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A sequential reaction process to assemble polysubstituted indolizidines, quinolizidines and quinolizidine analogues

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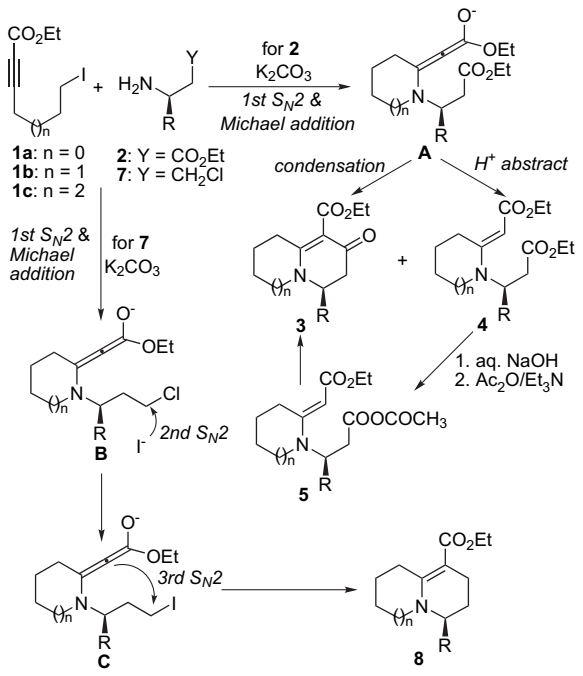
Abstract—The ω-iodo-α,β-alkynoates and their ketone, sulfone or phosphonate analogues react with δ-chloropropylamines in MeCN assisted with K_2CO_3 to undergo a sequential S_N2/Michael addition/S_N2/S_N2 reaction process, giving polysubstituted indolizidines or quinolizidines in good to excellent yields. This sequential reaction process is also compatible with three other substituted α,β-alkynoates, affording quinolizidine analogues in moderate to good yields.

1. Introduction

Fused nitrogen heterocyclic units of indolizidine and quinolizidine are found in a rather large class of alkaloids isolated from diverse natural sources and in human-made substances.[1] These compounds exhibit a considerable range of biological functions including neurological,[1–3] antiviral,[4] immunosuppressive,[5] antimalarial[6] and anti-tumor[7] activities. Because of the very limited amounts available to us from natural sources, total synthesis of natural indolizidines and quinolizidines has greatly facilitated their structural elucidation, as well as evaluation of their pharmacological profile in the past decades.[1,2] In order to assemble quickly the bicyclic skeletons of these compounds, several elegant methods have been developed and found extensive applications in the total synthesis of the targeted alkaloids.[8–13] However, more efficient protocols are still highly required to merit the increasing need for rapidly synthesizing these natural products, and their analogues for drug development and chemical biology.

During the studies aimed at synthesizing pyrrolizidine indolizidine and quinolizidine alkaloids,[14] we have developed a sequential S_N2/Michael addition/condensation reaction process[14a] to enantiopure quinolizidinones and indolizidinones **3** by refluxing enantiopure β-amino esters **2** and ω-iodo-α,β-alkynoates **1** in acetonitrile under the action of K_2CO_3 (Scheme 1). A plausible mechanism was that the amino group in a β-amino ester **2** first attacked the terminal carbon of ethyl 7-iodo-2-heptynoate **1a** or ethyl 7-iodo-2-hexynoate **1b** to form a secondary amine, which spontaneously attacked the electron-deficient triple bond to provide a heterocyclic intermediate **A**. Finally the vinylogous anion



Scheme 1.

Keywords: Sequential reaction process; Indolizidines; Quinolizidines; Michael addition, analogues.
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of **A** generated in the Michael addition step reacted with the carbonyl group of the β-amino ester **2** to give the bicyclic product **3**. Unfortunately, the efficiency of this process was greatly decreased by formation of a side product **4** through proton abstraction in intermediate **A**, although **4** could be converted into **3** through the mixed anhydrides **5**.[14a] In this article, we wish to report a new cascade process, which could deliver the desired bicyclic products exclusively in most cases.[15]

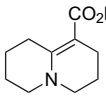
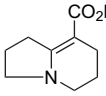
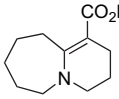
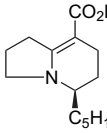
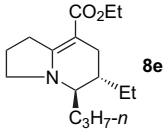
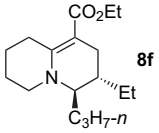
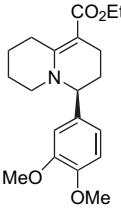
2. Results and discussion

2.1. Sequential S_N2/Michael addition/S_N2/S_N2 reaction process to indolizidines and quinolizidines

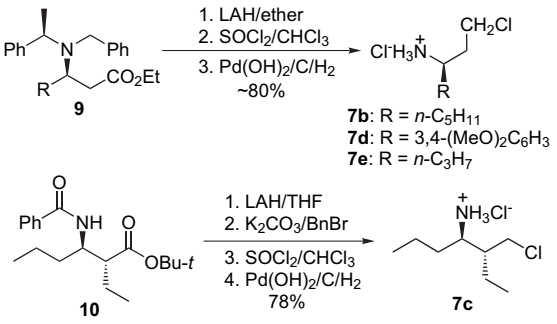
As depicted in Scheme 1, the successful transformation of **4** to **3** through the mixed anhydrides **5** implied that the lower reactivity of the ester moiety in **4** was the cause for incomplete conversion of the above sequential reaction process. One can easily think that increasing the reactivity of nucleophilic moiety of the bifunctional agents **2** would provide a cure for the above drawback. However, such substrates would probably lead to an intramolecular reaction between the amine group and this nucleophilic moiety. After careful analysis, we envisioned that if δ-amino chlorides **7** were used as the substrates, its amine group would first attack the terminal carbon of the ω-iodo-α,β-alkynoates **1** in an S_N2 reaction. Subsequently a Michael addition would occur spontaneously to form the intermediate **B** based on our previous observation.[16] At this time, the resultant iodine anion would probably undergo a halogen-exchange with the chloride, which in turn would generate a more reactive species to react with the allenolate moiety as depicted in intermediate **C**, thereby giving bicyclic products exclusively. Noteworthy is that the γ-amino chlorides have been investigated by Back and Nakajima for assembling piperidines, indolizidines and quinolizidines by reacting with acetylenic sulfones.[13e]

With the above idea in mind, a reaction of ethyl 7-iodo-2-heptynoate **1b** with 3-chloropropylamine hydrochloride **7a** was conducted in acetonitrile under the action of 3.5 equiv of K_2CO_3 and 4 Å MS. At room temperature the reaction gave only a monocyclic product **14** (see Scheme 3), which indicated that a single S_N2 and subsequent Michael reaction took place under these conditions. However, when the reaction temperature was raised to 65 °C, we were pleased to notice that indolizidine **8a** was isolated as a single product in 81% yield (Table 1, entry 1). Using acetonitrile was essential for this process because other solvents such as DMF gave relatively low yield due to formation of unidentified side products (entry 2). Further examination indicated that other iodides **1** with different length of chain also worked at different reaction temperatures to provide indolizidine **8b** (entry 3), or even a piperidinoazpine product **8c** (entry 4). Most importantly, either α-substituted or α,β-disubstituted δ-chloropropylamines was suitable for this process although higher reaction temperatures were needed (entries 5–8). Considering that these amines were readily available in enantiopure form from protected enantiopure β-amino esters **9**[17] or **10**[22c] based on the reaction sequence as outlined in Scheme 2, this method furnished an efficient protocol for synthesis of enantiopure polysubstituted indolizidines and quinolizidines.

Table 1. Reaction of ω-iodo-α,β-alkynoates **1** with δ-chloropropylamines[a]

Entry	Iodide	Amine	Temperature (°C)/time (h)	Product	Yield (%)[b]
1	**1b**	**7a**	65/36	 **8a**	81
2	**1b**	**7a**	50/24		60[c]
3	**1a**	**7a**	60/24	 **8b**	92
4	**1c**	**7a**	70/24	 **8c**	62
5	**1a**	**7b**	82/24	 **8d**	80
6	**1a**	**7c**	82/36	 **8e**	70
7	**1b**	**7c**	82/24	 **8f**	75
8	**1b**	**7d**	82/48	 **8g**	63

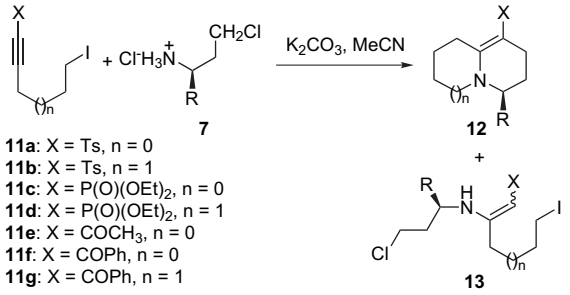
[a] Reaction conditions: **1** (0.2 mmol), **7** (0.2 mmol), K_2CO_3 (0.7 mmol) 4 Å MS (40 mg) in 3 mL of MeCN.
[b] Isolated yield.
[c] Reaction was carried out in DMF.



Scheme 2.

