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5g**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5g** was obtained as a brown solid (42.0 mg, 63% yield), mp 61.5–63.2 °C; $[\alpha]_D^{28}$ –129.5 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5g** was obtained as a brown solid (63.7 mg, 95% yield), mp 62.2–63.2 °C; $[\alpha]_D^{28}$ –129.8 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1744, 1658, 1590, 1523, 1434, 1365, 1273, 1206, 1180, 1046, 854, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 1.5 Hz, 1H), 7.49–7.35 (m, 3H), 6.59 (s, 1H), 6.35 (d, *J* = 0.9 Hz, 1H), 5.17 (dd, *J* = 9.3, 3.0 Hz, 1H), 3.82 (s, 3H), 3.34–3.20 (m, 1H), 3.20–3.07 (m, 1H), 2.64–2.46 (m, 1H), 2.40–2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.5,

161.5, 152.1, 150.5, 140.0, 134.9, 130.2, 129.3, 127.0, 125.1, 114.8, 100.8, 61.2, 52.8, 30.6, 26.3; HRMS (ESI-TOF) calcd for $C_{16}H_{14}Cl_1N_1Na_1O_3$ $(M+Na)^+$ 326.0560, found 326.0561.

*Methyl (S)-7-(3-nitrophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5h**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5h** was obtained as a brown solid (53.1 mg, 77% yield), mp 75.2–76.8 °C; $[\alpha]_D^{28}$ –146.8 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5h** was obtained as a brown solid (60.3 mg, 87% yield), mp 76.0–77.1 °C; $[\alpha]_D^{28}$ –147.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2955, 1744, 1659, 1593, 1435, 1349, 1206, 1180, 1046, 986, 806, 739, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 2.1, 1.8 Hz, 1H), 8.28 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.89 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 7.65 (dd, *J* = 8.1, 7.8 Hz, 1H), 6.63 (s, 1H), 6.42 (d, *J* = 1.2 Hz, 1H), 5.19 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.83 (s, 3H), 3.38–3.25 (m, 1H), 3.25–3.10 (m, 1H), 2.78–2.51 (m, 1H), 2.44–2.32 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.3, 161.4, 151.1, 150.8, 148.5, 139.8, 132.7, 130.0, 123.9, 121.7, 115.2, 100.3, 61.2, 52.8, 30.6, 26.2; HRMS (ESI-TOF) calcd for $C_{16}H_{14}N_2Na_1O_5$ $(M+Na)^+$ 337.0800, found 337.0795.

*Methyl (S)-7-(4-methoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5i**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5i** was obtained as a yellow solid (33.2 mg, 50% yield), mp 91.2–93.5 °C; $[\alpha]_D^{28}$ –123.6 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5i** was obtained as a yellow solid (58.8 mg, 89% yield), mp 91.0–93.1 °C; $[\alpha]_D^{28}$ –123.8 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2955, 1744, 1655, 1591, 1435, 1368, 1248, 1179, 1023, 986, 832, 814, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.58 (s, 1H),

6.38 (s, 1H), 5.15 (dd, J = 9.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.32–3.17 (m, 1H), 3.17–3.04 (m, 1H), 2.62–2.45 (m, 1H), 2.40–2.26 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.7, 161.8, 160.7, 152.9, 149.8, 130.3, 128.1, 114.3, 113.3, 100.7, 61.0, 55.4, 52.8, 30.5, 26.3; HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_1Na_1O_4$ $(M+Na)^+$ 322.1055, found 322.1054.

*Methyl (S)-7-(4-chlorophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5j**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5j** was obtained as a white solid (34.0 mg, 51% yield), mp 115.3–117.1 °C; $[\alpha]_D^{28}$ –125.5 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5j** was obtained as a white solid (64.3 mg, 96% yield), mp 116.0–117.2 °C; $[\alpha]_D^{28}$ –125.6 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 2925, 1745, 1659, 1590, 1496, 1366, 1270, 1206, 1180, 1091, 1021, 986, 861, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 1.1 Hz, 1H), 6.35 (d, J = 1.1 Hz, 1H), 5.16 (dd, J = 9.4, 3.1 Hz, 1H), 3.81 (s, 3H), 3.33–3.18 (m, 1H), 3.18–3.05 (m, 1H), 2.62–2.45 (m, 1H), 2.40–2.27 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.5, 161.6, 152.2, 150.4, 136.5, 135.5, 129.1, 128.1, 114.4, 100.7, 61.1, 52.8, 30.6, 26.2; HRMS (ESI-TOF) calcd for $C_{16}H_{14}Cl_1N_1Na_1O_3$ $(M+Na)^+$ 326.0560, found 326.0556.

