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Stereoselective Synthesis of Hexahydro-1*H*-pyrano- and thiopyrano[3,4-*c*]quinoline Derivatives through a Prins Cascade Cyclization

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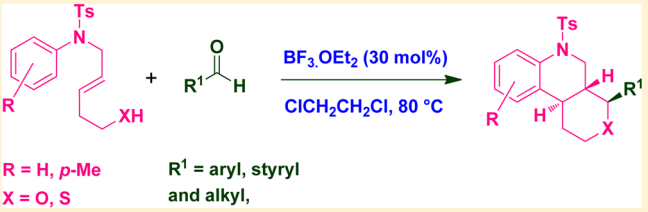
Supporting Information

ABSTRACT: A cascade reaction of (*E*)-5-(arylamino)pent-3-en-1-ols and thiols with various aldehydes in the presence of 30 mol % BF_3·OEt_2 in 1,2-dichloroethane at 80 °C affords a novel class of *trans*-fused hexahydro-1*H*-pyrano[3,4-*c*]quinolines and hexahydro-1*H*-thiopyrano[3,4-*c*]quinolines in good to excellent yields with high selectivity. The condensation of (*Z*)-5-(arylamino)pent-3-en-1-ol with aldehydes provides the corresponding *cis*-fused products under similar conditions.



The pyranoquinoline core is found in many alkaloids such as flindersine, oricine, veprisine, and (+)-orixalone D (Figure 1).[1] These alkaloids and their derivatives possess a wide

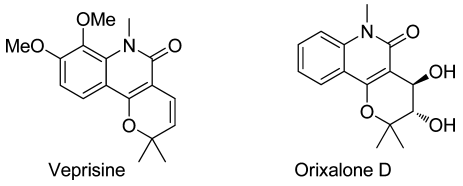


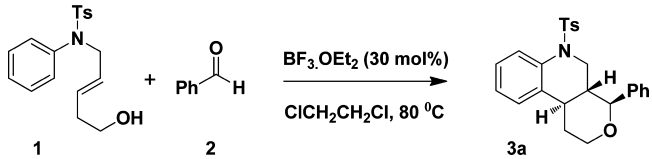
Figure 1. Examples of bioactive pyranoquinolines.

range of biological activities such as psychotropic, antiallergenic, anti-inflammatory, and estrogenic activities.[2] Thus, pyrano[3,2-*c*]quinolin-5-ones and their synthetic analogues are of great interest because of their potent biological activities.[3] Generally, the pyrano[3,4-*b*]quinolines are prepared by a well-known Povarov reaction that involves the reaction of aniline with benzaldehyde and alkene in the presence of an acid catalyst.[4]

Prins cyclization is a powerful strategy for the stereoselective synthesis of tetrahydropyran scaffolds.[5,6] In particular, the intramolecular version of the Prins cyclization provides a very attractive strategy to construct a variety of heterobicycles such as bicyclo[3.3.1]nonanes, azaspiro[4,4]nonanes, bicyclo[3,2,1]-octanes, and oxaspirobicycles in a single-step process.[7] Therefore, the Prins cyclization cascade has emerged as a powerful synthesis tool for the stereoselective construction of fused tetrahydropyran systems.[8] In spite of its potential application in natural products synthesis,[9,10] the scope of the tandem processes has not yet been explored to produce hexahydro-1*H*-pyrano[3,4-*c*]quinolines and hexahydro-1*H*-thiopyrano[3,4-*c*]quinolines from readily accessible aldehydes and (*E*)-5-(arylamino)pent-3-en-1-ols and thiols, respectively.

Following our research interest on tandem Prins-type cyclizations,[11] we report herein a novel strategy for the stereoselective synthesis of hexahydro-1*H*-pyrano[3,4-*c*]-quinolines and hexahydro-1*H*-thiopyrano[3,4-*c*]quinolines by means of a Prins-cascade process. As a model reaction, we first attempted the condensation of (*E*)-*N*-(5-hydroxypent-2-en-1-yl)-4-methyl-*N*-phenylbenzenesulfonamide (**1**) with benzaldehyde (**2**) using 30 mol % BF_3·OEt_2 in 1,2-dichloroethane. However, the reaction was slow at room temperature and required a long reaction time (8 h). The reaction was complete within a short time (20 min) by increasing the temperature to 80 °C, affording corresponding *trans*-4-phenyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline **3a** in a 90% yield as a single product (Scheme 1 and entry a, Table 1), which was confirmed by the ^{1}H NMR spectrum of the crude reaction mixture.

Scheme 1. Condensation of Arylamino Tethered Homoallyl Alcohol (1) with Benzaldehyde (2)



Insipired by the above results, we extendend our efforts to study the reactivity of various benzaldehydes containing different electron-withdrawing and donating substituents. As shown in Table 1, the corresponding *trans*-fused hexahydro-1*H*-pyrano[3,4-*c*]quinoline derivatives were obtained in good to

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Table 1. Synthesis of Hexahydro-1*H*-pyrano- and Hexahydro-1*H*-thiopyrano[3,4-*c*]quinolines

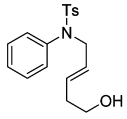
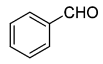
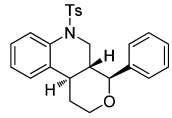
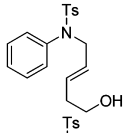
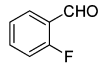
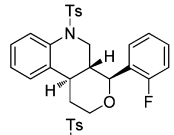
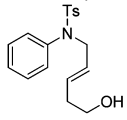
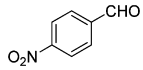
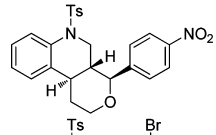
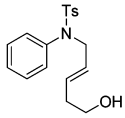
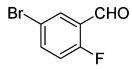
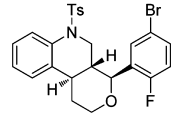
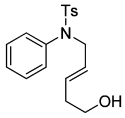
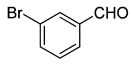
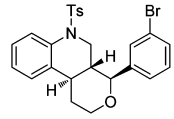
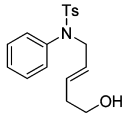
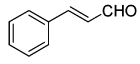
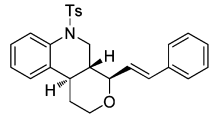
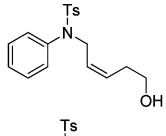
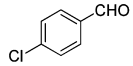
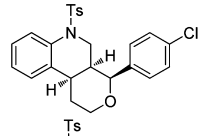
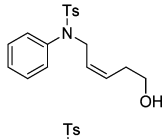
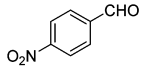
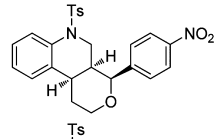
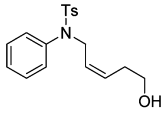
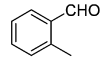
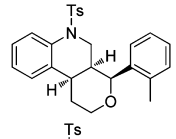
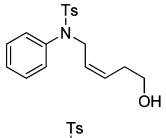
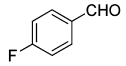
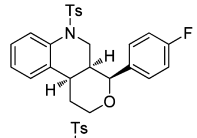
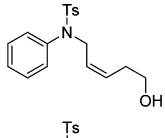
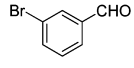
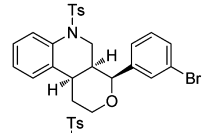
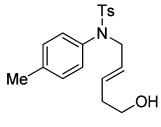
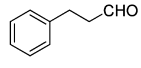
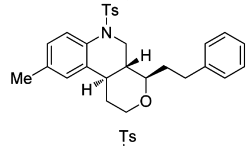
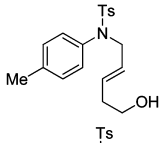
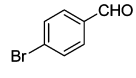
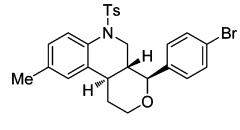
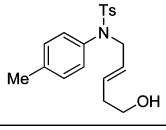
Entry	Homoallylic alcohol (**1**)	Aldehyde (**2**)	Product (**3**)[b]	Time (min)	Yield (%)[c]
a				20	90
b				25	85
c				20	78
d				25	86
e				20	90
f				35	70
g				35	90
h				35	76
i				35	88
j				35	92
k				35	94
l				45	70
m				15	92
n				20	95

