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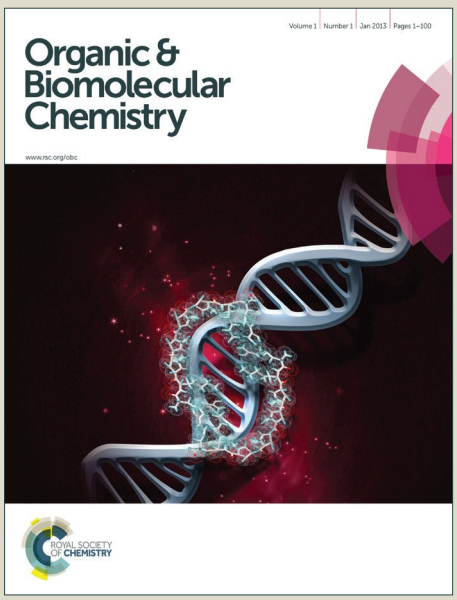

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ARTICLE

One-Pot, Highly Efficient, Asymmetric Synthesis of Ring-Fused Piperidine Derivatives Bearing N,O- or N,N-Acetal Moieties

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We successfully expand the application of lactol or cyclic hemiaminal as nucleophiles for the asymmetric synthesis of both N,O- and N,N-acetal moieties contained in the structure of ring-fused piperidine derivatives. This efficient one-pot protocol involves organocatalyzed asymmetric aza-Diels-Alder reaction and iminium ion induced cyclization sequence to ultimately deliver heterocyclic compounds with excellent stereoselectivity in high yield, containing three continuous stereogenic centers.

Introduction

The functionalized fused piperidine-based heterocyclic compounds, particularly containing N,O-acetal or N,N-acetal moieties, are widely present in many natural and bioactive sources, which exhibit various biological activities (Fig. 1).[1,2,3,4] Not surprisingly, because of their aforementioned potentially bioactive properties and impressive structures, the development of novel asymmetric catalytic methods to efficiently access these enantioenriched heterocyclic frameworks have become attractive targets in the area of medicinal and synthetic chemistry.

However, the synthesis of enantiopure ring-fused piperidine-based derivatives containing N,O- or N,N-acetal moieties have rarely succumbed to asymmetric catalysis, and among very few reported examples, they all suffered from restricted substrate or product scope. In 2012, Chen and co-workers[5] presented an asymmetric inverse-electron-demand aza-Diels-Alder reaction (ADAR) of aliphatic aldehydes and *N*-sulfonyl-1-aza-1,3-butadienes,[6] followed by a trifluoroacetic acid (TFA) triggered intramolecular *O*-Michael addition sequence providing ring-fused hydropyrano[2,3-b]pyridines with excellent stereoselectivity.[7] Recently, Wang et al. developed an efficient chiral BINOL-Ti(O*i*Pr)$_4$ complex catalyzed reaction of tertiary enamides with salicylaldehydes, which generated the desired enantiopure 4-chromanol derivatives in high yield.[8] However, according to the nature of both Chen's and Wang's sequential process, the bicyclic frameworks bearing only N,O-acetal moiety could be constructed. To the best of our knowledge, there is no reported method which is generally suitable for the asymmetric synthesis of piperidine-based both polycyclic aminal and hemiaminal structures.[9] Therefore, efficient stereoselective catalytic transformations that provide rapid accesses to N,O-acetal as well as N,N-acetal functionality remain desirable.

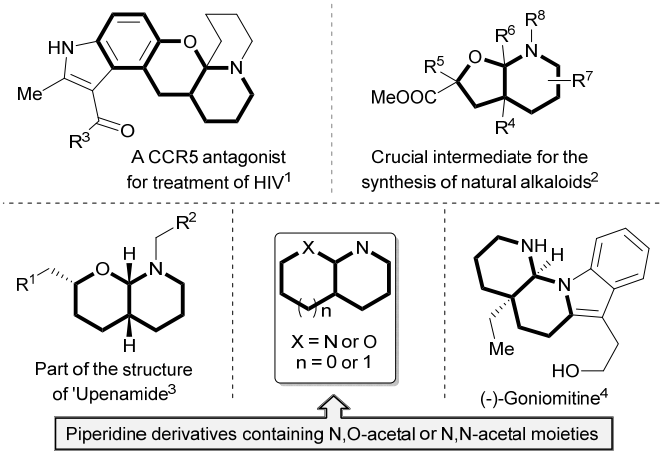

Fig. 1. Selected natural or bioactive ring-fused piperidine structures with different ring sizes bearing N,O-acetal or N,N-acetal motifs.

Iminium ions are widely recognized as important electrophilic intermediates in asymmetric reactions, especially in the synthesis of various heterocyclic structures.[10] Meanwhile, it is well known that this much unstable but highly reactive species could be easily derived from its relatively stable precursor N,O-acetal under proper acidic conditions, and normally directly used in situ as the electrophilic components.

Very recently, we were specifically interested in the application of lactol or cyclic hemiaminal as nucleophiles under enamine activation to produce chiral substituted lactones or

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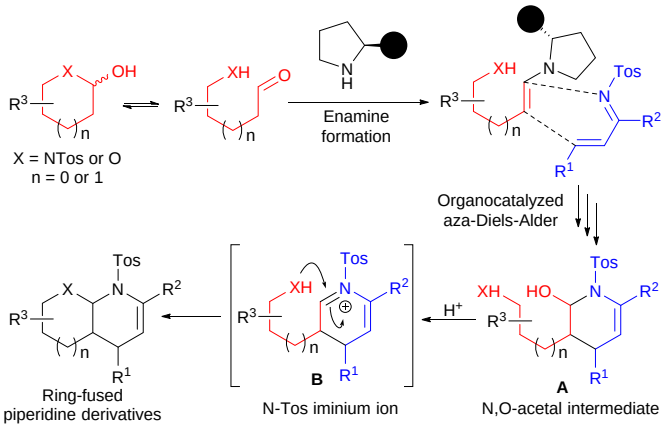


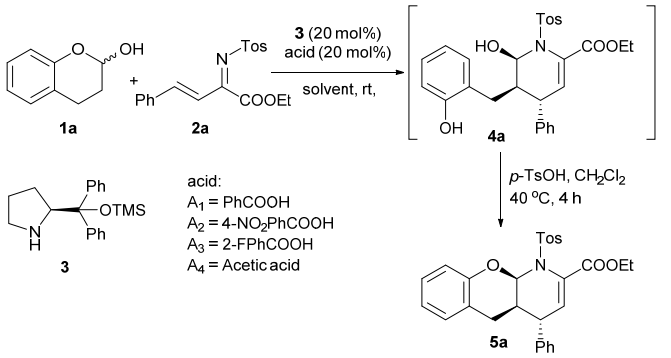
Scheme 1. Designed pathway to access ring-fused piperidine derivatives containing N,O- or N,N-acetal moieties.

lactams, which proceeded via oxidation sequence of O,O- or N,O-acetal intermediates.[11] We then questioned whether we could employ lactol or cyclic hemiaminal in the asymmetric ADAR strategy to produce ring-fused piperidine derivatives containing N,O- or N,N-acetal functionality (Scheme 1). In our designed plan, first, lactols or cyclic hemiaminals react with N-sulfonyl-1-aza-1,3-butadienes to generate the required N,O-acetal intermediate **A** via asymmetric ADAR, and then the free hydroxyl group in **A** could act as a leaving group under acidic conditions providing the crucial N-Tos iminium ion **B**, which would be attacked by the OH or TosNH group from the equilibrium content of lactol or cyclic hemiaminal, respectively, to form the functionalized fused piperidine-based structures bearing N,O- or N,N-acetal moieties containing three continuous stereogenic centers, and one of them is simultaneously attached to N,N or N,O two heteroatoms. Herein, we describe for the first time the application of lactol or cyclic hemiaminal in asymmetric ADAR towards the asymmetric synthesis of functionalized fused piperidine-based structures containing N,O- or N,N-acetal moieties via a one-pot, two-step sequential pathway under mild conditions.

