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SYNTHESIS OF DIHYDRO-1-BENZAZEPINES

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Abstract – A synthetic route toward the benzannulated dihydro-1-benzazepines (**8**) with two oxygenated groups starting with 2-methoxy-5-nitrophenol (**2**) in high total yield is described. Two key routes are carried by Claisen rearrangement of allyl phenyl ethers (**3**) and ring-closing metathesis of dienes (**7**).

INTRODUCTION

A 1-benzazepine ring system is a key pharmacophore for a drug candidate and its probability for clinical trials, for example, renal and cardiovascular agents, anti-tumor and neuroleptic agents, and potent inhibitors and antagonists.[1-6] It possesses a bicyclic benzannulated framework and is also known to be widespread among promising therapeutic agents. A considerable number of attempts have been made to develop the skeleton. The adopted synthetic routes are described in Figure 1.[7-12] Basically, the key transformations for enhancing the potential biological properties include intramolecular free radical ring-expansion,[7] Claisen-type condensation of dicarbonyl compounds,[8] Schmidt or Beckmann rearrangement of 1-tetralone, transition metal-mediated tandem coupling reaction of aniline with alkenes (e.g., Pd, Rh, Ir, Ru, Ni, Mo),[10,11] 1,3-dipolar cycloaddition of nitrone,[12] and other approaches.[13]

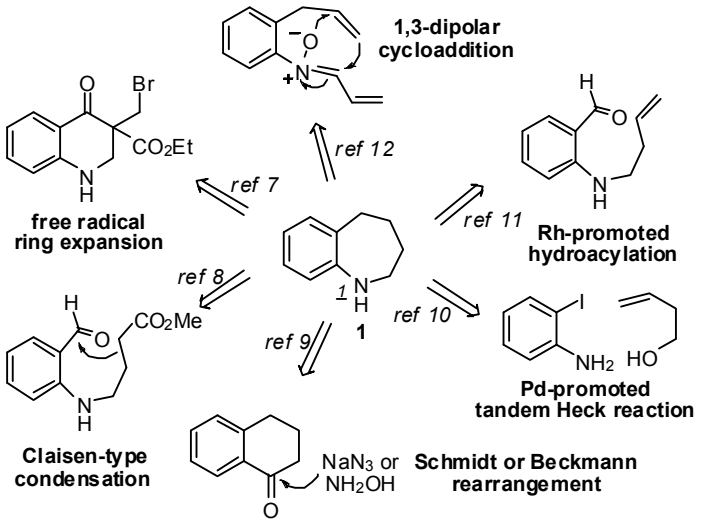
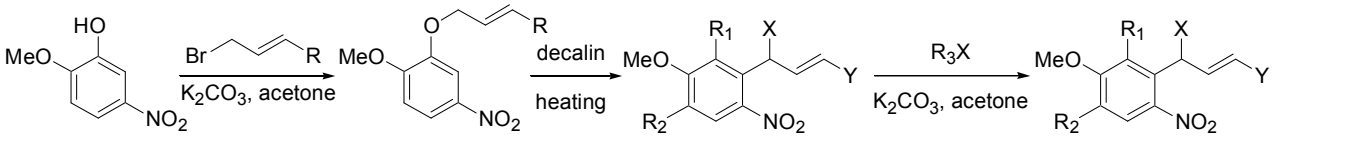


Figure 1. Synthetic Strategies toward 1-Benzazepine (**1**)

RESULTS AND DISCUSSION

Compounds **5a**~**5l** were easily acquired from commercially available 2-methoxy-5-nitrophenol (**2**) in moderate three-step yields overall, according to reported procedures, with a reaction sequence of O-allylation for **2** (R = H, allyl; R = Ph, cinnamyl; R = Me, crotyl) and a Claisen rearrangement of **3a**~**3c**, followed by O-alkylation of the corresponding **4a**~**4c** (R_3 = methyl, isopropyl, *n*-butyl, 3-phenylpropyl, *n*-octyl, *n*-dodecyl, cyclopentyl, benzyl, 3-methoxyphenylmethyl). There are a number of processes available to report this Claisen rearrangement, but generally, the skeleton of allyloxybenzene, with a nitro group, is not chosen as the best substrate because the nitro group exhibits a strong electron-withdrawing effect and thermal instability to easily generate complex results under the heating conditions.[14] To date, there have been few investigations into synthesizing the skeleton of 2-allyl-3-nitrophenol using a thermal Claisen rearrangement as the key step.[15] By controlling the reaction temperature and time, better results were detected in the refluxing decalin solution. After screening substrates, solvents, temperature and time, we found that entry 1 provided the optimized condition and a better yield, as shown in Table 1.



