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Synthesis of rodocaine

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ABSTRACT

A new method for synthesis of rodocaine (**1**) is presented. Two key steps were carried out by the *N*-bromosuccinimide (NBS)-mediated intermolecular addition of known enamine **5** with allyltrimethyl silane in presence of boron trifluoride etherate (BF_3/OEt_2) and the intramolecular ring-closing metathesis of triene **3**. The Diels–Alder cycloaddition of triene **3** with different ethyl propiolates was also studied.

1. Introduction

In preliminary studies,[1] we explored various reactions for preparing a series of interesting structural frameworks, including benzoisoquinoline, benzonaphthyridine, and 4-aryl-3-fluoropiperidine by 4-aryl-1,2,5,6-tetrahydropyridine. The basic skeleton of 4-aryl-1,2,5,6-tetrahydropyridine was easily synthesized from 4-hydroxypiperidine in high yields through sulfonation, Jones oxidation, Grignard addition, and dehydration. In order to continue our investigation on the skeleton of hydroxyl piperidine, 3-hydroxypiperidine was chosen to demonstrate the synthetic utility of our methodology. Herein, the synthesis of rodocaine (**1**) with a tetrahydropyrindine skeleton is reported. Rodocaine (**1**) is an ophthalmic anesthesia, which has attracted considerable attention due to its chemical structure and pharmacological properties.[2,3] To date, there are few reports on the synthesis of rodocaine (**1**) citations. Recently, Vasse et al. reported the novel synthesis of rodocaine (**1**) using the tandem hydrozirconation/Lewis acid-mediated cyclization sequence as the key steps.[2a] Lochte and Pittman developed a facile synthetic approach from the monocyanoethylation of the Stork enamine of cyclopentanone to the core of rodocaine (**1**) (Fig. 1).[2f]

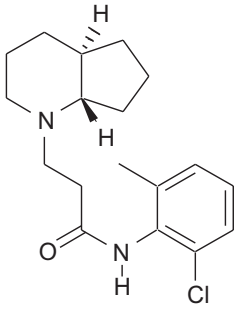

Fig. 1. Structure of rodocaine (**1**).

2. Results and discussion

Our approach to the synthesis of rodocaine (**1**) is shown in Scheme 1. An octahydropyrindine skeleton is expected to be achieved through (i) the intramolecular ring-closing metathesis of triene **3** with Grubbs' catalyst, (ii) a simple transformation from β-bromoacetate **4** to triene **3** via reduction, mesylation and elimination, and (iii) the intermolecular addition of enamine **5** with allyltrimethyl silane.

The known compound **5** was prepared in a facile four-step protocol, and it was chosen as a reasonable starting material in the synthesis of rodocaine (**1**) (Scheme 2).[1d] The synthesis of compound **5** is described as follows. 3-Hydroxypiperidine was treated with benzenesulfonyl chloride and triethylamine to produce *N*-benzenesulfonyl-3-piperidinol **6**. Jones oxidation of the resulting piperidinol **6** yielded piperidin-3-one **7**. The Wittig olefination of ketone **7** with ethyl triphenylphosphoranylidene acetate ($Ph_3P{=}CHCO_2Et$) gave α,β-unsaturated ester **8** a mixture of *E*-form

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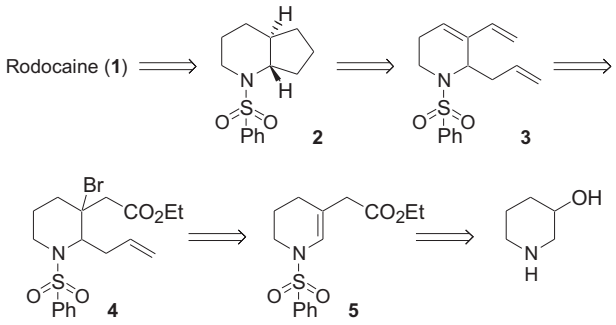
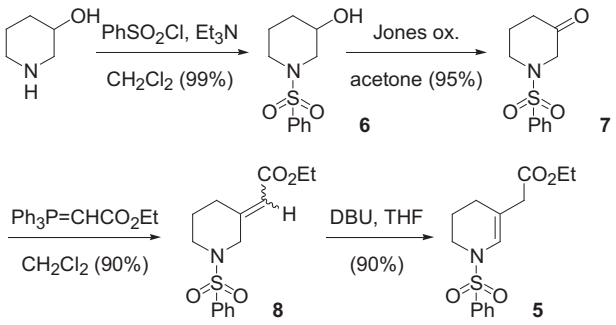


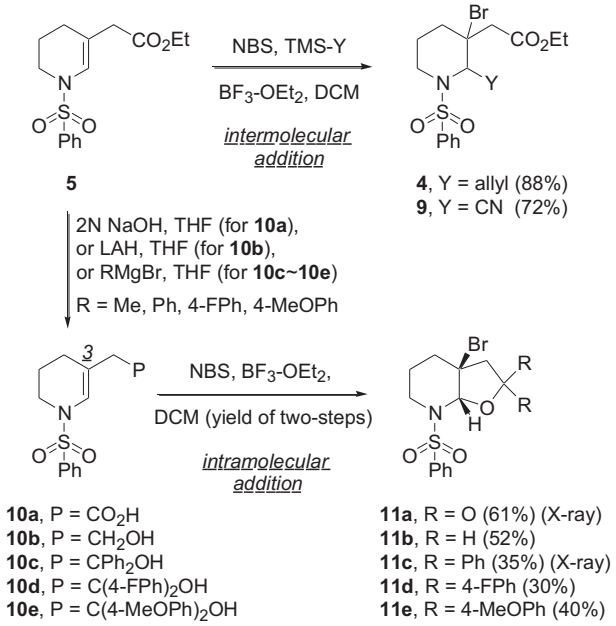
Scheme 1. Retrosynthesis of rodocaine (**1**).

isomer and *Z*-form isomer (a ratio of 2: 1). Furthermore, the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated deconjugation of skeleton **7** provided a sole β,γ-unsaturated ester **5** with a high yield of 90%.



Scheme 2. Synthesis of compound **5**.

Next, β-bromoacetate **4** resulted in a sole isomer through an NBS-mediated intermolecular addition reaction of the enamine **5** with BF_3/OEt_2 in the co-solvent of allyltrimethyl silane and DCM at rt (Scheme 3). After changing the trimethylsilyl-based nucleophile into trimethylsilyl cyanide, a sole isomer **9** was also isolated through an intermolecular addition reaction. The NBS-mediated intermolecular addition with allyltrimethyl silane in the presence of BF_3/OEt_2 had been developed in previous work.[1d] To explore the NBS-mediated intramolecular addition reaction with allyltrimethyl silane in the presence of BF_3/OEt_2, different enamine skeleton **10** was prepared. Under the abovementioned conditions, attempts to perform an intramolecular addition reaction of skeleton **10** with a carboxyl group, a primary hydroxyl group, or a tertiary hydroxyl group side chain on the C-3 position provided moderate yields.[4] Skeleton **10** with a structural framework of octahydrofuro[2,3-*b*] pyridine was easily generated from compound **5** via base-induced hydrolysis (for **10a**), lithium aluminum hydride-mediated reduction (for **10b**), or Grignard addition with the aryl group (for **10c**, R=Ph; for **10d**, R=4-FPh; for **10e**, R=4-MeOPh).