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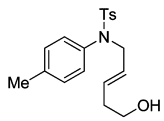
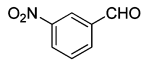
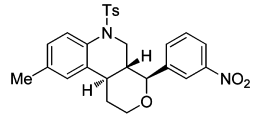
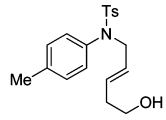
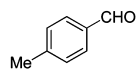
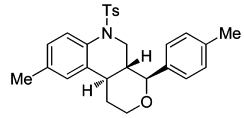
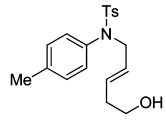
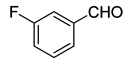
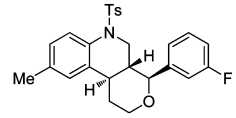
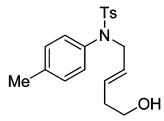
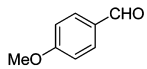
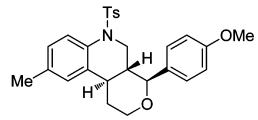
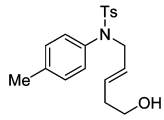
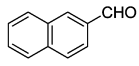
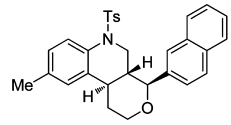
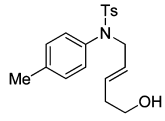
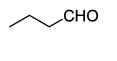
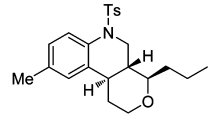
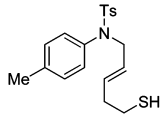
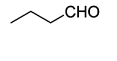
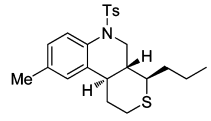
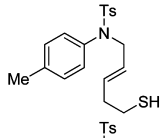
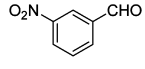
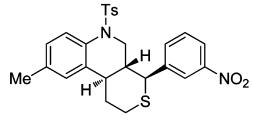
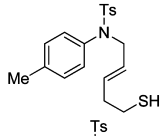
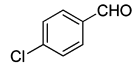
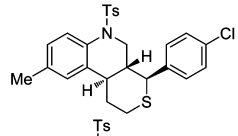
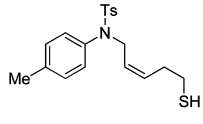
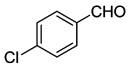
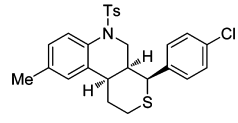
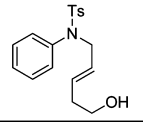
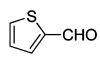
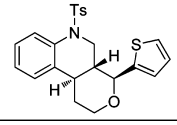
Table 1. continued

Entry	Homoallylic alcohol (**1**)	Aldehyde (**2**)	Product (**3**)[b]	Time (min)	Yield (%)[c]
o				25	75
p				20	90
q				25	88
r				40	78
s				20	80
t				60	75
u				30	70
v				25	75
w				20	90
x				30	85
Y				20	95

[a]All the products were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy. [b]Yield refers to pure product after column chromatography.

excellent yields. Furthermore, aliphatic substrates such as 3-phenylpropanaldehyde and *n*-butyraldehyde also gave the alkyl substituted *trans*-fused hexahydropyrano[3,4-*c*]quinolines in good yields (entries l and t, Table 1). The scope of the reaction is further illustrated with respect to various aldehydes and homoallylic substrates like (*E*)-*N*-(5-hydroxypent-2-en-1-yl)-4-methyl-*N*-(*p*-tolyl)benzenesulfonamide and (*Z*)-*N*-(5-hydroxypent-2-en-1-yl)-4-methyl-*N*-phenylbenzenesulfonamide. The substituents present on the aromatic ring had shown some effect on the conversion. It was observed that activated aromatic aldehydes (entry r, Table 1) and deactivated aromatic aldehydes (entries c, h, and o, Table 1) gave the products in slightly lower yields than their halogenated aromatic counterparts. As depicted in Table 1, aliphatic aldehydes gave slightly lower yields than their aromatic counterparts (entries l, t, and u, Table 1). The scope of this reaction is also illustrated with respect to heterocyclic aldehydes, for instance, thiophene-2-carboxaldehyde to produce the *trans*-fused thienyl-substituted hexahydropyrano[3,4-*c*]quinoline in good yield (entry y, Table 1) .

The condensation of the *cis*-alkenol (*Z*)-*N*-(5-hydroxypent-2-en-1-yl)-4-methyl-*N*-phenylbenzenesulfonamide with aromatic

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aldehydes gave the *cis*-fused hexahydropyrano[3,4-*c*]quinolines (entries g–k, Table 1). The geometry of the olefin controls the stereoselectivity of the reaction. It is known that cis-olefins gives cis-fused products exclusively, whereas trans-olefins provide trans-fused products predominantly.[11] This method is effective even with acid-sensitive cinnamaldehyde and sterically hindered 2-naphthaldehyde to provide the respective *trans*-fused hexahydropyrano[3,4-*c*]quinoline in good yields (entries f and s, Table 1). The structures of **3d** and **3i** were confirmed by X-ray crystallography (Figures 2 and 3). Furthermore, the structures and stereochemistries of **3j** and **3q** were established by detailed 1D and 2D NMR experiments (Supporting Information).[12]

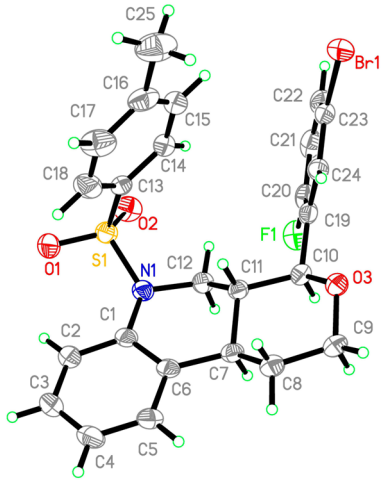


Figure 2. ORTEP diagram for product **3d** (entry d, Table 1).

