Tetrahedron 67 (2011) 4552–4558

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of tetrahydrobenzoisoquinolinols, tetrahydropyrindines, and hexahydroquinolines from 4-aryltetrahydropyridines

Meng-Yang Chang *, Ming-Fang Lee, Yeh-Long Chen

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan

ARTICLE INFO

Article history:
Received 3 March 2011
Received in revised form 17 April 2011
Accepted 22 April 2011
Available online 5 May 2011

Keywords:
Tetrahydrobenzoisoquinolinols
Tetrahydropyrindines
Hexahydroquinolines
Friedel–Crafts cyclization
Ring-closing metathesis

ABSTRACT

A straightforward synthesis of tetrahydrobenzoisoquinolinols **2**, tetrahydropyrindines **3**, and hexahydroquinolines **4** from versatile intermediate **6** is reported. Two key transformations were carried out by intramolecular Friedel–Crafts cyclization and ring-closing metathesis in moderate yields. Skeleton **6** was easily prepared from the known starting material 4-aryl-4-methoxypiperidin-3-ones **7** via Wittig olefination with $Ph_3P{=}CHCO_2Et$, deconjugation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and boron trifluoride etherate ($BF_3{-}OEt_2$)-catalyzed addition of the corresponding iminium ion with allyltrimethylsilane.

1. Introduction

The importance of heterocycles with nitrogen-containing functional groups in natural and synthetic products has stimulated the development of efficient methodologies.[1] Recently, we have introduced a straightforward approach for synthesizing diarylhexahydrobenzo[*f*]isoquinolines **5** with a 3-azadecalin system via the rearrangement reaction from the structural skeleton of 4-aryl-1,2,5,6-tetrahydropyridines **1**.[2] To demonstrate the synthetic application of 4-aryl-1,2,5,6-tetrahydropyridines **1**, the synthetic strategies for tetrahydrobenzo[*f*]isoquinolinols **2**,[3] tetrahydropyrindines **3**,[4] and hexahydroquinolines **4**[5] were investigated. The synthetic strategy of skeletons **2**, **3**, and **4** was shown in Fig. 1.

2. Results and discussion

These styrene-type substructures have been synthesized from various sources, and some of them show interesting biological activities.[3–5] These moieties are also important part of other more complex products. Considering the molecular diversity of target skeletons **2**, **3**, and **4** using the versatile intermediate **6** is a major challenge. Functionalization of the acetate group at C-3 position of intermediate **6** is probably one of the most promising strategies toward this purpose. The direct introduction of acetate functional group into vinyl, allyl, and carboxylate group is indeed expected to shorten the syntheses of targets by utilizing simple synthetic transformation without the protecting group manipulation.

As shown in Scheme 1, skeleton **6** was provided from skeleton **8** via deconjugation and Lewis acid-promoted the intermolecular addition with allyltrimethylsilane in 50–65% overall yield of two-steps, respectively. Therefore, an easy five-step synthetic step of skeleton **8** from skeleton **1** (P=Bs, Ar=**a**, Ph; **b**, 4-FPh; **c**, 3-CF_3Ph; **d**, 3-CF_3-4-ClPh; P=Ms **e**, Ph) involves: (1) selenium dioxide-mediated *trans*-methoxyhydroxylation reaction of skeleton **1** with hydrogen peroxide in methanol; (2) Jones oxidation of the resulting secondary methoxyalcohol; (3) Wittig olefination of ketone **7**; (4) deconjugation of skeleton **8** with 1,8-diazabicyclo[5.4.0]undec-7-ene, and (5) a boron trifluoride etherate-promoted addition of the corresponding iminium ion with allyltrimethylsilane.[2b,c] The 3-acetate functional group plays an important role to allow the different carbon–carbon bond formation as a useful activating arm. The structure of compound **6a** was determined using single-crystal X-ray analysis.[6]

With the skeleton **6** in hand, synthesis of skeleton **2** was examined. The intramolecular Friedel–Crafts cyclization was chosen as the key step to produce skeleton **2** with tricyclic ring system.[7] As shown in Scheme 2, compound **2a** or **2b** was isolated in 40% and 35% yield of three-steps by (i) hydrolysis of skeleton **6** with aqueous sodium hydroxide solution (2 N) at reflux for 10–15 h, (ii) acylation of the corresponding acid with thionyl chloride at reflux temperature for 10–15 h, and (iii) intramolecular Friedel–Crafts cyclization and with aluminum trichloride in dichloromethane for 2–3 h,

* Corresponding author. Tel.: +886 7 3121101x2220; e-mail address: mychang@kmu.edu.tw (M.-Y. Chang).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.04.089

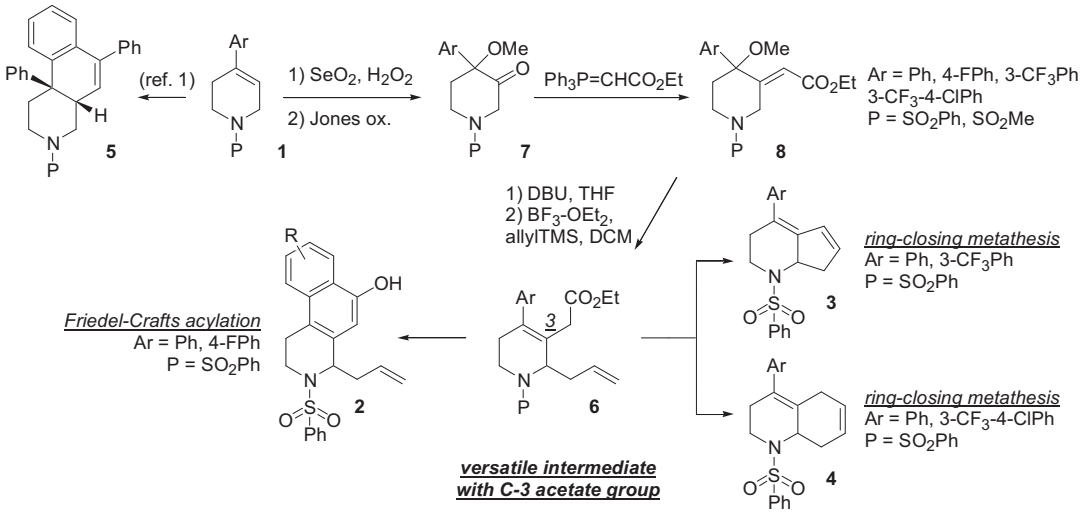


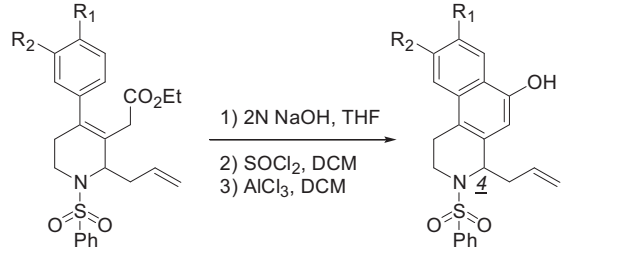
Fig. 1. Synthetic strategy toward tetrahydrobenzoisoquinolinols **2**, tetrahydropyrindines **3**, and hexahydroquinolines **4**.

P = SO_2Ph
8a, $R_1 = R_2 = H$
8b, $R_1 = F$, $R_2 = H$
8c, $R_1 = H$, $R_2 = CF_3$
8d, $R_1 = Cl$, $R_2 = CF_3$
P = SO_2Me
8e, $R_1 = R_2 = H$

P = SO_2Ph
6a, $R_1 = R_2 = H$ (56%)
6b, $R_1 = F$, $R_2 = H$ (60%)
6c, $R_1 = H$, $R_2 = CF_3$ (65%)
6d, $R_1 = Cl$, $R_2 = CF_3$ (50%)
P = SO_2Me
6e, $R_1 = R_2 = H$ (61%)

Scheme 1. Synthesis of skeleton **6**.

followed by a tautomeric aromaticity. This experimental procedure offers a general and efficient alternative to the intramolecular Friedel–Crafts cyclization. According to literature report, an extended conjugation at C-4 position of benzo[*f*]isoquinoline skeleton can possess some potential biological activity.[3a–c] The allyl functional group is a key ingredient in many therapeutic agents,[3a] as important bioactive components in pharmaceutical research.