Scheme 3. Synthesis of skeletons **4**, **9** and **11**.

This methodology showed a concise and efficient synthetic route to construct 2,3-disubstituted piperidines **4** and **9**, and five bicyclic octahydrofuro[2,3-*b*]pyridines **11a**–**e** from compound **5** via the NBS-mediated intermolecular or intramolecular addition in the presence of BF_3/OEt_2. This distribution of the overall yield suggested that the diarylmethanoyl group with a slightly steric hindrance could not be easily introduced into the bromonium ion, and the resulting products **11c**–**e** could only be generated in 30–40% yields. The structures of compounds **11a** and **11c** were determined by single-crystal X-ray analysis (for **11c**, see Fig. 2).[5] This typical experimental procedure has afforded a general and efficient alternative to the skeleton of 2,3-disubstituted 3-bromopiperidine.

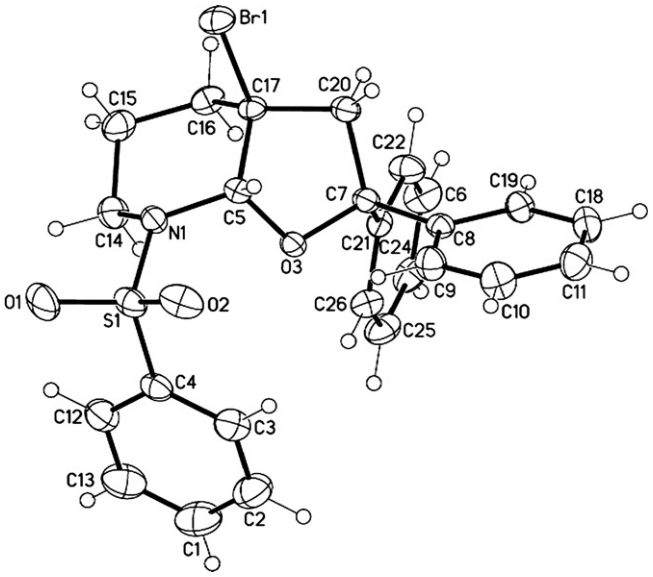
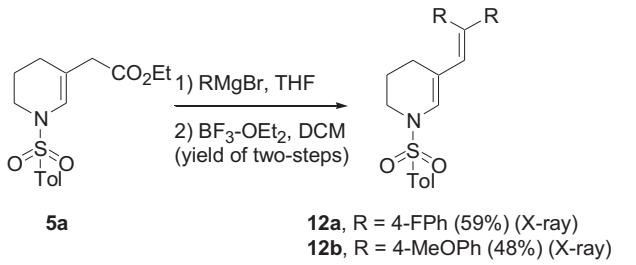


Fig. 2. X-ray structure of compound **11c**.

As shown in Scheme 4, the BF_3/OEt_2-mediated reaction of the tertiary alcohols (from the Grignard reaction of compound **5a**, R=4-FPh and 4-MeOPh) without the addition of NBS afforded dienylamines **12a** and **12b** in 59% and 48% yields in a two-step reaction[1d] The conjugated skeleton with an electronic 'push–pull' nature was isolated as a sole conformer. The synthetic procedure of compound **5a** was the same as that for compound **5**. This typical experimental procedure offered a facile alternative to the skeleton of 3-diarylmethenyl-1,2,3,4-tetrahydropyridine. The structures of compounds **12a** and **12b** were determined by single-crystal X-ray analysis (for **12a**, see Fig. 3).[5]

Based on the known results, the reduction reaction of compound **4** was then undertaken (Scheme 5 and Table 1). Attempts to perform the reaction with different reducing reagents (i.e., $LiBH_4$ or $LiAlH_4$) and under different reaction conditions (−78 °C, 0 °C or rt) afforded complex mixtures due to the factor of the 3-bromo group on the piperidine skeleton (entries 1–4). When the reduction of



Scheme 4. Synthesis of skeleton **12**.

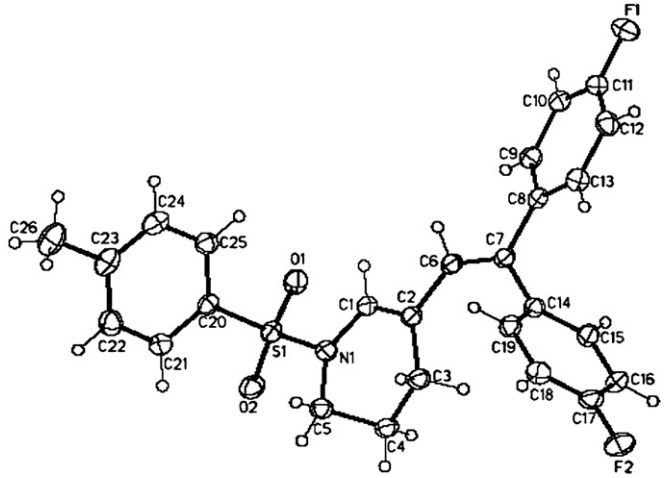
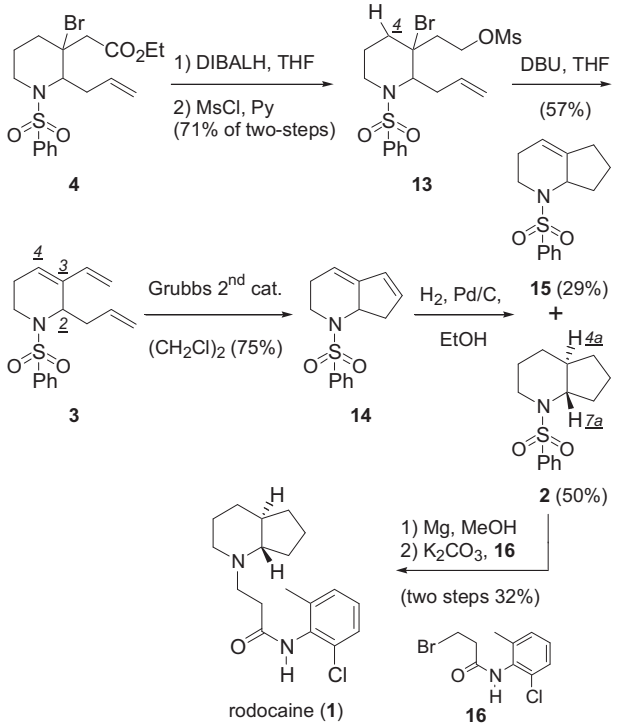


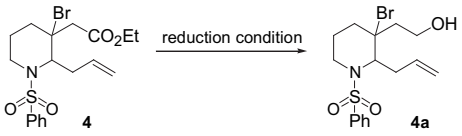
Fig. 3. X-ray structure of compound **12a**.

compound **4** was treated with diisobutylaluminium hydride (DIBALH) in THF (entries 5–6) at 0 °C or rt, crude primary alcohol **4a** was smoothly obtained in 50% or 84% yield. Noticeably, β-bromoalcohol **4a** was unstable via the column purification. Without purification, mesylation of the resulting alcohol **4a** with methanesulfonyl chloride (MsCl) in pyridine provided mesylate **13** in a 71% yielded in a two-step reaction.



Scheme 5. Synthesis of rodocaine (**1**).