*Methyl (S)-7-(4-nitrophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5k**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5k** was obtained as a yellow solid (50.0 mg, 72% yield), mp 130.8–132.6 °C; $[\alpha]_D^{27}$ –130.8 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5k** was obtained as a yellow solid (65.8 mg, 95% yield), mp 131.0–132.5 °C; $[\alpha]_D^{28}$ –131.5 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2955, 1744, 1660, 1589, 1528, 1435, 1344, 1206, 1155, 1108, 986, 847, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 8.9 Hz, 2H), 6.77 (brs, 1H), 6.38 (d, *J* = 1.1 Hz, 1H), 5.18 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.83 (s, 3H), 3.37–3.22 (m, 1H), 3.22–3.10 (m, 1H), 2.68–2.50 (m, 1H), 2.45–2.30 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.3, 161.2, 151.1, 151.0, 148.2, 144.5, 127.8, 124.1, 115.7, 100.4, 61.2, 52.8, 30.6, 26.2; HRMS (ESI-TOF) calcd for $C_{16}H_{14}N_2Na_1O_5$ $(M+Na)^+$ 337.0800, found 337.0794.

Methyl (S)-7-[4-(methoxycarbonyl)phenyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate ***(5l)****.*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5l** was obtained as a yellow solid (38.0 mg, 53% yield), mp 117.2–119.4 °C; $[\alpha]_D^{27}$ –126.3 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5l** was obtained as a yellow solid (64.5 mg, 89% yield), mp 118.0–120.1 °C; $[\alpha]_D^{28}$ –126.6 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 2845, 1745, 1718, 1659, 1592, 1434, 1364, 1276, 1205, 1106, 849, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 6.63 (s, 1H), 6.39 (d, *J* = 1.0 Hz, 1H), 5.17 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 3.35–3.20 (m, 1H), 3.20–3.07 (m, 1H), 2.65–2.48 (m, 1H), 2.42–2.29 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.5, 166.5, 161.5, 152.3, 150.5, 142.4, 130.7, 126.9, 115.1, 100.7, 61.1, 52.8, 52.2, 30.6, 26.2; HRMS (ESI-TOF) calcd for $C_{18}H_{17}N_1Na_1O_5$ $(M+Na)^+$ 350.1004, found 350.1007.

*Methyl (S)-7-(4-aminophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (****5m****).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/MeOH = 9:1), the product **5m** was obtained as a yellow solid (33.3 mg, 53% yield), mp 214.2–215.6 °C; $[\alpha]_D^{29}$ –113.4 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc/MeOH = 9:1), the product **5m** was obtained as a yellow solid (56.8 mg, 91% yield), mp 215.0–217.1 °C; $[\alpha]_D^{28}$ –115.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 3437, 3330, 2957, 1747, 1651, 1569, 1435, 1372, 1245, 1192, 989, 820, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.55 (s, 1H), 6.37 (s, 1H), 5.14 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.79 (s, 3H), 3.30–3.24 (m, 1H), 3.24–3.01 (m, 1H), 2.61–2.44 (m, 1H), 2.38–2.26 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.8, 161.9, 153.1, 149.6, 147.9, 128.0, 127.5, 115.0, 112.2, 100.5, 60.9, 52.7, 30.5, 26.3; HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O_3$ $(M+H)^+$ 285.1239, found 285.1237.

*Methyl (S)-7-(2-naphthalenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5n**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5n** was obtained as a yellow solid (52.1 mg, 74% yield), mp 168.7–170.2 °C; $[\alpha]_D^{28}$ –131.9 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5n** was obtained as a yellow solid (68.3 mg, 97% yield), mp 169.0–170.1 °C; $[\alpha]_D^{28}$ –133.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1744, 1656, 1590, 1435, 1377, 1272, 1205, 1180, 1155, 986, 852, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.91–7.80 (m, 3H), 7.64 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.55–7.46 (m, 2H), 6.73 (s, 1H), 6.50 (s, 1H), 5.16 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.81 (s, 3H), 3.32–3.17 (m, 1H), 3.17–3.04 (m, 1H), 2.62–2.43 (m, 1H), 2.39–2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.6, 161.6, 153.2, 150.1, 135.2, 133.4, 133.1, 128.6, 128.4, 127.5, 126.8, 126.5, 126.3, 124.3, 114.5, 101.0, 61.0, 52.7, 30.5, 26.2; HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_1Na_1O_3$ $(M+Na)^+$ 342.1106, found 342.1100.

*Methyl (S)-5-oxo-7-(3-thioenyl)-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5o**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5o** was obtained as brown oil (37.7 mg, 62% yield), $[\alpha]_D^{28}$ –134.1 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5o** was obtained as brown oil (51.4 mg, 85% yield), $[\alpha]_D^{28}$ –135.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1743, 1655, 1586, 1434, 1336, 1275, 1204, 1180, 1045, 986, 846, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.39 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.34 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.63 (s, 1H), 6.40 (d, *J* = 1.1 Hz, 1H), 5.14 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.79 (s, 3H), 3.31–3.17 (m, 1H), 3.17–3.04 (m, 1H), 2.62–2.45 (m, 1H), 2.38–2.26 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.5, 161.9, 150.1, 147.3, 139.2, 126.8, 125.8, 123.7, 113.0, 100.4, 61.0, 52.7, 30.4, 26.2; HRMS (ESI-TOF) calcd for $C_{14}H_{13}N_1Na_1O_3S$ $(M+Na)^+$ 298.0514, found 298.0511.