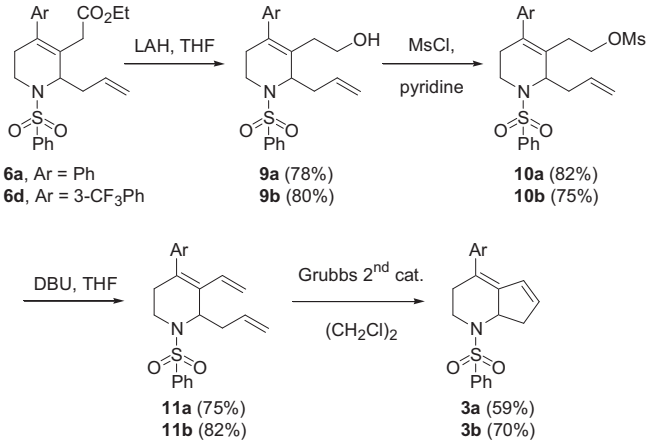


6a, $R_1 = R_2 = H$
6b, $R_1 = F$, $R_2 = H$

2a, $R_1 = R_2 = H$ (40%)
2b, $R_1 = F$, $R_2 = H$ (35%)

Scheme 2. Synthesis of tetrahydrobenzoisoquinolinols **2**.

With the successful results, we further expanded the scope of the strategy to ring-closing metathesis. Ring-closing metathesis was chosen as the next key step to produce skeletons **3** or **4** with bicyclic ring system.[8] As shown in Scheme 3, skeleton **3** (Ar=**a**, Ph; **b**, 3-CF_3Ph) were prepared using the simple four-steps protocol and are described as follows: (i) by reduction of ester **6** with lithium aluminum hydride at rt for 2–3 h; (ii) mesylation of alcohol **9** with mesyl chloride in pyridine at rt for 10–12 h; (iii) 1,8-diazabicyclo [5.4.0]undec-7-ene-promoted elimination of mesylate **10** at reflux for 10–12 h; and (iv) ring-closing metathesis of skeleton **11** with the second generation Grubbs' catalyst at reflux for 1–2 h. Skeleton **3** exhibited a conformationally restricted character of *s-trans* dienyl conformer.



6a, Ar = Ph
6d, Ar = 3-CF_3Ph

9a (78%)
9b (80%)

10a (82%)
10b (75%)

11a (75%)
11b (82%)

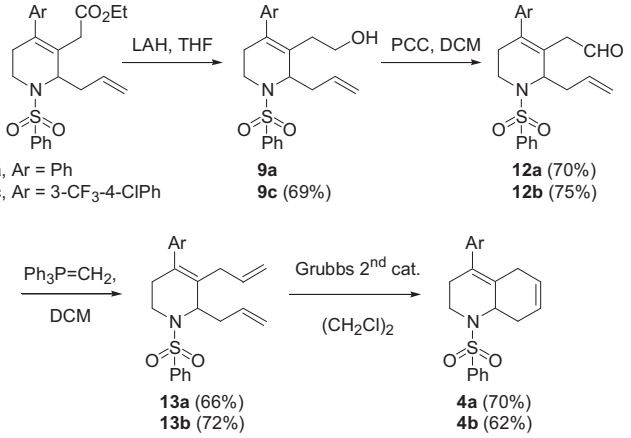
3a (59%)
3b (70%)

Scheme 3. Synthesis of tetrahydropyrindines **3**.

When skeleton **11** was subjected to a ring-closing metathesis reaction employing first generation Grubbs' catalyst, the expected bicyclic skeleton **3** was generated in low yield (for **3a**, 19%; for **3b**, 13%) under a number of conditions (prolonged reaction time, elevated temperature, different solvents). The ring strain existed in the desired bicyclic [4.3.0] product might retard the normally facile intramolecular annulation. The amino group in the piperidine ring might potentially chelate the metal center of the first generation Grubbs' catalyst to form unproductive complex. Therefore, we next turn our attention to examine the second generation Grubbs' catalyst, which has higher thermal stability and lower sensitivity to double bond migration. Using similar reaction conditions, compound **3a** or **3b** was obtained as the major product in 59% or 70% yield, respectively.

Furthermore, synthetic approach of skeleton **4** is similar to skeleton **3** by the four-step protocol as shown in Scheme 4.

Aldehydes **12a** and **b** were yielded by reduction of skeleton **6** (Ar=**a**, Ph; **b**, 3-CF_3-4-ClPh) with lithium aluminum hydride, and followed by PCC-mediated oxidation of alcohol **6**. Then, Wittig olefination of skeleton **12** and ring-closing metathesis of skeleton **13** were provided skeleton **4**. This typical experimental procedure offers a general and efficient alternative to the ring-closing metathesis.



Scheme 4. Synthesis of hexahydroquinolines **4**.

3. Conclusion

In summary, we have successfully presented a new and straightforward synthetic methodology for producing the structural skeletons of tetrahydrobenzo[*f*]isoquinolinols **2**, tetrahydropyrindines **3**, and hexahydroquinolines **4** by the two key steps of intramolecular Friedel–Crafts cyclization and ring-closing metathesis in moderate yields. Further investigation is required regarding the synthesis of desulfonated compounds of skeletons **2**, **3**, and **4** and their structure–activity in the context of psychotomimetic effects. Considering the utility of these heterocyclic aromatic compounds, the development of these general synthetic approaches is significant.

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 an 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. A representative procedure of skeleton 8 is as follows[2]

A solution of hydrogen peroxide in methanol (2 mL) was added dropwise to a solution of compound **1** (1.0 mmol) with selenium dioxide (222 mg, 2.0 mmol) in methanol (20 mL) at rt. The reaction mixture was stirred at reflux temperature for 5 h. Saturated sodium bicarbonate solution (2 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Jones reagent (3 mL) was added to a solution of the resulting crude α-methoxyalcohol in acetone (15 mL) at rt. The reaction mixture was stirred at rt for 20 min. Isopropanol (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude skeleton **7**. Without further purification, ethyl triphenylphosphoranylidene acetate (348 mg, 1.0 mmol) was added to a solution of the resulting crude product in dichloromethane (15 mL). The reaction mixture was stirred at reflux temperature for 3 h and then the solvent was concentrated. The reaction mixture was extracted with dichloromethane (3×15 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt=4/1) afforded skeleton **8**.

*4.2.1. (1-Benzenesulfonyl-4-methoxy-4-phenylpiperidin-3-ylidene) acetic acid ethyl ester (**8a**).* Yield 75% (three-steps); viscous oil; IR ($CHCl_3$) 3526, 2946, 1769, 1164 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_5S$ 416.1532, found 416.1533; ^{1}H NMR (400 MHz): δ 7.85–7.82 (m, 2H), 7.62–7.50 (m, 3H), 7.37–7.27 (m, 3H), 7.21–7.18 (m, 2H), 5.74 (s, 1H), 4.93 (d, J=14.0 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 4.00 (d, J=14.0 Hz, 1H), 3.58–3.52 (m, 1H), 3.31–3.25 (m, 1H), 2.97 (s, 3H), 2.40–2.33 (m, 1H), 2.03–1.97 (m, 1H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 165.66, 151.04, 138.54, 137.44, 132.71, 129.06 (2×), 128.55 (2×), 127.97, 127.62 (2×), 127.38 (2×), 120.25, 79.84, 60.62, 50.82, 43.72, 42.32, 35.67, 14.16; Anal. Calcd for $C_{22}H_{25}NO_5S$: C, 63.59; H, 6.06; N, 3.37. Found: C, 63.71; H, 5.92; N, 3.52.