In view of this encouraging result, other iodides **11a**–**11g** bearing different electron-withdrawing groups at the terminal of the acetylene were prepared[18] in order to further explore the scope of this process. As summarized in Table 2, it was found that reaction of tosylate **11a** or **11b** with **7** delivered corresponding indolizidines or quinolizidines **12**, but

Table 2. Reaction of iodides **11** with δ-chloropropylamines[a]



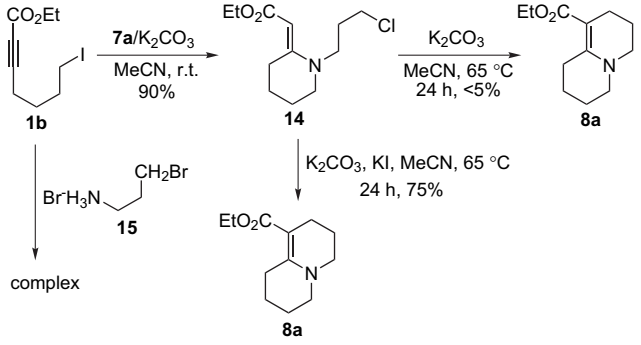
11a: X = Ts, n = 0
11b: X = Ts, n = 1
11c: X = P(O)(OEt)$_2$, n = 0
11d: X = P(O)(OEt)$_2$, n = 1
11e: X = COCH$_3$, n = 0
11f: X = COPh, n = 0
11g: X = COPh, n = 1

Entry	Iodide	Amine	Temperature (°C)/time (h)	Product	Yield (%)[b]
1	**11a**	**7a**	82/24	**12a**	87
2	**11b**	**7a**	82/18	**12b**	83
3	**11a**	**7e**	82/26	**12c**	84
4	**11c**	**7a**	82/36	**12d**	84
5	**11d**	**7a**	82/36	**12e**	77
6	**11c**	**7e**	82/48	**12f**	72
7	**11d**	**7b**	82/48	**12g**	70
8	**11e**	**7a**	30–60/24	**12h**	0 (80)[c]
9	**11f**	**7a**	30–60/24	**12i**	70 (20)[c]
10	**11g**	**7a**	30–60/24	**12j**	~10 (75)[c]
11	**11g**	**7d**	30–60/24	**12k**	55 (20)[c]

[a] Reaction conditions: **11** (0.2 mmol), **7** (0.2 mmol), K_2CO_3 (0.7 mmol), 4 Å MS (40 mg) in 3 mL of MeCN.
[b] Isolated yield.
[c] Yields in parentheses are for direct Michael addition products.

refluxing temperature was required to ensure good yields (entries 1–3). Phosphonates **11c** and **11d** gave similar results under these conditions but needed longer reaction time to complete the conversion (entries 4–7). Then we moved our attention to ketone-derived iodides **11e–11g** and observed that the reaction of **11e** with **7a** only produced a direct Michael addition product **13** (entry 8). This result indicated that for **11e** the ynone moiety was the target for the first attack of the amine group, which should result from the higher electron-withdrawing ability of methyl ketone. Consequently we chose less reactive phenyl ketones as substrates and noticed that reaction of **11f** with **7a** provided the desired indolizidine **12i** in 70% yield (entry 9). In this case some direct Michael addition product was still isolated. Dramatically, when phenyl ketone **11g** was used, the reaction only gave the desired quinolizidine **12j** in less than 10% yield, together with a direct Michael addition product in 70% yield (entry 10), which illustrated that subtle change in structures of ketone substrates would greatly alter the reaction sequence. Moreover, the priority for the first nucleophilic attack site was also dependant on the nature of nucleophiles because when **11g** reacted with sterically hindered amino chloride **7d**, desired bicyclic product **12k** was obtained in 55% yield (entry 11). It is notable that for ketone substrates the reaction mixture should be heated at 30 °C for 12 h first to avoid forming more direct Michael addition products, and then 60 °C for 12 h to complete the conversion. From all the reaction results it was seen that reactivity order for this process was ketone>ester>tosylate>phosphonate, which was consistent with the order of electron-withdrawing ability for the corresponding functional groups.

As mentioned before, the reaction of iodide **1b** and δ-chloropropylamine **7a** at room temperature only gave a monocyclic product **14** (Scheme 3). This result clearly indicated that the formation of the second ring was a rate-determining step for the present process. In order to check if halogen-exchange was important for the second cyclization, controlled experiments as depicted in Scheme 3 were conducted. It was observed when **14** and K_2CO_3 were heated in acetonitrile at 65 °C for 24 h, quinolizidine **8a** was isolated in less than 5% yield. However, when catalytic amount of KI was added to this reaction system, **8a** was obtained in 75% yield. These results demonstrated that the halogen-exchange is necessary for closure of the second ring in satisfactory conversion. The additional evidence came from the fact that reaction of either **11a** or **11b** with **7** gave bicyclic products in good yields (entries 1–3, Table 2), while in a Back's report it was mentioned that addition of δ-chloropropylamines to acetylenic sulfones in several refluxed solvents did not give any cyclization products directly.[13e] On the other hand, we found that when 3-bromopropylamine hydrobromide **15** was used as the substrate, only some polar, unidentified side products and unreacted **1b** were obtained, which implied that **15** was not stable at this reaction condition. Based on these results, we concluded that both the δ-chloropropylamine substrates and the reaction sequence (S_N2/Michael addition/S_N2/S_N2) depicted in Scheme 1 are the key elements for obtaining the target molecules in high yields.



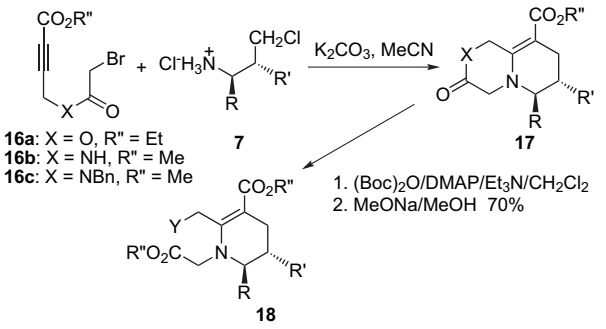
Scheme 3.

Noteworthy is that the present methodology is very useful for quickly assembling natural indolizidines and quinolizidines. For example, from products **8b**, **8d** and **12c** we could prepare tashiromine,[19] indolizidine 209B[20] and indolizidine 167B[21] following the known procedures, respectively.

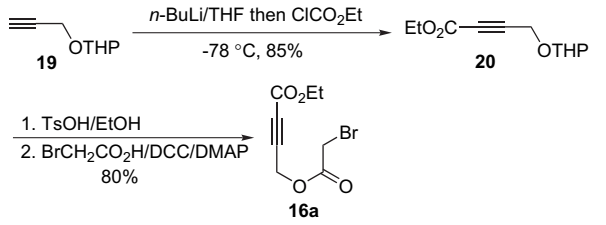
2.2. Sequential S_N2/Michael addition/S_N2/S_N2 reaction process to quinolizidine analogues

Encouraged by the above success, we decided to explore the possibility of substituted α,β-alkynoates **16** as the substrates. If they worked for the above cascade process, we would be able to obtain some quinolizidine analogues **17**. These molecules not only are of interest for further biological evaluation, but also serve as the precusors for elaborating polysubstituted piperidines **18** (Scheme 4).

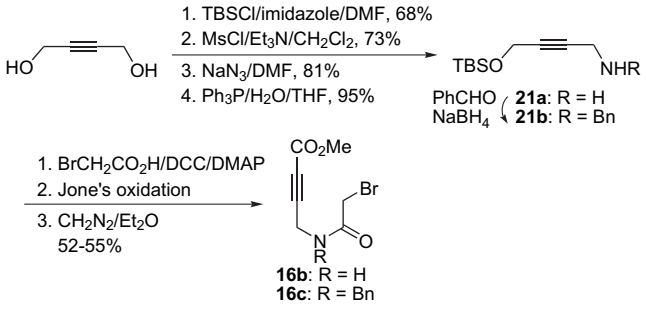
The required substrates **16** were prepared from the corresponding γ-substituted α,β-alkynoates as outline in Schemes 5 and 6. From protected propargyl alcohol **19**, ester **20** was obtained. Removal of the protecting group of **20**



Scheme 4.



Scheme 5.



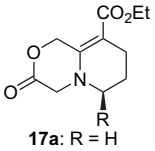
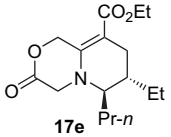
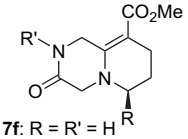
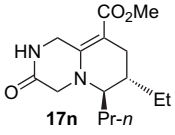
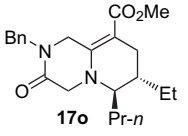
Scheme 6.

followed by coupling with bromoacetic acid provided **16a** in 80% yield.

In a parallel procedure, 2-butyn-1,4-diol was monoprotected and the left hydroxy group was converted into azide through its mesylate. This azide was reduced with triphenylphosphine and water yielded amine **21a**, which was transformed into benzyl amine **21b** via reductive amination. Coupling of amines **21** with bromoacetic acid and subsequent Jone's oxidation and esterification with diazomethane produced the desired amides **16b** and **16c**.