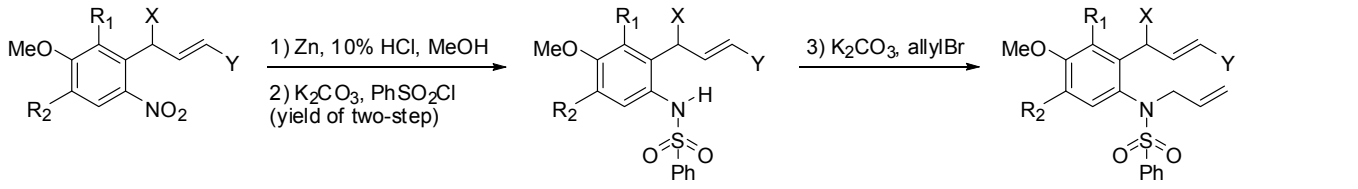
Scheme 1. Synthesis of skeleton (**5**)

Table 1. Claisen rearrangement conditions of skeleton (**3**)[a-b]

Entry	Reactant **3**	Solvent	Temp (°C)	Time (h)	**4** / **3**, Yield (%)[c]
1	**3a**	decalin	reflux	1.5	**4a**, 72 / **3a**, trace
2	**3a**	decalin	reflux	3.0	**4a**, 25 / **3a**, trace
3	**3a**	decalin	140	3.0	**4a**, 30 / **3a**, 45
4	**3a**	decalin	140	6.0	**4a**, 35 / **3a**, 36
5	**3a**	DMF	reflux	1.5	**4a**, 40 / **3a**, 43
6	**3a**	$PhNMe_2$	reflux	1.5	**4a**, 30 / **3a**, 13
7	**3a**	toluene	reflux	1.5	**4a**, ~10 / **3a**, 78
8	**3b**	decalin	reflux	1.0	**4b**, 70 / **3b**, 14
9	**3b**	decalin	reflux	1.5	**4b**, 80 / **3b**, trace
10	**3c**	decalin	reflux	1.5	**4c**, 66 / **3c**, 11

[a]The reactions were run on a 3.0 mmol scale with **3a**~**3c**. [b]**4a**~**4c** was >95% pure as determined by NMR analysis. [c]The unknown mixture was isolated in different yield (entry 1, 15%; entry 2, 58%; entry 3, 16%; entry 4, 22%; entry 5, 10%; entry 6; 50%; entry 7, <10%; entry 8, 11%; entry 9, <10%; entry 10, 17%).

For the generation of **4a**, the optimal reaction condition of Claisen rearrangement should be in a refluxing decalin for a period of 1.5 h. When the reaction time is increased to 3 h, the desired **4a** is isolated in a 25% yield and the insoluble black solid is isolated as the unknown product (58%). To decrease the generation of major unknown products, we tried to decrease the reaction temperature and increase the reaction time. However, the major **3a** is recovered and an unknown mixture is still produced, as shown in entries 3~4. When changing the reaction solvent to three other solvents (DMF, $PhNMe_2$, toluene), **4a** provided poorer yields than entry 1 (see entries 5~7). Also, entries 8~10 exhibited similar results for the formation of **4b** and **4c**.[16]



5a-j/5l

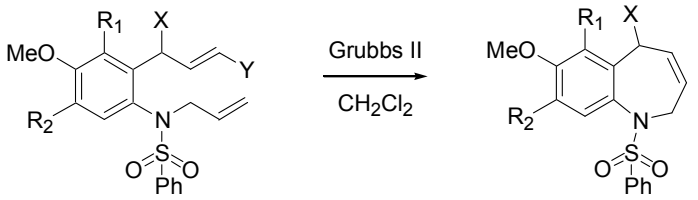
R_2=X=Y=H, R_1=,
6a, OMe (80%); **6b**, O-*n*-C_4H_9 (70%)
6c, O-$(CH_2)_3$Ph (70%); **6d**, O-*n*-C_8H_{17} (77%)
6e, O-*n*-$C_{12}H_{25}$ (72%)
R_1=X=H, Y=Ph, R_2=, **6f**, OMe (47%)
R_2=Y=H, X=Me, R_1=,
6g, OMe (74%)
R_2=X=Y=H, R_1=,
6h, OH (from **5b**, 80%; **5g**, 68%; **5h**, 75%; **5i**, 69%)