Results and discussion

We first investigated the reaction of lactol **1a** and easily prepared N-tosyl-1-aza-1,3-butadiene **2a** in the presence of commercially available chiral catalyst **3**[12] and Benzoic acid in CH_3CN as solvent at room temperature, and after the asymmetric ADAR was completed, the isolated hemiaminal intermediate **4a** was then cyclized via the *p*-TsOH triggered N-Tos iminium ion formation leading to the fused piperidine-based polycycles.[13] Pleasingly, the desired octahydro-2H-pyrano[2,3-b]pyridine **5a** was produced in 72% isolated yield with excellent enantioselectivity as a single diastereomer (Table 1, entry 1, >99% ee). Encouraged by this elegant result, more detailed optimization was carried out. Surprisingly, not only acids but also solvents have almost no effect on stereoselectivity of this sequence, only slightly lower yields as well as longer reaction time were observed when nonpolar

Table 1. Conditions screening[a]



Entry	Acid	Solvent	Time[b] (h)	Yield[c] (%)	ee[d] (%)
1	A_1	CH_3CN	12	72	>99
2	A_2	CH_3CN	10	77	>99
3	A_3	CH_3CN	12	77	>99
4	A_4	CH_3CN	12	81	>99
5[e]	A_2	CH_3CN	12	75	99
6	A_2	DMF	12	76	>99
7	A_2	toluene	36	61	>99
8	A_2	$CHCl_3$	>48	49	99
9[f]	A_2	CH_3CN	18	65	>99
10[g]	A_2	CH_3CN	20	60	>99
11[h]	A_2	CH_3CN	16	85	>99

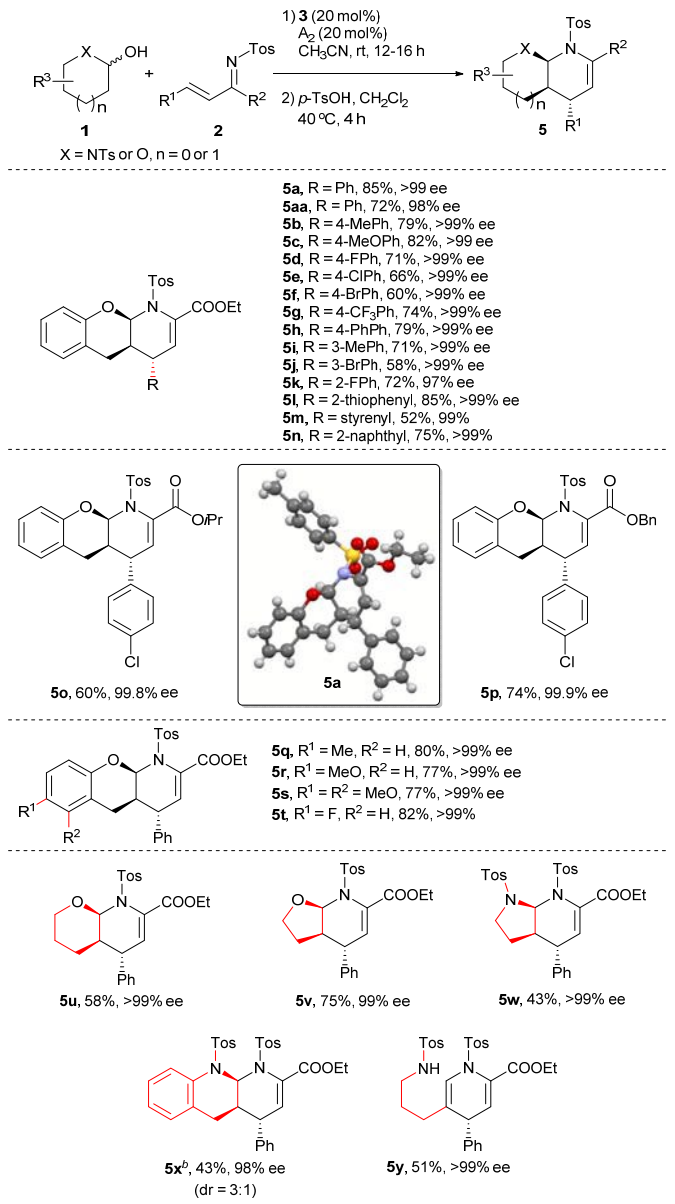
[a] See the Supporting Information for details. [b] For the first step. For entry 11, reaction time refers to two steps. [c] Isolated yields of product **5a**. [d] Determined by HPLC analysis over chiral stationary phases of **5a**. [e] 50 μL H_2O was added. [f] 10 mol% **3** was used. [g] 5 mol% **3** was used. [h] **5a** was obtained in one-pot. *p*-TsOH = *p*-toluenesulfonic acid, Tos = *p*-tolylsulfonyl, TMS = trimethylsilyl, DMF = N,N-Dimethylformamide.

solvents, such as toluene and $CHCl_3$, were employed (Table 1, entries 2-8). Interestingly, the additional H_2O had little effect on the reactivity of our system.[5] Moreover, this high level of stereoselectivity is maintained upon reducing the catalyst loading of **3** to 10 mol% or 5 mol%, giving **5a** with no erosion of yield, albeit with slightly longer reaction time (Table 1, entries 9-10). To further develop an operationally simple and step-economic route, we tried to combine these two reactions in a one-pot fashion. To our gratification, without the isolation of **4a**, this two-step sequence proceeded smoothly by simply changing the solvent from CH_3CN to DCM for the cyclization step. The desired **5a** was isolated with excellent enantioselectivity in even higher yield (Table 1, entry 11).[14]

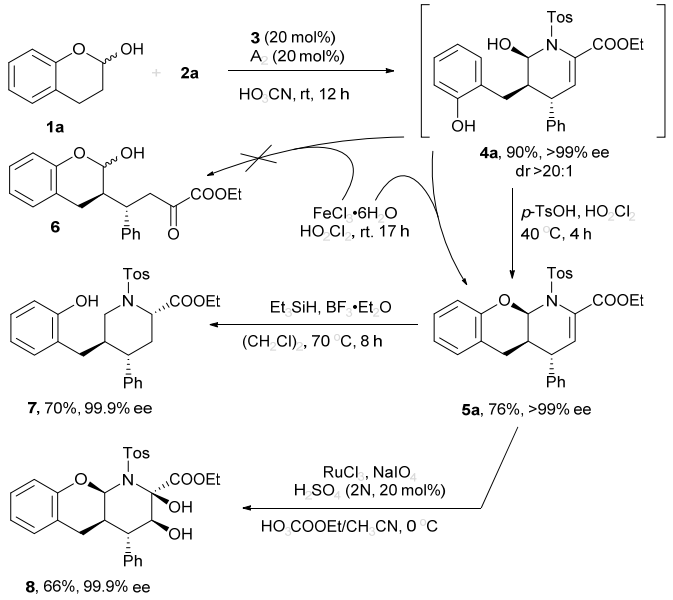
Under the optimized conditions (Table 1, entry 11), we further surveyed the scope and limitations of this one-pot, two-step sequence by varying the structure of both **1** and **2**. As summarized in Table 2, in general, both the position and electronic properties of the substituents on the aromatic ring in the structure of N-tosyl-1-aza-1,3-butadiene **2** had no or little effect on the outcome affording the corresponding products (**5a**-**k**) in high yields and excellent enantioselectivities. The opposite configuration of the product **5a** could be easily

accessed by simply selecting the appropriate enantiomer of the catalyst **3** (Table 2, **5aa**). Moreover, **2** bearing thiophenyl, styrenyl, and even more sterically bulky 2-naphthalene moiety were also investigated providing the desired cycloadducts **5l**-**n** in good to high yields (52–85 %). Excellent results were attained for N-tosyl-1-aza-1,3-butadiene **2** with differently ester groups (Table 2, **5o** and **5p**). Another attractive feature of this domino process is the highly tolerant of the structural modifications of lactol **1**, pleasingly, not only substituted chroman-2-ol derivatives but also simple lactols have a very limited effect on the enantioselectivities (Table 1, **5q**-**v**). Noticeably, except for lactols, the cyclic hemiaminals also exhibited high reactivity, and **5w** and **5x** were obtained in moderate isolated yield without any lowing of the enantioselectivity, albeit moderate diastereoselectivity was achieved for the case of **5x**.[13] In contrast, under the above-mentioned conditions, the reaction of hemiaminal **1y** with **2a** failed to give the cyclized product, while the dehydrated **5y** was finally obtained.