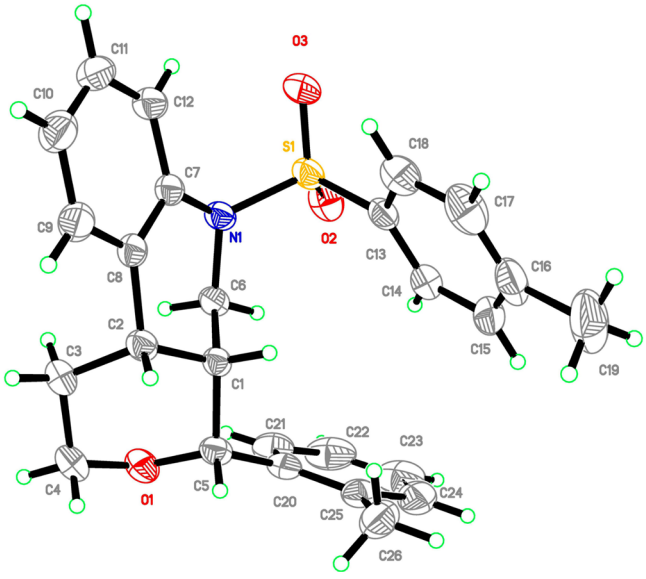
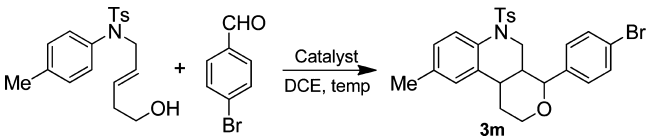


Figure 3. ORTEP diagram for product **3i** (entry i, Table 1).

The above results provided a gateway to extend this process to a thia-Prins/Friedel–Crafts cyclization.[13] For instance, aryl-tethered homoallylic mercaptan (i.e., (*E*)-*N*-(5-mercaptopent-2-en-1-yl)-4-methyl-*N*-(*p*-tolyl)benzenesulfonamide) underwent a smooth condensation with *n*-butanal under similar conditions to give the respective *trans*-hexahydro-1*H*-thiopyrano[3,4-*c*]quinoline **3u** in a 70% yield (entry u, Table 1). Similarly, aryl aldehydes like 3-nitrobenzaldehyde and 4-chlorobenzaldehyde also afforded the corresponding *trans*-fused hexahydro-1*H*-thiopyrano[3,4-*c*]quinolines in good yields (entries v and w, Table 1). However, the coupling of (*Z*)-*N*-(5-mercaptopent-2-en-1-yl)-4-methyl-*N*-(*p*-tolyl)-benzenesulfonamide with 4-chlorobenzaldehyde afforded the *cis*-fused hexahydro-1*H*-thiopyrano[3,4-*c*]quinoline in 85% yield (entry x, Table 1) . The steriochemistry of **3x** was established by 1D and 2D NMR experiments (Supporting Information).[12]

The reactions were performed with various acid catalysts to evaluate their efficiency, and the results are presented in Table 2. Brønsted acids such as *p*-toluenesulfonic acid (*p*-TSA) and

Table 2. Screening of Various Acid Catalysts in the Synthesis of 3m



entry	catalyst	mol %	temp (°C)	time	yield (%)
a	Sc(OTf)3	10	rt	16 h	25
b	Sc(OTf)3	30	rt	16 h	30
c	$Sc(OTf)_3$ + TsOH	10:30	rt	16 h	30
d	In(OTf)3	30	rt	24 h	10
e	$InCl_3$	30	rt	24 h	0
f	CSA	30	rt	24 h	0
g	$BF_3{\cdot}OEt_2$	30	rt	24 h	40
h	$BF_3{\cdot}OEt_2$	30	80	15 min	92

camphorsulfonic acid (CSA) as well as Lewis acids such as $BF_3{\cdot}OEt_2$, $InCl_3$, $In(OTf)_3$, and $Sc(OTf)_3$ were screened. Among them, 30 mol % $BF_3{\cdot}OEt_2$ gave the best results in terms of conversion and reaction time. Next, we examined the effect of various solvents such as 1,2-dichloroethane, acetonitrile, toluene, and tetrahydrofuran, and we found that 1,2-dichloroethane gave the best results. The reaction is assumed to proceed via the formation of an oxocarbenium ion from the hemiacetal that is formed in situ from the aldehyde and a homoallylic alcohol, likely after activation with $BF_3{\cdot}OEt_2$. The oxocarbenium ion is attacked by an internal olefin resulting in the formation of a carbocation that is simultaneously trapped by a tethered aryl group, leading to the formation of hexahydro-1*H*-pyrano[3,2-*c*]quinoline, as depicted in Scheme 2.

A tandem Prins-cyclization process has been developed for the stereoselective synthesis of a novel series of hexahydro-1*H*-pyrano- and thiopyrano[3,4-*c*]quinoline derivatives. This is the first report on the synthesis of pyrano- and thiopyrano-quinolines via tandem Prins cyclization. This method is a highly stereoselective to produce cis- and trans-fused quinoline derivatives. It provides direct access to the synthesis of biologically interesting pyrano- and thiopyrano-quinolines, of which some are reported as potent psychotropic and anti-inflammatory agents. The new products are under biological screening, in particular for their CNS activity.

EXPERIMENTAL SECTION

General Information. All solvents were dried according to standard literature procedures. The reactions were performed in oven-dried round-bottomed flasks fitted with rubber septa under a nitrogen atmosphere. Glass syringes were used to transfer the solvents.