Table 1
Reduction reaction of compound **4**[a]



Entry	Condition (reagents, solvent, temp, time)	Results[b,c]
1	$LiAlH_4$ (3.0 equiv), THF, rt, 1 h	Complex
2	$LiAlH_4$ (3.0 equiv), THF, 0 °C, 3 h	Complex
3	$LiAlH_4$ (3.0 equiv), THF, −78 °C, 5 h	Complex
4	$LiBH_4$ (3.0 equiv), THF, −78 °C, 5 h	Complex
5	DIBALH (3.0 equiv), THF, 0 °C, 3 h	50%
6	DIBALH (5.0 equiv), THF, rt, 5 h	84%

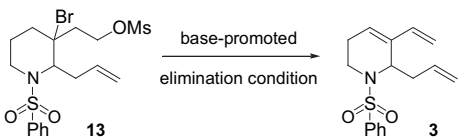
[a] The reactions were run on a 0.3 mmol scale with **4**.
[b] The results were determined by ^1H NMR analysis.
[c] The provided yields were based on the crude products **4a**.

In order to investigate the one-pot dehydrobromination and dehydromesylation reaction, some commercial tertiary amines were tested under a number of conditions (prolonged reaction time and different solvents). When compound **13** was treated with 4-dimethylaminopyridine (DMAP) in THF at reflux, the complex mixture was isolated (entry 1). For the treatment of compound **13** with triethylamine (Et_3N) in THF at reflux, the starting material **13** was recovered as the major product (entries 2–3). During the experimental procedures, compound **3** was generated in a 57% yield by an excess amount of DBU at reflux (entry 4). Two new olefins were formed via the concise dehydrobromination and dehydromesylation (Table 2).

In other words, the unique trienyl isomer **3** possessed a C-2 allyl group and a conjugated diene functional group with a C-3 vinyl group and an *endo*-olefinic group at the C3 and C4 positions. For the reaction condition, we found that DBU provided better regioselectivity and a moderate yield for the double elimination reaction. We expected the DBU (a bulky base) to be used to trap C-4 hydrogen with less steric hindrance via the initial dehydrobromination reaction. When the resulting olefinic group was formed in the position of C-3 and C-4, the dehydromesylation reaction was initiated to generate the C-3 vinyl group. This study verified that DBU can serve as a better base for the sequential regioselective elimination.

To construct the octahydropyrindine skeleton, compound **3** was subjected to a ring-closing metathesis (RCM) reaction.[6] When compound **3** was subjected to a ring-closing metathesis reaction

Table 2
Base-promoted elimination reaction of compound **13**[a]

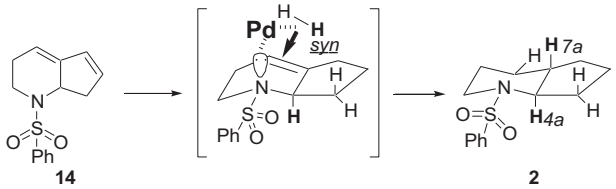


Entry	Condition (reagents, solvent, temp, time)	Results[b,c]
1	DMAP (3.0 equiv), THF, reflux, 2 h	Complex
2	Et_3N (3.0 equiv), THF, reflux, 2 h	No reaction
3	Et_3N (5.0 equiv), THF, reflux, 5 h	No reaction
4	DBU (5.0 equiv), THF, reflux, 5 h	57%

[a] The reactions were run on a 0.19 mmol scale with **13**.
[b] The results were determined by ^1H NMR analysis.
[c] The provided yields were based on the isolated products.

employing a first generation Grubbs' catalyst, the expected bicyclic skeleton **14** was generated in low yield (ca. 12%). During the ring closure process, compound **3** could be affected by Grubbs' first catalyst, as isomerization of the double bond occurred. The ring strain existing in the desired 5,6-fused product might retard the normally facile cyclization. We then checked the second generation Grubbs' catalyst, which has higher thermal stability and lower sensitivity to double bond migration. Using a similar reaction condition, treatment of compound **3** with Grubbs' second catalyst produced compound **14** with a moderate yield (75%) in 1,2-dichloroethane at reflux for 1 h. Compound **14** exhibited a conformationally restricted character of *s*-trans diene conformer.

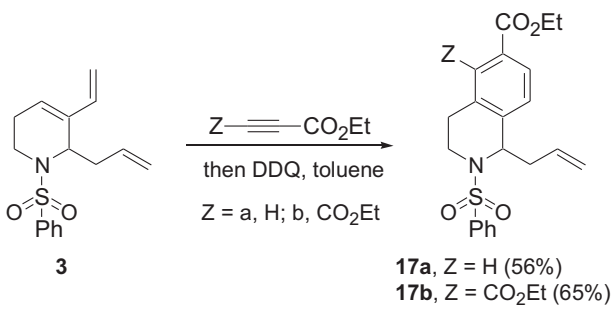
The hydrogenation reaction was then achieved by treatment of compound **14** with hydrogen on 10% Pd-activated carbon in ethanol to yield compound **2** at a yield of 50%.[7] In particular, partially hydrogenated compound **15** was isolated at a yield of 29%. To increase the overall yield of rodocaine (**1**), treatment of compound **15** with hydrogen and palladium hydroxide on carbon (Pearlman's catalyst) transformed to rodocaine core **2** as the major product (76%). The stereochemical outcome in this case implied that the sulfonylamino group-directed hydrogenation,[7a,b] wherein the substrate was bound to the catalyst surface on the same side, thereby resulting in the addition of hydrogen *syn* to the coordinating moiety (Scheme 6).



Scheme 6. Stereochemical assignments of compound **2**.

Although the ^{1}H and ^{13}C NMR spectral data of compound **2** with the benzenesulfonyl group were similar to the core skeleton with the *tert*-butyloxycarbonyl group reported in the literature,[2a] the authentic stereochemical center of the bicyclo [4.3.0] ring junction was still re-examined. Because the *trans*-stereochemistry of core **2** at the ring juncture was not evident from a 2D $^{1}H-^{1}H$ NOESY NMR revealing the NOE enhancement between H-4a and H-7a, compound **2** was further converted into target 1 for comparing the real structure in the next stage. Following the procedure suggested by previous literature,[8] desulfonation of compound **2** with magnesium in methanol and coupling of the resulting amine with bromide **16** afforded the target rodocaine (**1**) in a 32% overall yield in a two-step reaction. The ^{1}H and ^{13}C NMR spectra of the racemic rodocaine (**1**) were identical to those reported by Professor Jean-Luc Vasse.

For exploring the synthetic application of compound **3**, the Diels–Alder cycloaddition of diene **3** with alkyne was then studied (Scheme 7). Two propiolate analogs were chosen as the dienophile. When compound **3** was subjected to a regioselective Diels–Alder cycloaddition employing two ethyl propiolates (Z=a, H; b, CO_2Et),



Scheme 7. Diels–Alder cycloaddition of compound **3** with two propiolates.

the expected bicyclic skeleton was generated. The total synthetic procedure was monitored by TLC until the reaction was complete. Without further purification, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was further added to the reaction mixture and two compounds, **17a** and **17b**, with the skeleton of 1-allyl-1,2,3,4-tetrahydroisoquinoline were isolated in 56% and 65% yields, respectively, in a two-step reaction. This typical experimental procedure has afforded a general and efficient alternative to the synthesis of tetrahydroisoquinoline.