Table 2. Substrate scope[a]



[a] See the Supporting Information for experimental details. Yields are of the isolated **5**. Enantiomeric excess was determined by HPLC on chiral stationary phase. Diastereomeric ratios were determined by Chiral HPLC analysis. The absolute configuration of **5a** was determined by X-ray analysis, and the others were assigned by analogy.[15] **5aa** was obtained with the opposite enantiomer of **3**. [b] For the major isomer.



Scheme 2. Further improved synthesis of **5a** and useful transformations.

To further improve the efficiency of this sequential protocol and also to illustrate the practicality of this method, we then performed the second step of the reaction by directly adding DCM to the reaction mixture while no need to remove the previous solvent, CH_3CN.[16] Significantly, this strategy results in a substantial operational simplicity, while affording **5a** with promising results, albeit with slightly lower yield (Scheme 2). It is surprising that the hemiaminal **4a** did not undergo hydrolysis in the presence of $FeCl_3$•$6H_2O$ to generate **6**,[5a] while gave the cyclized product **5a**.[13] Meanwhile, the stable hemiaminal **4a** was also analysed for the first time with excellent stereoselectivity in high chemical yield (90%, >99% ee, dr >20:1). Promoted by BF_3•Et_2O and Et_3SiH, the subsequent reduction and ring-opening reaction of **5a** took place to lead to stereoselective polysubstituted piperidine **7** as a single diastereomer.[15,17] To further demonstrating the synthetic transformations, **5a** can be readily dihydroxylated affording hetero-polycycles **8** in 66% yield with excellent enantioselectivity as a single diastereomer.[18] Notably, **8** is a really complicated structure, which bearing five continuous stereogenic centers on a fully substituted piperidine ring, and one of them is a N,O-contained chiral quaternary carbon center.

Conclusions

In conclusion, we have developed an effective method for synthesizing ring-fused piperidine-based derivatives bearing N,O- or N,N-acetal moieties under mild conditions and low catalyst loadings (5 mol%). Upon dienamine-activation induced aza-Diels-Alder reaction of lactol or cyclic hemiaminal with N-tosyl-1-aza-1,3-butadiene, the desired polyfunctionalized cyclic structures were obtained with excellent stereoselectivity in high yield, which containing three continuous stereogenic centers, and one of them is attached simultaneously to N,N or N,O two heteroatoms. It should be noted that this is the first reported method which is suitable for the asymmetric synthesis of polycyclic aminal as well as hemiaminal structures. Moreover, these products could be easily transformed into polyfunctionalized heterocycles with multiple stereogenic centers. We believe this methodology will significantly expand the utility of lactol or cyclic hemiaminal to rapidly assemble complex molecular architectures, and more applications of this highly efficient method is still in progress.

Experimental

General methods

Reagents and solvents were purchased from commercial suppliers and used as received, without further purification. Chromatographic purification of products was accomplished using force-flow chromatography (FC) on silica gel (200-400 mesh). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate or basic aqueous potassium permangante ($KMnO_4$) as stain developing solutions. ^{1}H NMR spectra were measured with a Bruker Avance 500 MHz spectrometer. Chemical shifts were reported in δ (ppm) units relative to tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were measured at 125 MHz; chemical shifts were reported in ppm relative to TMS with the solvent resonance as the internal standard. Infrared spectra were obtained with a Bruker ALPHA-P spectrometer or a Perkin Elmer Spectrum One spectrometer. High resolution mass spectra (electron spray ionization) were measured with a Bruker APEX IV Fourier-Transform mass spectrometer. Enantiomeric excesses (*ee*) were determined by chiral HPLC analysis using an Agilent 1200 LC instrument with a Daicel Chiralpak IA, IB or IC column with *i*-PrOH/*n*-hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by mixture of two enantiomeric final products obtained using (*S*) and (*R*) catalyst.

Materials

(*S*) and (*R*)-diphenylprolinol silyl ether **3** are commercially available from Daicel chiral Technologies. All the cyclic hemiaminals[18] and lactol[19] were synthesized according to literature procedures. The N-Tos-1-aza-1,3-butadienes[20] were prepared from α,β-unsaturated ketones and *p*-toluenesulfonamide according to the literature procedures.

General procedure

The reaction was carried out with **1** (0.12 mmol, 1.2 equiv) and N-Tos-1-aza-1,3-butadienes **2** (0.1 mmol, 1.0 equiv) in the presence of **3** (6.5 mg, 0.02 mmol), A_2 (3.4 mg, 0.02 mmol) in CH_3CN (0.5 mL) at room temperature. After full conversion of the first step (monitored by TLC), the CH_3CN solvent was removed under vacuum to afford the crude product **4**. Then DCM (1.2 mL) and *p*-TsOH (5.0 equiv) were added to the reaction mixture and stirred at 40 °C for 4 hours. After the reaction completed, the solution was concentrated under vacuum and the residue was purified by flash chromatography on silica gel to afford the fused heterocyclic products **5**.

(4*S*,5*R*,6*R*)-ethyl 6-hydroxy-5-(2-hydroxybenzyl)-4-phenyl-1-tosyl-1,4,5,6-tetrahydropyridine-2-carboxylate (4a, Table 1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.30–7.27 (m, 3H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.14–7.10 (m, 1H), 6.96 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.90 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.77 (dd, *J* = 6.2, 0.9 Hz, 1H), 6.76 (dd, *J* = 6.15, 0.9 Hz, 1H), 6.40 (d, *J* = 7.5 Hz, 1H), 6.15 (d, *J* = 3.2 Hz, 1H), 5.28 (d, *J* = 2.4 Hz, 1H), 4.63–4.49 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.34 (dd, *J* = 11.2, 3.2 Hz, 1H), 2.69 (dd, *J* = 14.0, 11.5 Hz, 1H), 2.43 (s, 4H), 2.20–2.14 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.43, 154.51, 144.28, 140.27, 134.32, 130.81, 130.10, 128.83, 128.75, 128.71, 128.03, 127.96, 127.71, 127.51, 124.45, 120.49, 116.65, 78.32, 77.33, 77.11, 76.90, 62.19, 43.56, 43.18, 28.92, 21.71, 14.18. **HRMS**: $[M+H]^+$ calcd. For $C_{28}H_{30}NO_6S$ m/z: 508.1794; found: 508.1793. **$[\alpha]_D^{20}$** +28.89 (c = 1.125 in $CHCl_3$). The diastereomeric ratio was determined by both NMR and HPLC analysis, dr > 20:1. The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 20.80 min, t_{minor} = 15.94 min, *ee* = 99.3%.