R_2=X=Y=H, R_1=,
7a, OMe (90%); **7b**, O-*n*-C_4H_9 (83%)
7c, O-$(CH_2)_3$Ph (84%); **7d**, O-*n*-C_8H_{17} (87%)
7e, O-*n*-$C_{12}H_{25}$ (82%)
R_1=X=H, Y=Ph, R_2=,
7f, OMe (40%)
R_2=Y=H, X=Me, R_1=,
7g, OMe (81%)
R_2=X=Y=H, R_1=,
7h, *O*-allyl (85%)

Scheme 2. Synthesis of skeleton (**7**)

Furthermore, conversion of skeleton **5** into **6** affords 47%~80% yields via the activated zinc-mediated reduction with the presence of 10% HCl in MeOH at rt for 2 h followed by treatment of the corresponding aniline with phenylsulfonyl chloride ($PhSO_2Cl$) and K_2CO_3 at rt for 4 h, as shown in Scheme 2. Then, **7a**~**7h** are prepared by allylation of **6a**~**6h** in 40%~90% yields. Under the above mentioned conditions, compounds **5b**, **5g**, **5h** and **5i**, are converted to **6h** in 80%, 68%, 75% and 69% yields, respectively. Notably, the R_1 group of **5b** (isopropyloxy), **5g** (cyclopentyloxy), **5h** (benzyloxy) and **5i** (3-methoxybenzyloxy) are easily transformed to the hydroxyl group due to the sensitivity of the secondary alkyl or benzyl group under the acidic reduction condition. The structure of **6h** was determined using single-crystal X-ray analysis.[17] For two N-sulfonylation and allylation reactions, the isolated yields of **6f** and **7f** from **5j** and **6f** (Y = Ph) are relatively poorer (47% or 40%). We envisioned that N-sulfonylation should exhibit in the methylene position between the phenyl and cinnamyl group to cause the complex reaction under a mild basic condition. Because acetone could be used as the same reaction solvent for N-sulfonylation and N-allylation, a combination of the two steps was required. We chose **5a** as the substrate to examine the one-pot reaction. In comparing the two routes, we found that the one-pot

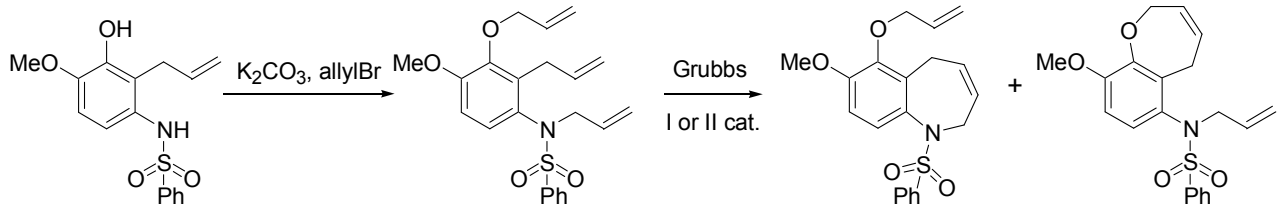
reaction provided **7a** in a higher yield (80%) than the three-step reaction process (72%) did. The one-pot method provides a rapid process to generate **7**. To construct **8**, **7** with the diallyl group was subjected to an intramolecular ring-closing metathesis (RCM) by using Grubbs second generation catalyst in CH_2Cl_2 according to reported conditions.[18-20] **8a**~**8g** in 80%~93% yields were isolated, as shown in Scheme 3. With the results, a rapid synthetic route for establishing the dihydro-1-benzazepine skeleton could be found.