*4.2.2. [1-Benzenesulfonyl-4-methoxy-4-(4-fluorophenyl)piperidin-3-ylidene]acetic acid ethyl ester (**8b**).* Yield 56% (three-steps); viscous oil; IR ($CHCl_3$) 3525, 2944, 1767, 1168 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{25}FNO_5S$ 434.1438, found 434.1435; ^{1}H NMR (400 MHz): δ 7.84–7.81 (m, 2H), 7.62–7.50 (m, 3H), 7.20–7.15 (m, 2H), 7.06–7.00 (m, 2H), 5.69 (s, 1H), 4.92 (d, J=14.0 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 3.97 (d, J=14.0 Hz, 1H), 3.56–3.51 (m, 1H), 3.25 (dt, J=3.2, 10.0 Hz, 1H), 2.95 (s, 3H), 2.33 (ddd, J=4.0, 10.0, 14.0 Hz, 1H), 2.01 (ddd, J=3.2, 5.6, 14.0 Hz, 1H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 165.54, 163.46, 161.00, 151.01, 137.29, 134.38, 132.77, 129.25, 129.08 (2×), 127.61 (2×), 120.21, 115.61, 115.40, 79.46, 60.69, 50.72, 43.66, 42.24, 35.57, 14.14; Anal. Calcd for $C_{22}H_{24}FNO_5S$: C, 60.95; H, 5.58; N, 3.23. Found: C, 61.22; H, 5.82; N, 3.43.

*4.2.3. [1-Benzenesulfonyl-4-methoxy-4-(3-trifluoromethylphenyl)piperidin-3-ylidene]acetic acid ethyl ester (**8c**).* Yield 69% (three-steps); viscous oil; IR ($CHCl_3$) 3529, 2933, 1766, 1170 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{25}F_3NO_5S$ 484.1406, found 484.1407; ^{1}H NMR (400 MHz): δ 7.87–7.84 (m, 2H), 7.64–7.47 (m, 5H), 7.41–7.37 (m, 2H), 5.60 (d, J=0.8 Hz, 1H), 5.24 (dd, J=1.2, 14.0 Hz, 1H), 4.21 (q, J=7.2 Hz, 2H), 3.77 (dd, J=1.2, 14.0 Hz, 1H), 3.68–3.62 (m, 1H), 3.26–3.19 (m, 1H), 3.00 (s, 3H), 2.26 (ddd, J=4.4, 10.4, 14.0 Hz, 1H), 2.00 (ddd, J=8.4, 11.2, 14.0 Hz, 1H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 165.29, 162.86, 149.81, 140.38, 137.40, 132.88, 130.86, 129.14 (2×), 127.61 (2×), 124.88, 124.85, 123.88, 123.85, 121.12, 79.87, 60.84, 51.11, 43.67, 42.04, 36.59, 14.12; Anal. Calcd for $C_{23}H_{24}F_3NO_5S$: C, 57.13; H, 5.00; N, 2.90. Found: C, 57.44; H, 5.31; N, 3.12.

*4.2.4. [1-Benzenesulfonyl-4-methoxy-4-(4-chloro-3-trifluoromethylphenyl)piperidin-3-ylidene]acetic acid ethyl ester (**8d**).* Yield 78% (three-steps); viscous oil; IR ($CHCl_3$) 3523, 2952, 1766,

1166 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{24}ClF_3NO_5S$ 518.1016, found 518.1018; ^1H NMR (400 MHz): δ 7.86–7.83 (m, 2H), 7.64–7.48 (m, 5H), 7.30 (dd, *J*=2.4, 10.8 Hz, 1H), 5.60 (d, *J*=0.4 Hz, 1H), 5.27 (d, *J*=14.8 Hz, 1H), 4.21 (q, *J*=7.2 Hz, 2H), 3.71 (d, *J*=14.8 Hz, 1H), 3.68–3.62 (m, 1H), 3.22–3.15 (m, 1H), 2.99 (s, 3H), 2.22 (ddd, *J*=4.4, 10.8, 14.8 Hz, 1H), 1.99 (dd, *J*=3.6, 14.0 Hz, 1H), 1.30 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 165.11, 149.52, 138.70, 137.32, 132.91, 131.92, 131.75, 129.16 (2×), 128.80, 127.59 (2×), 126.26, 126.16, 123.95, 121.16, 79.65, 60.92, 51.12, 43.64, 41.92, 36.54, 14.10.

*4.2.5. (1-Methanesulfonyl-4-methoxy-4-phenylpiperidin-3-ylidene) acetic acid ethyl ester (**8e**).* Yield 60% (three-steps); viscous oil; IR ($CHCl_3$) 3522, 2943, 1765, 1165 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{17}H_{24}NO_5S$ 354.1375, found 354.1377; ^1H NMR (400 MHz): δ 7.41–7.32 (m, 5H), 5.91 (s, 1H), 4.62 (d, *J*=14.0 Hz, 1H), 4.48 (d, *J*=14.0 Hz, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 3.58–3.54 (m, 2H), 3.06 (s, 3H), 2.88 (s, 3H), 2.54 (ddd, *J*=4.4, 8.0, 14.0 Hz, 1H), 2.13–2.07 (ddd, *J*=4.0, 6.4, 14.0 Hz, 1H), 1.27 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 165.87, 151.87, 137.94, 128.72 (2×), 128.27, 127.60 (2×), 119.45, 79.79, 60.66, 50.72, 43.32, 42.11, 37.05, 35.11, 14.11; Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.77; H, 6.56; N, 3.96. Found: C, 57.48; H, 6.29; N, 4.21.

4.3. A representative procedure of skeleton 6 is as follows

1,8-Diazabicyclo[5.4.0]undec-7-ene (1.52 g, 10.0 mmol) was added to a solution of skeleton **8** (0.8 mmol) in tetrahydrofuran (10 mL) at reflux temperature. The reaction mixture was stirred at reflux temperature for 20 min. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Without further purification, a solution of boron trifluoride etherate (0.5 mL) in dichloromethane (1 mL) was added to a stirred solution of the resulting enamine product in allyltrimethylsilane (1 mL) and dichloromethane (3 mL) at rt. The reaction mixture was stirred at rt for 15 min. 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=6/1–3/1) afforded skeleton **6**.

*4.3.1. (2-Allyl-1-benzenesulfonyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)acetic acid ethyl ester (**6a**).* Yield 56% (two-steps); mp=99–101 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3540, 2934, 1765 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{24}H_{28}NO_4S$ 426.1739, found 426.1742; ^1H NMR (400 MHz): δ 8.01–7.98 (m, 2H), 7.58–7.47 (m, 3H), 7.26–7.18 (m, 3H), 6.81–6.78 (m, 2H), 6.01–5.90 (m, 1H), 5.16–5.10 (m, 2H), 4.70–4.67 (m, 1H), 4.19–4.16 (m, 2H), 3.88 (dd, *J*=6.4, 14.0 Hz, 1H), 3.42–3.24 (m, 1H), 2.99 (d, *J*=16.4 Hz, 1H), 2.89 (d, *J*=16.4 Hz, 1H), 2.64–2.57 (m, 1H), 2.48–2.40 (m, 1H), 1.93–1.78 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 170.98, 141.59, 140.99, 136.78, 134.64, 132.35, 128.83 (2×), 128.33 (2×), 127.56 (2×), 127.33 (2×), 127.14, 126.71, 117.41, 60.83, 55.68, 38.05, 37.25, 36.68, 29.45, 14.17; Anal. Calcd for $C_{24}H_{27}NO_4S$: C, 67.74; H, 6.40; N, 3.29. Found: C, 67.91; H, 6.29; N, 3.60.