*Methyl (S)-5-oxo-7-(3-pyridinyl)-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5p**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5p** was obtained as brown oil (35.9 mg, 60% yield), $[\alpha]_D^{29}$ –146.2 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5p** was obtained as brown oil (55.5 mg, 93% yield), $[\alpha]_D^{28}$ –145.9 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2954, 1742, 1656, 1588, 1524, 1434, 1367, 1206, 1021, 806, 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.8 Hz, 1H), 8.66 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86 (ddd, *J* = 7.9, 2.1, 1.8 Hz, 1H), 7.39 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.61 (s, 1H), 6.39 (d, *J* = 1.1 Hz, 1H), 5.18 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.82 (s, 3H), 3.36–3.22 (m, 1H), 3.21–3.09 (m, 1H), 2.67–2.50 (m, 1H), 2.43–2.39 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.4, 161.3, 150.9, 150.2, 147.7, 134.2,

133.7, 123.6, 114.9, 100.4, 61.1, 52.8, 30.6, 26.1; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O_3$ $(M+H)^+$ 271.1083, found 271.1078.

*Methyl (S)-7-butyl-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5q**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5q** was obtained as brown oil (33.6 mg, 61% yield), $[\alpha]_D^{28}$ –149.6 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5q** was obtained as brown oil (50.8 mg, 93% yield), $[\alpha]_D^{28}$ –150.9 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2955, 1746, 1661, 1586, 1434, 1362, 1202, 1180, 1043, 988, 849, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (s, 1H), 6.00 (s, 1H), 5.08 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.78 (s, 3H), 3.22–3.19 (m, 1H), 3.18–2.95 (m, 1H), 2.56–2.40 (m, 3H), 2.33–2.20 (m, 1H), 1.62–1.50 (m, 2H), 1.42–1.28 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.7, 161.7, 157.1, 149.1, 115.4, 102.9, 60.8, 52.6, 35.3, 31.4, 30.2, 26.2, 22.1, 13.7; HRMS (ESI-TOF) calcd for $C_{14}H_{19}N_1Na_1O_3$ $(M+Na)^+$ 272.1263, found 272.1256.

*Methyl (S)-7-(tert-butyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5r**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5r** was obtained as a yellow solid (34.9 mg, 64% yield), mp 102.7–104.1 °C; $[\alpha]_D^{28}$ –191.8 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5r** was obtained as a yellow solid (51.8 mg, 94% yield), mp 103.0–104.3 °C; $[\alpha]_D^{28}$ –191.0 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2958, 1746, 1658, 1586, 1435, 1358, 1204, 1179, 1043, 987, 855, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 1H), 6.19 (s, 1H), 5.08 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.79 (s, 3H), 3.24–3.10 (m, 1H), 3.10–2.98 (m, 1H), 2.58–2.40 (m, 3H), 2.35–2.20 (m, 1H), 1.23 (s, 9H);

$^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 170.7, 165.0, 162.0, 148.7, 112.7, 100.4, 60.8, 52.7, 35.1, 30.3, 29.9, 26.3; HRMS (ESI-TOF) calcd for $C_{14}H_{19}N_1Na_1O_3$ $(M+Na)^+$ 272.1263, found 272.1251.

*Methyl (S)-7-(3-hydroxypropyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5s**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/MeOH = 9:1), the product **5s** was obtained as brown oil (36.9 mg, 66% yield), $[\alpha]_D^{29}$ –137.9 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc/MeOH = 9:1), the product **5s** was obtained as brown oil (52.6 mg, 95% yield), $[\alpha]_D^{28}$ –137.6 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 3376, 2951, 1714, 1655, 1574, 1435, 1380, 1277, 1206, 1043, 987, 820, 776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (s, 1H), 6.04 (d, *J* = 1.2 Hz, 1H), 5.09 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.78 (s, 3H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.24–3.09 (m, 1H), 3.09–2.97 (m, 1H), 2.58–2.42 (m, 3H), 2.34–2.22 (m, 1H), 1.89–1.78 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 170.7, 161.8, 156.7, 149.4, 115.4, 103.1, 61.6, 60.9, 52.7, 32.1, 31.9, 30.2, 26.2; HRMS (ESI-TOF) calcd for $C_{13}H_{18}N_1O_4$ $(M+H)^+$ 252.1236, found 252.1226.

*N,N'-Methoxymethyl (S)-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3-carboxamide (**5t**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5s** was obtained as a yellow solid (27.8 mg, 42% yield), mp 134.3–137.1 °C; $[\alpha]_D^{29}$ –34.9 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5s** was obtained as a yellow solid (61.9 mg, 94% yield), mp 135.0–137.3 °C; $[\alpha]_D^{28}$ –38.6 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2942, 1652, 1574, 1524, 1444, 1370, 1317, 1178, 1156, 993, 853, 765, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.51 (m, 2H), 7.48–7.39 (m, 3H), 6.58 (s, 1H), 6.39 (d, *J*

= 0.8 Hz, 1H), 5.62 (dd, *J* = 9.3, 1.6 Hz, 1H), 3.95 (s, 3H), 3.41–3.29 (m, 1H), 3.27 (s, 3H), 3.15–3.03 (m, 1H), 2.56–2.40 (m, 1H), 2.30–2.18 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 169.8, 161.8, 153.5, 151.1, 138.3, 129.1, 128.7, 126.8, 114.0, 100.9, 61.4, 58.7, 32.0, 30.6, 26.0; HRMS (ESI-TOF) calcd for $C_{17}H_{18}N_2Na_1O_3$ $(M+Na)^+$ 321.1215, found 321.1210.