(4*S*,4a*R*,10a*R*)-ethyl 4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5a, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.35–7.28 (m, 3H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 6.7 Hz, 2H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 7.1 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.25 (d, *J* = 3.0 Hz, 1H), 6.25 (d, *J* = 3.0 Hz, 1H), 5.76 (d, *J* = 2.3 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.25 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.98 (dd, *J* = 17.0, 5.7 Hz, 1H), 2.58 (d, *J* = 17.1 Hz, 1H), 2.46 (s, 3H), 2.36 (dd, *J* = 10.9, 5.7 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.31, 152.65, 144.35, 140.04, 136.20, 129.76, 129.69, 128.86, 128.64, 127.87, 127.82, 127.62, 127.50, 127.17, 121.67, 118.47, 117.21, 82.43, 77.26, 77.01, 76.76, 61.66, 40.22, 35.81, 28.11, 21.65, 14.05. **HRMS**: $[M+H]^+$ calcd. For $C_{28}H_{28}NO_5S$ m/z: 490.1688; found: 490.1685. **$[\alpha]_D^{20}$** -56.20 (c = 1.38 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 15.84 min, t_{minor} = 12.13 min, *ee* = 99.4%.

(4*R*,4a*S*,10a*S*)-ethyl 4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5aa, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.36–7.27 (m, 3H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.09–7.05 (m, 2H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.90 (dd, *J* = 7.4, 1.0 Hz, 1H), 6.86 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.25 (d, *J* = 3.1 Hz, 1H), 5.77 (d, *J* = 2.4 Hz, 1H), 4.30 (q, *J* = 7.5 Hz, 2H), 3.25 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.98 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.58 (d, *J* =

16.9 Hz, 1H), 2.46 (s, 3H), 2.35 (dd, *J* = 11.0, 6.1 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.99, 155.31, 147.02, 142.69, 138.85, 132.43, 132.36, 131.52, 131.30, 130.53, 130.48, 130.28, 130.16, 129.85, 124.34, 121.15, 119.87, 85.09, 79.93, 79.67, 79.42, 64.33, 42.88, 38.47, 30.77, 24.31, 16.70. **HRMS**: $[M+H]^+$ calcd. For $C_{28}H_{28}NO_5S$ m/z: 490.1688; found: 490.1685. **$[\alpha]_D^{20}$** +63.83 (c = 1.25 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 12.12 min, t_{minor} = 16.08 min, *ee* = 98.2%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(p-tolyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5b, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 6.7 Hz, 3H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.90 (t, *J* = 6.9 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 5.76 (d, *J* = 2.3 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.22 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.97 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.57 (d, *J* = 16.9 Hz, 1H), 2.46 (s, 3H), 2.35 (s, 3H), 2.31 (s, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.35, 152.65, 144.32, 137.23, 136.91, 129.76, 129.68, 129.52, 128.51, 127.83, 127.81, 127.49, 121.64, 118.54, 117.20, 82.46, 77.26, 77.00, 76.75, 61.63, 39.80, 35.77, 28.13, 21.64, 21.06, 14.04. **HRMS**:$[M+H]^+$ calcd. For $C_{29}H_{30}NO_5S$ m/z: 504.1845; found: 504.1842. **$[\alpha]_D^{20}$** -37.36 (c = 1.06 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 14.42 min, t_{minor} = 11.48 min, *ee* = 99.3%.

(4S,4aR,10aR)-ethyl 4-(4-methoxyphenyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5c, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.04–6.97 (m, 3H), 6.90 (t, *J* = 7.1 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 3H), 6.23 (d, *J* = 3.1 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.20 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.98 (dd, *J* = 17.0, 5.8 Hz, 1H), 2.57 (d, *J* = 16.9 Hz, 1H), 2.46 (s, 3H), 2.32 (dd, *J* = 10.8, 6.0 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$)δ 164.35, 158.98, 152.66, 144.33, 136.20, 131.84, 129.76, 129.68, 129.61, 127.83, 127.81, 127.61, 121.64, 118.54, 117.20, 114.24, 82.49, 77.26, 77.01, 76.75, 61.63, 55.31, 39.40, 35.91, 28.11, 21.64, 14.04. **HRMS**:$[M+H]^+$ calcd. For $C_{29}H_{30}NO_6S$ m/z: 520.1794; found: 520.1796. **$[\alpha]_D^{20}$** -23.83 (c = 1.54 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 22.19 min, t_{minor} = 19.29 min, *ee* = 99.3%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(4-fluorophenyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5d, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.08–6.97 (m, 5H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.21 (d, *J* = 3.0 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 4.29 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.25 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.00 (dd, *J* = 17.0, 5.8 Hz, 1H), 2.54 (d, *J* = 17.0 Hz, 1H), 2.46 (s, 3H), 2.33 (dd, *J* = 11.0, 6.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.21, 163.13, 161.17, 152.59, 144.41, 136.14, 135.73, 130.14, 130.08, 129.74, 129.69, 127.94, 127.81, 126.75, 121.74, 118.30, 117.23, 115.84, 115.67, 82.35, 77.25, 77.00, 76.74, 61.72, 39.47, 36.00, 28.06, 21.64, 14.03. **HRMS**:$[M+H]^+$ calcd. For $C_{28}H_{27}FNO_5S$ m/z: 508.1594; found: 508.1591. **$[\alpha]_D^{20}$** -71.88 (c = 1.06 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IB column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 13.93 min, t_{minor} = 12.80 min, *ee* = 99.5%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(4-chlorophenyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5e, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.05–6.99 (m, 3H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.19 (d, *J* = 3.0 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 4.29 (dd, *J* = 7.1, 2.9 Hz, 2H), 3.25 (d, *J* = 11.1 Hz, 1H), 3.00 (dd, *J* = 17.1, 5.7 Hz, 1H), 2.53 (d, *J* = 17.1 Hz, 1H), 2.46 (s, 3H), 2.33 (dd, *J* = 13.0, 9.2 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.17, 152.55, 144.44, 138.56, 136.11, 133.40, 129.94, 129.73, 129.70, 129.04, 127.97, 127.81, 126.30, 121.77, 118.23, 117.24, 82.29, 77.25, 77.00, 76.74, 61.74, 39.60, 35.86, 28.07, 21.65, 14.02. **HRMS**: $[M+H]^+$ calcd. For $C_{28}H_{27}ClNO_5S$ m/z: 524.1298; found: 524.1294. **$[\alpha]_D^{20}$** -9.31 (c = 1.74 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IB column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 7.57 min, t_{minor} = 9.37 min, *ee* = 99.5%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(4-bromophenyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5f, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.18 (d, *J* = 3.0 Hz, 1H), 5.75 (d, *J* = 2.2 Hz, 1H), 4.29 (dd, *J* = 7.1, 2.7 Hz, 2H), 3.23 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.00 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.53 (d, *J* = 17.1 Hz, 1H), 2.46 (s, 3H), 2.33 (dd, *J* = 11.0, 5.7 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, CDCl3) δ 164.15, 152.54, 144.44, 139.10, 136.10, 132.00, 130.30, 129.72, 129.70, 127.97, 127.96, 127.81, 126.16, 121.78, 121.45, 118.22, 117.24, 82.28, 77.25, 77.00, 76.74, 61.75, 39.68, 35.81, 28.07, 21.65, 14.02. **HRMS**:$[M+H]^+$ calcd. For $C_{28}H_{27}BrNO_5S$ m/z: 568.0793; found: 568.0789. **$[\alpha]_D^{20}$** -12.13 (c = 0.89 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 7.81 min, t_{minor} = 9.70 min, *ee* = 99.8%.