7a~7g

R_2=X=Y=H, R_1=,
8a, OMe (93%); **8b**, O-*n*-C_4H_9 (84%)
8c, O-$(CH_2)_3$Ph (88%); **8d**, O-*n*-C_8H_{17} (90%)
8e, O-*n*-$C_{12}H_{25}$ (88%)
R_1=X=H, Y=Ph, R_2=,
8f, OMe (80%)
R_2=Y=H, X=Me, R_1=,
8g, OMe (82%)

Scheme 3. Synthesis of skeleton (**8**)



6h

7h (85%)

Grubbs II cat., **8h** (62%)
Grubbs I cat., **8h** (47%)

9 (30%)
9 (44%)

Scheme 4. Synthesis of compounds (**8h**) and (**9**)

Under this synthetic sequence, **8h** and **9** were synthesized in 62% and 30% via the double allylation of **6h** and ring-closing metathesis of **7h** with three allyl groups, as shown in Scheme 4. Attempts to achieve sole O- or N-allylation of **6h** failed due to the competitive allylation of **6h**. Interestingly, when reaction of **7h** was treated with Grubbs first generation catalyst in CH_2Cl_2, the yields from **8h** (47%) and **9** (44%) provided a nearly 1/1 ratio. For the two kinds of Grubbs catalysts, both major products were **8h** during reaction conditions.

CONCLUSION

In summary, we have successfully presented a synthetic route for the synthesis of **8a**~**8h** via Claisen rearrangement, reduction, sulfonylation, allylation and ring-closing metathesis. This synthesis begins with

simple starting materials and reagents, and provides a new synthetic route toward the skeleton of 1-benzazepines.

EXPERIMENTAL

General. 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. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and at 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.

A representative synthetic procedure of skeleton (3) *is as follows:* K_2CO_3 (1.38 g, 10.0 mmol) was added to a solution of **2** (845 mg, 5.0 mmol) in acetone (30 mL) at rt. The reaction mixture was stirred at rt for 10 min. Different allylic bromide (7.5 mmol, for **3a**, allyl bromide 900 mg; for **3b**, cinnamyl bromide, 1.48 g; for **3c**, crotyl bromide, 1.00 g) was added to the reaction mixture at rt. The reaction mixture was stirred at reflux for 10 h. The reaction was monitored by TLC until **2a** was consumed. The reaction mixture was cooled to rt, concentrated, and partitioned with EtOAc (3 x 30 mL) and water. The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc=10/1~8/1) afforded **3a**~**3c**.

2-Allyloxy-1-methoxy-4-nitrobenzene (3a). Yield 95% (995 mg); Yellowish solid; mp 85-87 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{10}H_{12}NO_4$ 210.0766, found 210.0770; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.91 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.75 (d, *J* = 2.8 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.13-6.03 (m, 1H), 5.46 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.36 (dq, *J* = 1.6, 10.4 Hz, 1H), 4.68 (dt, *J* = 1.6, 5.6 Hz, 2H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.83, 147.69, 141.30, 131.94, 119.09, 117.93, 110.04, 108.12, 70.05, 56.41; Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.62; H, 5.22; N, 6.92.

2-Cinnamyloxy-1-methoxy-4-nitrobenzene (3b). Yield 92% (1.31 g); Yellowish solid; mp 112-114 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{16}H_{16}NO_4$ 286.1079, found 286.1083; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, *J*=2.4, 8.8 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.42-7.41 (m, 2H), 7.36-7.24 (m, 3H), 6.89 (d, *J* = 9.2 Hz, 1H), 6.77 (d, *J* = 16.0 Hz, 1H), 6.43 (dt, *J* = 6.0,

16.0 Hz, 1H), 4.78 (d, *J*=6.0 Hz, 2H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.65, 147.48, 141.01, 135.82, 134.14, 128.36 (2x), 127.92, 126.45 (2x), 122.75, 117.71, 109.87, 107.81, 69.66, 56.15; Anal. Calcd for $C_{16}H_{16}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 57.62; H, 5.22; N, 5.19.

2-But-2-enyloxy-1-methoxy-4-nitrobenzene (3c). Yield 90% (1.01 g); Yellowish solid; mp 70-72 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{11}H_{14}NO_4$ 224.0923, found 224.0928; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 9.2 Hz, 1H), 5.97-5.88 (m, 1H), 5.80-5.72 (m, 1H), 4.59 (dd, *J* = 1.2, 6.0 Hz, 2H), 3.96 (s, 3H), 1.77 (dd, *J* = 1.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.80, 147.83, 141.30, 132.14, 124.78, 117.69, 109.90, 107.88, 69.94, 56.38, 17.86; Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.41; H, 6.02; N, 6.56.