With the above building blocks in hand, we next explored their reaction with several δ-chloropropylamines and the results are summarized in Table 3. In all cases catalytic amount of *n*-Bu_4NI was added to facilitate all S_N2 reactions through halogen-exchange. When diester **16a** was used, its reaction with **7a** was initially carried out under our standard conditions as mentioned above. In this case low yield was observed although the desired bicyclic product **17a** was isolated (entry 1). After some experiment, we found that if a relatively weak base, $NaHCO_3$ was employed, the yield was improved (entry 2). Using these new reaction conditions some α-substituted or α,β-disubstituted δ-chloropropylamines were checked and the corresponding cyclization

Table 3. Reaction of ω-iodo-α,β-alkynoates **16** with δ-chloropropylamines[a]

Entry	Bromide	Amine	Product	Yield (%)[b]
1	**16a**	**7a**	 **17a**: R = H	22
2	**16a**	**7a**	**17a**	57
3	**16a**	**7b**	**17b**: R=*n*-C_5H_{11}	46
4	**16a**	**7d**	**17c**: R=3,4-$(MeO)_2C_6H_3$	41
5	**16a**	**7f**	**17d**: R=Me	49
6	**16a**	**7c**	 **17e** Pr-*n*	37
7	**16b**	**7a**	 **17f**: R = R' = H	74
8	**16c**	**7a**	**17g**: R=H, R′=Bn	82
9	**16b**	**7b**	**17h**: R=*n*-C_5H_{11}, R′=H	68
10	**16b**	**7d**	**17i**: R=3,4-$(MeO)_2C_6H_3$, R′=H	63
11	**16b**	**7f**	**17j**: R=Me, R′=H	71
12	**16c**	**7b**	**17k**: R=*n*-C_5H_{11}, R′=Bn	81
13	**16c**	**7d**	**17l**: R=3,4-$(MeO)_2C_6H_3$, R′=Bn	74
14	**16c**	**7f**	**17m**: R=Me, R′=Bn	78
15	**16b**	**7c**	 **17n** Pr-*n*	59
16	**16c**	**7c**	 **17o** Pr-*n*	72

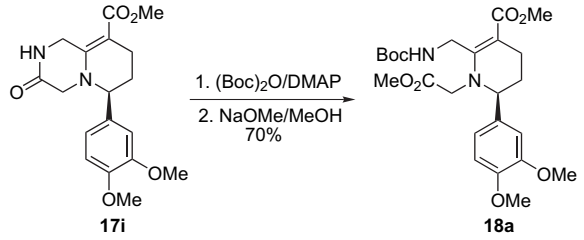
[a] Reaction conditions: **16** (0.2 mmol), **7** (0.2 mmol), Na_2CO_3 (0.7 mmol) [or $NaHCO_3$ (0.7 mmol) for entries 2–6], Bu_4NI (0.02 mmol), 4 Å MS (40 mg) in 3 mL of MeCN.
[b] Isolated yield.

products were isolated in moderate yields (entries 3–6). We reasoned that unsatisfactory yields might result from the bromoacetate moiety in **16a** that was too active and some side reactions might occur. Therefore, less reactive amide **16b** was investigated. As expected, reaction of **16b** with **7a** under the action of Na_2CO_3 worked well, giving **17f** in 74% yield. Using *N*-benzyl amide **16c**, better yield was observed (entry 8).

Further studies revealed that reactions of **16b** and **16c** with some α-substituted (entries 9–14) or α,β-disubstituted (entries 15 and 16) δ-chloropropylamines all proceeded smoothly, delivering the corresponding quinolizidine analogues in good yields. These results indicated that the α-substitutents or α,β-disubstitutents only slightly alter the cascade process, and this process is reliable for elaborating polysubstituted quinolizidine analogues in reasonable diversity.

We next attempted to assemble polysubstituted piperidines using our bicyclic products. Accordingly, treatment of **17i**

with di-*tert*-butyl dicarbonate in the presence of DMAP provided a carbamate. Ring opening of this intermediate with sodium methoxide in methanol afforded tetrasubstituted piperidine **18a** in 70% overall yield (Scheme 7). Obviously, other related bicyclic products **17f**, **17h**, **17j** and **17n** could be converted into corresponding piperidines in the same procedure. Thus, combination of our cascade process and ring-opening transformation gave a facile protocol for elaboration of polysubstituted piperidines.[22]



Scheme 7.

3. Conclusions

In conclusion, we have demonstrated here a sequential S_N2/Michael addition/S_N2/S_N2 reaction process, which allows effectively assembling polysubstituted indolizidines, or quinolizidines and their analogues with a great diversity. This process should find further application in the total synthesis of natural products and designed molecules for biological evaluation.

4. Experimental

4.1. (*R*)-1-Chloro-3-octylamine hydrochloride salt (7b)

To a stirred suspension of LAH (544 mg, 14.3 mmol) in dry diethyl ether (40 mL) was added dropwise β-amino ester **9b** (5.5 g, 14.3 mmol) in dry diethyl ether (40 mL) at 0 °C. After the reaction mixture was stirred at 20 °C for 1 h, water (0.57 mL), 15% NaOH (0.57 mL) and more water (1.71 mL) was added successively. Stirring was continued until a white precipitate formed, then it was filtered through Celite, and the filtrate was dried over $MgSO_4$, concentrated and purified via chromatography to give 4.85 g (100%) of amino alcohol as a viscous oil. $[\alpha]_D^{20}$ −38.9 (*c* 1.1, $CHCl_3$); IR (film) 2931, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.20 (m, 10H), 3.95 (t, *J*=6.9 Hz, 1H), 3.85 (d, *J*=13.7 Hz, 1H), 3.68 (d, *J*=13.7 Hz, 1H), 3.52–3.46 (m, 1H), 3.22–3.15 (m, 1H), 2.80–2.76 (m, 2H), 1.71–1.67 (m, 1H), 1.57–1.50 (m, 1H), 1.46–1.26 (m, 11H), 0.91 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 140.7, 129.1, 128.4, 128.1, 128.0, 126.9, 61.9, 56.6, 55.2, 49.8, 33.7, 32.6, 32.2, 27.4, 22.7, 14.9, 14.1; HRMS calcd for $C_{23}H_{34}NO$ 340.2635 $(M+H)^+$, found 340.2624.

To a stirred solution of the above amino alcohol (339 mg, 5.5 mmol) in $CHCl_3$ (15 mL) was slowly added a solution of $SOCl_2$ (0.8 mL, 10.9 mmol) in $CHCl_3$ (3 mL) at 0 °C. The reaction mixture was refluxed for 1 h, and then evaporated. The residue was dissolved directly in methanol (40 mL), and hydrogenated over 20% $Pd(OH)_2$ (400 mg) under 50 atm hydrogen atmosphere at 30 °C for 48 h. The reaction mixture was filtered off, and the filtrate was concentrated in vacuum to afford 0.9 g (85%) of crude **7b** as a light yellow solid, which was directly used due to its instability. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.49–8.47 (m, 3H), 3.86–3.82 (m, 1H), 3.75–3.69 (m, 1H), 3.52–3.48 (m, 1H), 2.2–2.24 (m, 1H), 2.17–2.13 (m, 1H), 1.82–1.29 (m, 8H), 0.91 (t, *J*=6.6 Hz, 3H).

4.2. General procedure for reaction of ω-iodo-α,β-alkynoates 1 with δ-chloropropylamines (7)

A mixture of **1** (0.22 mmol), **7** (0.23 mmol), anhydrous K_2CO_3 (0.7 mmol) and 4 Å MS (40 mg) in 3 mL of MeCN was stirred at the indicated temperatures until the starting materials disappeared as monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:10 to 1:1 ethyl acetate/petroleum ether to afford **8**.

4.2.1. 3,4,6,7,8,9-Hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8a).[19] ^1H NMR ($CDCl_3$, 300 MHz) δ 4.08 (q, *J*=7.2 Hz, 2H), 3.13–3.06 (m, 4H), 3.01 (t, *J*=6.4 Hz, 2H), 2.38 (t, *J*=12.9 Hz, 2H), 1.80–1.73 (m, 4H), 1.63–1.59 (m, 2H), 1.24 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 209 $(M)^+$.

4.2.2. 1,2,3,5,6,7-Hexahydroindolizine-8-carboxylic acid ethyl ester (8b).[19] ^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, *J*=7.2 Hz, 2H), 3.28 (t, *J*=7.1 Hz, 2H), 3.14 (t, *J*=5.8 Hz, 2H), 3.05 (t, *J*=7.8 Hz, 2H), 2.35 (t, *J*=6.5 Hz, 2H), 1.94–1.81 (m, 4H), 1.25 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 195 $(M)^+$.

4.2.3. 2,3,4,6,7,8,9,10-Octahydropyrido[1,2-*a*]azepine-1-carboxylic acid ethyl ester (8c).[19] ^1H NMR ($CDCl_3$, 300 MHz) δ 4.10 (q, *J*=7.2 Hz, 2H), 3.37–3.34 (m, 2H), 3.21 (t, *J*=5.8 Hz, 2H), 3.15 (t, *J*=4.7 Hz, 2H), 2.37 (t, *J*=6.3 Hz, 2H), 1.81–1.77 (m, 2H), 1.65–1.57 (m, 6H), 1.25 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 223 $(M)^+$.