(4*S*,4a*R*,10a*R*)-ethyl1-tosyl-4-(4-(trifluoromethyl)phenyl)-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5g, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.92 (t, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.19 (d, *J* = 3.0 Hz, 1H), 5.77 (d, *J* = 2.3 Hz, 1H), 4.30 (dd, *J* = 7.1, 4.0 Hz, 2H), 3.35 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.03 (dd, *J* = 17.1, 5.7 Hz, 1H), 2.53 (d, *J* = 17.1 Hz, 1H), 2.47 (s, 3H), 2.39 (dd, *J* = 10.1, 5.1 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.08, 152.51, 144.50, 144.31, 136.08, 129.72, 129.03, 128.22, 128.05, 127.82, 125.83, 125.60, 121.85, 118.10, 117.27, 82.20, 77.25, 76.99, 76.74, 61.80, 40.04, 35.85, 28.08, 21.65, 14.02. **HRMS**:$[M+H]^+$ calcd. For $C_{29}H_{27}F_3NO_5S$ m/z: 558.1562; found: 558.1564. **$[\alpha]_D^{20}$** -47.31 (c = 1.08 in CHCl3). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-

hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 9.68 min, t_{minor} = 11.01 min, *ee* = 99.4%.

(4*S*,4a*R*,10a*R*)-ethyl 4-([1,1'-biphenyl]-4-yl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5h, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (dd, *J* = 18.4, 7.7 Hz, 3H), 7.15 (t, *J* = 9.4 Hz, 3H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.29 (d, *J* = 2.7 Hz, 1H), 5.79 (d, *J* = 1.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.31 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.02 (dd, *J* = 17.0, 5.3 Hz, 1H), 2.64 (d, *J* = 17.1 Hz, 1H), 2.47 (s, 3H), 2.41 (dd, *J* = 9.1, 3.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.30, 152.66, 144.37, 140.55, 139.05, 136.21, 129.79, 129.71, 129.06, 128.81, 127.90, 127.84, 127.69, 127.58, 127.40, 127.06, 127.03, 121.71, 118.49, 117.24, 82.43, 77.26, 77.01, 76.75, 61.69, 39.89, 35.83, 28.20, 21.67, 14.05. **HRMS**:$[M+H]^+$ calcd. For $C_{34}H_{32}NO_5S$ m/z: 566.2001; found: 566.2003. **$[\alpha]_D^{20}$** +39.41 (c = 1.37 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 34.78 min, t_{minor} = 20.64 min, *ee* = 99.3%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(m-tolyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5i, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 3H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.16–7.11 (m, 2H), 7.01 (t, *J* = 8.5 Hz, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.16 (d, *J* = 2.7 Hz, 1H), 5.76 (d, *J* = 1.7 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.22 (dd, *J* = 11.1, 2.7 Hz, 1H), 2.97 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.51 (d, *J* = 16.6 Hz, 1H), 2.47 (s, 3H), 2.16 (dd, *J* = 10.3, 5.7 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.39, 152.64, 144.33, 139.87, 138.64, 136.18, 129.75, 129.71, 129.07, 128.67, 128.28, 127.83, 127.81, 127.39, 125.87, 121.65, 118.54, 117.22, 82.45, 77.25, 77.00, 76.74, 61.66, 40.14, 35.56, 28.12, 21.65, 21.38, 14.04. **HRMS**:$[M+H]^+$ calcd. For $C_{29}H_{30}NO_5S$ m/z: 504.1845; found: 504.1841. **$[\alpha]_D^{20}$** -50.91 (c = 1.32 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 12.34 min, t_{minor} = 9.54 min, *ee* = 99.4%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(3-bromophenyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5j, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.7 Hz, 3H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.16–7.11 (m, 2H), 7.01 (t, *J* = 8.5 Hz, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.16 (d, *J* = 2.7 Hz, 1H), 5.76 (d, *J* = 1.7 Hz, 1H), 3.21 (d, *J* = 11.2 Hz, 1H), 2.97 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.51 (d, *J* = 16.6 Hz, 1H), 2.47 (s, 3H), 2.16 (dd, *J* = 10.7, 5.4 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.31, 152.48, 144.61, 142.32, 135.85, 131.25, 130.76, 130.41, 129.87, 129.72, 128.00, 127.76, 127.49, 125.99, 122.91, 121.82, 118.13, 117.29, 82.31, 77.26, 77.01, 76.75, 61.85, 39.89, 35.32, 28.02, 21.72, 14.05. **HRMS**:$[M+H]^+$ calcd. For $C_{28}H_{27}BrNO_5S$ m/z: 568.0793; found: 568.0798. **$[\alpha]_D^{20}$** -29.92 (c = 1.27 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 13.05 min, t_{minor} = 11.94 min, *ee* = 99.4%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(2-fluorophenyl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5k, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.27 (s, 1H), 7.14 (dt, *J* = 15.2, 5.1 Hz, 3H), 7.07–7.00 (m, 2H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.22 (d, *J* = 3.1 Hz, 1H), 6.22 (d, *J* = 3.1 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.70 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.02 (dd, *J* = 16.9, 5.7 Hz, 1H), 2.56 (d, *J* = 17.1 Hz, 1H), 2.46 (s, 4H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ164.19, 160.02, 152.50, 144.34, 136.22, 130.02, 129.99, 129.87, 129.68, 129.13, 129.07, 127.82, 126.29, 124.75, 121.71, 118.43, 117.11, 115.80, 115.62, 82.34, 77.26, 77.01, 76.75, 61.69, 35.23, 33.02, 28.40, 21.64, 14.03. **HRMS**:$[M+H]^+$ calcd. For $C_{28}H_{27}FNO_5S$ m/z: 508.1594; found: 508.1597. **$[\alpha]_D^{20}$** -42.43 (c = 1.15 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IB column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 15.22 min, t_{minor} = 11.93 min, *ee* = 97.2%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(thiophen-2-yl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5l, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 5.7 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.90 (td, *J* = 7.4, 0.9 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 2.8 Hz, 1H), 6.22 (d, *J* = 3.0 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 4.34–4.26 (m, 2H), 3.60 (dd, *J* = 11.2, 3.0 Hz, 1H), 3.03 (d, *J* = 5.8 Hz, 1H), 2.69 (d, *J* = 17.1 Hz, 1H), 2.46 (s, 3H), 2.32 (dd, *J* = 11.1, 6.1 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.21, 152.48, 144.39, 142.54, 136.09, 129.81, 129.76, 127.89, 127.73, 127.03, 126.03, 125.81, 124.74, 121.77, 118.28, 117.26, 82.26, 77.26, 77.00, 76.75, 61.76, 35.98, 35.27, 28.48, 21.65, 14.03. **HRMS**:$[M+H]^+$ calcd. For $C_{26}H_{26}NO_5S_2$ m/z: 496.1252; found: 496.1250. **$[\alpha]_D^{20}$** -77.87 (c = 1.08 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 17.85 min, t_{minor} = 14.70 min, *ee* = 99.3%.

(4*S*,4a*R*,10a*R*)-ethyl 4-((E)-styryl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5m, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, **J** = 8.3 Hz, 2H), 7.40–7.30 (m, 6H), 7.27 (d, **J** = 7.2 Hz, 1H), 7.12 (t, **J** = 7.8 Hz, 1H), 7.04 (d, **J** = 7.4 Hz, 1H), 6.90 (t, **J** = 7.4 Hz, 1H), 6.83 (d, **J** = 8.1 Hz, 1H), 6.41 (d, **J** = 15.7 Hz, 1H), 6.19 (d, **J** = 3.2 Hz, 1H), 6.19 (d, **J** = 3.2 Hz, 1H), 5.96 (dd, **J** = 15.7, 9.0 Hz, 1H), 5.74 (d, **J** = 2.3 Hz, 1H), 4.30 (dd, **J** = 8.6, 7.2 Hz, 2H), 3.12 (dd, **J** = 17.0, 5.9 Hz, 1H), 2.92–2.82 (m, 1H), 2.77 (d, **J** = 17.0 Hz, 1H), 2.45 (s, 3H), 2.23 (dd, **J** = 10.2, 6.3 Hz, 1H), 1.31 (t, **J** = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.26, 152.71, 144.29, 136.40, 136.30, 133.75, 129.81, 129.63, 128.65, 127.86, 127.79, 127.74, 127.51, 126.28, 126.15, 121.61, 118.55, 117.20, 81.80, 77.26, 77.01, 76.75, 61.70, 37.99, 34.03, 28.26, 21.64, 14.03. **HRMS**:$[M+H]^+$ calcd. For $C_{30}H_{30}NO_5S$ m/z: 516.1845; found: 516.1844. **$[\alpha]_D^{20}$** +26.32 (c = 1.63 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 18.02 min, t_{minor} = 22.19 min, *ee* = 99.3%.