3. Conclusion

In summary, we present a simple synthesis of rodocaine (**1**) via the NBS-mediated intermolecular cross coupling of enamine **5** with allyltrimethyl silane in presence of BF_3/OEt_2 and the intramolecular ring-closing metathesis of triene **3**. The Diels–Alder cycloaddition of triene **3** with different ethyl propiolate was also studied. This method started from simple starting material and reagents and provided a potential intermediate for chemical biology research.

4. Experimental section

4.1. General

Tetrahydrofuran (THF) was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus. Infrared spectra were recorded with a Perkin–Elmer 100 series FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 200/400 and at 50/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN–OS–Rapid Analyzer or Elementar Vario EL III.

4.2. (1-Benzenesulfonyl-1,4,5,6-tetrahydro-pyridin-3-yl)-acetic acid ethyl ester (5)[1d]

A solution of benzenesulfonyl chloride (1.87 g, 10.6 mmol) in DCM (5 mL) was added to a rapidly stirred solution of 3-hydroxypiperidine (1.01 g, 10.0 mmol) and triethylamine (3.3 g, 32.6 mmol) in DCM (20 mL) at ice bath. The mixture was stirred at rt for 5 h, and the reaction was concentrated under reduced pressure. Water (20 mL) was added to the residue and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product **6**. Recrystallization from EtOAc and hexane yielded compound **6** (2.39 g, 99%) under reduced pressure. Without further purification, excess Jones reagent was added to a solution of the crude product **6** (2.40 g, 10.0 mmol) in acetone (30 mL) at ice bath. The mixture was stirred at rt for 30 min, and the reaction mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Recrystallization from EtOAc and hexane yielded the compound **7** (2.26 g, 95%) as a white solid. Mp=77–78 °C (recrystallized from hexane and EtOAc); IR ($CHCl_3$) 3320, 2910, 1745, 1120 cm^{-1}; ^{1}H NMR (200 MHz):

δ 7.80–7.76 (m, 2H), 7.62–7.55 (m, 3H), 3.62 (s, 2H), 331 (t, *J*=6.0 Hz, 2H), 2.34 (t, *J*=6.0 Hz, 2H), 2.05–2.02 (m, 2H). A solution of compound **7** (2.2 g, 9.2 mmol) in DCM (5 mL) was added to a rapidly stirred solution of ethyl triphenylphosphoranylidene acetate (3.48 g, 10.0 mmol) in DCM (10 mL), then stirred at reflux for 4 h. The resulting mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=10/1) afforded compound **8** (2.56 g, 90%) with *E*-form isomer and *Z*-form isomer (a ratio of 2: 1). Colorless oil; IR ($CHCl_3$) 3325, 2932, 1762, 1141 cm^{-1}; For *E*-form isomer: ^1H NMR (200 MHz): δ 7.80–7.75 (m, 2H), 7.60–7.51 (m, 3H), 5.68 (s, 1H), 4.32 (s, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 3.33–3.18 (m, 2H), 2.22 (t, *J*=6.0 Hz, 2H), 1.81–1.73 (m, 2H), 1.29 (t, *J*=7.2 Hz, 3H). For *Z*-form isomer: ^1H NMR (200 MHz): δ 7.80–7.75 (m, 2H), 7.60–7.51 (m, 3H), 5.78 (s, 1H), 4.32 (s, 2H), 4.18 (q, *J*=7.2 Hz, 2H), 3.33–3.18 (m, 2H), 2.80 (t, *J*=6.0 Hz, 2H), 1.81–1.73 (m, 2H), 1.26 (t, *J*=7.2 Hz, 3H). DBU (1.2 g, 7.9 mmol) was added to a solution of compound **8** (2.16 g, 7.0 mmol) in THF (10 mL) at rt. The mixture was stirred at reflux for 2 h, and the reaction mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=10/1) afforded compound **5** (1.94 g, 90%). Colorless oil; IR ($CHCl_3$) 3342, 2921, 1761, 1132 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{15}H_{20}NO_4S$ 310.1113, found 310.1112; ^1H NMR (200 MHz): δ 7.80–7.74 (m, 2H), 7.68–7.49 (m, 3H), 6.61 (s, 1H), 4.10 (q, *J*=6.8 Hz, 2H), 3.33 (t, *J*=5.8 Hz, 2H), 2.94 (s, 2H), 1.94 (t, *J*=5.8 Hz, 2H), 1.67–1.60 (m, 2H), 1.22 (t, *J*=6.8 Hz, 3H).

4.3. (2-Allyl-1-benzenesulfonyl-3-bromo-piperidin-3-yl)-acetic acid ethyl ester (4) and (1-benzenesulfonyl-3-bromo-2-cyano-piperidin-3-yl)-acetic acid ethyl ester (9)

NBS (400 mg, 2.2 mmol) was added to a solution of compound **5** (620 mg, 2.0 mmol) in the co-solvent of DCM (10 mL) and trimethylsilane cyanide (for **9**, 3 mL) or allyltrimethyl silane (for **4**, 3 mL) at rt. The reaction mixture was stirred at rt for 5 min. A solution of BF_3/OEt_2 (~4.0 mmol, 0.5 mL) in DCM (5 mL) was added to a stirred solution of the reaction mixture at ice bath. The reaction mixture was stirred at rt for 5 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=10/1) afforded compound **4** (755 mg, 88%) or compound **9** (600 mg, 72%). For compound **4**: Colorless oil; IR ($CHCl_3$) 3342, 2927, 1768, 1182 cm^{-1}; HRMS (ESI, M^++Na) calcd for $C_{18}H_{24}BrNO_4SNa$ 452.0507, found 452.0505; ^1H NMR (400 MHz): δ 7.91–7.88 (m, 2H), 7.54–7.49 (m, 1H), 7.47–7.42 (m, 2H), 5.84–5.73 (m, 1H), 5.06–4.96 (m, 2H), 4.20 (dq, *J*=1.6, 7.2 Hz, 2H), 3.3.68 (ddd, *J*=1.6, 3.2, 12.8 Hz, 1H), 2.93 (d, *J*=15.6 Hz, 1H), 2.85 (d, *J*=15.6 Hz, 1H), 2.51–2.44 (m, 1H), 2.39–2.31 (m, 1H), 2.12–2.07 (m, 2H), 1.98–1.74 (m, 3H), 1.55–1.50 (m, 1H), 1.29 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 168.66, 141.05, 134.00, 132.14, 128.45 (2×), 127.61 (2×), 117.74, 66.65, 62.09, 60.95, 47.66, 39.51, 34.47, 32.79, 21.62, 14.14; Anal. Calcd for $C_{18}H_{24}BrNO_4S$: C, 50.24; H, 5.62; N, 3.25. Found: C, 50.43; H, 5.89; N, 3.54. For compound **9**: Colorless oil; IR ($CHCl_3$) 3346, 2930, 2154, 1758, 1132 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{16}H_{20}BrN_2O_4S$ 415.0327, found 415.0330; ^1H NMR (400 MHz): δ 7.88–7.83 (m, 2H), 7.67–7.63 (m, 1H), 7.60–7.56 (m, 2H), 5.76 (s, 1H), 4.26 (q, *J*=7.2 Hz, 2H), 3.91 (dd, *J*=3.6, 12.8 Hz, 1H), 3.13 (d, *J*=16.4 Hz, 1H), 3.05 (d, *J*=16.4 Hz, 1H), 2.78 (dt, *J*=2.8, 12.8 Hz, 1H), 2.27–2.08 (m, 2H), 1.82–1.71 (m, 2H), 1.33 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 168.11, 137.01, 133.67, 129.33 (2×), 127.69, 127.62, 112.44, 61.52, 59.37, 54.84, 46.82, 42.10, 35.76, 21.31, 14.10.