A representative synthetic procedure of skeleton (4) is as follows: Decalin (8 mL) was added to a solution of **3** (3.0 mmol) at rt. The reaction mixture was stirred at reflux for 1.5 h. The reaction mixture was cooled to rt. Decalin was evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1~4/1) afforded **4**a~**4c**.

2-Allyl-6-methoxy-3-nitrophenol (4a). In Table 1, entry 1; Yield 72% (450 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{10}H_{12}NO_4$ 210.0766, found 210.0771; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 9.2 Hz, 1H), 6.80 (d, *J* = 9.2 Hz, 1H), 6.05-6.95 (m, 1H), 5.96 (s, 1H), 5.07 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.04 (dq, *J* = 1.6, 10.4 Hz, 1H), 3.98 (s, 3H), 3.74 (dt, *J* = 1.6, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.86 (2x), 144.18, 134.61, 121.88, 117.56, 115.90, 107.47, 56.37, 29.74.

2-Methoxy-5-nitro-4-(3-phenylallyl)phenol (4b). In Table 1, entry 9; Yield 80% (684 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{16}H_{16}NO_4$ 286.1079, found 286.1083; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.37-7.20 (m, 5H), 6.77 (s, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.36 (dt, *J* = 6.4, 16.0 Hz, 1H), 5.75 (s, 1H), 3.96 (s, 3H), 3.84 (dt, *J* = 1.2, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.47, 144.03, 137.09, 131.85, 130.14, 129.30, 128.52 (2x), 127.34, 127.21, 126.17 (2x), 112.54, 111.66, 56.35, 36.73.

6-Methoxy-2-(1-methylallyl)-3-nitrophenol (4c). In Table 1, entry 10; Yield 66% (441 mg); Yellowish solid; mp 100-102 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{11}H_{14}NO_4$ 224.0923, found 224.0924; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.31-6.22 (m, 1H), 6.04 (s, 1H), 5.10 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.05 (dt, *J* = 1.6, 10.4 Hz, 1H), 4.03-3.99 (m, 1H), 3.96 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.42, 144.41, 140.15 (2x), 125.58, 116.58, 114.52, 107.47, 56.36, 36.45, 17.91; Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.35; H, 5.98; N, 6.45.

A representative synthetic procedure of skeleton (5) is as follows: K_2CO_3 (280 mg, 2.0 mmol) was added

to a solution of **4** (1.0 mmol) in acetone (10 mL) at rt. The reaction mixture was stirred at rt for 10 min. Different alkyl halide (1.5 mmol, for **5a**, **5j** and **5l**, methyl iodide, 210 mg; for **5b**, isopropyl bromide, 185 mg; for **5c** and **5k**, *n*-butyl bromide, 206 mg; for **5d**, 3-phenylpropyl bromide, 300 mg; for **5e**, *n*-octyl bromide, 290 mg; for **5f**, *n*-dodecyl bromide, 375 mg; for **5g**, cyclopentyl bromide, 225 mg; for **5h**, benzyl bromide, 260 mg; for **5i**, 3-methoxyphenylmethyl bromide, 305 mg) was added to the reaction mixture at rt. The reaction mixture was stirred at reflux for 10 h. The reaction mixture was cooled to rt, concentrated, and partitioned with EtOAc (3 x 30 mL) and water. The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~8/1) afforded **5a**~**5l**.

2-Allyl-3,4-dimethoxy-1-nitrobenzene (5a). Yield 92% (205 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{11}H_{14}NO_4$ 224.0923, found 224.0928; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.03-5.93 (m, 1H), 5.05-4.98 (m, 2H), 3.95 (s, 3H), 3.84 (s, 3H), 3.77 (dt, *J* = 1.6, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.85, 147.58, 142.90, 134.39, 130.40, 121.93, 115.93, 109.29, 61.10, 56.06, 30.04.

2-Allyl-3-isopropoxy-4-methoxy-1-nitrobenzene (5b). Yield 88% (221 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{13}H_{18}NO_4$ 252.1236, found 252.1242; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 9.2 Hz, 1H), 5.95-5.85 (m, 1H), 5.02-4.95 (m, 2H), 4.60-4.54 (m, 1H), 3.92 (s, 3H), 3.80 (dt, *J* = 1.6, 6.0 Hz, 2H), 1.29 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.75, 145.29, 142.88, 134.92, 130.39, 121.29, 115.87, 108.96, 75.42, 55.97, 30.18, 22.50 (2x).