4.2.4. (2*R*)-3,4,6,7,8,9-Hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8d). $[\alpha]_D^{30}$ −1.05 (*c* 1.2, EtOH); IR (film) 2932, 1680, 1593, 1282 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, *J*=7.2 Hz, 2H), 3.51 (dt, *J*=9.3, 7.0 Hz, 1H), 3.24–3.14 (m, 2H), 3.10–3.04 (m, 2H), 2.44 (dt, *J*=15.8, 5.1 Hz, 1H), 2.27–2.16 (m, 1H), 1.97–1.85 (m, 2H), 1.86–1.75 (m, 2H), 1.68–1.55 (m, 2H), 1.38–1.23 (m, 1H), 0.89 (t, *J*=7.2 Hz, 3H); MS *m*/*z* 265 $(M)^+$; HRMS calcd for $C_{16}H_{29}NO_2$ 266.2115, found 266.2119.

4.2.5. (2*R*,3*S*)-6-Ethyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylic acid ethyl ester (8e). $[\alpha]_D^{17}$ −26.3 (*c* 0.75, $CHCl_3$); IR (film) 1678, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, *J*=7.2 Hz, 2H), 3.56 (dt, *J*=9.3, 7.1 Hz, 1H), 3.24–3.17 (m, 1H), 3.09–3.01 (m, 3H), 2.39–2.19 (m, 2H), 1.97–1.86 (m, 2H), 1.65 (m, 1H), 1.53 (m, 1H), 1.40–1.23 (m, 6H), 1.17–1.10 (m, 2H), 0.95–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 157.2, 84.6, 58.3, 58.0, 52.4, 35.4, 34.7, 32.7, 25.3, 22.3, 21.2, 19.2, 14.8, 14.1, 12.0; MS *m*/*z* 265 $(M)^+$; HRMS calcd for $C_{16}H_{28}NO_2$ 266.2115 $(M+H)^+$, found 266.2113.

4.2.6. (2*R*,3*S*)-3-Ethyl-4-propyl-3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8f). $[\alpha]_D^{18}$ −139.2 (*c* 0.5, $CHCl_3$); IR (film) 1730, 1673, 1556 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.08 (q, *J*=7.0 Hz, 2H), 3.35–3.10 (m, 3H), 2.90–2.81 (m, 2H), 2.37–2.23 (m, 2H), 1.74–1.64 (m, 3H), 1.57–1.52 (m, 4H), 1.34–1.16 (m, 7H), 0.94–0.88 (m, 6H); MS *m*/*z* 265 $(M)^+$; HRMS calcd for $C_{17}H_{30}NO_2$ 280.2271 $(M+H)^+$, found 280.2277.

4.2.7. (2*S*)-4-(3,4-Dimethoxyphenyl)-3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylic acid ethyl ester (8g). $[\alpha]_D^{19}$ +44.3 (*c* 1.4, $CHCl_3$); IR (film) 2939, 1669, 1549 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.83–6.81 (m, 1H), 6.72–6.69 (m, 2H), 4.20 (br s, 1H), 4.11–4.06 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.21–3.15 (m, 4H), 2.57–2.45 (m, 1H), 2.10–1.69 (m, 7H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 156.4, 148.9, 147.9, 135.1, 118.3, 111.0, 109.3, 91.5, 62.9, 58.5, 55.9, 55.8, 49.6, 28.6, 27.6, 23.4, 20.4, 19.2, 14.7; ESI-MS *m*/*z* 346 $(M+H)^+$; HRMS calcd for $C_{20}H_{28}NO_4$ 346.2013 $(M+H)^+$, found 346.2013.

4.2.8. 1-(6-Iodohex-1-yne-1-sulfonyl)-4-methylbenzene (11b). A mixture of selenosulfonate (3.4 g, 10.8 mmol), 5-hexyn-1-ol (1.05 g, 10.8 mmol) and AIBN (80 mg) was refluxed in chloroform (100 mL) under an argon atmosphere for 24 h. The solvent was evaporated on vacuum, and the residue was chromatographed to give the addition product, which was dissolved in dichloromethane (30 mL) and *n*-hexane (180 mL). With vigorous stirring, *m*-CPBA (70%, 2.52 g) was added in small portions at room temperature. After 10 min, a white precipitate formed, which was filtered and washed with diethyl ether, and then dried on vacuum. The white solid was suspended in chloroform (100 mL) and refluxed for 3 h. The solvent was removed, and the residue was purified via chromatograph to afford 1.5 g (57%) of alcohol. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J*=8.2 Hz, 2H), 7.37 (d, *J*=8.6 Hz, 2H), 3.64 (t, *J*=5.8 Hz, 2H), 2.47 (s, 3H), 2.44–2.40 (m, 2H), 1.67–1.62 (m, 4H); MS *m*/*z* 252 $(M)^+$; HRMS calcd for $C_{13}H_{16}O_3S$ 252.0820 $(M)^+$, found 252.0808.

To a solution of the above alcohol (0.58 g, 2.3 mmol) and Et_3N (0.5 mL, 3.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (0.22 mL, 2.8 mmol). The reaction mixture was stirred at room temperature for 1 h, and then quenched with methanol (0.2 mL). The mixture was washed with water and brine, dried over Na_2SO_4 and evaporated to give the crude product, which was dissolved in acetone (25 mL). Sodium iodide (0.82 g, 5.4 mmol) was added, and the reaction mixture was stirred in dark for 72 h. The solvent was removed, and the residue was diluted with dichloromethane, washed with saturated $Na_2S_2O_3$ and dried over Na_2SO_4. The organic phase was concentrated and the residue was chromatographed to give 0.7 g (84%) of **11b** as a viscous oil. IR (film) 2935, 1596, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J*=8.2 Hz, 2H), 7.39–7.37 (m, 2H), 3.15 (t, *J*=6.7 Hz, 2H), 2.47 (s, 3H), 2.40 (t, *J*=6.8 Hz, 2H), 1.88–1.81 (m, 2H), 1.73–1.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.3, 140.0, 130.0, 127.3, 95.9, 32.1, 27.7, 21.8, 18.0, 5.1; MS *m*/*z* 362 $(M)^+$; HRMS calcd for $C_{13}H_{15}O_2SI$ 361.9838 $(M)^+$, found 361.9859.

4.2.9. 1-(5-Iodopent-1-yne-1-sulfonyl)-4-methylbenzene (11a). Following a similar procedure from 5-hexyn-1-ol to **11b**, **11a** was prepared from 4-pentyn-1-ol in 48% yield. IR (film) 2203, 1596, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J*=8.4 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 3.19 (t, *J*=7.2 Hz, 2H), 2.53 (t, *J*=7.5 Hz, 2H), 2.47 (s, 3H), 2.08–1.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.4, 138.8, 130.0, 127.3, 94.7, 79.3, 30.4, 21.8, 20.1, 4.0; MS *m*/*z* 348 $(M)^+$; ESI-HRMS calcd for $C_{12}H_{13}O_2SINa$ 370.9573 $(M+Na)^+$, found 370.9592.

4.2.10. (5-Iodopent-1-ynyl)phosphonic acid diethyl ester (11c). To a solution of 2-(4-pentyn-1-oxy)tetrahydrofuran (0.74 g, 4.4 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in hexane, 2.8 mL, 4.9 mmol) dropwise at −78 °C under an argon atmosphere. The resultant solution was stirred for 30 min, and then diethylchlorophosphate (0.7 mL, 4.8 mmol) in THF (5 mL) was added slowly. After the reaction mixture was stirred for a further 1 h at −78 °C, it was quenched with brine, and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in methanol (50 mL) before 20 mg of *p*-TsOH was added. After the reaction mixture was stirred at room temperature for 24 h, it was concentrated in vacuo. The residue was purified by chromatography to give 0.87 g (90%) of phosphonate as a viscous oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21–4.10 (m, 4H), 3.79–3.73 (m, 2H), 2.54–2.47 (m, 2H), 1.89–1.81 (m, 2H), 1.36–1.33 (m, 6H); MS *m*/*z* 220 $(M)^+$; HRMS calcd for $C_9H_{17}O_4P$ 220.0865 $(M)^+$, found 220.0871.

To a solution of the above phosphonate (0.51 g, 2.3 mmol) and Et_3N (0.5 mL, 3.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (0.22 mL, 2.8 mmol). The reaction mixture was stirred at room temperature for 1 h before 0.2 mL of MeOH was added to quench the reaction. The mixture was washed with water and brine, dried over Na_2SO_4 and evaporated to give the crude product, which was dissolved in acetone (25 mL). After sodium iodide (0.82 g, 5.4 mmol) was added, the reaction mixture was stirred in dark for 72 h. The solvent was removed, and the residue was diluted with dichloromethane, washed with saturated $Na_2S_2O_3$ and dried over Na_2SO_4. The organic phase was concentrated and the residue was chromatographed to give 0.68 g (90%) of **11c** as a viscous oil. IR (film) 2208, 1259, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21–4.11 (m, 4H), 3.29 (t, *J*=6.6 Hz, 2H), 2.55–2.49 (m, 2H), 2.11–2.02 (m, 2H), 1.38 (t, *J*=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 100.7, 100.0, 63.0, 62.9, 20.2, 20.1, 16.1, 16.0, 4.1; MS *m*/*z* 330 $(M)^+$; HRMS calcd for $C_9H_{16}O_3PI$ 329.9882 $(M)^+$, found 329.9904.