*Methyl (S)-5-imino-7-phenyl-1,2,3,5-tetrahydroindolizine-3-carboxylate (**5u**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **5u** was obtained as a brown solid (43.0 mg, 73% yield), mp 137.3–139.7 °C; $[\alpha]_D^{28}$ –201.7 (*c* 1.0, $CHCl_3$).

Following the general procedure of condition B and purification by flash column chromatography (EtOAc), the product **5u** was obtained as a brown solid (52.6 mg, 89% yield), mp 139.0–140.0 °C; $[\alpha]_D^{28}$ –202.5 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 3054, 1743, 1666, 1588, 1575, 1433, 1328, 1217, 1183, 984, 870, 770, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.71–7.60 (m, 2H), 7.53–7.40 (m, 3H), 6.84 (s, 1H), 6.45–6.37 (m, 1H), 3.89 (s, 3H), 3.24–3.09 (m, 2H), 2.79–2.60 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 168.2, 154.0, 153.9, 150.8, 135.5, 130.6, 129.1, 127.2, 109.9, 106.7, 65.0, 53.6, 29.6, 27.4; HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O_2$ $(M+H)^+$ 269.1290, found 269.1289.

*Dimethyl (S)-7-(2-methoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6b**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6b** was obtained as a brown solid (13.5 mg, 17% yield), mp 73.5–76.0 °C; $[\alpha]_D^{28}$ –146.9 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2952, 2840, 1733, 1647, 1595, 1435, 1250, 1110, 1023, 821, 755, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.20 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.98 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.16 (s, 1H), 5.15 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.61 (s, 3H), 3.34–3.18 (m, 1H), 3.15–3.04 (m, 1H), 2.63–2.45 (m, 1H), 2.40–2.28 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 170.3, 166.4, 158.6, 155.7,

151.8, 150.7, 130.2, 129.2, 127.4, 121.2, 120.6, 110.9, 104.2, 61.6, 55.4, 52.8, 51.8, 30.8, 26.1; HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_1Na_1O_6$ $(M+Na)^+$ 380.1110, found 380.1115.

*Dimethyl (S)-7-(2-iso-propoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6c**)*.

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6c** was obtained as brown oil (11.1 mg, 13% yield), $[\alpha]_D^{27}$ –139.1 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2977, 1734, 1650, 1595, 1528, 1490, 1439, 1374, 1246, 1207, 1108, 951, 818, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 1H), 7.19 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.01–6.89 (m, 2H), 6.18 (s, 1H), 5.17 (dd, *J* = 9.4, 3.0 Hz, 1H), 4.52–4.39 (m, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 3.45–3.28 (m, 1H), 3.27–3.04 (m, 1H), 2.62–2.45 (m, 1H), 2.40–2.28 (m, 1H), 1.23 (d, *J* = 5.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.3, 166.3, 158.7, 154.2, 152.5, 150.3, 129.9, 129.4, 129.0, 120.7, 114.8, 104.5, 71.4, 61.6, 52.8, 51.8, 30.7, 26.1, 22.0, 21.9; HRMS (ESI-TOF) calcd for $C_{21}H_{23}N_1Na_1O_6$ $(M+Na)^+$ 408.1423, found 408.1429.

*Dimethyl (S)-7-(2-chlorophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6d**)*.

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6d** was obtained as a brown solid (11.8 mg, 15% yield), mp 146.4–147.9 °C; $[\alpha]_D^{26}$ –148.7 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1732, 1650, 1601, 1529, 1435, 1376, 1271, 1208, 1107, 1056, 812, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.40 (m, 1H), 7.35–7.25 (m, 3H), 6.11 (s, 1H), 5.18 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 3.37–3.20 (m, 1H), 3.20–3.05 (m, 1H), 2.65–2.48 (m, 1H), 2.41–2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.1, 165.7, 158.4, 152.4, 151.4, 137.3, 129.7, 129.6, 129.4, 126.6, 121.3, 103.5, 61.8, 52.9, 52.0, 30.9, 26.1; HRMS (ESI-TOF) calcd for $C_{18}H_{16}Cl_1N_1Na_1O_5$ $(M+Na)^+$ 384.0615, found 384.0615.

*Dimethyl (S)-7-(2-bromophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6e**)*.

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6e** was obtained as a brown solid (9.7 mg, 11% yield), mp 79.1–81.3 °C; $[\alpha]_D^{28}$ –139.3 (*c* 0.9, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1743, 1658, 1594, 1523, 1434, 1369, 1267, 1206, 1180, 1108, 1022, 760, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.59 (m, 1H), 7.40–7.13 (m, 3H), 6.09 (s, 1H), 5.21 (dd, *J* = 9.3, 2.7 Hz, 1H), 3.84 (s, 3H), 3.60 (s, 3H), 3.51–3.24 (m, 1H), 3.24–3.05 (m, 1H), 2.69–2.46 (m, 1H), 2.44–2.30 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.2, 165.6, 158.5, 154.0, 151.5, 139.3, 132.9, 132.7, 129.8, 129.4, 129.0, 127.1, 121.0, 103.5, 61.8, 52.9, 52.0, 30.9, 26.0; HRMS (ESI-TOF) calcd for $C_{18}H_{16}Br_1N_1Na_1O_5$ $(M+Na)^+$ 428.0110, found 428.0106.