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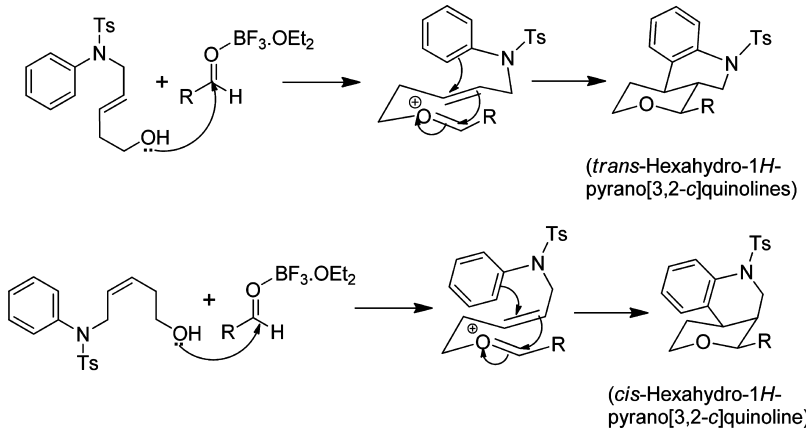
Scheme 2. Plausible Reaction Pathway



The crude products were purified by column chromatography on silica gel of 60−120 or 100−200 mesh. Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to a methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporator at 35−40 °C. IR spectra were recorded on FT−IR spectrometer. ^{1}H and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on a 200, 300, 400, or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer using the electrospray ionization (ESI) or the atmospheric pressure chemical ionization (APCI) technique.

Typical Procedure for the Intramolecular Prins/Friedel−Crafts Cyclization. To a mixture of (*E*)-*N*-(5-hydroxypent-2-en-1-yl)-4-methyl-*N*-phenylbenzenesulfonamide (0.50 mmol) and benzaldehyde (0.60 mmol) in anhydrous 1,2-dichloroethane (5 mL) was added $BF_3{\cdot}OEt_2$ (30 mol %) in 1,2-dichloroethane. The resulting mixture was allowed to stir at 80 °C under a nitrogen atmosphere for the specified time (Table 1). After completion of the reaction (indicated by TLC), the mixture was quenched with a saturated $NaHCO_3$ solution (0.5 mL) and extracted with dichloromethane (2 × 5 mL). The organic phases were combined, washed with brine (3 × 2 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using ethyl acetate/hexane gradients to afford pure product **3a** (Table 1).

3a: (4*S*,4a*R*,10b*R*)-4-Phenyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 188 mg, 90%. mp 162−164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (dd, J = 8.3, 1.5 Hz, 1H), 7.40−7.32 (m, 5H), 7.29−7.15 (m, 6H), 7.1 (d, J = 7.5 Hz, 1H), 4.25−4.18 (m, 1H), 3.91 (d, J = 9.8 Hz, 1H), 3.57 (dt, J = 12.0, 1.5 Hz, 1H), 3.39 (dd, J = 12.8, 6.7 Hz, 1H), 3.28 (dd, J = 12.8, 10.5 Hz, 1H), 2.41 (s, 3H), 2.15−2.05 (m, 1H), 1.9 (dt, J = 11.3, 3.7 Hz, 1H), 1.75−1.61 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 138.9, 136.1, 135.9, 134.6, 129.5, 128.6, 128.5, 126.9, 125.5, 125.3, 124.0, 83.8, 67.8, 47.6, 44.3, 37.5, 28.6, 21.4. IR (KBr): ν 3032, 2923, 2850, 1598, 1487, 1452, 1350, 1228, 1165, 1102, 1080, 904, 814, 760, 664 cm^{-1}. MS−ESI: m/z 420 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{25}O_3NNaS$ $[M + Na]^+$: 442.1447; found, 442.1454.

3b: (4*S*,4a*R*,10b*R*)-4-(2-Fluorophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 183 mg, 85%. mp 111−113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77−7.73 (m, 1H), 7.39−7.05 (m, 11H), 4.34 (d, J = 9.6 Hz, 1H), 4.23−4.16 (m, 1H), 3.56 (dt, J = 12.0, 2.0 Hz, 1H), 3.50−3.42 (m, 1H), 3.39−3.30 (m, 1H), 2.41 (s, 3H), 2.13−2.05 (m, 1H), 1.87 (dt, J = 11.3, 3.5 Hz, 1H), 1.75−1.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 158.2, 143.6, 136.1, 135.8, 134.4, 129.9, 129.8,129.5, 129.1, 128.8, 128.1, 127.9, 127.7, 127.0, 126.4, 126.2, 125.7, 125.4, 124.5, 124.0, 115.6, 115.3, 75.8, 68.0, 46.8, 44.3, 37.5, 28.6, 21.5. IR (KBr): ν 3065, 2924, 2853, 1595, 1490, 1454, 1352, 1230, 1165, 1091, 911, 815, 759, 663 cm^{-1}. MS−ESI: m/z 438 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{25}O_3NFS$ $[M + H]^+$: 438.1533; found, 438.1542.

3c: (4*S*,4a*R*,10b*R*)-4-(4-Nitrophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 180 mg, 78%. mp 208−210 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.28−7.17 (m, 4H), 7.11 (d, J = 7.2 Hz, 1H), 4.24 (dd, J = 11.4, 4.1 Hz, 1H), 4.07 (d, J = 9.3 Hz, 1H), 3.61 (t, J = 11.4 Hz, 1H), 3.36−3.33 (m, 2H), 2.41 (s, 3H), 2.18−2.13 (m, 1H), 2.02 (dt, J = 11.4, 3.1 Hz, 1H), 1.74−1.66 (m, 1H), 1.65−1.57 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 146.2, 143.8, 135.9, 135.7, 134.0, 129.5, 127.9, 127.2, 126.9, 125.5, 125.3, 124.1, 123.8, 82.5, 67.8, 47.2, 44.4, 37.3, 28.4, 21.5. IR (KBr): ν 3030, 2936, 2853, 1601, 1522, 1452, 1348, 1227, 1164, 1094, 854, 757, 663 cm^{-1}. MS−ESI: m/z 487 $[M + Na]^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{24}O_5N_2NaS$ $[M + Na]^+$: 487.1298; found, 487.1308.

3d: (4*S*,4a*R*,10b*R*)-4-(5-Bromo-2-fluorophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Pale-yellow solid. Yield 221 mg, 86%. mp 165−167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82−7.78 (m, 1H), 7.47−7.39 (m, 2H), 7.32−7.21 (m, 5H), 7.20−7.16 (m, 1H), 7.13−7.08 (m, 1H), 7.04−6.97 (m, 1H), 4.31 (d, J = 9.8, 1H), 4.22−4.16 (m, 1H), 3.6−3.5 (m, 2H), 3.38−3.28 (m, 1H), 2.42 (s, 3H), 2.16−2.07 (m, 1H), 2.05−1.95 (m, 1H), 1.64−1.53 (m, 1H), 1.50−1.37 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 157.0, 143.7, 136.0, 135.8, 133.5, 132.7, 132.6, 131.1, 131.0, 129.6, 129.2, 129.0, 128.9, 128.7, 127.8, 127.7, 127.1, 127.0, 125.7, 125.5, 124.2, 117.4, 117.1, 74.9, 68.1, 46.6, 43.9, 38.0, 28.8, 21.5. IR (KBr): ν 3031, 2925, 2854, 1598, 1485, 1353, 1238, 1165, 1095, 1074, 920, 869, 815, 757, 664 cm^{-1}. MS−ESI: m/z 518 $[(M + 2) + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{24}O_3NBrFS$ $[M + H]^+$: 516.0638; found, 516.0642.