4.4. 7-Benzenesulfonyl-3a-bromo-hexahydrofuro[2,3-*b*] pyridin-2-one (11a)

A solution of compound **5** (155 mg, 0.5 mmol) and $NaOH_{(aq)}$ (2 N, 5 mL) in THF (10 mL) was refluxed for 6 h. The reaction was traced by TLC until compound **5** was completely consumed. The reaction solution was cooled to rt and concentrated until one third of the solution remained. The remained solution was extracted with EtOAc (3×10 mL). The aqueous phase was cooled in ice bath and acidified by adding concentrated $HCl_{(aq)}$ to pH 2. The aqueous solution was extracted with EtOAc (3×20 mL), and the extracts were washed with brine. The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product **10a** under reduced pressure. Without further purification, NBS (98 mg, 0.55 mmol) was added to a solution of crude product **10a** in DCM (10 mL) at rt. The reaction mixture was stirred at rt for 5 min. A solution of BF_3/OEt_2 (~0.8 mmol, 0.1 mL) in DCM (1 mL) was added to a stirred solution of the reaction mixture at ice bath. The reaction mixture was stirred at rt for 5 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=5/1) afforded compound **11a** (110 mg, 61% of two-step). White solid; mp=98–100 °C (recrystallized from hexane and EtOAc); IR ($CHCl_3$) 3328, 2937, 1771, 1394, 1174 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{13}H_{15}BrNO_4S$ 359.9905, found 359.9905; ^1H NMR (400 MHz): δ 7.90–7.87 (m, 2H), 7.64–7.60 (m, 1H), 7.56–7.51 (m, 2H), 6.35 (s, 1H), 3.73–3.69 (m, 1H), 3.21 (d, *J*=16.4 Hz, 1H), 2.95 (d, *J*=16.4 Hz, 1H), 2.73 (dt, *J*=2.8, 12.8 Hz, 1H), 2.23–2.18 (m, 1H), 2.06–1.94 (m, 1H), 1.79–1.65 (m, 2H); ^{13}C NMR (100 MHz): δ 169.84, 137.79, 133.48, 129.17 (2×), 127.89 (2×), 89.87, 52.83, 47.66, 39.71, 34.27, 20.44; Anal. Calcd for $C_{13}H_{14}BrNO_4S$: C, 43.34; H, 3.92; N, 3.89. Found: C, 43.61; H, 4.11; N, 4.02. Single-crystal X-ray diagram: crystal of compound **11a** was grown by slow diffusion of EtOAc into a solution of compound **11a** in DCM to yield colorless prism. The compound crystallizes in the orthorhombic crystal system, space group *Pna* 21, *a*=19.7744(9) Å, *b*=11.3857(5) Å, *c*=6.5135(2) Å, *V*=1466.48(10) $Å^3$, *Z*=4, d_{calcd}=1.632 g/cm^3, *F*(000)=728, 2θ range 2.06–26.38°, *R* indices (all data) *R*1=0.0590, *wR*2=0.1144.

4.5. 7-Benzenesulfonyl-3a-bromo-octahydrofuro[2,3-*b*] pyridine (11b)

LAH (50 mg, 1.3 mmol) was added to a stirred solution of compound **5** (155 mg, 0.5 mmol) in THF (10 mL) at ice bath. The mixture was further stirred for 5 h at rt. The reaction was quenched with $NH_4Cl_{(aq)}$ (15%, 1 mL) at ice bath and the mixture was concentrated under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to give crude product **10b**. Without further purification, NBS (98 mg, 0.55 mmol) was added to a solution of crude product **10b** in DCM (10 mL) at rt. The reaction mixture was stirred at rt for 5 min. A solution of BF_3/OEt_2 (~0.8 mmol, 0.1 mL) in DCM (1 mL) was added to a stirred solution of the reaction mixture at ice bath. The reaction mixture was stirred at rt for 5 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product

under reduced pressure. Purification on silica gel (hexane/EtOAc=8/1) afforded compound **11b** (90 mg, 52% of two-step). Colorless oil; IR ($CHCl_3$) 3331, 2934, 1324, 1122 cm^{-1}; HRMS (ESI, M^++Na) calcd for $C_{13}H_{16}BrNO_3SNa$ 367.9932, found 367.9930; ^1H NMR (400 MHz): δ 7.93–7.90 (m, 2H), 7.59–7.54 (m, 1H), 7.51–7.47 (m, 2H), 5.64 (s, 1H), 3.97–3.85 (m, 2H), 3.54–3.50 (m, 1H), 2.79 (dt, J=2.8, 12.0 Hz, 1H), 2.64 (dt, J=9.6, 12.8 Hz, 1H), 2.34 (ddd, J=3.2, 7.6, 12.8 Hz, 1H), 2.08–2.03 (m, 1H), 1.96–1.88 (m, 1H), 1.86–1.78 (m, 1H), 1.60–1.58 (m, 1H); ^{13}C NMR (100 MHz): δ 138.99, 132.74, 128.74 (2x), 127.94 (2x), 89.39, 63.73, 57.97, 40.98, 39.63, 33.99, 20.97.

4.6. A representative procedure of compounds 11c–e is as follows

A solution of different Grignard reagent (1.0 M in THF, 1.5 mL, 1.5 mmol; for compound **11c**, phenylmagnesium bromide; for compound **11d**, 4-fluorophenylmagnesium bromide; for compound **11e**, 4-methoxyphenylmagnesium bromide) was added to a stirred solution of compound **5** (155 mg, 0.5 mmol) in THF (10 mL) at ice bath. The reaction mixture was stirred at rt for 5 h. Water (5 mL) was added to the reaction mixture and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford different crude product **10c**, **10d** or **10e** under reduced pressure. Without further purification, NBS (98 mg, 0.55 mmol) was added to a solution of crude product **10c**, **10d** or **10e** in DCM (10 mL) at rt. The reaction mixture was stirred at rt for 5 min. A solution of BF_3/OEt_2 ($\sim$0.8 mmol, 0.1 mL) in DCM (1 mL) was added to a stirred solution of the reaction mixture at ice bath. The reaction mixture was stirred at rt for 5 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=8/1–4/1) afforded compound **11c**, **11d** or **11e**.