2-Allyl-3-butoxy-4-methoxy-1-nitrobenzene (5c). Yield 88% (233 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{14}H_{20}NO_4$ 266.1392, found 266.1394; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 9.2 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.01-5.91 (m, 1H), 5.03-4.97 (m, 2H), 3.94 (t, *J* = 6.8 Hz, 2H), 3.93 (s, 3H), 3.78 (dt, *J* = 1.6, 6.0 Hz, 2H), 1.81-1.74 (m, 2H), 1.57-1.46 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.93, 146.89, 142.50, 135.39, 130.39, 121.75, 115.82, 109.18, 73.41, 56.03, 32.22, 30.04, 19.10, 13.86.

2-Allyl-3-(1-phenylpropyloxy)-4-methoxy-1-nitrobenzene (5d). Yield 92% (300 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4$ 328.1549, found 328.1552; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.33-7.29 (m, 1H), 7.26-7.19 (m, 3H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.02-5.92 (m, 1H), 5.03-4.96 (m, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 3.91 (s, 3H), 3.78 (dt, *J* = 1.2, 5.6 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.17-2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.85, 146.76, 142.96, 141.57, 135.34, 130.35, 128.43 (2x), 128.38 (2x), 125.93, 121.83, 115.86, 109.18, 72.81, 55.98, 32.11, 31.76, 30.09.

2-Allyl-4-methoxy-1-nitro-3-octyloxybenzene (5e). Yield 91% (292 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{28}NO_4$ 322.2018, found 322.2022; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 9.2 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.01-5.92 (m, 1H), 5.03-4.96 (m, 2H), 3.93 (t, *J* = 6.8 Hz, 2H), 3.93 (s,

3H), 3.78 (dt, *J* = 2.0, 6.4 Hz, 2H), 1.82-1.75 (m, 2H), 1.50-1.42 (m, 2H), 1.37-1.28 (m, 8H), 0.89 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.94, 146.86, 142.93, 135.38, 130.40, 121.79, 115.82, 109.13, 73.73, 56.03, 31.81, 30.14, 20.06, 29.37, 29.23, 25.86, 22.64, 14.01.

2-Allyl-3-dodecyloxy-4-methoxy-1-nitrobenzene (5f). Yield 85% (320 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{22}H_{36}NO_4$ 378.2644, found 378.2646; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 9.2 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.01-5.91 (m, 1H), 5.03-4.96 (m, 2H), 3.93 (t, *J* = 6.8 Hz, 2H), 3.93 (s, 3H), 3.78 (dt, *J* = 2.0, 6.4 Hz, 2H), 1.92-1.75 (m, 2H), 1.50-1.42 (m, 2H), 1.36-1.26 (m, 16H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.93, 146.88, 142.96, 135.38, 130.40, 121.75, 115.82, 109.16, 73.74, 56.03, 31.91, 31.15, 30.06, 29.65, 29.62, 29.60, 29.57, 29.41, 29.34, 25.87, 22.67, 14.11.

2-Allyl-3-cyclopentyloxy-4-methoxy-1-nitrobenzene (5g). Yield 88% (244 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{15}H_{20}NO_4$ 278.1392, found 278.1397; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 9.2 Hz, 1H), 5.95-5.85 (m, 1H), 5.01-4.94 (m, 2H), 4.91-4.87 (m, 1H), 3.92 (s, 3H), 3.77 (dt, *J* = 1.6, 6.0 Hz, 2H), 1.89-1.59 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.53, 145.66, 142.33, 134.93, 130.19, 121.15, 115.79, 109.13, 85.29, 55.97, 32.81 (2x), 30.05, 23.60 (2x).

2-Allyl-3-benzyloxy-4-methoxy-1-nitrobenzene (5h). Yield 92% (275 mg); Yellowish solid; mp 68-70 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{17}H_{18}NO_4$ 300.1236, found 300.1242; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.2 Hz, 1H), 7.47-7.33 (m, 5H), 6.89 (d, *J* = 9.2 Hz, 1H), 5.99-5.89 (m, 1H), 5.02-4.93 (m, 2H), 5.01 (s, 2H), 3.97 (s, 3H), 3.76 (dt, *J* = 1.6, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.88, 146.37, 143.06, 136.99, 135.26, 130.66, 128.49 (2x), 128.21, 128.07 (2x), 122.08, 115.97, 109.31, 75.07, 56.11, 30.15; Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.45; H, 6.10; N, 4.82.