3e: (4*S*,4a*R*,10b*R*)-4-(3-Bromophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Pale-yellow solid. Yield 223 mg, 90%. mp 129−131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79−7.40 (m, 1H), 7.52−7.41 (m, 2H), 7.37−7.08 (m, 9H), 4.2 (dd, J = 11.7, 3.2 Hz, 1H), 3.89 (d, J = 9.6 Hz, 1H), 3.60−3.52 (m, 1H), 3.45 (dd, J = 13.0, 5.8 Hz, 1H), 3.31−3.21 (m, 1H), 2.42 (s, 3H), 2.16−2.07 (m, 1H), 2.03−1.92 (m, 1H), 1.70−1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 141.3, 136.0, 135.8, 134.0, 131.7, 130.0, 129.9, 129.5, 127.0, 126.9, 125.8, 124.4, 124.1, 122.9, 82.9, 67.9, 47.3, 43.9, 37.7, 28.7, 21.5. IR (KBr): ν 3030, 2923, 2849, 1570, 1451, 1350, 1221, 1164, 1089, 1071, 771 cm^{-1}. MS−ESI: m/z 498 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{25}O_3NBrS$ $[M + H]^+$: 498.0733; found, 498.0731.

3f: (4*R*,4a*R*,10b*R*)-4-((*E*)-Styryl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Pale-yellow solid. Yield 155 mg, 70%. mp 136−138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (dd, J = 7.9, 0.9 Hz, 1H), 7.48−7.14 (m, 11H), 7.06 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 15.8 Hz, 1H), 6.05 (dd, J = 15.8, 7.3 Hz, 1H), 4.19−4.11 (m, 1H), 3.83 (dd, J = 13.0, 6.2 Hz, 1H), 3.65−3.57 (m, 1H),

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3.54−3.44 (m, 1H), 3.38 (dd, J = 12.8, 10.9 Hz, 1H), 2.40 (s, 3H), 2.08−1.99 (m, 1H), 1.84−1.73 (m, 1H), 1.60−1.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 136.1, 136.0, 134.8, 133.4, 129.5, 128.5, 128.0, 127.0, 126.6, 125.5, 125.4, 123.9, 81.6, 67.2, 47.6, 43.7, 37.0, 28.4, 21.5. IR (KBr): ν 3028, 2936, 2849, 1722, 1598, 1488, 1551, 1350, 1222, 1165, 1092, 1073, 971, 914, 757, 665 cm^{-1}. MS−ESI: m/z 468 [M + Na]$^+$. HRMS (Orbitrap ESI) calcd for $C_{27}H_{28}O_3NS$ [M + H]$^+$: 446.1784; found, 446.1793.

3g: (4*S*,4a*S*,10b*R*)-4-(4-Chlorophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 203 mg, 90%. mp 140−141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.28−7.05 (m, 10H), 4.54 (d, J = 3.0 Hz, 1H), 4.09 (dd, J = 12.0, 3.7 Hz, 1H), 3.68−3.54 (m, 2H), 3.51−3.40 (m, 1H), 3.02−2.92 (m, 1H), 2.40 (t, 3H), 1.89−1.80 (m, 1H), 1.66−1.47 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 143.6, 137.9, 135.8, 135.4, 133.0, 132.9, 129.4, 128.7, 128.4, 127.1, 126.9, 126.6, 124.7, 124.1, 78.7, 68.0, 41.6, 37.1, 35.5, 30.4, 21.5. IR (KBr): ν 3445, 3065, 2974, 2943, 2851, 1597, 1487, 1453, 1326, 1161, 1089, 1060, 1014, 946, 848, 810, 766, 682, 652, 557, 531 cm^{-1}. MS−ESI: m/z 476 [M + Na]$^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{25}O_3NClS$ [M + H]$^+$: 454.1238; found, 454.1238.

3h: (4*S*,4a*S*,10b*R*)-4-(4-Nitrophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Yellow solid. Yield 176 mg, 76%. mp 160−161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.30−7.07 (m, 7H), 4.67 (d, J = 3.0 Hz, 1H), 4.14 (dd, J = 11.3, 3.7 Hz, 1H), 3.66 (dt, J = 12.0, 2.2 Hz, 1H), 3.49−3.45 (m, 2H), 3.08−2.99 (m, 1H), 2.41 (s, 3H), 2.07−1.97 (m, 1H), 1.70−1.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 147.0, 143.8, 136.2, 135.4, 132.6, 129.5, 128.7, 127.1, 126.1, 124.8, 124.0, 123.5, 78.6, 68.1, 41.6, 37.3, 35.8, 30.3, 21.5. IR (KBr): ν 3446, 3066, 2941, 2838, 1601, 1519, 1348, 1162, 1093, 1065, 857, 817, 766, 676, 558 cm^{-1}. MS−ESI: m/z 465 [M + H]$^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{25}O_5N_2S$ [M + H]$^+$: 465.1478; found, 465.1482.

3i: (4*S*,4a*S*,10b*R*)- 4-(*o*-Tolyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 190 mg, 88%. mp 180−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J =7.5 Hz, 1H), 7.38−7.05 (m, 11H), 4.65 (d, J = 2.2 Hz, 1H), 4.14−4.06 (m, 1H), 3.74−3.56 (m, 3H), 3.0−2.91 (m, 1H), 2.38 (s, 3H), 2.02 (s, 3H), 1.67−1.53 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 143.2, 137.3, 135.8, 135.5, 133.0, 132.9, 130.3, 129.6, 128.7, 127.3, 126.9, 126.1, 126.0, 124.5, 124.2, 77.2, 68.4, 41.9, 37.3, 32.9, 30.6, 21.4, 19.0. IR (KBr): ν 3446, 3063, 2948, 2850, 1598, 1486, 1347, 1162, 1088, 947, 811, 749, 677, 560 cm^{-1}. MS−ESI: m/z 434 [M + H]$^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{28}O_3NS$ [M + H]$^+$: 434.1784; found, 434.1781.

3j: (4*S*,4a*S*,10b*R*)-4-(4-Fluorophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 201 mg, 92%. mp 140−143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, J = 8.3 Hz, 1H), 7.28−7.05 (m, 11H), 4.54 (d, J = 2.2 Hz, 1H), 4.09 (dd, J = 11.7, 4.1 Hz, 1H), 3.68−3.58 (m, 2H), 3.52−3.42 (m, 1H), 3.01−2.91 (m, 1H), 2.40 (s, 3H), 1.86−1.77 (m, 1H), 1.64−1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6, 160.3, 143.5, 136.1, 135.5, 135.3, 135.2, 132.9, 129.4, 128.7, 127.1, 126.9, 126.9, 126.8, 124.6, 124.0, 115.3, 78.9, 68.1, 41.7, 37.3, 35.8, 30.5, 21.4. IR (KBr): ν 3322, 3065, 2950, 2862, 1729, 1694, 1509, 1344, 1219, 1160, 1087, 850, 758, 675, 569, 544 cm^{-1}. MS−ESI: m/z 438 [M + H]$^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{25}O_3NFS$ [M + H]$^+$: 438.1533; found, 438.1531.