4.2.11. (6-Iodohex-1-ynyl)phosphonic acid diethyl ester (11d). Following a similar procedure from 2-(4-pentyn-1-oxy)tetrahydrofuran to **11c**, **11d** was prepared in 78% yield from 2-(5-hexyn-1-oxy)tetrahydrofuran. IR (film) 2985, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21–4.11 (m, 4H), 3.21 (t, *J*=6.6 Hz, 2H), 2.43–2.37 (m, 2H), 1.97–1.92 (m, 2H), 1.75–1.70 (m, 2H), 1.40–1.35 (m, 6H); MS *m*/*z* 344 $(M)^+$; ESI-HRMS calcd for $C_{10}H_{19}O_3PI$ 345.0111 $(M+H)^+$, found 345.0099.

4.2.12. 6-Iodo-1-phenylhex-2-yn-1-one (11f). To a stirred solution of 2-(4-pentyn-1-oxy)tetrahydrofuran (1.51 g, 9.0 mmol) in dry THF (20 mL) was added *n*-BuLi (1.6 M in hexane, 6.2 mL, 10.0 mmol) at −78 °C. The reaction mixture was stirred for 30 min, and then a solution of PhCHO (1.1 mL, 10.8 mmol) in THF (5 mL) was added slowly. The reaction mixture was stirred for a further 30 min before saturated NH_4Cl was added at −78 °C to quench the reaction. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and purified via chromatograph to give 2.33 g (95%) of the desired alcohol.

To a solution of oxalyl chloride (1.54 mL, 18.0 mmol) in dichloromethane (40 mL) was added methyl sulfoxide (1.9 mL, 20.9 mmol) in dichloromethane (6 mL) at −78 °C. After 15 min, a solution of the above alcohol (2.33 g, 8.57 mmol) in dichloromethane (15 mL) was added slowly. After the solution was stirred for a further 15 min at −78 °C, triethylamine (6.2 mL) was added dropwise. The reaction mixture was warmed to room temperature, and stirring was continued for 30 min. After saturated $NaHCO_3$ was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, evaporated and purified via chromatograph to give 2.1 g (90%) of ketone.

A solution of the above ketone (2.1 g, 7.72 mmol) and *p*-TsOH (10 mg) in MeOH (30 mL) and water (1.5 mL) was stirred at room temperature for 24 h. The solvent was removed under vacuum, and the residue was dissolved in ethyl acetate, washed with brine and dried over Na_2SO_4. Evaporation on vacuum followed by chromatography afforded 1.2 g (83%) of alcohol, which was converted to iodide **11f** through its mesylate in 92% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15–8.12 (m, 2H), 7.62–7.59 (m, 1H), 7.52–7.47 (m, 2H), 3.36 (t, J=6.5 Hz, 2H), 2.69 (t, J=6.8 Hz, 2H), 2.19–2.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.0, 134.1, 129.6, 128.6, 93.9, 80.4, 31.1, 20.3, 4.6; MS *m*/*z* 298 $(M)^+$.

4.2.13. 7-Iodo-1-phenylhept-2-yn-1-one (11g). Following a similar procedure from 2-(4-pentyn-1-oxy)tetrahydrofuran to **11b**, **11g** was prepared in 63% overall yield from 2-(5-hexyn-1-oxy)tetrahydrofuran. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16–8.12 (m, 2H), 7.65–7.60 (m, 1H), 7.52–7.47 (m, 2H), 3.25 (t, J=6.6 Hz, 2H), 2.56 (t, J=7.1 Hz, 2H), 2.07–1.98 (m, 2H), 1.86–1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.1, 136.8, 134.0, 129.6, 128.6, 95.4, 80.1, 32.4, 28.5, 18.3, 5.6; ESI-HRMS calcd for $C_{13}H_{14}O_6I$ 313.0084 $(M+H)^+$, found 313.0083.

4.3. General procedure for reaction of iodides 11 with δ-chloropropylamines (7)

A mixture of **11** (0.22 mmol), **7** (0.23 mmol), anhydrous K_2CO_3 (0.7 mmol) and 4 Å MS (40 mg) in 3 mL of MeCN was stirred at the indicated temperatures until the starting materials disappeared as monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:1 to 1:10 ethyl acetate/petroleum ether to afford **12**.

4.3.1. 8-(Toluene-4-sulfonyl)-1,2,3,5,6,7-hexahydroindolizine (12a). IR (film) 2847, 1592 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.68 (m, 2H), 7.28–7.23 (m, 2H), 3.28 (t, J=7.2 Hz, 2H), 3.14–3.09 (m, 4H), 2.40 (s. 3H), 2.33 (t, J=6.0 Hz, 2H), 1.98–1.88 (m, 2H), 1.86–1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 142.2, 129.7, 126.6, 93.0, 53.3, 45.0, 31.6, 22.5, 21.8, 21.7, 21.3; MS *m*/*z* 277 $(M)^+$; HRMS calcd for $C_{15}H_{19}NSO_2$ 277.1180 $(M)^+$, found 277.1158.

4.3.2. 9-(Toluene-4-sulfonyl)-1,3,4,6,7,8-hexahydro-2*H*-quinolizine (12b). IR (film) 2948, 1558, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71–7.68 (m, 2H), 7.27–7.24 (m, 2H), 3.12–3.04 (m, 4H), 2.84 (t, J=6.5 Hz, 2H), 2.53 (t, J=6.2 Hz, 2H), 2.40 (s, 3H), 1.83–1.77 (m, 2H), 1.74–1.68 (m, 2H), 1.60–1.55 (m, 2H); MS *m*/*z* 291 $(M)^+$; HRMS calcd for $C_{16}H_{21}NSO_2$ 291.1315 $(M)^+$, found 291.1304.

4.3.3. (5*R*)-5-Propyl-8-(toluene-4-sulfonyl)-1,2,3,5,6,7-hexahydroindolizine (12c). $[\alpha]_D^{19}$ +3.0 (*c* 1.1, $CHCl_3$); IR (film) 2956, 1596, 1274 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, J=8.5 Hz, 2H), 7.27–7.23 (m, 3H), 3.51 (dt, J=9.6, 6.9 Hz, 1H), 3.23–3.08 (m, 4H), 2.43 (s, 3H), 2.38–2.25 (m, 2H), 1.91 (q, J=7.3 Hz, 2H), 1.80–1.74 (m, 1H), 1.65–1.50 (m, 1H), 1.39–1.20 (m, 4H), 0.91 (t, J=6.8 Hz, 3H); MS *m*/*z* 319 $(M)^+$; HRMS calcd for $C_{18}H_{26}NSO_2Na^+$ 320.1679 $(M+Na)^+$, found 320.1682.

4.3.4. (1,2,3,5,6,7-Hexahydroindolizin-8-yl)phosphonic acid diethyl ester (12d). IR (film) 2979, 1610, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.04–3.90 (m, 4H), 3.22 (t, J=6.9 Hz, 2H), 3.15 (t, J=5.8 Hz, 2H), 2.90 (t, J=7.4 Hz, 2H), 2.18 (q, J=6.1 Hz, 2H), 1.92–1.81 (m, 4H), 1.29 (t, J=7.2 Hz, 6H); MS *m*/*z* 259 $(M)^+$; HRMS calcd for $C_{12}H_{23}NPO_3$ 260.1410 $(M+H)^+$, found 260.1415.

4.3.5. (3,4,6,7,8,9-Hexahydro-2*H*-quinolizin-1-yl)phosphonic acid diethyl ester (12e). IR (film) 2939, 1577, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.06–3.96 (m, 4H), 3.07–3.01 (m, 4H), 2.80 (br s, 2H), 2.27–2.21 (m, 2H), 1.85–1.73 (m, 4H), 1.64–1.58 (m, 2H), 1.34–1.28 (m, 6H); MS *m*/*z* 273 $(M)^+$; HRMS calcd for $C_{13}H_{25}NPO_3$ 274.1567 $(M+H)^+$, found 274.1565.

4.3.6. (5*R*)-(5-Propyl-1,2,3,5,6,7-hexahydroindolizin-8-yl)phosphonic acid diethyl ester (12f). $[\alpha]_D^{18}$ +2.4 (*c* 1.0, $CHCl_3$); IR (film) 2962, 1707, 1606, 1292 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.04–3.91 (m, 4H), 3.47 (dt, J=9.1, 6.5 Hz, 1H), 3.27–3.20 (m, 1H), 3.12 (dt, J=8.7, 6.9 Hz, 1H), 2.94–2.88 (m, 2H), 2.17–2.07 (m, 2H), 1.92–1.82 (m, 2H), 1.75–1.54 (m, 2H), 1.37–1.25 (m, 10H), 0.96–0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.4, 60.3, 53.7, 51.1, 34.9, 31.7, 25.0, 24.9, 21.4, 19.6, 19.4, 19.0, 16.5, 16.4, 14.2; MS *m*/*z* 301 $(M)^+$; HRMS calcd for $C_{15}H_{29}NPO_3$ 302.1880 $(M+H)^+$, found 302.1886.