*Dimethyl (S)-7-(3-methoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6f**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6f** was obtained as a white solid (18.0 mg, 23% yield), mp 72.5–73.9 °C; $[\alpha]_D^{28}$ –139.5 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1731, 1647, 1598, 1434, 1374, 1263, 1107, 1043, 816, 788, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 2H), 6.99–6.89 (m, 2H), 6.20 (s, 1H), 5.16 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.35–3.19 (m, 1H), 3.19–3.05 (m, 1H), 2.52–2.46 (m, 1H), 2.40–2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.2, 166.2, 159.6, 158.5, 153.0, 151.0, 139.4, 129.7, 121.0, 119.7, 114.9, 112.8, 102.9, 61.5, 55.3, 52.9, 52.2, 30.8, 26.2; HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_1Na_1O_6$ $(M+Na)^+$ 380.1110, found 380.1117.

*Dimethyl (S)-7-(3-chlorophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6g**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6g** was obtained as a yellow solid (14.9 mg, 19% yield), mp 135.4–137.1 °C; $[\alpha]_D^{28}$ –142.8 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2925, 1733, 1650, 1602, 1531, 1436, 1374, 1271, 1209, 1110, 1079, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.22 (m, 4H), 6.16 (s, 1H), 5.17 (dd, *J* = 9.4, 3.0 Hz, 1H),

3.82 (s, 3H), 3.67 (s, 3H), 3.37–3.20 (m, 1H), 3.18–3.07 (m, 1H), 2.63–2.47 (m, 1H), 2.41–2.28 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 170.1, 166.4, 158.4, 151.7, 151.5, 139.8, 134.6, 129.8, 129.2, 127.5, 125.6, 121.2, 102.5, 61.7, 52.9, 52.3, 30.9, 26.2; HRMS (ESI-TOF) calcd for $C_{18}H_{16}Cl_1N_1Na_1O_5$ $(M+Na)^+$ 384.0615, found 384.0613.

*Dimethyl (S)-7-(3-nitrophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6h**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6h** was obtained as a brown solid (13.0 mg, 16% yield), mp 71.6–73.5 C; $[\alpha]_D^{28}$ –125.7 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2954, 2854, 1732, 1649, 1529, 1435, 1351, 1208, 1110, 935, 809, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30–8.24 (m, 2H), 7.71 (ddd, *J* = 7.8, 1.4, 1.4 Hz, 1H), 7.60 (dd, *J* = 8.8, 7.8 Hz, 1H), 6.21 (s, 1H), 5.19 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.48–3.24 (m, 1H), 3.23–3.10 (m, 1H), 2.68–2.50 (m, 1H), 2.43–2.30 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 169.9, 166.1, 158.2, 152.2, 150.8, 148.3, 139.7, 133.4, 129.6, 123.8, 122.5, 102.3, 61.8, 53.0, 52.4, 31.0, 26.1; HRMS (ESI-TOF) calcd for $C_{18}H_{16}N_2Na_1O_7$ $(M+Na)^+$ 395.0855, found 395.0843.

*Dimethyl (S)-7-(4-methoxyphenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6i**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6i** was obtained as a white solid (11.2 mg, 14% yield), mp 166.1–167.0 °C; $[\alpha]_D^{28}$ –111.3 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2952, 2842, 1729, 1646, 1599, 1435, 1377, 1251, 1172, 1101, 1027, 815, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 1H), 5.15 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.68 (s, 3H), 3.33–3.18 (m, 1H), 3.17–3.05 (m, 1H), 2.62–2.45 (m, 1H), 2.40–2.28 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 170.2, 167.2, 160.4, 158.7, 152.7, 150.7, 130.3, 128.9, 120.4, 114.1, 103.0, 61.5, 55.3, 52.9,

52.2, 30.7, 26.2; HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_1Na_1O_6$ $(M+Na)^+$ 380.1110, found 380.1127.

*Dimethyl (S)-7-(4-chlorophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6j**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6j** was obtained as a white solid (17.8 mg, 22% yield), mp 201.8–203.2 °C; $[\alpha]_D^{28}$ –141.2 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 2852, 1730, 1647, 1528, 1435, 1375, 1271, 1171, 1101, 1013, 815, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.15 (s, 1H), 5.16 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.35–3.19 (m, 1H), 3.18–3.05 (m, 1H), 2.62–2.45 (m, 1H), 2.40–2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.1, 166.6, 158.4, 152.0, 151.4, 136.5, 135.3, 128.8, 128.7, 120.9, 102.7, 61.6, 52.9, 52.3, 30.8, 26.1; HRMS (ESI-TOF) calcd for $C_{18}H_{16}Cl_1N_1Na_1O_5$ $(M+Na)^+$ 384.0615, found 384.0615.