3k: (4*S*,4a*S*,10b*R*)-4-(3-Bromophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 233 mg, 94%. mp 146−148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.33−7.05 (m, 10H), 4.50 (d, J = 2.4 Hz, 1H), 4.13−4.05 (m, 1H), 3.68−3.55 (m, 2H), 3.51−3.40 (m, 1H), 2.98−2.89 (m, 1H), 2.41 (s, 3H), 1.76−1.67 (m, 1H), 1.63−1.51 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 141.9, 136.0, 135.4, 132.9, 130.4, 129.9, 129.5, 128.7, 128.3, 127.0, 126.9, 124.8, 124.3, 123.9, 122.4, 78.6, 68.0, 41.6, 37.1, 35.2, 30.6, 21.4. IR (KBr): ν 3449, 3063, 2848, 1919, 1728, 1596, 1481, 1353, 1298, 1166, 1086, 951, 802, 755, 676, 563 cm^{-1}. MS−ESI: m/z 498 [M + H]$^+$. HRMS (Orbitrap ESI) calcd for $C_{25}H_{24}O_3NBrNaS$ [M + Na]$^+$: 520.0552; found, 520.0550.

3l: (4*R*,4a*R*,10b*R*)-9-Methyl-4-phenethyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Off-white solid. Yield 161 mg, 70%. mp 130−133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J = 7.9 Hz, 1H), 7.37−7.29 (m, 4H), 7.24−7.18 (m, 3H), 7.13 (d, J = 8.9 Hz, 2H), 7.04 (d, J = 7.9 Hz, 1H), 6.79 (s, 1H), 4.1−4.06 (m, 1H), 3.79−3.75 (m, 1H), 3.30−3.22 (m, 2H), 2.91−2.86 (m, 1H), 2.85−2.78 (m, 1H), 2.66−2.59 (m, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.94−1.88 (m, 1H), 1.86−1.79 (m, 1H), 1.66−1.58 (m, 1H), 1.55−1.40 (m, 2H), 1.37−1.28 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 141.8, 135.9, 135.5, 135.2, 133.3, 129.4, 128.5, 128.3, 127.5, 126.9, 125.8, 125.7, 124.3, 79.6, 67.2, 47.3, 43.8, 36.6, 34.9, 31.2, 28.4, 21.4, 21.1. IR (KBr): ν 3027, 2924, 2850, 1599, 1494, 1454, 1350, 1245, 1165, 1090, 1020, 908, 815, 754 cm^{-1}. MS−ESI: m/z 462 [M + H]$^+$. HRMS (Orbitrap ESI) calcd for $C_{28}H_{32}O_3NS$ [M + H]$^+$: 462.2097; found, 462.2095.

3m: (4*S*,4a*R*,10b*R*)-4-(4-Bromophenyl)-9-methyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 235 mg, 92%. mp 162−164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 7.7 Hz, 2H), 7.23 (d, J = 7.7 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 4.2 (dd, J = 11.0, 4.4 Hz, 1H), 3.89 (d, J = 9.9 Hz, 1H), 3.56 (t, J = 12.1 Hz, 1H), 3.35 (dd, J = 13.2, 6.6 Hz, 1H), 3.26 (dd, J = 13.2, 11.0 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 3H), 2.12−2.07 (m, 1H), 1.92−1.85 (m, 1H), 1.71−1.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 138.1, 135.9, 135.1, 134.2, 133.4, 131.7, 129.5, 128.7, 127.6, 127.0, 125.4, 124.6, 122.3, 83.1, 67.8, 47.3, 44.4, 37.4, 28.6, 21.5, 21.0. IR (KBr): ν 3029, 2923, 2851, 1596, 1491, 1349, 1220, 1164, 1082, 911, 815, 771 cm^{-1}. MS−ESI: m/z 514 [(M + 2) + H]$^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_3NBrNaS$ [M + Na]$^+$: 534.0709; found, 534.0736.

3n: (4*S*,4a*R*,10b*R*)-4-(4-Chlorophenyl)-9-methyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 221 mg, 95%. mp 144−146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.23−7.18 (m, 4H), 7.06 (d, J = 7.9 Hz, 1H), 6.89 (s, 1H), 4.21−4.16 (m, 1H), 3.89 (d, J = 8.9 Hz, 1H), 3.54 (t, J = 11.9 Hz, 1H), 3.34 (dd, J = 12.9, 5.9 Hz, 1H), 3.27−3.21 (m, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 2.08 (dd, J = 12.9, 2.0 Hz, 1H), 1.87 (dt, J = 10.9, 2.9 Hz, 1H), 1.69−1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 137.6, 135.9, 135.1, 134.3, 133.5, 129.5, 128.8, 128.4, 127.6, 127.0, 125.4, 124.6, 83.0, 67.9, 47.3, 44.5, 37.4, 28.6, 21.5, 21.0. IR (KBr) ν 3029, 2922, 2851, 1598, 1492, 1349, 1221, 1164, 1090, 1015, 997, 911, 817, 768 cm^{-1}. MS−ESI: m/z 468 [M + H]$^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{27}O_3NClS$ [M + H]$^+$: 468.1394; found, 468.1396.

3o: (4*S*,4a*R*,10b*R*)-9-Methyl-4-(3-nitrophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Pale-yellow solid. Yield 179 mg, 75%. mp 191−193 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 7.9 Hz, 1H), 8.15 (s, 1H), 7.64−7.54 (m, 3H), 7.32 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 7.07 (d, J = 7.9 Hz, 1H), 6.91 (s, 1H), 4.2 (dd, J = 11.9, 3.9 Hz, 1H), 4.04 (d, J = 9.9 Hz, 1H), 3.59 (t, J = 11.9 Hz, 1H), 3.40 (dd, J = 12.9, 5.9 Hz, 1H), 3.30−3.24 (m, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 2.13 (d, J = 12.9 Hz, 1H), 2.04−1.97 (m, 1H), 1.69−1.52 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 143.8, 141.3, 135.8, 135.3, 133.5, 133.3, 133.2, 129.5, 127.8, 126.9, 125.4, 124.8, 123.4, 122.0, 82.4, 67.9, 47.1, 44.0, 37.7, 28.7, 21.5, 21.0. IR (KBr): ν 3027, 2923, 2854, 1597, 1530, 1493, 1349, 1221, 1164, 1087, 813, 766, 686 cm^{-1}. MS−ESI: m/z 501 [M + Na]$^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{26}O_5N_2$ NaS [M + Na]$^+$: 501.1454; found, 501.1456.