4.3.7. (4*R*)-(4-Pentyl-3,4,6,7,8,9-hexahydro-2*H*-quinolizin-1-yl)phosphonic acid diethyl ester (12g). $[\alpha]_D^{19}$ −26.1 (*c* 0.53, $CHCl_3$); IR (film) 2926, 1577, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.03–3.93 (m, 4H), 3.21–3.15 (m, 1H), 3.09–3.03 (m, 1H), 3.01–2.99 (m, 1H), 2.92–2.84

(m, 1H), 2.68–2.61 (m, 1H), 2.28–2.08 (m, 2H), 1.79–1.47 (m, 6H), 1.36–1.25 (m, 14H), 0.89 (t, J=6.8 Hz, 3H); MS m/z 343 $(M)^+$; HRMS calcd for $C_{18}H_{35}NPO_3$ 344.2349 $(M+H)^+$, found 344.2348.

4.3.8. (1,2,3,5,6,7-Hexahydroindolizin-8-yl)phenylmethanone (12i). IR (film) 2926, 1531, 1290 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.32 (m, 5H), 3.40–3.36 (m, 2H), 3.28–3.24 (m, 2H), 2.79 (t, J=7.8 Hz, 2H), 2.46 (t, J=6.0 Hz, 2H), 1.92–1.82 (m, 4H); ESI-MS m/z 228 $(M+H)^+$; HRMS calcd for $C_{15}H_{18}NO$ 228.1383 $(M+H)^+$, found 228.1389.

4.3.9. (2*S*)-[4-(3,4-Dimethoxyphenyl)-3,4,6,7,8,9-hexahydro-2*H*-quinolizin-1-yl]-phenylmethanone 12k. $[\alpha]_D^{21}$ +144.9 (c 1.2, $CHCl_3$); IR (film) 2933, 1712, 1595, 1516 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49–7.46 (m, 2H), 7.40–7.30 (m, 3H), 6.89–6.86 (m, 1H), 6.79–6.74 (m, 2H), 4.29 (t, J=3.9 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.29–3.00 (m, 4H), 2.32–2.19 (m, 2H), 2.03–1.96 (m, 1H), 1.88–1.64 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7, 158.6, 149.1, 148.2, 143.9, 135.0, 129.3 (2C), 127.9 (2C), 127.6 (2C), 118.4, 111.1, 109.3, 102.5, 63.5, 55.9, 49.5, 29.4, 28.8, 23.2, 22.6, 20.4; ESI-HRMS calcd for $C_{24}H_{28}NO_3$ 378.2070 $(M+H)^+$, found 378.2064.

4.3.10. [1-(3-Chloropropyl)piperidin-2-ylidene]acetic acid ethyl ester (14). ^1H NMR ($CDCl_3$, 300 MHz) δ 4.56 (s, 1H), 4.06 (q, J=7.2 Hz, 2H), 3.58 (t, J=12.3 Hz, 2H), 3.35 (t, J=14.4 Hz, 2H), 3.26 (t, J=12.3 Hz, 2H), 3.10 (t, J=12.9 Hz, 2H), 2.11–2.06 (m, 2H), 1.80–1.74 (m, 2H), 1.66–1.62 (m, 2H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 161.8, 82.0, 58.2, 50.4, 49.2, 42.5, 28.2, 26.5, 23.3, 19.5, 14.7; ESI-MS m/z 246 $(M+H)^+$; ESI-HRMS calcd for $C_{12}H_{21}NO_2Cl$ 246.1255 $(M+H)^+$, found 246.1257.

4.3.11. Ethyl 4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-ynoate (20). To a stirred solution of **19** (4.36 g, 31.2 mmol) in dry ethyl ether (100 mL) at −78 °C under N_2 atmosphere was added dropwise *n*-butyllithium (1.6 M in hexane, 20.0 mL, 32.0 mmol). The resultant solution was stirred for 30 min, and ethyl chloroformate (4.5 mL, 47.1 mmol) was added dropwise. The solution was stirred for 30 min and the solution was warmed to room temperature before it was quenched with saturated NH_4Cl. The separated organic layer was washed with brine and water, dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/20 ethyl acetate/petroleum ether to give 5.62 g of **20** in 85% yield. IR (film) 2946, 2241, 1718, 1254, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81 (m, 1H), 4.25 (m, 2H), 4.18 (m, 1H), 3.82 (m, 1H), 3.52 (m, 1H), 2.41 (m, 1H), 1.77–1.42 (m, 6H), 1.29 (m, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 144.1, 96.8, 79.8, 73.9, 67.7, 62.0, 54.0, 30.2, 25.3, 19.0, 18.9; MS m/z 212.2 $(M)^+$.

4.3.12. Ethyl 4-(2-bromoacetoxy)but-2-ynoate (16a). To a solution of **20** (2.55 g, 12.0 mmol) in ethanol (20 mL) was added TsOH (0.23 g, 1.20 mmol). The resultant solution was stirred overnight and concentrated to remove the solvent. The residue was diluted with dichloromethane and washed with saturated $NaHCO_3$, brine and water sequentially. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 1.39 g of alcohol, which was dissolved in dry CH_2Cl_2 (15 mL). To this solution were added bromoacetic acid (1.81 g, 13.0 mmol), DMAP (0.14 g, 1.10 mmol) and DCC (2.68 g, 13.0 mmol) sequentially. The resultant mixture was stirred for 3 h before it was filtered and concentrated in vacuo. The residue was purified by chromatography eluting with 1/10 ethyl acetate/petroleum ether to give 2.29 g of **16a** (80% yield for two steps). IR (film) 2987, 2252, 1752, 1716, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (s, 2H), 4.27 (q, J=6.9 Hz, 2H), 3.91 (s, 2H), 1.33 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 152.6, 79.5, 78.7, 62.4, 52.8, 24.8, 13.9; MS m/z 248.2 $(M)^+$.

4.3.13. *N*-Benzyl-4-(*tert*-butyldimethylsilyloxy)but-2-yn-1-amine (21b). To a stirred solution of 2-butyne-1,4-diol (17.22 g, 0.20 mol) in DMF (200 mL) were added imidazole (20.42 g, 0.30 mol) and *tert*-butyldimethylsilyl chloride (36.02 g, 0.24 mol). The resultant solution was stirred for 24 h, and then quenched with methanol (25 mL) and water (200 mL). The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 27.19 g of silyl ether in 68% yield.

To a solution of the above silyl ether (19.10 g, 98.5 mmol) in dry CH_2Cl_2 (150 mL) were added Et_3N (19.2 mL, 138 mmol) and MsCl (9.2 mL, 118 mmol) successively at 0 °C under nitrogen atmosphere. The resultant solution was stirred overnight, and then washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/8 ethyl acetate/petroleum ether to give 19.30 g of mesylate in 73% yield.

To a stirred solution of above mesylate (8.80 g, 31.7 mmol) in DMF (50 mL) was added NaN_3 (2.47 g, 38.0 mmol) and stirred for 2 h, and then quenched with water (200 mL). The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/20 ethyl acetate/petroleum ether to give 5.78 g of azide in 81% yield.

A solution of above azide (5.78 g, 25.7 mmol), Ph_3P (7.41 g, 28.3 mmol) and water (0.70 mL, 38.9 mmol) in THF (100 mL) was stirred for 2 days at room temperature. After the solution was concentrated in vacuo, the residual oil was purified by chromatography eluting with ethyl acetate to give 4.86 g of **21a** in 95% yield.

A mixture of **21a** (0.85 g, 4.27 mmol) and PhCHO (0.44 g, 4.33 mmol) in ethanol (20 mL) was stirred for 3 h before $NaBH_4$ (0.24 g, 6.39 mmol) was added. After the resultant solution was refluxed for 3 h, it was concentrated and then diluted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/4 ethyl acetate/petroleum ether to give 0.55 g of **21b** in 45% yield. IR (film) 2930, 2858, 1472, 1255,

1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H), 4.36 (t, J=1.8 Hz, 2H), 3.90 (s, 3H), 3.46 (t, J=1.8 Hz, 2H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.57, 128.41, 128.39, 127.10, 82.91, 82.12, 52.43, 51.86, 37.75, 25.86, 18.34, −5.11; ESI-MS *m/z* 290.2 $(M-H)^+$; HRMS calcd for $C_{17}H_{28}NOSi$ 290.1935 $(M+H)^+$, found 290.1945.

4.3.14. Methyl 4-(2-bromoacetamido)but-2-ynoate (16b). A solution of **21a** (8.1 g, 29.3 mmol), bromoacetic acid (4.07 g, 29.3 mmol), DMAP (0.30 g, 2.44 mmol) and DCC (6.03 g, 29.3 mmol) in 100 mL of CH_2Cl_2 was stirred for 3 h before it was filtered and concentrated in vacuo. The residue was purified by chromatography eluting with 1/4 ethyl acetate/petroleum ether to give 7.42 g of amide in 95% yield.