2-Allyl-3-(3-methoxybenzyloxy)-4-methoxy-1-nitrobenzene (5i). Yield 90% (296 mg); Yellowish gum; HRMS (ESI, M^++1) calcd for $C_{18}H_{20}NO_5$ 330.1342, found 330.1348; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.2 Hz, 1H), 7.31 (t, *J* = 9.2 Hz, 1H), 7.04 (s, 1H), 7.03 (d, *J* = 9.2 Hz, 1H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.00-5.90 (m, 1H), 5.03-4.95 (m, 2H), 4.99 (s, 2H), 3.96 (s, 3H), 3.83 (s, 3H), 3.77 (dt, *J* = 1.6, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.61, 156.78, 146.16, 142.79, 138.42, 135.19, 130.41, 129.39, 122.00, 120.04, 115.83, 113.55, 113.33, 109.24, 74.74, 55.99, 55.09, 30.05.

4,5-Dimethoxy-1-nitro-2-(3-phenylallyl)benzene (5j). Yield 70% (209 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{17}H_{18}NO_4$ 300.1236, found 300.1243; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.36-7.19 (m, 5H), 6.79 (s, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.37 (dt, *J* = 6.4, 16.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.87 (dd, *J* = 1.2, 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.14, 147.38, 137.09, 131.92, 130.47, 128.52 (2x), 127.35, 127.07, 126.70, 126.18 (2x), 113.13, 108.23, 56.34, 56.31, 36.89.

5-n-Butoxy-4-methoxy-1-nitro-2-(3-phenylallyl)benzene (5k). Yield 60% (205 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{24}NO_4$ 342.1705, found 342.1711; ^{1}H NMR (400 MHz): δ 7.63 (s, 1H),

7.36-7.15 (m, 5H), 6.77 (s, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.35 (dt, *J* = 6.4, 16.0 Hz, 1H), 4.07 (t, *J* = 5.8 Hz, 2H), 3.93 (s, 3H), 3.86 (dd, *J* = 0.8, 6.4 Hz, 2H), 1.89-1.82 (m, 2H), 1.52-1.46 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz): δ 153.51, 146.94, 137.13, 131.84, 130.19, 128.74, 128.51 (2x), 127.32, 127.18, 126.17 (2x), 113.29, 109.38, 69.13, 56.34, 36.90, 30.93, 19.12, 13.79.

1,2-Dimethoxy-3-(1-methylallyl)-4-nitrobenzene (5l). Yield 82% (194 mg); Yellowish oil; HRMS (ESI, M^++1) calcd for $C_{12}H_{16}NO_4$ 238.1079, found 238.1081; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 9.2 Hz, 1H), 6.14 (ddd, *J* = 6.0, 10.4, 16.4 Hz, 1H), 5.08-5.02 (m, 2H), 4.02-3.98 (m, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 1.48 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.11, 147.95, 141.02, 134.30, 121.87, 120.59, 114.19, 109.40, 60.89, 56.97, 36.15, 18.84.

A representative synthetic procedure of skeleton (6) is as follows: Activated zinc (24 mg, 1.2 mmol) was added to a solution of **5** (1.0 mmol) in MeOH (8 mL) at rt. Then, 10% HCl aqueous solution was added to the mixture, and stirring occurred at rt for 2 h. The reaction mixture was filtered and evaporated to yield crude product. Without further purification, K_2CO_3 (280 mg, 2.0 mmol) was added to a solution of crude product in acetone (10 mL) at rt. The reaction mixture was stirred at rt for 10 min. Then, benzenesulfonyl chloride (265 mg, 1.5 mmol) was added to reaction mixture. The reaction mixture was stirred at rt for 4 h. The reaction mixture was concentrated, and partitioned with EtOAc (3 x 30 mL) and water. The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~8/1) afforded **6a**~**6h**.