3p: (4*S*,4a*R*,10b*R*)-9-Methyl-4-(*p*-tolyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Off-white solid. Yield 201 mg, 90%. mp 141−143 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.6 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.17−7.11 (m, 4H), 7.05 (d, J = 7.1 Hz, 1H), 6.89 (s, 1H), 4.18 (dd, J = 11.2, 4.0 Hz, 1H), 3.85 (d, J = 10.2 Hz, 1H), 3.56−3.50 (m, 1H), 3.37 (dd, J = 13.2, 7.1 Hz, 1H), 3.26−3.21 (m, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H), 2.08−2.03 (m, 1H), 1.84 (dt, J = 11.2, 3.0, Hz 1H), 1.69−1.58 (m, 2H). ^{13}C NMR (75 MHz,

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$CDCl_3$): δ 143.4, 138.2, 136.0, 135.0, 134.6, 133.5, 129.4, 129.2, 127.5, 127.0, 126.9, 125.4, 124.6, 83.7, 67.8, 47.5, 44.3, 37.5, 28.7, 21.4, 21.1, 21.0. IR (KBr): ν 3448, 3028, 2960, 2916, 2846, 1597, 1491, 1341, 1160, 1075, 1051, 992, 922, 882, 815, 684 cm^{-1}. MS−ESI: *m*/*z* 448 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{27}H_{29}O_3NNaS$ $[M + Na]^+$: 470.1760; found, 470.1781.

3q: (4*S*,4a*R*,10b*R*)-4-(3-Fluorophenyl)-9-methyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. White solid. Yield 198 mg, 88%. mp 141−142 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 7.1 Hz, 2H), 7.08−7.01 (m, 4H), 6.95 (d, *J* = 10.2 Hz, 1H), 6.90 (s, 1H), 4.19 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.90 (d, *J* = 9.2 Hz, 1H), 3.58−3.52 (m, 1H), 3.40 (dd, *J* = 13.2, 5.1 Hz, 1H), 3.27−3.22 (m, 1H), 2.42 (s, 3H), 2.34 (s, 3H), 2.09 (d, *J* = 13.2 Hz, 1H), 1.95−1.89 (m, 1H), 1.67−1.60 (m, 1H), 1.53−1.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 161.2, 143.6, 141.5, 141.6, 135.8, 135.1, 133.9, 133.4, 130.2, 130.0, 129.5, 127.7, 126.9, 125.4, 124.7, 122.8, 115.6, 115.3, 114.0, 113.7, 83.0, 67.9, 47.2, 44.0, 37.6, 28.7, 21.5, 21.0. IR (KBr): ν 3029, 2923, 2851, 1593, 1492, 1449, 1349, 1245, 1219, 1164, 1106, 1084, 814, 771 cm^{-1}. MS−ESI: *m*/*z* 452 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{27}O_3NFS$ $[M + H]^+$: 452.1690; found, 452.1686.

3r: (4*S*,4a*R*,10b*R*)-4-(4-Methoxyphenyl)-9-methyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Yellow solid. Yield 180 mg, 78%. mp 154−156 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.6 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.90−6.86 (m, 3H), 4.17 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.86−3.79 (m, 4H), 3.56−3.50 (m, 1H), 3.37 (dd, *J* = 13.0, 6.0 Hz, 1H), 3.26−3.19 (m, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 2.05 (d, *J* = 13.0 Hz, 1H), 1.86−1.80 (m, 1H), 1.68−1.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 143.4, 136.0, 135.1, 134.7, 133.5, 131.2, 129.4, 128.2, 127.5, 127.0, 125.4, 124.6, 114.0, 83.4, 67.9, 55.2, 47.5, 44.5, 37.5, 28.7, 21.5, 21.0. IR (KBr): ν 2924, 2844, 1611, 1513, 1493, 1349, 1249, 1164, 1092, 1034, 818, 771 cm^{-1}. MS−ESI: *m*/*z* 464 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{27}H_{30}O_4NS$ $[M + H]^+$: 464.1890; found, 464.1889.

3s: (4*S*,4a*R*,10b*R*)-9-Methyl-4-(naphthalen-2-yl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Off-white solid. Yield 193 mg, 80%. mp 145−147 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.86−7.82 (m, 3H), 7.73 (s, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.50−7.48 (m, 2H), 7.38−7.34 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 4.24 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.08 (d, *J* = 10.0, 1H), 3.64−3.58 (m, 1H), 3.39−3.30 (m, 2H), 2.41 (s, 3H), 2.35 (s, 3H), 2.14−2.09 (m, 1H), 1.97−1.91 (m, 1H), 1.78−1.67 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 136.4, 136.0, 135.1, 134.5, 133.5, 133.4, 133.1, 129.4, 128.5, 128.0, 127.6, 127.0, 126.3, 126.2, 126.1, 125.4, 124.7, 124.5, 83.9, 67.9, 47.5, 44.3, 37.5, 28.7, 21.4, 21.0. IR (KBr): ν 3028, 2922, 2851, 1599, 1492, 1348, 1218, 1164, 101, 995, 898, 816, 753 cm^{-1}. MS−ESI: *m*/*z* 484 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{30}H_{30}O_3NS$ $[M + H]^+$: 484.1940; found, 484.1940.

3t: (4*R*,4a*R*,10b*R*)-9-Methyl-4-propyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-*c*]quinoline. Colorless oil. Yield 149 mg, 75%. ^1H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.3 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.09−7.03 (m, 1H), 6.81 (s, 1H), 4.14−4.04 (m, 1H), 3.85−3.77 (m, 1H), 3.35−3.25 (m, 2H), 2.97−2.90 (m, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 1.95−1.89 (m, 1H), 1.55−1.44 (m, 3H), 1.36−1.23 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 135.8, 135.5, 135.1, 133.2, 129.4, 127.4, 126.8, 125.6, 124.4, 80.4, 67.1, 47.5, 43.7, 36.5, 35.2, 28.4, 21.4, 21.1, 18.2, 14.0. IR (neat): ν 3450, 2957, 2870, 1598, 1493, 1459, 1350, 1165, 1095, 916, 815, 757, 656 cm^{-1}. MS−ESI: *m*/*z* 400 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{23}H_{30}O_3NS$ $[M + H]^+$: 400.1940; found, 400.1948.