To a stirred solution of above amide (1.04 g, 3.25 mmol) in acetone (20 mL) was added Jone's reagent (5.0 mL) at −10 °C for 2 h. The resultant solution was warmed to room temperature and stirred for 4 h. After the solution was diluted with water (100 mL), it was extracted with ethyl ether. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give crude acid. The crude acid was dissolved in ethyl ether and a solution of CH_2N_2 in ethyl ether was added at 0 °C. After it was stirred for 0.5 h, the solution was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resultant oil was purified by chromatography eluting with 1/2 ethyl acetate/petroleum ether to give 0.41 g of **16b** in 54% yield. IR (film) 3300, 2247, 1717, 1668, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J=5.7 Hz, 2H), 3.92 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 153.4, 82.3, 75.3, 52.9, 29.8, 28.4; MS *m/z* 234.0 $(M+H)^+$; HRMS calcd for $C_7H_9BrNO_3$ 232.9688 $(M+H)^+$, found 232.9685.

4.3.15. Methyl 4-(*N*-benzyl-2-bromoacetamido)but-2-ynoate (16c). Following the same procedure from **21b** to **16b**, **16c** was prepared from **21c** in 52% yield. IR (film) 2955, 2242, 1716, 1656, 1436, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 4.72 (d, J=7.8 Hz, 2H), 4.33 (s, 1H), 4.18 (s, 1H), 3.97 (s, 1H), 3.93 (s, 1H), 3.79 (d, J=8.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 134.7, 129.3, 129.2, 128.9, 128.4, 82.0, 75.8, 52.8, 51.5, 34.7, 25.7; ESI-MS 324.0 $(M+H)^+$; HRMS calcd for $C_{14}H_{14}BrNO_3$ 323.0157 $(M)^+$, found 323.0157.

4.4. General procedure for reaction of iodides 16 with δ-chloropropylamines (7)

A mixture of **16** (0.22 mmol), **7** (0.23 mmol), anhydrous $NaHCO_3$ (0.7 mmol) or Na_2CO_3 (0.7 mmol) and 4 Å MS (40 mg) in 3 mL of MeCN was stirred at the indicated temperatures until the starting materials disappeared monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:0 to 1:10 ethyl acetate/petroleum ether to afford **17**.

4.4.1. 3-Oxo-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17a). IR (film) 3426, 1737, 1656, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (s, 2H), 4.13 (q, J=7.2 Hz, 2H), 3.90 (s, 2H), 3.19 (t, J=5.4 Hz, 2H), 2.42 (t, J=6.0 Hz, 2H), 1.91 (m, 2H), 1.27 (t, J=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.7, 147.0, 95.4, 66.3, 59.5, 50.9, 49.2, 22.2, 20.9, 14.5; ESI-MS 226.15 $(M+H)^+$; HRMS calcd for $C_{11}H_{15}NO_4Na$ 248.0893 $(M+Na)^+$, found 248.0884.

4.4.2. (*R*)-3-Oxo-6-pentyl-1,3,4,6,7,8-hexahydropyrido-[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17b). $[\alpha]_D^{20}$ +0.81 (*c* 0.64, $CHCl_3$); IR (film) 2932, 1770, 1677, 1592, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, J=15.6 Hz, 1H), 5.51 (d, J=15.6 Hz, 1H), 4.13 (q, J=6.9 Hz, 2H), 4.00 (d, J=16.8 Hz, 1H), 3.89 (d, J=16.8 Hz, 1H), 3.18 (m, 1H), 2.54 (m, 1H), 2.21 (m, 1H), 1.68 (m, 1H), 1.51–1.26 (m, 8H), 0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.7, 145.7, 94.5, 66.0, 59.5, 58.1, 50.4, 31.7, 31.2, 25.3, 23.2, 22.5, 18.4, 14.5, 13.9; ESI-MS 296.1 $(M+H)^+$.

4.4.3. (*S*)-6-(3,4-Dimethoxyphenyl)-3-oxo-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17c). $[\alpha]_D^{20}$ +48.8 (*c* 0.83, $CHCl_3$); IR (film) 2932, 1768, 1675, 1597, 1517, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J=8.1 Hz, 1H), 6.69–6.63 (m, 2H), 5.80 (d, J=16.2 Hz, 1H), 5.63 (d, J=15.6 Hz, 1H), 4.27 (m, 1H), 4.15 (q, J=6.9 Hz, 2H), 3.92 (s, 3H), 3.88 (m, 3H), 3.90 (d, J=16.8 Hz, 1H), 3.78 (d, J=16.8 Hz, 1H), 2.49 (m, 1H), 2.25 (m, 1H), 2.05–1.97 (m, 2H), 1.28 (t, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.25, 167.52, 149.64, 148.91, 146.99, 132.96, 118.47, 111.56, 109.27, 95.97, 65.84, 61.74, 59.66, 56.02, 55.99, 49.33, 29.18, 19.25, 14.46; ESI-MS 362.1 $(M+H)^+$.

4.4.4. (*R*)-6-Methyl-3-oxo-1,3,4,6,7,8-hexahydropyrido-[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17d). $[\alpha]_D^{20}$ +48.3 (*c* 0.61, $CHCl_3$); IR (film) 2976, 1768, 1673, 1591, 1281 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (d, J=13.2 Hz, 1H), 5.40 (dd, J=15.9, 1.2 Hz, 1H), 4.13 (q, J=7.2 Hz, 2H), 4.00 (d, J=16.5 Hz, 1H), 3.85 (d, J=16.5 Hz, 1H), 3.39 (m, 1H), 2.57 (m, 1H), 2.31 (m, 1H), 1.87–1.70 (m, 2H), 1.30 (t, J=7.2 Hz, 3H), 1.15 (d, J=5.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 167.7, 145.8, 94.7, 66.1, 59.5, 53.1, 49.3, 26.5, 18.4, 17.4, 14.5; ESI-MS 240.20 $(M+H)^+$; HRMS calcd for $C_{12}H_{18}NO_4$ 240.1230 $(M+H)^+$, found 240.1240.

4.4.5. (6*R*,7*S*)-7-Ethyl-3-oxo-6-propyl-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic acid ethyl ester (17e). $[\alpha]_D^{20}$ −24.2 (*c* 0.28, $CHCl_3$); IR (film) 2961, 2929, 2855, 1769, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (d, J=15.3 Hz, 1H), 5.55 (dd, J=15.3, 0.9 Hz, 1H), 4.13 (q, J=6.9 Hz, 2H), 4.04 (d, J=13.8 Hz, 1H), 3.91 (d, J=16.2 Hz, 1H), 2.92 (m, 1H), 2.42–2.26 (m, 3H), 1.70–1.17 (m, 6H), 1.01–0.85 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 168.2, 144.8, 92.5, 65.8, 62.6, 59.5, 51.3, 35.2, 34.1, 31.9, 25.4, 22.7, 19.2, 14.5, 11.9; ESI-MS 296.2 $(M+H)^+$; HRMS calcd for $C_{16}H_{26}NO_4$ 296.2856 $(M+H)^+$, found 296.1865.

4.4.6. 3-Oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17f). IR (film) 1702, 1676, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 4.80 (s, 2H), 3.78 (s, 2H), 3.65 (s, 3H), 3.19 (t, J=5.7 Hz, 2H), 2.40 (t, J=6.3 Hz, 2H), 1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 168.4, 148.9,

62.5, 53.2, 50.6, 50.0, 42.5, 22.4, 21.0; ESI-MS 211.3 $(M+H)^+$; HRMS calcd for $C_{10}H_{14}N_2O_3Na$ 233.0897 $(M+Na)^+$, found 233.0893.

4.4.7. 2-Benzyl-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido-[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17g). IR (film) 3406, 2952, 1737, 1681, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.73 (s, 2H), 4.64 (s, 2H), 3.81 (s, 2H), 3.60 (s, 3H), 3.16 (t, J=5.4 Hz, 2H), 2.36 (t, J=5.4 Hz, 2H), 1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 165.8, 149.3, 136.0, 128.9, 128.7, 127.7, 92.4, 53.5, 50.6, 49.7, 47.6, 29.7, 22.3, 20.9; ESI-MS 301.2 $(M+H)^+$; HRMS calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366 $(M+Na)^+$, found 323.1360.

4.4.8. (*R*)-3-Oxo-6-pentyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17h). $[\alpha]_D^{20}$ −78.2 (*c* 0.25, $CHCl_3$); IR (film) 2931, 2858, 1686, 1574 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 4.85 (dd, J=18.0, 3.6 Hz, 2H), 3.90 (d, J=9.0 Hz, 1H), 3.76 (d, J=9.0 Hz, 1H), 3.63 (s, 3H), 3.17 (m, 1H), 2.50 (m, 1H), 2.24 (m, 1H), 1.90 (m, 1H), 1.72–1.30 (m, 9H), 0.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.6, 147.8, 91.8, 58.8, 53.0, 50.7, 42.2, 31.07, 31.0, 25.4, 23.2, 22.5, 18.4, 14.1; ESI-MS 281.25 $(M+H)^+$; HRMS calcd for $C_{15}H_{25}N_2O_3$ 281.1860 $(M+H)^+$, found 281.1864.