*Dimethyl (S)-7-(4-nitrophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6k**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6k** was obtained as a brown solid (10.8 mg, 13% yield), mp 159.0–161.4 °C; $[\alpha]_D^{28}$ –138.3 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2954, 1731, 1649, 1596, 1437, 1347, 1263, 1207, 1170, 1102, 915, 850, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 6.15 (s, 1H), 5.19 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 3.47–3.22 (m, 1H), 3.21–3.09 (m, 1H), 2.67–2.50 (m, 1H), 2.45–2.32 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.9, 166.0, 158.2, 152.2, 151.3, 148.1, 144.6, 128.5, 123.8, 121.2, 102.1, 61.8, 53.0, 52.4, 31.0, 26.1; HRMS (ESI-TOF) calcd for $C_{18}H_{16}N_2Na_1O_7$ $(M+Na)^+$ 395.0855, found 395.0863.

*Dimethyl (S)-7-[(4-methoxycarbonyl)phenyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6l**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6l** was obtained as a white solid (15.4 mg, 18% yield), mp 176.1–177.9 °C; $[\alpha]_D^{27}$ –137.1 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2953, 1721, 1647, 1599, 1530, 1435, 1374, 1277, 1208, 1101, 1018, 820, 776, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 6.18 (s, 1H), 5.17 (dd, *J* = 9.5, 3.1 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 3.63 (s, 3H), 3.36–3.21 (m, 1H), 3.20–3.08 (m, 1H), 2.64–2.49 (m, 1H), 2.42–2.31 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.1, 166.5, 166.3, 158.4, 152.3, 151.6, 142.6, 130.6, 129.8, 127.4, 121.1, 102.5, 61.6, 52.9, 52.3, 30.9, 26.1; HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_1Na_1O_7$ $(M+Na)^+$ 408.1059, found 408.1069.

*Dimethyl (S)-7-(4-aminophenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6m**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/MeOH = 9:1), the product **6m** was obtained as a brown solid (7.6 mg, 10% yield), mp 205.6–206.8 °C; $[\alpha]_D^{29}$ –95.7 (*c* 0.6, $CHCl_3$).

IR (UATR) ν_{max} 3453, 3345, 2952, 1727, 1641, 1603, 1585, 1528, 1434, 1378, 1259, 1210, 1174, 1107, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.21 (s, 1H), 5.15 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.33–3.19 (m, 1H), 3.18–3.04 (m, 1H), 2.61–2.45 (m, 1H), 2.40–2.28 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.3, 167.5, 158.8, 153.0, 150.5, 147.6, 128.8, 127.6, 119.8, 114.8, 102.9, 61.4, 52.8, 52.2, 30.7, 26.2; HRMS (ESI-TOF) calcd for $C_{18}H_{18}N_2Na_1O_5$ $(M+Na)^+$ 365.1113, found 365.1107.

*Dimethyl (S)-7-(2-naphthalenyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6n**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6n** was obtained as a brown solid (10.0 mg, 12% yield), mp 164.7–166.5 °C; $[\alpha]_D^{28}$ –132.1 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2952, 1729, 1646, 1595, 1434, 1386, 1263, 1206, 1103, 974, 817, 732, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.81 (m, 4H), 7.56–7.50 (m, 2H), 7.48 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.31 (s, 1H), 5.19 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 3.38–3.22 (m, 1H), 3.20–3.08 (m, 1H), 2.63–2.48 (m, 1H), 2.41–2.29 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.2, 166.8, 158.6, 153.2, 151.1, 135.5, 133.3, 133.0, 128.4, 127.7, 126.93, 126.89, 126.7, 124.9, 121.1, 103.1, 61.6, 52.9, 52.2, 30.8, 26.2; HRMS (ESI-TOF) calcd for $C_{22}H_{19}N_1Na_1O_5$ $(M+Na)^+$ 400.1161, found 400.1148.

*Dimethyl (S)-5-oxo-7-(3-thioenyl)-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6o**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6o** was obtained as a brown solid (19.2 mg, 26% yield), mp 128.4–130.1 °C; $[\alpha]_D^{28}$ –137.4 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2952, 1728, 1645, 1599, 1434, 1347, 1263, 1206, 1105, 974, 795, , 731, 673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.36 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.25 (s, 1H), 5.14 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.43–3.18 (m, 1H), 3.17–3.05 (m, 1H), 2.61–2.45 (m, 1H), 2.40–2.27 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.1, 167.2, 158.7, 150.8, 146.6, 138.1, 126.9, 126.5, 125.0, 120.3, 102.3, 61.4, 52.9, 52.4, 30.7, 26.1; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_1Na_1O_5S$ $(M+Na)^+$ 356.0569, found 356.0574.

*Dimethyl (S)-5-oxo-7-(3-pyridinyl)-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6p**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6p** was obtained as brown oil (5.0 mg, 7% yield), $[\alpha]_D^{29}$ –118.4 (*c* 0.4, $CHCl_3$).