(4*S*,4a*R*,10a*R*)-ethyl 4-(naphthalen-2-yl)-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5n,

Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$)δ 8.06 (d, *J* = 8.3 Hz, 2H), 7.87–7.77 (m, 3H), 7.53 (s, 1H), 7.51–7.46 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.20 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.93 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.31 (d, *J* = 3.1 Hz, 1H), 6.31 (d, *J* = 3.1 Hz, 1H), 5.81 (d, *J* = 2.3 Hz, 1H), 5.81 (d, *J* = 2.3 Hz, 1H), 4.31 (q, *J* = 6.9 Hz, 2H), 3.43 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.99 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.62 (d, *J* = 17.1 Hz, 1H), 2.46 (d, *J* = 10.1 Hz, 4H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.35, 152.67, 144.42, 137.33, 136.17, 133.39, 132.75, 129.81, 129.74, 128.76, 127.91, 127.86, 127.76, 127.70, 127.57, 127.06, 126.41, 126.27, 126.04, 121.74, 118.52, 117.28, 82.43, 77.27, 77.02, 76.76, 61.72, 40.40, 35.68, 28.14, 21.68, 14.04. **HRMS**:$[M+H]^+$ calcd. For $C_{32}H_{30}NO_5S$ m/z: 540.1845; found: 540.1849. **$[\alpha]_D^{20}$** +35 (c = 2.02 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IB column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 8.81 min, t_{minor} = 10.68 min, *ee* = 99.4%.

(4*S*,4a*R*,10a*R*)-isopropyl 4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5o, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.13 (dd, *J* = 14.8, 8.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.15 (d, *J* = 3.1 Hz, 1H), 5.75 (d, *J* = 2.4 Hz, 1H), 5.16 (dt, *J* = 12.5, 6.3 Hz, 1H), 3.25 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.01 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.54 (d, *J* = 17.0 Hz, 1H), 2.46 (s, 3H), 2.37 (dd, *J* = 13.2, 3.9 Hz, 1H), 1.32 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.29, 155.23, 147.01, 141.35, 138.90, 136.04, 132.65, 132.39, 132.31, 131.70, 130.88, 130.60, 130.51, 128.42, 124.40, 120.94, 119.91, 84.92, 79.92, 79.67, 79.41, 72.10, 42.25, 38.60, 30.66, 24.40, 24.31, 24.18. **HRMS**:$[M+H]^+$ calcd. For $C_{29}H_{29}ClNO_5S$ m/z: 538.1455; found: 538.1454. **$[\alpha]_D^{20}$** -18.48 (c = 1.25 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH =90/10, 1 mL/min], λ = 210 nm, t_{major} = 12.57 min, t_{minor} = 11.02 min, *ee* = 99.8%.

(4*S*,4a*R*,10a*R*)-benzyl 4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5p, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.42–7.32 (m, 5H), 7.31 (s, 4H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 3H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 5.73 (d, *J* = 2.3 Hz, 1H), 5.27 (s, 2H), 3.24 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.02 (d, *J* = 5.7 Hz, 1H), 2.54 (d, *J* = 17.1 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, *J* = 10.2, 4.9 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.04, 152.52, 144.44, 138.44, 135.86, 135.38, 133.42, 129.95, 129.73, 129.66, 129.06, 128.57, 128.48, 128.27, 127.97, 127.88, 127.61, 126.98, 121.78, 118.21, 117.22, 82.24, 77.26, 77.01, 76.75, 67.46, 39.69, 35.90, 28.06, 21.65. **HRMS**:$[M+H]^+$ calcd. For $C_{33}H_{29}ClNO_5S$ m/z: 586.1455; found: 586.1456. **$[\alpha]_D^{20}$** -35.15 (c = 1.34 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH =90/10, 1 mL/min], λ = 210 nm, t_{major} = 27.56 min, t_{minor} = 18.22 min, *ee* = 99.9%.

(4*S*,4a*R*,10a*R*)-ethyl 7-methyl-4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5q, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.35–7.28 (m, 3H), 7.08 (d, *J* = 6.9 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.82 (s, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.25 (d, *J* = 2.9 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.26 (d, *J* = 14.0 Hz, 1H), 2.94 (dd, *J* = 17.1, 5.7 Hz, 1H), 2.53 (d, *J* = 17.1 Hz, 1H), 2.46 (s, 3H), 2.32 (dd, *J* = 10.7, 5.6 Hz, 1H), 2.25 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, CDCl3)δ 164.36, 150.41, 144.31, 140.12, 136.21, 130.95, 130.02, 129.68, 128.83, 128.66, 128.50, 127.81, 127.63, 127.46, 127.24, 118.10, 116.95, 82.44, 77.27, 77.01, 76.76, 61.65, 40.33, 35.89, 28.06, 21.64, 20.50, 14.04. **HRMS**:$[M+H]^+$ calcd. For $C_{29}H_{30}NO_5S$ m/z: 504.1845; found: 504.1847. **$[\alpha]_D^{20}$** -58.84 (c = 1.29 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], λ = 210 nm, t_{major} = 16.05 min, t_{minor} = 13.22 min, *ee* = 99.4%.

(4*S*,4a*R*,10a*R*)-ethyl 7-methoxy-4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5r, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.35–7.27 (m, 3H), 7.07 (t, *J* = 7.8 Hz, 2H), 6.79 (d, *J* = 8.9 Hz, 1H), 6.70 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.25 (d, *J* = 3.0 Hz, 1H), 5.71 (d, *J* = 2.2 Hz, 1H), 4.31 (d, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 3.26 (dd, *J* = 11.1, 3.0 Hz, 1H), 2.96 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.54 (d, *J* = 17.1 Hz, 1H), 2.46 (s, 3H), 2.31 (dd, *J* = 10.8, 6.0 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.35, 154.27, 146.51, 144.33, 140.04, 136.19, 129.69, 128.85, 128.66, 127.81, 127.66, 127.49, 127.20, 119.15, 117.90, 114.16, 113.78, 82.45, 77.27, 76.94, 76.76, 61.66, 55.66, 40.32, 35.79, 28.40, 21.64, 14.04. **HRMS**:$[M+H]^+$ calcd. m/z: 520.1794; found: 520.1790. **$[\alpha]_D^{20}$** -51.45 (*c* = 1.45 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IC column [*n*-hexane/*i*-PrOH = 80/20, 1mL/min], *λ* = 210 nm, t_{major} = 46.55 min, t_{minor} = 25.96 min, *ee* = 99.3%.