*4.3.2. [2-Allyl-1-benzenesulfonyl-4-(4-fluorophenyl)-1,2,5,6-tetrahydropyridin-3-yl]acetic acid ethyl ester (**6b**).* Yield 60% (two-steps); mp=84–86 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3544, 2930, 1767 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{24}H_{27}FNO_4S$ 444.1645, found 444.1644; ^1H NMR (400 MHz): δ 7.99–7.96 (m, 2H), 7.58–7.54 (m, 1H), 7.51–7.47 (m, 2H), 6.96–6.90 (m, 2H), 6.79–6.74 (m, 2H), 5.98–5.88 (m, 1H), 5.14–5.10 (m, 2H), 4.66–4.63 (m, 1H), 4.19–4.08 (m, 2H), 3.87 (dd, *J*=6.4, 14.0 Hz, 1H), 3.41–3.33 (m, 1H), 2.95 (d, *J*=16.4 Hz, 1H), 2.88 (d, *J*=16.4 Hz, 1H), 2.62–2.56 (m, 1H), 2.46–2.38 (m, 1H), 1.91–1.77 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 170.89, 163.07, 160.62, 141.52, 136.81, 136.79, 135.86, 134.54, 132.31, 129.23, 128.85 (2×), 127.33 (2×), 117.51, 115.40, 115.19, 60.95, 55.72, 38.00, 37.17, 36.68, 29.59, 14.17; Anal. Calcd for $C_{24}H_{26}FNO_4S$: C, 64.99; H, 5.91; N, 3.16. Found: C, 65.29; H, 6.21; N, 3.45.

*4.3.3. [2-Allyl-1-benzenesulfonyl-4-(3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridin-3-yl]acetic acid ethyl ester (**6c**).* Yield 65% (two-steps); viscous oil; IR ($CHCl_3$) 3538, 2929, 1766 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{25}H_{27}F_3NO_4S$ 494.1613, found 494.1617; ^1H NMR (400 MHz): δ 8.00–7.97 (m, 2H), 7.60–47 (m, 4H), 7.37 (t, *J*=7.6 Hz, 1H), 7.03 (d, *J*=7.6 Hz, 1H), 6.96 (s, 1H), 5.99–5.89 (m, 1H), 5.16–5.11 (m, 2H), 4.69–4.66 (m, 1H), 4.19–4.07 (m, 2H), 3.95–3.90 (m, 1H), 3.43–3.35 (m, 1H), 2.88 (s, 2H), 2.63–2.57 (m, 1H), 2.47–2.39 (m, 1H), 1.92–1.85 (m, 2H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 170.59, 141.61, 141.48, 135.57, 134.42, 132.54, 131.02, 128.92 (2×), 128.14, 127.39 (2×), 124.64, 124.57, 124.10, 124.03, 123.99, 117.61, 61.07, 55.83, 37.87, 37.04, 36.79, 29.35, 14.08.

*4.3.4. [2-Allyl-1-benzenesulfonyl-4-(4-chloro-3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridin-3-yl] acetic acid ethyl ester (**6d**).* Yield 50% (two-steps); viscous oil; IR ($CHCl_3$) 3541, 2936, 1767 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{25}H_{26}ClF_3NO_4S$ 528.1223, found 528.1225; ^1H NMR (400 MHz): δ 7.98–7.95 (m, 2H), 7.59–7.47 (m, 3H), 7.39 (d, *J*=8.0 Hz, 1H), 7.03 (d, *J*=2.0 Hz, 1H), 6.97 (dd, *J*=2.0, 8.0 Hz, 1H), 5.97–5.87 (m, 1H), 5.14–5.10 (m, 2H), 4.67–4.63 (m, 1H), 4.19–4.07 (m, 2H), 3.94–3.89 (m, 1H), 3.41–3.33 (m, 1H), 2.89 (d, *J*=16.4 Hz, 1H), 2.84 (d, *J*=16.4 Hz, 1H), 2.61–2.55 (m, 1H), 2.45–2.33 (m, 1H), 1.89–1.82 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 170.42, 141.38, 139.68, 134.60, 134.28, 132.57, 132.17, 131.57, 128.91 (2×), 128.80, 127.36 (2×), 127.01, 126.92, 123.95, 121.23, 117.67, 61.18, 55.81, 37.76, 36.95, 36.79, 29.24, 14.05.

*4.3.5. (2-Allyl-1-methanesulfonyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)acetic acid ethyl ester (**6e**).* Yield 61% (two-steps); mp=67–69 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3544, 2938, 1766 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{19}H_{26}NO_4S$ 364.1583, found 364.1585; ^1H NMR (400 MHz): δ 7.36–7.26 (m, 3H), 7.11–7.08 (m, 2H), 5.97–5.87 (m, 1H), 5.16–5.11 (m, 2H), 4.31 (dd, *J*=3.6, 9.2 Hz, 1H), 4.12 (q, *J*=7.2 Hz, 2H), 3.98 (ddt, *J*=1.2, 7.5, 15.2 Hz, 1H), 3.43 (ddd, *J*=5.2, 12.0, 15.2 Hz, 1H), 3.12 (d, *J*=17.2 Hz, 1H), 3.07 (s, 3H), 2.89 (d, *J*=17.2 Hz, 1H), 2.62–2.52 (m, 2H), 2.48–2.39 (m, 1H), 2.28 (ddd, *J*=0.8, 4.4, 18.4 Hz, 1H), 1.23 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 172.54, 140.85, 136.72, 134.57, 128.62 (2×), 127.71 (2×), 127.58, 127.48, 117.39, 61.01, 54.90, 39.80, 37.99, 36.82, 36.24, 30.01, 14.12; Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.78; H, 6.93; N, 3.85. Found: C, 62.97; H, 7.21; N, 3.98.

4.4. A representative procedure of skeleton 2 is as follows

A solution of skeleton **6** (0.5 mmol) and sodium hydroxide solution (2 N, 5 mL) in tetrahydrofuran (10 mL) was refluxed for 10–15 h. The reaction was traced by TLC until the skeleton **6** 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 ethyl acetate (3×10 mL). The aqueous phase was cooled in ice-bath and acidified by adding concentrated hydrochloric acid to pH 2. The aqueous solution was extracted with ethyl acetate (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 under

reduced pressure. Without further purification, thionyl chloride (5 mL) was added to a stirred solution of the resulting acid product in dichloromethane (5 mL) at rt. The reaction mixture was stirred at reflux for 10–15 h and the solvent was concentrated under reduced pressure. Aluminum chloride (134 mg, 1.0 mmol) was added to a stirred solution of the residue in dichloromethane (10 mL) at rt. The reaction mixture was stirred at rt for 2–3 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=6/1–3/1) afforded skeleton **2**.

*4.4.1. 4-Allyl-3-benzenesulfonyl-1,2,3,4-tetrahydrobenzo[f]isoquinolin-6-ol (**2a**).* Yield 40% (three-steps); viscous oil; IR ($CHCl_3$) 3650, 3298, 2929, 1149 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{22}NO_3S$ 380.1320, found 380.1322; ^1H NMR (400 MHz): δ 8.15–8.13 (m, 1H), 7.74 (d, J=7.2 Hz, 2H), 7.63–7.61 (m, 1H), 7.46–7.42 (m, 2H), 7.35–7.32 (m, 1H), 7.26–7.18 (m, 2H), 6.52 (s, 1H), 5.98 (br s, 1H), 5.93–5.83 (m, 1H), 5.12–5.05 (m, 3H), 4.11 (dd, J=6.8 Hz, 1H), 3.60–3.52 (m, 1H), 2.84 (dd, J=4.4, 16.8 Hz, 1H), 2.70–2.57 (m, 3H); ^{13}C NMR (100 MHz): δ 150.20, 140.74, 134.52, 133.03, 132.82, 132.38, 128.72 (2×), 126.91 (2×), 126.83, 124.95, 123.91, 122.47, 122.18, 120.15, 117.70, 107.17, 56.46, 41.04, 38.58, 22.63; Anal. Calcd for $C_{22}H_{21}NO_3S$: C, 69.63; H, 5.58; N, 3.69. Found: C, 69.87; H, 5.79; N, 3.94.