IR (UATR) ν_{max} 2924, 1731, 1647, 1600, 1530, 1443, 1376, 1264, 1207, 1108, 1025, 811, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66–8.61 (m, 2H), 7.72 (ddd, *J* = 7.9, 2.2, 1.8 Hz, 1H), 7.35 (dd, *J* = 7.9, 5.0 Hz, 1H), 6.17 (s, 1H), 5.19 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.83 (s, 3H), 3.68 (s,

3H), 3.38–3.24 (m, 1H), 3.22–3.09 (m, 1H), 2.63–2.49 (m, 1H), 2.43–2.31 (m, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 170.0, 166.2, 158.3, 152.9, 150.1, 150.0, 148.0, 134.9, 134.1, 123.2, 102.5, 61.7, 53.0, 52.4, 30.9, 26.1; HRMS (ESI-TOF) calcd for $C_{17}H_{16}N_2Na_1O_5$ $(M+Na)^+$ 351.0957, found 351.0953.

*Dimethyl (S)-7-butyl-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6q**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6q** was obtained as yellow oil (7.3 mg, 11% yield), $[\alpha]_D^{28}$ –155.1 (*c* 0.8, $CHCl_3$).

IR (UATR) ν_{max} 2955, 2872, 1730, 1651, 1598, 1443, 1378, 1264, 1128, 1046, 984, 811, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 5.08 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.27–3.12 (m, 1H), 3.11–2.99 (m, 1H), 2.61–2.40 (m, 3H), 2.35–2.20 (m, 1H), 1.62–1.50 (m, 2H), 1.42–1.29 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 172.3, 167.0, 158.7, 156.5, 150.7, 120.7, 103.0, 61.4, 52.8, 52.2, 33.7, 32.0, 30.6, 26.1, 22.6, 13.8; HRMS (ESI-TOF) calcd for $C_{16}H_{21}N_1Na_1O_5$ $(M+Na)^+$ 330.1317, found 330.1322.

*Dimethyl (S)-7-(tert-butyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6r**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6r** was obtained as a yellow solid (14.3 mg, 21% yield), mp 220.5–221.4 °C; $[\alpha]_D^{28}$ –147.9 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2956, 2923, 1741, 1639, 1588, 1439, 1366, 1211, 1109, 1003, 972, 834, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.05 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.29–3.12 (m, 1H), 3.10–2.98 (m, 1H), 2.55–2.38 (m, 3H), 2.35–2.20 (m, 1H), 1.31 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 170.2, 168.9, 160.2, 159.5, 148.9, 121.3, 100.6, 61.2, 52.8, 52.3, 36.4, 30.5, 30.2, 26.3; HRMS (ESI-TOF) calcd for $C_{16}H_{21}N_1Na_1O_5$ $(M+Na)^+$ 330.1317, found 330.1314.

*Dimethyl (S)-7-(3-hydroxypropyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**6s**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6s** was obtained as a brown solid (10.3 mg, 15% yield), mp 107.6–109.8 °C; $[\alpha]_D^{29}$ –187.9 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max}3420, 2953, 1729, 1646, 1586, 1542, 1437, 1381, 1266, 1208, 1128, 1045, 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.09 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.28–3.14 (m, 1H), 3.12–3.00 (m, 1H), 2.64 (t, *J* = 7.3 Hz, 2H), 2.57–2.41 (m, 1H), 2.35–2.24 (m, 1H), 1.93–1.81 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.2, 167.6, 158.6, 156.2, 151.3, 120.9, 102.8, 61.4, 61.0, 52.8, 52.5, 32.5, 30.6, 30.0, 26.0; HRMS (ESI-TOF) calcd for $C_{15}H_{19}N_1Na_1O_6$ $(M+Na)^+$ 332.1110, found 332.1112.

*Methyl (S)-3-[methoxy(methyl)carbamoyl]-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-6-carboxylate (**6t**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6t** was obtained as a brown solid (6.9 mg, 9% yield), mp 160.5–162.5 °C; $[\alpha]_D^{29}$ –32.7 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2925, 1730, 1644, 1594, 1530, 1443, 1378, 1260, 1172, 1107, 1076, 768, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.35 (m, 5H), 6.21 (s, 1H), 5.63 (dd, *J* = 9.4, 1.7 Hz, 1H), 3.95 (s, 3H), 3.60 (s, 3H), 3.44–3.30 (m, 1H), 3.26 (s, 3H), 3.15–3.03 (m, 1H), 2.57–2.39 (m, 1H), 2.30–2.18 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.1, 167.0, 158.8, 153.3, 152.2, 138.3, 128.9, 128.5, 127.4, 120.5, 103.0, 61.7, 59.1, 52.1, 32.0, 31.0, 26.0; HRMS (ESI-TOF) calcd for $C_{19}H_{20}N_2Na_1O_5$ $(M+Na)^+$ 379.1270, found 379.1269.

*Methyl (S)-6-cyano-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3-carboxylate (**6u**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6u** was obtained as a brown solid (7.9 mg, 12% yield), mp 213.9–215.1 °C; $[\alpha]_D^{28}$ –164.1 (*c* 0.5, $CHCl_3$).