*4.6.1. 7-Benzenesulfonyl-3a-bromo-2,2-diphenyl-octahydrofuro[2,3-b]pyridine (**11c**).* Yield (87 mg, 35% of two-step); White solid; mp=165–166 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3345, 2939, 1420, 1138, 764, 681 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{25}H_{25}BrNO_3S$ 498.0739, found 498.0740; ^1H NMR (400 MHz): δ 8.07–8.04 (m, 2H), 7.69–7.58 (m, 3H), 7.36–7.29 (m, 4H), 7.22–7.11 (m, 6H), 5.90 (s, 1H), 3.73–3.69 (m, 1H), 3.37 (d, J=13.2 Hz, 1H), 3.30 (d, J=13.2 Hz, 1H), 2.92 (dt, J=2.4, 12.0 Hz, 1H), 1.97–1.85 (m, 2H), 1.64–1.56 (m, 1H), 1.52–1.46 (m, 1H); ^{13}C NMR (100 MHz): δ 147.34, 146.12, 139.18, 132.88, 128.76 (2×), 128.48 (2×), 128.39 (2×), 127.97 (2×), 127.02, 126.76, 124.59 (2×), 124.43 (2×), 89.04, 83.45, 58.62, 54.14, 40.29, 34.47, 21.15; Anal. Calcd for $C_{25}H_{24}BrNO_3S$: C, 60.24; H, 4.85; N, 2.81. Found: C, 59.98; H, 5.01; N, 2.99. Single-crystal X-ray diagram: crystal of compound **11c** was grown by slow diffusion of EtOAc into a solution of compound **11c** in DCM to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group $P1\ 21/c1$, a=8.6459(3) Å, b=31.0413(11) Å, c=8.5495(3) Å, V=2211.73(13) $Å^3$, Z=4, d_{calcd}=1.497 g/cm^3, $F(000)$=1024, 2θ range 2.44–26.81°, R indices (all data) $R1$=0.0516, $wR2$=0.0728.

*4.6.2. 7-Benzenesulfonyl-3a-bromo-2,2-di-(4-fluorophenyl)-octahydrofuro[2,3-b]pyridine (**11d**).* Yield (80 mg, 30% of two-step); White solid; mp=142–143 °C (recrystallized from hexane and EtOAc); IR ($CHCl_3$) 3348, 2941, 1422, 1141, 762, 682 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{25}H_{23}BrF_2NO_3S$ 534.0550, found 534.0552; ^1H NMR (400 MHz): δ 8.02–7.99 (m, 2H), 7.68–7.64 (m, 1H), 7.60–7.56 (m, 2H), 7.30–7.25 (m, 2H), 7.19–7.14 (m, 2H), 7.02–6.96 (m, 2H), 6.94–6.89 (m, 2H), 5.86 (s, 1H), 3.70–3.67 (m, 1H), 3.31 (d, J=13.2 Hz, 1H), 3.23 (d, J=13.2 Hz, 1H), 2.90 (dt, J=2.8, 12.4 Hz, 1H), 1.94–1.83 (m, 2H), 1.61–1.48 (m, 2H); ^{13}C NMR (100 MHz): δ 162.85 (d, J=25.0 Hz), 160.40 (d, J=24.3 Hz), 142.98 (d, J=3.0 Hz), 141.87 (d, J=3.0), 139.18, 132.98, 128.82 (2×), 127.90 (2×), 126.40, 126.32, 126.18, 126.10, 115.56, 115.50, 115.34, 115.28, 89.12, 82.82, 58.28, 54.31, 40.29, 34.54, 21.07.

*4.6.3. 7-Benzenesulfonyl-3a-bromo-2,2-di-(4-methoxyphenyl)-octahydrofuro[2,3-b]pyridine (**11e**).* Yield (110 mg, 40% of two-step); Colorless oil; IR ($CHCl_3$) 3342, 2931, 1423, 1140, 759, 679 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{27}H_{29}BrNO_5S$ 558.0950, found 558.0951; ^1H NMR (400 MHz): δ 8.03–8.00 (m, 2H), 7.66–7.62 (m, 1H), 7.59–7.55 (m, 2H), 7.24–7.20 (m, 2H), 7.11–7.07 (m, 2H), 6.85–6.81 (m, 2H), 6.75–6.71 (m, 2H), 5.88 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.70–3.65 (m, 1H), 3.31 (d, J=13.2 Hz, 1H), 3.19 (d, J=13.2 Hz, 1H), 2.89 (dt, J=2.8, 12.4 Hz, 1H), 1.93–1.85 (m, 2H), 1.68–1.60 (m, 1H), 1.52–1.46 (m, 1H); ^{13}C NMR (100 MHz): δ 158.46, 158.17, 139.87, 139.25, 138.74, 132.83, 128.73 (2×), 128.04 (2×), 125.92 (2×), 125.66 (2×), 113.80 (2×), 113.68 (2×), 89.07, 83.22, 58.92, 55.26, 55.15, 54.27, 40.32, 34.65, 21.21.

4.7. A representative procedure of compounds 12a,12b is as follows

A solution of different Grignard reagent (1.0 M in THF, 1.5 mL, 1.5 mmol; for compound **12a**, 4-fluorophenylmagnesium bromide; for compound **12b**, 4-methoxyphenylmagnesium bromide) was added to a stirred solution of compound **5a** (162 mg, 0.5 mmol) in THF (10 mL) at ice bath. The reaction mixture was stirred at rt for 5 h. Water (5 mL) was added to the reaction mixture and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford different crude tertiary alcohol under reduced pressure. Without further purification, BF_3/OEt_2 ($\sim$0.8 mmol, 0.1 mL) was added to a solution of crude tertiary alcohol in DCM (10 mL) at ice bath. The reaction mixture was stirred at rt for 5 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=8/1–4/1) afforded compound **12a** or **12b**.

*4.7.1. 1-(4-Methylphenylsulfonyl)-5-[2,2-bis-(4-fluorophenyl)-vinyl]-1,2,3,4-tetrahydropyridine (**12a**).* Yield (134 mg, 59% of two-step); White solid; mp=198–200 °C (recrystallized from hexane and EtOAc); IR ($CHCl_3$) 3328, 2931, 1431, 1130, 723 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{26}H_{24}F_2NO_2S$ 452.1496, found 452.1497; ^1H NMR (400 MHz): δ 7.62 (d, J=8.4 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.14–7.08 (m, 4H), 7.02–6.91 (m, 4H), 6.90 (s, 1H), 6.44 (s, 1H), 3.30–3.27 (m, 2H), 2.44 (s, 3H), 1.52–1.47 (m, 4H); ^{13}C NMR (100 MHz): δ 163.28, 163.24, 160.83, 160.80, 143.82, 139.53, 136.72, 135.80, 134.99, 132.07, 131.99, 129.82 (2x), 129.06, 128.63, 128.54, 128.22, 126.97 (2x), 118.29, 115.09, 114.88, 43.37, 24.46, 21.59, 21.00. Single-crystal X-ray diagram: crystal of compound **12a** was grown by slow diffusion of EtOAc into a solution of compound **12a** in DCM to yield colorless prism. The compound crystallizes in the triclinic crystal system, space group $P-1$, a=9.9560(7) Å, b=9.9819(7) Å, c=11.1142(8) Å, V=1096.10(13) $Å^3$, Z=2, d_{calcd}=1.368 g/cm^3, $F(000)$=472, 2θ range 1.84–28.25°, R indices (all data) $R1$=0.0531, $wR2$=0.1123.