*4.4.2. 4-Allyl-3-benzenesulfonyl-8-fluoro-1,2,3,4-tetrahydrobenzo[f]isoquinolin-6-ol (**2b**).* Yield 35% (three-steps); mp=166–169 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3661, 3320, 2934, 1157 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{21}FNO_3S$ 398.1226, found 398.1230; ^1H NMR (400 MHz): δ 7.78–7.75 (m, 2H), 7.70 (dd, J=2.8, 10.4 Hz, 1H), 7.60 (dd, J=5.6, 9.2 Hz, 1H), 7.37 (tt, J=1.2, 6.8 Hz, 1H), 7.30–7.25 (m, 2H), 7.20 (ddd, J=2.8, 8.4, 12.0 Hz, 1H), 6.58 (s, 1H), 5.96 (s, 1H), 5.91–5.81 (m, 1H), 5.11–5.04 (m, 3H), 4.09 (ddt, J=1.2, 6.8, 14.8 Hz, 1H), 3.54 (ddd, J=4.8, 11.6, 14.8 Hz, 1H), 2.83 (dd, J=1.2, 4.8 Hz, 1H), 2.80–2.55 (m, 3H); ^{13}C NMR (100 MHz): δ 161.45, 159.01, 149.69, 140.55, 134.44, 132.51, 132.27, 129.82, 128.76 (2×), 127.01 (2×), 124.95, 124.91, 120.24, 116.65, 107.98, 106.35, 56.24, 40.93, 38.46, 22.80.

4.5. A representative procedure of skeleton 9 is as follows

Lithium aluminum hydride (76 mg, 2.0 mmol) was added to a stirred solution of skeleton **6** (0.5 mmol) in tetrahydrofuran (5 mL) at ice-bath. The mixture was further stirred for 2–3 h at rt. The reaction was quenched with 15% ammonium chloride solution (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 under reduced pressure. Purification on silica gel (hexane/ethyl acetate=3/1–1/1) afforded skeleton **9**.

*4.5.1. 2-(2-Allyl-1-benzenesulfonyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)ethanol (**9a**).* Yield 78%; viscous oil; IR ($CHCl_3$) 3610, 2938, 1191 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_3S$ 384.1633, found 384.1635; ^1H NMR (400 MHz): δ 7.94–7.91 (m, 2H), 7.62–7.58 (m, 1H), 7.53–7.49 (m, 2H), 7.28–7.18 (m, 3H), 6.81–6.78 (m, 2H), 5.81–5.70 (m, 1H), 5.10–5.02 (m, 2H), 4.41 (dd, J=3.2, 9.6 Hz, 1H), 4.00 (dd, J=6.8, 14.8 Hz, 1H), 3.51 (dd, J=6.4, 12.0 Hz, 2H), 3.39 (ddd, J=5.2, 12.0, 15.2 Hz, 1H), 2.60–2.53 (m, 1H), 2.43–2.32 (m, 2H), 2.25–2.16 (m, 1H), 2.04–1.91 (m, 2H), 1.65 (br s, 1H); ^{13}C NMR (100 MHz): δ 141.63, 141.02, 135.14, 134.65, 132.53, 130.31, 128.91 (2×), 128.39 (2×), 127.67 (2×), 127.44 (2×), 126.81, 117.19, 61.06, 55.01, 37.91, 37.17, 33.48, 20.03; Anal. Calcd for $C_{22}H_{25}NO_3S$: C, 68.90; H, 6.57; N, 3.65. Found: C, 69.21; H, 6.39; N, 3.32.

*4.5.2. 2-(2-Allyl-1-benzenesulfonyl-4-(3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridin-3-yl)ethanol (**9b**).* Yield 80%; viscous oil; IR ($CHCl_3$) 3623, 2946, 1198 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{25}F_3NO_3S$ 452.1447, found 452.1450; ^1H NMR (400 MHz): δ 7.95–7.92 (m, 2H), 7.63–7.58 (m, 1H), 7.53–7.45 (m, 3H), 7.40–7.36 (m, 1H), 7.04 (d, J=7.6 Hz, 1H), 6.97 (s, 1H), 5.81–5.70 (m, 1H), 5.10–5.02 (m, 2H), 4.46 (dd, J=3.2, 9.6 Hz, 1H), 4.01 (dd, J=7.2, 14.8 Hz, 1H), 3.55–3.51 (m, 2H), 3.39 (ddd, J=5.2, 12.0, 15.2 Hz, 1H), 2.61–2.54 (m, 1H), 2.42–2.32 (m, 1H), 2.30–2.21 (m, 1H), 2.19–2.12 (m, 1H), 2.05–1.98 (m, 1H), 1.93–1.92 (m, 1H), 1.89 (br s, 1H); ^{13}C NMR (100 MHz): δ 141.63, 141.05, 135.44, 134.14, 132.75, 130.96, 129.85, 129.24, 129.15 (2×), 127.24 (2×), 124.32, 124.26, 124.10, 123.99, 117.69, 66.91, 54.93, 37.61, 37.02, 30.21, 29.74.

*4.5.3. 2-(2-Allyl-1-benzenesulfonyl-4-(4-chloro-3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridin-3-yl) ethanol (**9c**).* Yield 69%; viscous oil; IR ($CHCl_3$) 3618, 2944, 1199 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{24}ClF_3NO_3S$ 486.1118, found 486.1121; ^1H NMR (400 MHz): δ 7.94–7.92 (m, 2H), 7.63–7.58 (m, 1H), 7.53–7.48 (m, 2H), 7.40 (d, J=8.0 Hz, 1H), 7.08 (d, J=2.0 Hz, 1H), 7.01 (dd, J=2.0, 8.0 Hz, 1H), 5.77–5.67 (m, 1H), 5.10–5.01 (m, 2H), 4.46–4.43 (m, 1H), 4.00 (dd, J=7.2, 14.8 Hz, 1H), 3.61–3.50 (m, 2H), 3.38 (ddd, J=4.8, 12.0, 15.2 Hz, 1H), 2.58–2.52 (m, 1H), 2.40–2.23 (m, 2H), 2.19–2.10 (m, 1H), 2.06–1.99 (m, 1H), 1.92–1.86 (m, 2H); ^{13}C NMR (100 MHz): δ 140.81, 140.41, 134.31, 132.76, 132.71, 132.62, 132.49, 131.55, 128.94 (3×), 127.51 (3×), 127.17, 127.02, 117.41, 60.54, 54.74, 37.62, 36.95, 33.31, 29.77; Anal. Calcd for $C_{23}H_{23}ClF_3NO_3S$: C, 56.85; H, 4.77; N, 2.88. Found: C, 57.09; H, 4.93; N, 3.11.

4.6. A representative procedure of skeleton 10 is as follows

Methanesulfonyl chloride (230 mg, 2.0 mmol) was added to a stirred solution of skeleton **9** (0.5 mmol) in the co-solvent of pyridine (5 mL) and dichloromethane (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/ethyl acetate=3/1–1/1) afforded skeleton **10**.