(4*S*,4a*R*,10a*R*)-ethyl 6,7-dimethoxy-4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5s, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.35–7.28 (m, 3H), 7.08 (d, *J* = 6.8 Hz, 2H), 6.46 (d, *J* = 16.0 Hz, 2H), 6.26 (d, *J* = 3.1 Hz, 1H), 5.70 (d, *J* = 2.2 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 6H), 3.27 (dd, *J* = 11.0, 3.1 Hz, 1H), 2.91 (dd, *J* = 16.8, 5.9 Hz, 1H), 2.48 (d, *J* = 6.9 Hz, 1H), 2.46 (s, 3H), 2.31 (dd, *J* = 11.9, 5.5 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.40, 148.78, 146.29, 144.38, 144.08, 140.10, 136.10, 129.73, 128.84, 128.65, 127.86, 127.50, 127.47, 112.01, 108.85, 101.30, 82.47, 77.26, 77.01, 76.75, 61.67, 56.43, 55.89, 40.29, 35.88, 27.69, 21.65, 14.06. **HRMS**:$[M+H]^+$ calcd. For $C_{30}H_{32}NO_7S$ m/z: 550.1899; found: 550.1892. **$[\alpha]_D^{20}$** -64.56 (*c* = 1.075 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IB column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], *λ* = 210 nm, t_{major} = 13.74 min, t_{minor} = 15.62 min, *ee* = 99.6%.

(4*S*,4a*R*,10a*R*)-ethyl 7-fluoro-4-phenyl-1-tosyl-4,4a,5,10a-tetrahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (5t, Table 2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.35–7.29 (m, 3H), 7.07 (d, *J* = 6.6 Hz, 2H), 6.82 (dd, *J* = 11.3, 3.7 Hz, 2H), 6.73 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.25 (d, *J* = 3.1 Hz, 1H), 5.74 (d, *J* = 2.3 Hz, 1H), 4.30 (q, *J* = 6.8 Hz, 2H), 3.22 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.96 (dd, *J* = 17.3, 5.8 Hz,

1H), 2.55 (d, *J* = 17.2 Hz, 1H), 2.46 (s, 3H), 2.32 (dd, *J* = 10.1, 5.0 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.26, 158.45, 156.54, 148.57, 144.43, 139.77, 136.09, 129.73, 128.92, 128.60, 127.82, 127.61, 126.96, 119.75, 119.69, 118.32, 118.26, 115.66, 115.47, 114.86, 114.68, 82.47, 77.26, 77.00, 76.75, 61.71, 40.26, 35.46, 28.26, 21.65, 14.04. **HRMS**:$[M+H]^+$ calcd. For $C_{28}H_{27}FNO_5Sm$/z: 508.1594; found: 508.1591. **$[\alpha]_D^{20}$** -57.96 (*c* = 1.175 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], *λ* = 210 nm, t_{major} = 16.97 min, t_{minor} = 15.02 min, *ee* = 99.7%.

(4a*R*,5*S*,8a*R*)-ethyl 5-phenyl-8-tosyl-3,4,4a,5,8,8a-hexahydro-2H-pyrano[2,3-b]pyridine-7-carboxylate (5u, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 16.6 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.28 (dd, *J* = 13.6, 6.2 Hz, 4H), 7.04 (d, *J* = 6.7 Hz, 2H), 6.22 (d, *J* = 3.3 Hz, 1H), 5.10 (d, *J* = 2.5 Hz, 1H), 4.33–4.21 (m, 2H), 4.11 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.60 – 3.54 (m, 2H), 2.45 (s, 3H), 1.78 (d, *J* = 12.6 Hz, 1H), 1.65 (d, *J* = 14.2 Hz, 1H), 1.57 (d, *J* = 13.4 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.69, 144.07, 140.76, 136.19, 129.65, 128.67, 128.55, 128.32, 127.68, 127.26, 126.75, 84.82, 77.25, 77.00, 76.74, 69.33, 61.60, 39.64, 37.66, 24.59, 21.61, 20.01, 13.99. **HRMS**:$[M+H]^+$ calcd. For $C_{24}H_{28}NO_5S$ m/z: 442.1688; found: 442.1682. **$[\alpha]_D^{20}$** +52.89 (*c* = 0.83 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], *λ* = 210 nm, t_{major} = 15.82 min, t_{minor} = 23.32 min, *ee* = 99.8%.

(3a*R*,4*S*,7a*R*)-ethyl 4-phenyl-7-tosyl-2,3,3a,4,7,7a-hexahydrofuro[2,3-b]pyridine-6-carboxylate (5v, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.31 (dd, *J* = 13.5, 6.1 Hz, 4H), 7.28–7.24 (m, 2H), 7.18 (d, *J* = 7.1 Hz, 2H), 6.45 (d, *J* = 6.0 Hz, 1H), 5.69 (d, *J* = 5.7 Hz, 1H), 4.31–4.20 (m, 2H), 3.96 (dd, *J* = 16.0, 7.7 Hz, 1H), 3.83 (td, *J* = 8.5, 4.9 Hz, 1H), 3.43 – 3.37 (m, 1H), 2.65 (dt, *J* = 10.8, 5.4 Hz, 1H), 2.42 (s, 3H), 2.15 (dt, *J* = 20.2, 7.6 Hz, 1H), 1.88 (td, *J* = 12.7, 5.2 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$)δ 164.21, 143.67, 140.37, 137.14, 130.60, 129.32, 128.92, 127.86, 127.75, 127.23, 126.18, 86.75, 77.26, 77.00, 76.75, 65.42, 61.59, 44.61, 41.60, 29.65, 21.59, 13.99. **HRMS**:$[M+H]^+$ calcd. For $C_{23}H_{26}NO_5S$ m/z: 428.1532; found: 428.1537. **$[\alpha]_D^{20}$** +68.41 (*c* = 1.20 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 90/10, 1 mL/min], *λ* = 210 nm, t_{major} = 22.26 min, t_{minor} = 28.80 min, *ee* = 98.6%.

(3a*R*,4*S*,7a*S*)-ethyl 4-phenyl-1,7-ditosyl-2,3,3a,4,7,7a-hexahydro-1H-pyrrolo[2,3-b]pyridine-6-carboxylate (5w, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 4H), 7.31–7.22 (m, 4H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 6.8 Hz, 2H), 6.66 (d, *J* = 4.8 Hz, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 4.31–4.19 (m, 2H), 3.61 (dd, *J* = 12.6, 7.6 Hz, 1H), 3.51 (dd, *J* = 18.9, 9.3 Hz, 1H), 3.25 (t, *J* = 5.6 Hz, 1H), 2.51 (d, *J* = 1.0 Hz, 1H), 2.48 (s, 3H), 2.40 (s, 3H), 1.66–1.61 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.89, 144.54, 143.48, 140.69, 135.14, 134.87, 131.47, 129.47, 129.32, 128.96, 128.07, 127.90, 127.62, 127.41, 77.25, 77.00, 76.74, 73.36, 61.45, 46.35, 43.41, 43.30, 29.04, 21.73, 21.52, 14.08. **HRMS**:$[M+H]^+$ calcd. For $C_{30}H_{33}N_2O_6S_2$ m/z: 581.1780; found: 581.1775. **$[\alpha]_D^{20}$** +107.87 (*c* = 0.775 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH = 80/20, 1 mL/min], *λ* = 210 nm, t_{major} = 26.66 min, t_{minor} = 32.46 min, *ee* = 99.6%.