*4.7.2. 1-(4-Methylphenylsulfonyl)-5-[2,2-bis-(4-methoxyphenyl)-vinyl]-1,2,3,4-tetrahydropyridine (**12b**).* Yield (114 mg, 48% of two-step); White solid; mp=176–177 °C (recrystallized from hexane

and EtOAc); IR ($CHCl_3$) 3321, 2928, 1428, 1122, 718 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{28}H_{30}NO_4S$ 476.1896, found 476.1897; ^1H NMR (400 MHz): δ 7.63 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.12 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.0 Hz, 2H), 6.89 (s, 1H), 6.83 (d, J=8.0 Hz, 2H), 6.79 (d, J=8.8 Hz, 2H), 6.42 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.28 (t, J=5.6 Hz, 2H), 2.42 (s, 3H), 1.58–1.52 (m, 2H), 1.51–1.43 (m, 2H); ^{13}C NMR (100 MHz): δ 158.58, 158.54, 143.58, 137.26, 136.45, 134.85, 133.27, 131.46 (2×), 129.69 (2×), 128.16 (2×), 126.88 (2×), 126.85 (2×), 119.31, 113.36 (2×), 113.12 (2×), 55.15, 55.06, 43.36, 24.39, 21.46, 20.92. Single-crystal X-ray diagram: crystal of compound **12b** was grown by slow diffusion of EtOAc into a solution of compound **12b** in DCM to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group $P1\,21/n1$, a=14.3704(11) Å, b=10.2927(8) Å, c=16.1666(13) Å, V=2383.1(3) $Å^3$, Z=4, d_{calcd}=1.326 g/cm^3, $F(000)$=1008, 2θ range 1.82–26.41°, R indices (all data) $R1$=0.0463, $wR2$=0.1107.

4.8. Methanesulfonic acid 2-(2-allyl-1-benzenesulfonyl-3-bromo-piperidin-3-yl)-ethyl ester (13)

A solution of DIBALH (1.0 M in THF, 1.5 mL, 1.5 mmol) was added to a stirred solution of compound **4** (130 mg, 0.3 mmol) in THF (10 mL) at ice bath. The mixture was further stirred for 5 h at rt. The reaction was quenched with $NH_4Cl_{(aq)}$ (15%, 1 mL) at ice bath and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude bromoalcohol product **4a** under reduced pressure. ^1H NMR (200 MHz): δ 7.92–7.87 (m, 2H), 7.51–7.45 (m, 3H), 5.91–5.67 (m, 1H), 5.17–4.98 (m, 2H), 4.58–4.43 (m, 1H), 4.02 (t, J=6.6 Hz, 2H), 3.73–3.60 (m, 1H), 2.99–2.84 (m, 1H), 2.58–2.29 (m, 3H), 2.08–1.45 (m, 6H). Without further purification, methanesulfonyl chloride (115 mg, 1.0 mmol) was added to a stirred solution of crude product **4a** in the co-solvent of pyridine (5 mL) and DCM (10 mL) at ice bath. The reaction mixture was stirred at rt for 10–12 h. Water (5 mL) was added to the reaction mixture and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=4/1) afforded compound **13** (100 mg, 71% of two-steps). Colorless oil; IR ($CHCl_3$) 3372, 2948, 1428, 1119, 821 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{17}H_{25}BrNO_5S_2$ 466.0358, found 466.0361; ^1H NMR (400 MHz): δ 7.90–7.87 (m, 2H), 7.56–7.52 (m, 1H), 7.49–7.45 (m, 2H), 5.79–5.69 (m, 1H), 5.11–5.00 (m, 2H), 4.60 (t, J=7.2 Hz, 2H), 4.44 (dd, J=5.6, 9.2 Hz, 1H), 3.66 (ddd, J=1.6, 4.0, 13.2 Hz, 1H), 3.06 (s, 3H), 2.92 (dt, J=3.2, 13.2 Hz, 1H), 2.46–2.25 (m, 4H), 2.00–1.81 (m, 3H), 1.56–1.53 (m, 1H); ^{13}C NMR (100 MHz): δ 140.80, 133.55, 132.36, 128.59 (2x), 127.62 (2x), 118.43, 70.48, 67.63, 62.75, 41.75, 39.42, 37.51, 34.28, 32.72, 21.57; Anal. Calcd for $C_{17}H_{24}BrNO_5S_2$: C, 43.78; H, 5.19; N, 3.00. Found: C, 44.01; H, 5.31; N, 3.20.

4.9. 6-Allyl-1-benzenesulfonyl-5-vinyl-1,2,3,6-tetrahydropyridine (3)

DBU (150 mg, 1.0 mmol) was added to a solution of compound **13** (90 mg, 0.19 mmol) in THF (10 mL) at reflux. The reaction mixture was stirred at reflux for 2 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=10/1) afforded compound 3 (32 mg, 57%). Colorless oil; IR ($CHCl_3$) 3352, 2940, 1429, 1138, 712 cm^{-1}; HRMS (ESI, M^++Na) calcd for $C_{16}H_{19}NO_2SNa$ 312.1034, found 312.1037; ^1H NMR (400 MHz): δ 7.81–7.76 (m, 2H), 7.52–7.48 (m, 1H), 7.44–7.34 (m, 2H), 6.09 (dd, J=11.2, 17.6 Hz, 1H), 5.96–5.86 (m, 1H), 5.47 (t, J=4.0 Hz, 1H), 5.18–5.03 (m, 4H), 4.70 (d, J=10.0 Hz, 1H), 3.86 (dt, J=4.0, 15.2 Hz, 1H), 3.29 (dt, J=8.4, 16.8 Hz, 1H), 2.57–2.51 (m, 1H), 2.39–2.31 (m, 1H), 1.88–1.85 (m, 2H); ^{13}C NMR (100 MHz): δ 141.25, 136.80, 136.61, 134.87, 132.32, 128.71 (2×), 126.94 (2×), 126.30, 117.00, 111.98, 52.84, 37.62, 37.40, 23.21.

4.10. 1-Benzenesulfonyl-2,3,7,7a-tetrahydro-1*H*-[1]pyrindine (14)

Grubbs second catalyst (12 mg, 1.4% mmol) was added to a solution of compound **3** (61 mg, 0.21 mmol) in 1,2-dichloroethane (5 mL) at reflux. The reaction mixture was stirred at reflux for 1 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=8/1) afforded compound **14** (41 mg, 75%). Colorless oil; IR ($CHCl_3$) 3361, 2952, 1460, 1152, 972, 722 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{14}H_{16}NO_2S$ 262.0902, found 262.0904; ^1H NMR (400 MHz): δ 7.82–7.72 (m, 2H), 7.65–7.48 (m, 3H), 6.19–6.08 (m, 1H), 6.00–5.98 (m, 1H), 5.54 (dd, J=4.0, 7.2 Hz, 1H), 3.73 (ddd, J=4.0, 4.8, 11.6 Hz, 1H), 3.56 (ddt, J=2.0, 4.8, 13.6 Hz, 1H), 2.87–2.81 (m, 1H), 2.75 (ddd, J=4.8, 9.2, 13.6 Hz, 1H), 2.40–2.33 (m, 2H), 2.06–2.00 (m, 1H); ^{13}C NMR (100 MHz): δ 134.30, 132.85, 130.08, 129.15, 129.07 (2×), 127.94, 127.77 (2×), 114.94, 58.87, 45.65, 39.21, 24.99.