*4.6.1. Methanesulfonic acid 2-(2-allyl-1-benzenesulfonyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)ethyl ester (**10a**).* Yield 82%; viscous oil; IR ($CHCl_3$) 3498, 2930, 1151 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{28}NO_5S_2$ 462.1409, found 462.1411; ^1H NMR (400 MHz): δ 7.91–7.88 (m, 2H), 7.62–7.57 (m, 1H), 7.55–7.50 (m, 2H), 7.27–7.18 (m, 3H), 6.74–6.71 (m, 2H), 5.91–5.81 (m, 1H), 5.13–5.07 (m, 2H), 4.45 (dd, J=2.8, 9.2 Hz, 1H), 3.95 (t, J=6.8 Hz, 2H), 3.91 (dd, J=7.2, 15.2 Hz, 1H), 3.34 (ddd, J=5.2, 12.0, 15.2 Hz, 1H), 2.89 (s, 3H), 2.59–2.35 (m, 3H), 2.27–2.11 (m, 1H), 2.10–2.04 (m, 1H), 1.88 (dd, J=4.8, 17.2 Hz, 1H); ^{13}C NMR (100 MHz): δ 141.11, 141.90, 136.69, 134.35, 132.58, 128.06 (2×), 128.58 (2×), 128.34, 127.30 (2×), 127.14 (3×), 117.49, 67.40, 55.13, 37.76, 37.26, 37.14, 30.14, 29.78; Anal. Calcd for $C_{23}H_{27}NO_5S_2$: C, 59.85; H, 5.90; N, 3.03. Found: C, 59.62; H, 6.24; N, 3.41.

*4.6.2. Methanesulfonic acid 2-(2-allyl-1-benzenesulfonyl-4-(3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridin-3-yl)ethyl ester (**10b**).* Yield 75%; mp=95–97 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3476, 2938, 1151 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{24}H_{27}F_3NO_5S_2$ 530.1283, found 530.1285; ^1H NMR (400 MHz):

δ 7.93–7.90 (m, 2H), 7.64–7.60 (m, 1H), 7.56–7.42 (m, 3H), 7.41–7.38 (m, 1H), 6.99 (d, *J*=7.6 Hz, 1H), 6.91 (br s, 1H), 5.91–5.81 (m, 1H), 5.14–5.09 (m, 2H), 4.50 (dd, *J*=3.2, 9.6 Hz, 1H), 4.01 (dt, *J*=1.2, 6.4 Hz, 2H), 3.94 (dd, *J*=7.2, 15.2 Hz, 1H), 3.38 (ddd, *J*=5.2, 12.0, 15.2 Hz, 1H), 2.95 (s, 3H), 2.60–2.54 (m, 1H), 2.44–2.36 (m, 2H), 2.30–2.25 (m, 1H), 2.12–2.03 (m, 1H), 1.89 (dd, *J*=5.2, 18.0 Hz, 1H); ^{13}C NMR (100 MHz): δ 142.27, 140.93, 134.44, 133.71, 132.66, 131.87, 131.25, 128.94 (2×), 128.92, 127.47 (3×), 124.69, 124.58, 123.70, 123.59, 117.30, 60.73, 54.93, 37.70, 36.99, 33.38, 29.82.

4.7. A representative procedure of skeleton 11 is as follows

DBU (460 mg, 3.0 mmol) was added to a solution of skeleton **10** (0.3 mmol) in tetrahydrofuran (10 mL) at reflux temperature. The reaction mixture was stirred at reflux temperature for 10–12 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (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/ethyl acetate=6/1–3/1) afforded skeleton **11**.

*4.7.1. 6-Allyl-1-benzenesulfonyl-4-phenyl-5-vinyl-1,2,3,6-tetrahydropyridine (**11a**).* Yield 75%; viscous oil; IR ($CHCl_3$) 3512, 2983, 1179 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{24}NO_2S$ 366.1528, found 366.1530; ^{1}H NMR (400 MHz): δ 7.86–7.83 (m, 2H), 7.57–7.53 (m, 1H), 7.47–7.43 (m, 2H), 7.24–7.19 (m, 3H), 6.64–6.60 (m, 2H), 6.11 (dd, *J*=11.2, 18.0 Hz, 1H), 6.06–5.96 (m, 1H), 5.22 (d, *J*=18.0 Hz, 1H), 5.16–5.11 (m, 2H), 5.00 (d, *J*=11.2 Hz, 1H), 4.88 (dd, *J*=2.0, 10.4 Hz, 1H), 4.05–3.98 (m, 1H), 3.49 (dt, *J*=8.8, 15.2 Hz, 1H), 2.65–2.59 (m, 1H), 2.48–2.34 (m, 1H), 2.09–2.05 (m, 2H); ^{13}C NMR (100 MHz): δ 141.38, 140.55, 136.55, 134.95, 133.40, 132.39, 131.47, 128.90 (2×), 128.13 (2×), 128.05 (2×), 127.13, 127.00 (2×), 116.97, 112.66, 52.71, 37.63, 37.60, 29.10.

*4.7.2. 6-Allyl-1-benzenesulfonyl-4-(3-trifluoromethylphenyl)-5-vinyl-1,2,3,6-tetrahydropyridine (**11b**).* Yield 82%; viscous oil; IR ($CHCl_3$) 3519, 2988, 1182 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{23}F_3NO_2S$ 434.1402, found 434.1404; ^{1}H NMR (400 MHz): δ 7.86–7.83 (m, 2H), 7.59–7.55 (m, 1H), 7.48–7.44 (m, 3H), 7.35 (t, *J*=7.6 Hz, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 6.71 (s, 1H), 6.06–5.95 (m, 2H), 5.29 (d, *J*=17.6 Hz, 1H), 5.17–5.13 (m, 2H), 5.07 (d, *J*=11.2 Hz, 1H), 4.88 (dd, *J*=2.0, 10.4 Hz, 1H), 4.09–4.03 (m, 1H), 3.54–3.45 (m, 1H), 2.64–2.58 (m, 1H), 2.48–2.40 (m, 1H), 2.09–2.05 (m, 2H); ^{13}C NMR (100 MHz): δ 141.30, 141.24, 134.96, 134.67, 132.69, 132.60, 131.49, 128.96 (2×), 128.67, 127.05 (2×), 125.07, 125.00, 124.03, 123.95, 123.91, 117.14, 113.89, 52.64, 37.48, 37.43, 28.95.

4.8. A representative procedure of skeleton 3 is as follows

Grubbs second catalyst (12 mg, 1.4% mmol) was added to a solution of skeleton **11** (0.3 mmol) in 1,2-dichloroethane (5 mL) at reflux temperature. The reaction mixture was stirred at reflux temperature for 1–2 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (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/ethyl acetate=6/1–3/1) afforded skeleton **3**.

*4.8.1. 1-Benzenesulfonyl-4-phenyl-2,3,7,7a-tetrahydro-1H-[1]pyrindine (**3a**).* Yield 59%; viscous oil; IR ($CHCl_3$) 3529, 2974, 1182 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{20}H_{20}NO_2S$ 338.7815, found 338.7822; ^{1}H NMR (200 MHz): δ 7.88–7.84 (m, 2H), 7.61–7.56 (m, 3H), 7.32–7.17 (m, 5H), 6.38 (d, *J*=8.4 Hz, 1H), 6.08–6.05 (m, 1H), 3.90–3.85 (m, 3H), 3.05–2.96 (m, 2H), 2.80–2.71 (m, 1H), 2.43–2.28 (m, 1H); ^{13}C NMR (50 MHz): δ 145.33, 137.29, 135.98, 133.82, 131.88, 128.23 (2×), 128.12 (2×), 127.62 (2×), 127.28 (2×), 126.82, 123.98, 113.22, 60.32, 40.29, 38.23, 31.22.