4.4.9. (*S*)-6-(3,4-Dimethoxyphenyl)-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17i). $[\alpha]_D^{20}$ +30.7 (*c* 0.47, $CHCl_3$); IR (film) 3302, 2952, 1868, 1517, 1272 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J=8.1 Hz, 1H), 6.69–6.63 (m, 2H), 6.38 (m, 1H), 4.95 (m, 2H), 4.30 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.79 (d, J=16.5 Hz, 1H), 3.68 (d, J=16.5 Hz, 1H), 3.66 (s, 3H), 2.50 (m, 1H), 2.18–1.91 (m, 2H), 1.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 168.4, 149.5, 148.9, 148.7, 133.4, 118.4, 111.5, 109.4, 93.1, 62.3, 56.0, 52.2, 50.8, 42.0, 29.7, 28.8, 18.7; ESI-MS 347.20 $(M+H)^+$; HRMS calcd for $C_{18}H_{23}N_2O_5$ 347.1602 $(M+H)^+$, found 347.1608.

4.4.10. (*R*)-6-Methyl-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17j). $[\alpha]_D^{20}$ +27.7 (*c* 0.89, $CHCl_3$); IR (film) 2954, 2850, 1686, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (m, 1H), 4.98 (dd, J=18.0, 3.6 Hz, 1H), 4.66 (d, J=16.8 Hz, 1H), 3.90 (d, J=16.5 Hz, 1H), 3.70 (d, J=16.5 Hz, 1H), 3.66 (s, 3H), 3.38 (m, 1H), 2.55 (m, 1H), 2.29 (m, 1H), 2.05 (m, 1H), 1.83–1.72 (m, 1H), 1.14 (d, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 168.6, 147.9, 92.0, 53.7, 51.9, 50.7, 42.2, 31.9, 26.4, 18.2; ESI-MS 225.15 $(M+H)^+$; HRMS calcd for $C_{11}H_{17}N_2O_3$ 225.1234 $(M+H)^+$, found 225.1242.

4.4.11. (*R*)-2-Benzyl-3-oxo-6-pentyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17k). $[\alpha]_D^{20}$ −43.0 (*c* 0.62, $CHCl_3$); IR (film) 2956, 2931, 2858, 1739, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.81 (d, J=17.7 Hz, 1H), 4.72 (d, J=17.7 Hz, 1H), 4.67 (d, J=14.4 Hz, 1H), 4.58 (d, J=14.4 Hz, 1H), 3.94 (d, J=15.9 Hz, 1H), 3.81 (d, J=16.5 Hz, 1H), 3.60 (s, 3H), 3.16 (m, 1H), 2.47 (dd, J=16.8, 4.5 Hz, 1H), 2.16 (m, 1H), 1.86 (m, 1H), 1.68–1.29 (m, 9H), 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.6, 148.3, 136.2, 128.7, 128.3, 127.7, 91.4, 58.3, 53.2, 50.5, 49.8, 47.3, 31.7, 31.0, 29.7, 25.4, 23.2, 18.3, 14.0; EIMS m/z 370 $(M)^+$.

4.4.12. (*S*)-2-Benzyl-6-(3,4-dimethoxyphenyl)-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17l). $[\alpha]_D^{20}$ +33.4 (*c* 0.89, $CHCl_3$); IR (film) 2924, 1674, 1642, 1562, 1278, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 6.80 (d, J=7.8 Hz, 1H), 6.65 (m, 2H), 4.91 (s, 2H), 4.74 (d, J=14.7 Hz, 1H), 4.58 (d, J=14.7 Hz, 1H), 4.28 (t, J=4.5 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.83 (d, J=13.8 Hz, 1H), 3.73 (d, J=13.8 Hz, 1H), 3.62 (s, 3H), 2.47 (m, 1H), 2.11–1.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 166.5, 149.5, 149.4, 148.7, 136.2, 133.5, 128.8, 128.4, 127.8, 118.4, 111.5, 109.4, 92.8, 62.0, 56.0, 52.5, 50.7, 49.8, 47.1, 31.9, 29.7, 22.7; ESI-MS 437.25 $(M+H)^+$; HRMS calcd for $C_{25}H_{29}N_2O_5$ 437.2071 $(M+H)^+$, found 437.2063.

4.4.13. (*R*)-2-Benzyl-6-methyl-3-oxo-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17m). $[\alpha]_D^{20}$ −10.3 (*c* 1.2, $CHCl_3$); IR (film) 3449, 1708, 1579, 1364 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.90 (d, J=17.7 Hz, 1H), 4.70–4.57 (m, 3H), 3.94 (d, J=16.8 Hz, 1H), 3.75 (d, J=16.5 Hz, 1H), 3.61 (s, 3H), 3.38 (m, 1H), 2.49 (dt, J=15.0, 4.2 Hz, 1H), 2.28 (m, 1H), 1.72 (m, 2H), 1.13 (d, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 166.6, 148.3, 136.1, 128.7, 128.3, 127.7, 91.4, 53.3, 52.1, 50.6, 49.8, 47.3, 31.9, 29.4, 22.7; ESI-MS 315.20 $(M+H)^+$; HRMS calcd for $C_{18}H_{23}N_2O_3$ 315.1703 $(M+H)^+$, found 315.1701.

4.4.14. (6*R*,7*S*)-7-Ethyl-3-oxo-6-propyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17n). $[\alpha]_D^{20}$ −30.8 (*c* 0.46, $CHCl_3$); IR (film) 2961, 2931, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 4.82 (m, 2H), 3.93–3.75 (m, 3H), 3.64 (s, 3H), 2.92 (m, 1H), 2.40–2.30 (m, 2H), 1.66 (m, 1H), 1.47–1.13 (m, 5H), 0.99–0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 168.8, 146.9, 89.6, 63.0, 53.8, 50.7, 42.0, 34.7, 34.1, 31.9, 29.4, 22.7, 19.2, 14.1; ESI-MS 281.25 $(M+H)^+$; HRMS calcd for $C_{15}H_{25}N_2O_3$ 281.1860 $(M+H)^+$, found 281.1866.

4.4.15. (6*R*,7*S*)-2-Benzyl-7-ethyl-3-oxo-6-propyl-2,3,4,6,7,8-hexahydro-1*H*-pyrido[1,2-*a*]pyrazine-9-carboxylic acid methyl ester (17o). $[\alpha]_D^{20}$ −36.8 (*c* 0.69, $CHCl_3$); IR (film) 2958, 1684, 1579, 1458, 1268 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.76 (s, 2H), 4.63 (m, 2H), 3.96 (d, J=16.8 Hz, 1H), 3.83 (d, J=16.5 Hz, 1H), 3.60 (s, 3H), 2.93 (m, 1H), 2.27 (m, 2H), 1.70–1.11 (m, 7H), 0.95–0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.6, 147.4, 136.2, 128.7, 128.2, 127.7, 89.2, 62.7, 54.2, 50.6, 49.7, 47.0, 35.0, 34.1, 31.9, 29.4, 25.3, 22.7, 14.1; ESI-MS 371.25 $(M+H)^+$; HRMS calcd for $C_{22}H_{31}N_2O_3$ 371.2329 $(M+H)^+$, found 371.2329.

4.4.16. (*S*)-2-((*tert*-Butoxycarbonyl)methyl)-6-(3,4-dimethoxyphenyl)-1-(2-methoxy-2-oxoethyl)-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester (18a). To a solution of **17i** (20 mg, 0.058 mmol) in methylene chloride were added triethylamine (8 μL, 0.058 mmol), di-*tert*-butyl

dicarbonate (25 mg, 0.116 mmol) and DMAP (7 mg, 0.058 mmol). The solution was stirred for 7 h at 25 °C under an argon atmosphere. The volatiles were removed, and the residue was purified by rapid chromatography on silica gel. Elution with 1/2 ethyl acetate/petroleum ether gave 21 mg of the desired *N*-Boc derivative, which was dissolved in 0.5 mL of methanol. Under an argon atmosphere, 0.40 mL (0.080 mmol) of a 0.2 M solution of sodium methoxide in methanol was added. After 10 min the solution was poured into brine and extracted with ether. After drying (Na_2SO_4) and concentration, the residue was chromatographed on silica gel. Elution with 1/4 ethyl acetate/petroleum ether afforded 19 mg of **18a** (70% from **17i**). $[\alpha]_D^{20}$ −34.0 (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J*=8.4 Hz, 1H), 6.69–6.63 (m, 2H), 5.86 (t, *J*=5.3 Hz, 1H), 5.07 (d, *J*=18.4 Hz, 1H), 4.31 (m, 2H), 4.22 (dd, *J*=14.9, 8.1 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.77 (d, *J*=18.7 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.50 (m, 1H), 2.09–1.93 (m, 3H), 1.43 (s, 9H); ESI-MS 479 $(M+H)^+$; HRMS calcd for $C_{24}H_{34}N_2O_8Na$ 501.2207 $(M+Na)^+$, found 501.2196.

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