IR (UATR) ν_{max} 2925, 2220, 1746, 1651, 1599, 1518, 1437, 1377, 1203, 1180, 1045, 766, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63–7.55 (m, 2H), 7.54–7.46 (m, 3H), 6.32 (s, 1H), 5.22 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.84 (s, 3H), 3.40–3.25 (m, 1H), 3.25–3.13 (m, 1H), 2.68–2.50 (m, 1H), 2.44–2.32 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.7, 161.2, 159.4, 154.9, 136.0, 130.6, 128.9, 128.0, 115.6, 103.1, 99.9, 62.0, 53.1, 31.4, 25.9; HRMS (ESI-TOF) calcd for $C_{17}H_{14}N_2Na_1O_3$ $(M+Na)^+$ 317.0902, found 317.0894.

*Methyl (S)-6-(4-nitrophenyl)-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3-carboxylate (**6v**).*

Following the general procedure of condition A and purification by preparative thin layer chromatography (EtOAc/DCM = 4:1), the product **6v** was obtained as a brown solid (35.9 mg, 42% yield), mp 106.8–108.1 °C; $[\alpha]_D^{28}$ –92.7 (*c* 1.0, $CHCl_3$).

IR (UATR) ν_{max} 2954, 1747, 1645, 1598, 1514, 1343, 1207, 1181, 1108, 853, 773, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.28–7.18 (m, 3H), 7.10–7.04 (m, 2H), 6.31 (s, 1H), 5.19 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.82 (s, 3H), 3.40–3.25 (m, 1H), 3.23–3.10 (m, 1H), 2.68–2.52 (m, 1H), 2.44–2.33 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.5, 160.2, 152.6, 149.7, 146.3, 142.7, 138.8, 132.3, 128.8, 128.4, 128.3, 124.6, 122.7, 104.3, 61.9, 52.9, 30.8, 26.2; HRMS (ESI-TOF) calcd for $C_{22}H_{19}N_2O_5$ $(M+H)^+$ 391.1294, found 391.1291.

Product variations from reaction in acidic EtOH at 100 and 150 °C.

In a pressurized tube, trimethyl chlorosilane (TMSCl, 0.3 mL, 2.4 mmol, 11 equiv) was added to a solution of 2-pyrone **4a** (100 mg, 0.22 mmol) in EtOH (3 mL), and the mixture was stirred at 100 or 150 °C for 1 h. Then, the volatile organic materials were removed under reduced pressure. The crude products were purified by preparative thin layer chromatography (EtOAc/DCM = 4:1). When the reaction was operated at 100 °C, the products **5a** (3.5 mg, 6% yield), **8a** as brown oil (13.0 mg, 21% yield), and **10a** as a brown solid (7.9 mg, 10% yield) were isolated. The observation of the products **8a** and **10a** suggested that the trans-esterification occurred and the

complete trans-esterification would be detected at higher temperature. As expectedly, GC-MS analysis of the crude reaction mixtures from the reaction at 150 °C revealed the ratio of **5a**:**8a**:**10a** to be 0.2:72.9:26.9 and only the trans-esterification products **8a** (42.5 mg, 68% yield) and **10a** (7.1 mg, 9% yield) could be isolated.

*Ethyl (S)-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3-carboxylate (**8a**).*

$[\alpha]_D^{28}$ –130.4 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 2981, 1740, 1655, 1590, 1525, 1374, 1195, 1026, 854, 766, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.52 (m, 2H), 7.47–7.38 (m, 3H), 6.61 (s, 1H), 6.38 (d, *J* = 1.1 Hz, 1H), 5.14 (dd, *J* = 9.3, 3.0 Hz, 1H), 4.35–4.19 (m, 2H), 3.32–3.17 (m, 1H), 3.17–3.05 (m, 1H), 2.60–2.46 (m, 1H), 2.38–2.25 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.1, 161.7, 153.4, 150.1, 138.1, 129.2, 128.8, 126.8, 114.3, 100.9, 61.8, 61.2, 30.5, 26.2, 14.0; HRMS (ESI-TOF) calcd for $C_{17}H_{18}N_1O_3$ $(M+H)^+$ 284.1281, found 284.1292.

*Diethyl (S)-5-oxo-7-phenyl-1,2,3,5-tetrahydroindolizine-3,6-dicarboxylate (**10a**).*

mp 69.5–71.4 °C; $[\alpha]_D^{28}$ –172.6 (*c* 1.0, $CHCl_3$); IR (UATR) ν_{max} 2982, 1728, 1647, 1598, 1530, 1444, 1377, 1257, 1197, 1104, 1020, 774, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 5H), 6.18 (s, 1H), 5.15 (dd, *J* = 9.5, 2.9 Hz, 1H), 4.35–4.19 (m, 2H), 4.15–4.04 (m, 2H), 3.34–3.20 (m, 1H), 3.17–3.05 (m, 1H), 2.61–2.45 (m, 1H), 2.37–2.27 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.7, 166.2, 158.5, 153.0, 151.1, 138.2, 128.9, 128.4, 127.4, 102.8, 61.9, 61.7, 61.1, 52.1, 30.7, 26.1, 14.0, 13.7; HRMS (ESI-TOF) calcd for $C_{20}H_{22}N_1O_5$ $(M+H)^+$ 356.1493, found 356.1501.

ASSOCIATED CONTENT

Supporting Information

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

^{1}H and ^{13}C NMR spectra for all new compounds (PDF) and HPLC chromatograms for **5a** and **6a**.

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Notes

The authors declare no competing financial interest.

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