*4.8.2. 1-Benzenesulfonyl-4-(3-trifluoromethylphenyl)-2,3,7,7a-tetrahydro-1H-[1]pyrindine (**3b**).* Yield 70%; viscous oil; IR ($CHCl_3$) 3533, 2975, 1184 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{21}H_{18}F_3NO_2S$ 406.1089, found 406.1092; ^{1}H NMR (200 MHz): δ 7.88–7.82 (m, 2H), 7.56–7.42 (m, 4H), 7.01 (d, *J*=7.6 Hz, 1H), 6.96 (br s, 1H), 6.44 (d, *J*=8.0 Hz, 1H), 6.12–6.08 (m, 1H), 3.91–3.87 (m, 3H), 3.06–2.95 (m, 2H), 2.81–2.73 (m, 1H), 2.44–2.32 (m, 1H); ^{13}C NMR (50 MHz): δ 141.88, 141.21, 135.00, 134.87, 132.92, 132.68, 131.33, 129.01 (3×), 128.90, 127.19 (3×), 126.19, 123.90, 114.14, 58.94, 39.78, 37.21, 29.09.

4.9. A representative procedure of skeleton 12 is as follows

A solution of skeleton **9** (0.5 mmol) in dichloromethane (5 mL) was added to a mixture of pyridinium chlorochromate (432 mg, 2.0 mmol) and Celite (200 mg) in dichloromethane (10 mL). After being stirred at rt for 2–3 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate=6/1–3/1) afforded skeleton **12**.

*4.9.1. (2-Allyl-1-benzenesulfonyl-4-phenyl-1,2,5,6-tetrahydropyridin-3-yl)acetaldehyde (**12a**).* Yield 70%; mp=85–88 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3532, 2943, 1754, 1162 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{24}NO_3S$ 382.1477, found 382.1478; ^{1}H NMR (400 MHz): δ 9.24 (t, *J*=2.0 Hz, 1H), 7.99–7.96 (m, 2H), 7.61–7.57 (m, 1H), 7.54–7.49 (m, 2H), 7.26–7.18 (m, 3H), 6.70–6.67 (m, 2H), 5.95–5.85 (m, 1H), 5.13–5.03 (m, 2H), 4.43 (dd, *J*=3.6, 9.2 Hz, 1H), 3.97 (dd, *J*=6.8, 14.8 Hz, 1H), 3.40 (ddd, *J*=5.6, 11.6, 15.2 Hz, 1H), 3.05 (d, *J*=17.2 Hz, 1H), 2.98 (dd, *J*=1.2, 17.2 Hz, 1H), 2.55–2.48 (m, 1H), 2.44–2.36 (m, 1H), 2.09–1.93 (m, 2H); ^{13}C NMR (100 MHz): δ 198.64, 141.28, 140.75, 137.90, 134.30, 132.48, 128.93 (3×), 128.54, 127.32, 127.26 (4×), 125.13, 117.56, 56.00, 46.15, 38.01, 36.97, 29.54.

*4.9.2. (2-Allyl-1-benzenesulfonyl-4-(4-chloro-3-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridin-3-yl)acetaldehyde (**12b**).* Yield 75%; viscous oil; IR ($CHCl_3$) 3540, 2949, 1758, 1170 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{22}ClF_3NO_3S$ 484.0961, found 484.0966; ^{1}H NMR (400 MHz): δ 9.42 (br s, 1H), 7.99–7.96 (m, 2H), 7.62–7.58 (m, 1H), 7.55–7.46 (m, 2H), 7.38 (d, *J*=8.0 Hz, 1H), 6.91 (d, *J*=2.0 Hz, 1H), 6.87 (dd, *J*=2.0, 8.0 Hz, 1H), 5.92–5.82 (m, 1H), 5.13–5.06 (m, 2H), 4.43 (dd, *J*=3.6, 9.2 Hz, 1H), 3.98 (dd, *J*=6.4, 14.8 Hz, 1H), 3.38 (ddd, *J*=5.2, 11.6, 14.8 Hz, 1H), 3.05 (d, *J*=17.2 Hz, 1H), 2.98 (dd, *J*=1.2, 17.2 Hz, 1H), 2.52–2.45 (m, 1H), 2.42–2.34 (m, 1H), 2.01–1.86 (m, 2H); ^{13}C NMR (100 MHz): δ 197.60, 141.20, 139.61, 135.65, 134.01, 132.71, 132.68, 131.93, 131.79, 129.01 (3×), 127.37 (3×), 126.55, 126.45, 117.85, 56.15, 46.24, 37.77, 36.86, 29.43.

4.10. A representative procedure of skeleton 13 is as follows

A solution of *n*-butyllithium (1.6 M in THF, 1.8 mmol) was added to a stirred solution of methyl triphenylphosphonium iodide (810 mg, 2.0 mmol) in tetrahydrofuran (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. A solution of skeleton **12** (0.5 mmol) in tetrahydrofuran (5 mL) was added to a reaction mixture. The reaction mixture was stirred at −30 °C for 1–2 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (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/ethyl acetate=6/1–3/1) afforded skeleton **13**.

*4.10.1. 5,6-Diallyl-1-benzenesulfonyl-4-phenyl-1,2,3,6-tetrahydropyridine (**13a**).* Yield 66%; viscous oil; IR ($CHCl_3$) 3522, 2976, 1187 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{23}H_{26}NO_2S$ 380.1684, found 380.1682; ^1H NMR (400 MHz): δ 7.89–7.86 (m, 2H), 7.61–7.55 (m, 1H), 7.52–7.43 (m, 2H), 7.26–7.17 (m, 3H), 6.69–6.67 (m, 2H), 5.99–5.90 (m, 1H), 5.56–5.46 (m, 1H), 5.20–4.94 (m, 4H), 4.44 (br s, *J*=6.4 Hz, 1H), 3.97 (dd, *J*=6.4, 14.8 Hz, 1H), 3.39 (ddd, *J*=5.2, 12.0, 17.6 Hz, 1H), 2.77 (dd, *J*=5.6, 15.2 Hz, 1H), 2.63–2.57 (m, 1H), 2.52–2.37 (m, 2H), 2.11–2.01 (m, 1H), 1.91 (dd, *J*=5.6, 17.6 Hz, 1H); ^{13}C NMR (100 MHz): δ 141.62, 141.46, 135.42, 134.89, 133.66, 132.33, 131.02, 128.83 (2×), 128.14 (2×), 127.61 (2×), 127.28 (2×), 126.79, 117.12, 117.07, 54.45, 38.38, 37.14, 35.46, 29.62.

*4.10.2. 5,6-Diallyl-1-benzenesulfonyl-4-(4-chloro-3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine (**13b**).* Yield 72%; viscous oil; IR ($CHCl_3$) 3520, 2968, 1182 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{24}H_{24}ClF_3NO_2S$ 482.1168, found 482.1170; ^1H NMR (400 MHz): δ 7.98–7.96 (m, 2H), 7.64–7.58 (m, 1H), 7.55–7.49 (m, 2H), 7.40 (d, *J*=8.0 Hz, 1H), 6.94 (d, *J*=2.0 Hz, 1H), 6.89 (dd, *J*=2.0, 8.0 Hz, 1H), 6.00–5.91 (m, 1H), 5.60–5.48 (m, 1H), 5.27–4.90 (m, 4H), 4.32 (br s, *J*=6.4 Hz, 1H), 3.91 (dd, *J*=6.4, 14.8 Hz, 1H), 3.22 (ddd, *J*=5.2, 12.0, 17.6 Hz, 1H), 2.64 (dd, *J*=5.6, 15.2 Hz, 1H), 2.60–2.51 (m, 1H), 2.50–2.38 (m, 2H), 2.10–2.00 (m, 1H), 1.88 (dd, *J*=5.6, 17.6 Hz, 1H); ^{13}C NMR (50 MHz): δ 142.10, 140.02, 135.82, 133.92, 132.81, 132.79, 131.67, 131.35, 129.33 (3×), 127.58 (3×), 127.61, 127.28, 126.59, 117.32, 116.88, 55.13, 40.12, 37.49, 36.92, 29.88.