4.11. 1-Benzenesulfonyl-octahydro-[1]pyrindine (rodocaine core, 2) and 1-benzenesulfonyl-2,3,5,6,7,7a-hexahydro-1*H*-[1]pyrindine (15)

Palladium on activated carbon (10%, 5 mg) was added to a solution of compound **14** (52 mg, 0.2 mmol) in EtOH (10 mL) at rt. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 20 h. The reaction mixture was filtered and evaporated to yield crude product. Purification on silica gel (hexane/EtOAc=4/1) afforded compounds **2** (26 mg, 50%) and **15** (15 mg, 29%). For compound **2**: Colorless oil; IR ($CHCl_3$) 3310, 2891, 1412, 1080 cm^{-1}; HRMS (ESI, M^++Na) calcd for $C_{14}H_{19}NO_2SNa$ 288.1034, found 288.1035; ^1H NMR (400 MHz): δ 7.83–7.79 (m, 2H), 7.57–7.52 (m, 1H), 7.51–7.46 (m, 2H), 4.24–4.18 (m, 1H), 3.76–3.72 (m, 1H), 2.79 (dt, J=2.8, 12.8 Hz, 1H), 1.92–1.85 (m, 1H), 1.68–1.31 (m, 9H), 1.10 (dq, J=3.6, 12.8 Hz, 1H); ^{13}C NMR (100 MHz): δ 140.57, 132.17, 128.90 (2×), 127.08 (2×), 57.12, 40.38, 36.78, 28.76, 25.59, 24.42, 22.46, 19.95. For compound **15**: Colorless oil; HRMS (ESI, M^++1) calcd for $C_{14}H_{18}NO_2S$ 264.1058, found 264.1059; ^1H NMR (400 MHz): δ 7.84–7.80 (m, 2H), 7.59–7.47 (m, 3H), 5.52–5.49 (m, 1H), 4.24–4.18 (m, 1H), 3.76–3.70 (m, 1H), 3.46–3.33 (m, 1H), 2.80 (dt, J=2.0, 13.2 Hz, 2H), 2.39–2.29 (m, 2H), 1.98–1.67 (m, 2H), 1.52–1.48 (m, 2H); ^{13}C NMR (100 MHz): δ 132.70, 132.59, 132.15, 128.88 (2×), 127.06 (2×), 116.61, 57.10, 40.37, 36.76, 28.75, 25.57, 24.39.

4.12. *N*-(2-Chloro-6-methylphenyl)-3-(octahydro-[1]pyrindin-1-yl)propionamide (rodocaine, 1)

Magnesium (10 mg, 0.42 mmol) was added to a solution of compound **2** (30 mg, 0.11 mmol) in MeOH (3 mL) at rt. The reaction mixture was stirred at reflux for 4 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Without further purification, potassium carbonate (28 mg, 0.20 mmol) was added to

a solution of the resulting crude secondary amine in DMF (1 mL) at rt. The reaction mixture was stirred at rt for 5 min. A solution of compound **16** (45 mg, 0.22 mmol) in DMF (1 mL) was added to a stirred solution of the reaction mixture at rt. The reaction mixture was stirred at rt for 20 h. Saturated $NaHCO_{3(aq)}$ (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc=1/1) afforded compound (**1**) (16 mg, 32% of two-steps). White solid; mp=97–98 °C (recrystallized from hexane and EtOAc); HRMS (ESI, M^++1) calcd for $C_{18}H_{26}ClN_2O$ 321.1734, found 321.1735; ^{1}H NMR (400 MHz): δ 10.83 (br s, 1H), 7.26 (dd, *J*=1.6, 7.6 Hz, 1H), 7.14 (dd, *J*=0.8, 7.6 Hz, 1H), 7.09 (t, *J*=7.6 Hz, 1H), 3.31 (dt, *J*=3.2, 11.2 Hz, 1H), 3.23 (dt, *J*=3.2, 12.0 Hz, 1H), 2.78 (ddd, *J*=4.4, 12.0, 17.6 Hz, 1H), 2.31 (dt, *J*=4.4, 17.6 Hz, 1H), 2.37 (dt, *J*=4.4, 12.8 Hz, 1H), 2.26 (s, 3H), 2.05–1.98 (m, 1H), 1.90–1.71 (m, 5H), 1.70–1.61 (m, 3H), 1.50–1.34 (m, 2H), 1.23–1.12 (m, 1H), 1.04 (dq, *J*=4.0, 12.4 Hz, 1H); ^{13}C NMR (100 MHz): δ 171.03, 137.74, 133.43, 131.29, 128.95, 127.26, 126.99, 70.87, 52.33, 51.45, 45.03, 32.15, 29.69, 29.32, 29.05, 26.01, 19.92, 19.05.

4.13. A representative procedure of compounds 17a,17b is as follows

A solution of ethyl propiolate (30 mg, 0.3 mmol) or diethyl acetylenedicarboxylate (51 mg, 0.3 mmol) was added to a stirred solution of compound **3** (61 mg, 0.21 mmol) in toluene (3 mL) at rt. The reaction mixture was stirred at reflux for 20 h. DDQ (160 mg, 0.7 mmol) was added to the reaction mixture at reflux. The reaction mixture was stirred at reflux for 10 h. Saturated sodium bicarbonate solution (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) afforded compound **17a** or **17b**.

*4.13.1. 1-Allyl-2-benzenesulfonyl-1,2,3,4-tetrahydro-isoquinoline-6-carboxylic acid ethyl ester (**17a**).* Yield (46 mg, 56% of two-step); Colorless oil; IR ($CHCl_3$) 3410, 2930, 1777, 1102, 875, 712 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{21}H_{24}NO_4S$ 386.1426, found 384.1425; ^{1}H NMR (200 MHz): δ 7.76–7.70 (m, 3H), 7.41–7.21 (m, 5H), 5.86–5.71 (m, 1H), 5.15–4.97 (m, 2H), 4.27 (q, *J*=7.2 Hz, 2H), 3.90–3.85 (m, 1H), 3.50 (ddd, *J*=5.4, 7.8, 14.6 Hz, 1H), 2.98–2.92 (m, 1H), 2.66–2.44 (m, 4H), 1.34 (t, *J*=7.2 Hz, 3H).

*4.13.2. 1-Allyl-2-benzenesulfonyl-1,2,3,4-tetrahydro-isoquinoline-5,6-dicarboxylic acid diethyl ester (**17b**).* Yield (62 mg, 65% of two-step); Colorless oil; IR ($CHCl_3$) 3438, 2939, 1771, 1110, 881, 727 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{24}H_{28}NO_6S$ 458.1637, found 458.1638; ^{1}H NMR (400 MHz): δ 7.79 (d, *J*=8.0 Hz, 1H), 7.72 (m, 2H), 7.49–7.44 (m, 1H), 7.37–7.34 (m, 2H), 7.18 (d, *J*=8.0 Hz, 1H), 5.83–5.73 (m, 1H), 5.12–5.01 (m, 2H), 4.39–4.33 (m, 1H), 4.31 (q, *J*=7.2 Hz, 4H), 3.88 (ddd, *J*=2.8, 6.4, 14.4 Hz, 1H), 3.46 (ddd, *J*=5.6, 7.6, 14.4 Hz, 1H), 2.64–2.47 (m, 4H), 1.34 (t, *J*=7.2 Hz, 3H), 1.32 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 168.43, 165.23, 140.70, 140.24, 135.85, 133.60, 132.71, 130.51, 128.95 (2×), 127.79, 127.49, 126.92 (2×), 126.61, 118.43, 61.54, 61.50, 56.22, 41.56, 38.30, 23.46, 14.12, 14.02.

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