(4S,4aR,10aS)-ethyl 4-phenyl-1,10-ditosyl-1,4,4a,5,10,10a-hexahydrobenzo[b][1,8]naphthyridine-2-carboxylate(5x,Table 2). **^{1}H NMR (500 MHz, cdcl$_3$)** δ 8.32 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.35–7.22 (m, 5H), 7.17 (d, *J* = 6.9 Hz, 2H), 7.11–6.99 (m, 4H), 6.71 (dd, *J* = 16.8, 7.9 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H), 5.03 (d, *J* = 10.4 Hz, 1H), 4.46–4.27 (m, 2H), 3.19 (dd, *J* = 10.3, 3.1 Hz, 1H), 2.66 (dd, *J* = 20.5, 10.3 Hz, 1H), 2.52 (s, 3H), 2.33 (s, 3H), 2.10 (d, *J* = 14.4 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR (125 MHz, cdcl$_3$)** δ 163.93, 144.15, 143.96, 138.82, 138.19, 135.93, 134.06, 133.75, 132.50, 129.91, 129.22, 129.09, 128.91, 128.79, 128.49, 128.43, 128.25, 127.73, 127.28, 127.19, 126.78, 126.67, 77.25, 76.99, 76.74, 76.58, 61.66, 49.69, 43.76, 29.34, 21.77, 21.53, 14.15. **HRMS**:$[M+H]^+$ *calcd*. For $C_{31}H_{35}N_2O_6S_2$ m/z: 643.1937 ; found: 643.1941. The diastereomeric ratio was determined by both NMR and HPLC analysis, ***dr* = 3:1**. The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH =80/20, 1 mL/min], *λ* = 210 nm, t_{major} = 21.39 min, t_{minor} =27.11 min, *ee* = 98%.

(R)-ethyl 5-(3-(4-methylphenylsulfonamido)propyl)-4-phenyl-1-tosyl-1,4-dihydropyridine-2-carboxylate (5y, Table 2). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.30 (dd, *J* = 7.5, 5.9 Hz, 4H), 7.25 (dd, *J* = 15.0, 7.8 Hz, 4H), 7.19 (d, *J* = 7.1 Hz, 2H), 6.97 (d, *J* = 11.0 Hz, 1H), 6.63 (s, 1H), 6.12 (s, 1H), 4.88 (d, *J* = 11.0 Hz, 1H), 3.90 (tdd, *J* = 10.8, 7.1, 3.7 Hz, 2H), 3.47–3.38 (m, 1H), 3.32–3.22 (m, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 1.81 (dt, *J* = 17.2, 5.8 Hz, 1H), 1.76–1.67 (m, 1H), 1.57–1.51 (m, 2H), 1.05 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.86, 144.09, 143.63, 141.62, 140.32, 135.61, 134.93, 129.70, 129.50, 128.73, 128.09, 127.75, 127.21, 127.13, 124.46, 122.08, 121.96, 77.25, 77.00, 76.74, 61.95, 48.47, 43.69, 29.68, 23.99, 21.52, 20.52, 13.88. **HRMS**:$[M+H]^+$ *calcd*. For $C_{31}H_{35}N_2O_6S_2$ m/z: 595.1937 ; found: 595.1934 . **$[\alpha]_D^{20}$** - 7.72 (*c* = 0.8 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH =90/10, 1 mL/min], *λ* = 210 nm, t_{major} = 20.80 min, t_{minor} =15.94 min, ***ee* = 99.3%**.

Procedure for the synthesis of compounds 7 and 8

(2*S*,4*S*,5*R*)-ethyl 5-(2-hydroxybenzyl)-4-phenyl-1-tosylpiperidine-2-carboxylate (7). To a $(CH_2Cl)_2$ solution (1.2 mL) of **5a** (20 mg, 0.04 mmol) and triethylsilane (20 µL, 0.3 mmol) was added trifluoroborane diethyl etherate (16 µL, 2.0 mmol) at 70 °C. After it was stirred for 8 h, the reaction mixture was slowly cooled to room temperature, and then the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 4 mL). The organic phase was combined and dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 1 : 5) to afford the **7** (14.0 mg, 70% yield). **^{1}H NMR** (500 MHz, cdcl$_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.37–7.29 (m, 4H), 7.23 (dd, *J* = 6.3, 5.2 Hz, 3H), 7.05 (td, *J* = 7.9, 1.5 Hz, 1H), 6.86 (dd, *J* = 7.4,

1.3 Hz, 1H), 6.79 (td, *J* = 7.4, 0.8 Hz, 1H), 6.72 (dd, *J* = 8.0, 0.5 Hz, 1H), 5.12 (s, 1H), 4.20–4.00 (m, 2H), 3.86 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.65 (dd, *J* = 12.2, 2.1 Hz, 1H), 2.58 (dd, *J* = 12.6, 5.5 Hz, 1H), 2.53 (d, *J* = 11.0 Hz, 1H), 2.44 (s, 3H), 2.34 (d, *J* = 8.3 Hz, 3H), 2.16 (dd, *J* = 14.9, 3.6 Hz, 1H), 2.08 (dd, *J* = 23.6, 12.2 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, cdcl$_3$) δ 171.13, 153.76, 143.85, 142.57, 130.91, 129.50, 128.79, 128.26, 127.68, 127.62, 127.03, 125.26, 120.73, 115.76, 77.25, 76.99, 76.74, 61.42, 59.02, 48.81, 45.79, 41.00, 36.25, 31.77, 21.57, 13.91. **HRMS**:[M+H]$^+$ calcd. For $C_{28}H_{32}NO_5S$ m/z: 494.2001; found: 494.2003. **$[\alpha]_D^{20}$** +23.24 (*c* = 0.58 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IA column [*n*-hexane/*i*-PrOH =90/10, 1 mL/min], λ = 210 nm, t_{major} = 44.83 min, t_{minor} = 42.34 min, *ee* = 99.9%.

(2*R*,3*S*,4*S*,4a*R*,10a*R*)-ethyl2,3-dihydroxy-4-phenyl-1-tosyl-2,3,4,4a,5,10a-hexahydro-1H-chromeno[2,3-b]pyridine-2-carboxylate (8). Sodium periodate (26.2 mg, 0.12 mmol, 3.00 eq.) was stirred in H_2O (0.5 mL) and 2N sulphuric acid (20 mol%). After the solid was dissolved, the solution was cooled to 0 °C. Ruthenium(III) chloride hydrate (4.1 mg, 0.02 mmol) was then added and the reaction was stirred until the colour turned bright yellow. Ethyl acetate (0.7 mL) and acetonitrile (0.7 mL) were added and stirring was continued for a further 5 min. **5a** (20 mg, 0.04 mmol, 1.00 eq.) was then added to the reaction and the slurry was stirred at room temperature for 5 min. The reaction mixture was poured into a mixture of aqueous saturated $NaHCO_3$ solution (5 mL). The organic phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and then concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate / petroleum ether 1 : 5) to afford the **8** (14.9 mg, 70% yield). **^{1}H NMR** (500 MHz, cdcl$_3$) δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.04 (dd, *J* = 13.2, 7.7 Hz, 3H), 6.82 (d, *J* = 6.4 Hz, 2H), 6.31 (d, *J* = 8.1 Hz, 1H), 6.02 (d, *J* = 2.0 Hz, 1H), 4.57 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.32 (t, *J* = 10.8 Hz, 1H), 2.94 (dd, *J* = 17.1, 6.3 Hz, 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.62 (dd, *J* = 11.9, 6.2 Hz, 1H), 2.51 (s, 3H), 2.32 (d, *J* = 17.0 Hz, 1H), 1.44 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (125 MHz, cdcl$_3$) δ 170.99, 152.51, 144.35, 138.22, 137.50, 129.28, 129.23, 129.07, 128.93, 128.37, 127.57, 127.43, 121.57, 118.51, 116.24, 86.12, 83.77, 77.26, 77.01, 76.75, 76.31, 64.05, 42.32, 36.92, 27.58, 21.70, 13.92. **HRMS**:[M+Na]$^+$ calcd. For $C_{28}H_{29}NNaO_7S$ m/z: 546.1562; found: 546.1559. **$[\alpha]_D^{20}$** -47.53 (*c* = 0.41 in $CHCl_3$). The enantiomeric excess was determined by HPLC using Chiralpak IB column [*n*-hexane/*i*-PrOH =95/5, 1 mL/min], λ = 310 nm, t_{major} = 23.03 min, t_{minor} = 14.18 min, *ee* = 99.9%.

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