4.11. A representative procedure of skeleton 4 is as follows

Grubbs second catalyst (12 mg, 1.4% mmol) was added to a solution of skeleton **13** (0.3 mmol) in 1,2-dichloroethane (5 mL) at reflux temperature. The reaction mixture was stirred at reflux temperature for 1–2 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with ethyl acetate (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/ethyl acetate=6/1–3/1) afforded skeleton **4**.

*4.11.1. 1-Benzenesulfonyl-4-phenyl-1,2,3,5,8,8a-hexahydroquinoline (**4a**).* Yield 70%; viscous oil; IR ($CHCl_3$) 3533, 2968, 1178 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{21}H_{22}NO_2S$ 352.1371, found 352.1377; ^1H NMR (200 MHz): δ 7.91–7.86 (m, 2H), 7.55–49 (m, 3H), 7.27–7.21 (m, 3H), 6.92–6.87 (m, 2H), 5.63–5.57 (m, 1H), 5.56–5.42 (m, 1H), 4.66–4.61 (m, 1H), 3.99–3.88 (m, 1H), 3.41–3.38 (m, 1H), 2.48–2.40 (m, 2H), 2.15–2.08 (m, 2H), 1.89–1.68 (m, 2H); ^{13}C NMR (50 MHz): δ 142.34, 136.12, 133.91, 132.33, 131.02, 128.66 (2×), 128.04 (2×), 127.72 (2×), 127.30 (2×), 126.53, 124.58, 117.79, 56.12, 38.79, 37.28, 35.88, 30.12.

*4.11.2. 1-Benzenesulfonyl-4-(4-chloro-3-trifluoromethylphenyl)-1,2,3,5,8,8a-hexahydroquinoline (**4b**).* Yield 62%; viscous oil; IR ($CHCl_3$) 3539, 2970, 1181 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{22}H_{19}ClF_3NO_2S$ 454.0855, found 454.0859; ^1H NMR (200 MHz): δ 7.93–7.89 (m, 2H), 7.60–7.55 (m, 1H), 7.50–7.44 (m, 2H), 7.32 (d, *J*=8.0 Hz, 1H), 6.89 (d, *J*=2.0 Hz, 1H), 6.84 (dd, *J*=2.0, 8.0 Hz, 1H), 5.66–5.61 (m, 1H), 5.56–5.50 (m, 1H), 4.76–4.70 (m, 1H), 4.04–3.92 (m, 1H), 3.20–3.16 (m, 1H), 2.44–2.38 (m, 2H), 2.21–2.15 (m, 2H), 1.92–1.87 (m, 2H); ^{13}C NMR (50 MHz): δ 142.38, 140.89, 134.12, 133.11, 132.71, 132.66, 131.52, 131.12, 129.00 (3×), 127.21 (3×), 126.88, 125.12, 117.98, 55.83, 41.23, 39.20, 36.88, 29.12.

Acknowledgements

The authors would like to thank the National Science Council of the Republic of China for its financial support (NSC 99-2113-M-037-006-MY3). The project is also supported by a grant from the Kaohsiung Medical Research Foundation (KMU-Q100004).

References and notes

1. For reviews on the synthesis of piperidine, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701; (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953; (c) Sorbera, L. A.; Serradell, N.; Bolos, J.; Rosa, E.; Bozzo, J. *Drugs Future* **2007**, *32*, 674; (d) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781; (e) Kallstrom, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601.
2. (a) Chang, M.-Y.; Lin, C.-H.; Chen, Y.-L.; Chang, C.-Y.; Hsu, R.-T. *Org. Lett.* **2010**, *12*, 1176; (b) Chang, M.-Y.; Lin, C.-H.; Chen, Y.-L. *Tetrahedron Lett.* **2010**, *51*, 1430; (c) Chang, M.-Y.; Lee, M.-F.; Lee, N.-C.; Huang, Y.-P.; Lin, C.-H. *Tetrahedron Lett.* **2011**, *52*, 588.
3. For synthesis of tetrahydrobenzo[*f*]isoquinoline: (a) Mikhailovskii, A. G.; Bubnov, Y. N.; Syropyatov, B. Y.; Dolzhenko, A. V.; Timofeeva, Y. P. *Pharm. Chem. J.* **1999**, *33*, 128; (b) Mikhailovskii, A. G.; Vakhrin, M. I. *Chem. Heterocycl. Compd.* **2002**, *38*, 205; (c) Polygalova, N. N.; Mikhailovskii, A. G. *Chem. Heterocycl. Compd.* **2006**, *42*, 959 For hexahydrobenzo[*f*]isoquinoline: (d) Russell, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Noble, A. J. *J. Med. Chem.* **1992**, *35*, 2025; (e) Wikstrom, H.; Andersson, B.; Elebring, T.; Svensson, K.; Carlsson, A.; Largent, B. *J. Med. Chem.* **1987**, *30*, 2169; (f) Van de Waterbeemd, H.; El Tayar, N.; Testa, B.; Wikstrom, H.; Largent, B. *J. Med. Chem.* **1987**, *30*, 2175; (g) Moriarty, E.; Carr, M.; Bonham, S.; Carty, M. P.; Aldabbagh, F. *Eur. J. Med. Chem.* **2010**, *45*, 3762; (h) Menard, M.; Rivest, P.; Morris, L.; Meunier, J.; Perron, Y. G. *Can. J. Chem.* **1974**, *52*, 2316; (i) Zimmerman, D. M. GB Patent 2,126,583, 1984. (j) Lalezari, I.; Nabahi, L. S. *J. Heterocycl. Chem.* **1980**, *17*, 1761; (k) Pratap, R.; Raghunandan, R.; Maulik, P. R.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 7982; (l) Ali, M.; El-Sayed, A. A.; Hammouda, H. A. *J. Prakt. Chem.* **1973**, *315*, 1090.
4. For synthesis of tetrahydropyrindine, see: (a) Hong, B.-C.; Wu, J.-L.; Gupta, A. K.; Hallur, M. S.; Liao, J. H. *Org. Lett.* **2004**, *6*, 3453 and cited references herein; (b) Larini, P.; Guarna, A.; Occhiato, E. G. *Org. Lett.* **2006**, *8*, 781; (c) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2003**, *5*, 1689; (d) Kolb, S.; Goddard, M. L.; Loukaci, A.; Mondésert, O.; Ducommun, B.; Braud, E.; Garbay, C. *Eur. J. Med. Chem.* **2010**, *45*, 896; (e) Sasaki, Y.; Shigenaga, A.; Fujii, N.; Otaka, A. *Tetrahedron* **2007**, *63*, 2000.
5. For synthesis of hexahydroquinoline, see: (a) Chou, S. S. P.; Cai, Y. L. *Tetrahedron* **2011**, *67*, 1183 and cited references herein; (b) Chou, S. S. P.; Chung, Y. C.; Chen, P. A.; Chiang, S. L.; Wu, C. J. *J. Org. Chem.* **2011**, *76*, 692.
6. CCDC 795949 (**6a**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
7. For Friedel–Crafts acylation reaction, see: (a) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 733; (b) Olah, G. A. In *Friedel–Crafts Chemistry*; John Wiley and Sons: New York, NY, 1973; For reviews on the intramolecular Friedel–Crafts acylation reaction, see: (c) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 753; (d) Sethna, S. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Interscience: New York, NY, 1964; Vol. 3, p 911; (e) Gore, P. H. *Chem. Rev.* **1955**, *55*, 229.
8. For ring-closing metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446; (b) Schmalz, H. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833; (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036; (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371; (e) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75; (f) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieraugel, H. *Eur. J. Org. Chem.* **1999**, *5*, 959; (g) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 75; (h) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073; (i) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *9*, 3693; (j) Cossy, J. *Chem. Rec.* **2005**, *5*, 70.