3u: (4*R*,4a*R*,10b*R*)-9-Methyl-4-propyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-thiopyrano[3,4-*c*]quinoline. Colorless oil. Yield 145 mg, 70%. ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.9 (s, 1H), 4.19−4.12 (m, 1H), 3.26 (dd, *J* = 13.5, 10.5 Hz, 1H), 2.66−2.48 (m, 4H), 2.43 (m, 1H), 2.39 (s, 3H), 2.32 (s, 3H), 1.78−1.61 (m, 2H), 1.55−1.26 (m, 4H), 0.94 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 136.4, 135.3, 134.8, 133.6, 129.4, 127.4, 127.0, 125.7, 125.5, 48.7, 46.6, 44.9, 39.9, 34.3, 31.3, 29.6, 28.4, 21.5, 21.1, 19.6, 14.0. IR (KBr): ν 3446, 3027, 2958, 2931, 2869, 1925, 1597, 1493, 1454, 1350, 1292, 1164, 1070, 872, 827, 708, 676 cm^{-1}. MS−ESI: *m*/*z* 438 $[M + Na]^+$. HRMS (Orbitrap ESI) calcd for $C_{23}H_{30}O_2NS_2$ $[M + H]^+$: 416.1712; found, 416.1706.

3v: (4*S*,4a*R*,10b*R*)-9-Methyl-4-(3-nitrophenyl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-thiopyrano[3,4-*c*]quinoline. White solid. Yield 185 mg, 75%. mp 160−162 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.23−8.15 (m, 2H), 7.63−7.53 (m, 3H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.01 (s, 1H), 3.68−3.57 (m, 2H), 3.10−3.00 (m, 1H), 2.97−2.86 (m, 1H), 2.77 (td, *J* = 13.5, 3.7 Hz, 1H), 2.67−2.58 (m, 1H), 2.44 (s, 3H), 2.35 (s, 3H), 2.12−2.03 (m, 1H), 1.95 (dt, *J* = 10.5, 4.5 Hz, 1H), 1.62−1.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 143.9, 141.0, 136.4, 135.4, 134.3, 133.8, 132.9, 129.9, 129.6, 127.8, 127.0, 126.1, 125.5, 123.2, 122.8, 50.3, 48.5, 44.3, 40.9, 31.4, 30.3, 21.5, 21.1. IR (KBr): ν 3447, 2922, 1596, 1530, 1493, 1349, 1156, 1089, 812, 678 cm^{-1}. MS−ESI: *m*/*z* 517 $[M + Na]^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{27}O_4N_2S_2$ $[M + H]^+$: 495.1406; found, 495.1407.

3w: (4*S*,4a*R*,10b*R*)-4-(4-Chlorophenyl)-9-methyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-thiopyrano[3,4-*c*]quinoline. White solid. Yield 217 mg, 90%. mp 180−182 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.27−7.18 (m, 4H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.99 (s, 1H), 3.56−3.51 (m, 2H), 3.10−3.04 (m, 1H), 2.88−2.81 (m, 1H), 2.76−2.71 (m, 1H), 2.61−2.56 (m, 1H), 2.42 (s, 3H), 2.34 (s, 3H), 2.00−1.91 (m, 2H), 1.65−1.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 137.2, 136.5, 135.3, 133.9, 133.7, 133.6, 129.5, 129.3, 129.0, 127.6, 127.1, 125.8, 125.4, 50.6, 48.5, 45.0, 40.6, 31.2, 30.2, 21.5, 21.1. IR (KBr): ν 3448, 2971, 1596, 1492, 1337, 1159, 1090, 883, 816, 680 cm^{-1}. MS−ESI: *m*/*z* 506 $[M + Na]^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{27}O_2NClS_2$ $[M + H]^+$: 484.1166; found, 484.1169.

3x: (4*S*,4a*S*,10b*R*)-4-(4-Chlorophenyl)-9-methyl-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-thiopyrano[3,4-c]quinoline. Yellow solid. Yield 205 mg, 85%. mp 85−87 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, *J* = 6.5, 1.9 Hz, 2H), 7.23−7.20 (m, 2H), 7.15−7.08 (m, 4H), 7.00 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 4.16 (d, *J* =3.0 Hz, 1H), 4.00 (dd, *J* = 13.2, 12.0 Hz, 1H), 3.75−3.70 (m, 1H), 2.86−2.79 (m, 1H), 2.69−2.59 (m, 2H), 2.37 (s, 3H), 2.28 (s, 3H), 2.05−2.00 (m, 1H), 1.79−1.73 (m, 1H), 1.28−1.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 138.1, 135.6, 134.0, 133.4, 133.0, 129.4, 129.2, 128.9, 128.7, 128.0, 127.1, 123.6, 49.3, 42.3, 41.2, 37.5, 30.0, 29.7, 21.4, 20.6. IR (KBr): ν 3453, 2921, 1657, 1597, 1492, 1349, 1163, 1089, 1053, 815, 670, 552 cm^{-1}. MS−ESI: *m*/*z* 484 $[M + H]^+$. HRMS (Orbitrap ESI) calcd for $C_{26}H_{27}O_2NClS_2$ $[M + H]^+$: 484.1166; found, 484.1165.

3y: (4*S*,4a*R*,10b*R*)-4-(Thiophen-2-yl)-6-tosyl-2,4,4a,5,6,10b-hexahydro-1*H*-pyrano[3,4-c]quinoline. Off-white solid. Yield 201 mg, 95%. mp 152−154 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.32 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 4.8 Hz, 1H), 7.28−7.24 (m, 1H), 7.23−7.16 (m, 3H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 7.00−6.97 (m, 1H), 4.24 (d, *J* = 9.6 Hz, 1H), 4.22−4.18 (m, 1H), 3.59−3.53 (m, 2H), 3.35−3.30 (m, 1H), 2.40 (s, 3H), 2.09−2.05 (m, 1H), 1.89−1.82 (m, 1H), 1.77−1.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 141.8, 136.1, 135.8, 134.6, 129.5, 127.0, 126.9, 126.5, 125.8, 125.6, 125.4, 123.9, 78.8, 67.9, 47.6, 45.6, 37.3, 28.2, 21.5. IR (KBr): ν 3455, 2967, 2913, 2842, 1598, 1486, 1448, 1341, 1314, 1161, 1096, 1069, 1038, 990, 769, 701, 662, 562, 540 cm^{-1}. MS−ESI: *m*/*z* 448 $[M + Na]^+$. HRMS (Orbitrap ESI) calcd for $C_{23}H_{24}O_3NS_2$ $[M + H]^+$: 426.1192; found, 426.1183.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray data for compounds **3d** and **3i** in CIF format. NOESY and DQFCOSY study of **3j**, **3q**, and **3x**. ^1H and ^{13}C NMR spectra of products **3a**−**3y**, **1a**, **1g**, **1l**, **1u**, and **1x**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) The crystallographic data (in CIF format) and the respective ORTEP diagram for the compound has been provided in the Supporting Information. CCDC 901997 contains the crystallographic data for structure **3d**. CCDC 922656 contains the crystallographic data for structure **3i**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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