N-(2-Allyl-3,4-dimethoxyphenyl)benzenesulfonamide (6a). Yield 80% (266 mg); Colorless solid; mp 121-123 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{17}H_{20}NO_4S$ 334.1113, found 334.1118; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.67 (m, 2H), 7.57-7.53 (m, 1H), 7.45-7.41 (m, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.48 (s, 1H), 5.83-5.73 (m, 1H), 5.03 (dd, *J* = 1.6, 10.4 Hz, 1H), 4.84 (dq, *J* = 1.6, 17.2 Hz, 1H), 3.84 (s, 3H), 3.69 (s, 3H), 2.97 (dt, *J* = 1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.48, 146.96, 139.60, 135.68, 132.76, 128.85 (2x), 128.14, 127.84, 126.86 (2x), 121.91, 115.93, 110.38, 60.86, 55.59, 28.62. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.52; H, 5.93; N, 4.36.

N-(2-Allyl-3-butoxy-4-methoxyphenyl)benzenesulfonamide (6b). Yield 70% (263 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{26}NO_4S$ 376.1583, found 376.1588; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H), 7.55-7.51 (m, 1H), 7.43-7.39 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.41 (s, 1H), 5.80-5.71 (m, 1H), 5.03 (dd, *J* = 1.6, 10.4 Hz, 1H), 4.83 (dq, *J* = 1.6, 17.2 Hz, 1H), 3.81 (s, 3H), 3.78 (t, *J* = 7.2 Hz, 2H), 2.90 (dt, *J* = 1.6, 5.6 Hz, 2H), 1.67-1.59 (m, 2H), 1.45-1.36 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.61, 146.23, 139.67, 135.76, 132.77, 128.90 (2x), 128.80, 127.95, 126.87 (2x), 121.73, 116.07, 110.44, 73.22, 55.66, 32.11, 28.75, 19.03, 13.77.

N-[2-Allyl-4-methoxy-3-(3-phenylpropoxy)phenyl]benzenesulfonamide (6c). Yield 70% (306 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{25}H_{28}NO_4S$ 438.1739, found 438.1743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H), 7.54-7.50 (m, 1H), 7.43-7.38 (m, 2H), 7.32-7.26 (m, 2H), 7.22-7.19 (m, 3H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.46 (s, 1H), 5.81-5.72 (m, 1H), 5.04 (dd, *J* = 1.6, 10.4 Hz, 1H), 4.85 (dq, *J* = 1.6, 17.2 Hz, 1H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 2.95 (dt, *J* = 1.6, 5.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.04-1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.50, 146.08, 141.61, 139.59, 135.65, 132.76, 128.87 (2x), 128.31 (2x), 128.24 (2x), 127.99, 127.93, 126.82 (2x), 125.76, 121.84, 116.06, 110.40, 72.66, 55.58, 32.06, 31.66, 28.77.

N-(2-Allyl-4-methoxy-3-octyloxyphenyl)benzenesulfonamide (6d). Yield 77% (332 mg); Colorless solid; mp 63-64 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{24}H_{34}NO_4S$ 432.2209, found 432.2213; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.64 (m, 2H), 7.59-7.52 (m, 1H), 7.44-7.39 (m, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.37 (s, 1H), 5.81-5.71 (m, 1H), 5.05 (dd, *J* = 1.6, 10.4 Hz, 1H), 4.84 (dq, *J* = 1.6, 17.2 Hz, 1H), 3.83 (s, 3H), 3.76 (t, *J* = 6.4 Hz, 2H), 2.89 (dt, *J* = 1.6, 5.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.39-1.24 (m, 10H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.64, 146.27, 139.72, 135.79, 133.84, 132.81, 129.24, 128.94 (2x), 126.90 (2x), 121.75, 116.18, 110.49, 73.63, 55.71, 31.79, 30.08, 29.32, 29.19, 28.80, 25.86, 22.61, 14.07. Anal. Calcd for $C_{24}H_{33}NO_4S$: C, 66.79; H, 7.71; N, 3.25. Found: C, 66.92; H, 7.56; N, 3.38.

N-(2-Allyl-3-dodecyloxy-4-methoxyphenyl)benzenesulfonamide (6e). Yield 72% (351 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{28}H_{42}NO_4S$ 488.2835, found 488.2836; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.64 (m, 2H), 7.58-7.51 (m, 1H), 7.43-7.39 (m, 2H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.40 (s, 1H), 5.81-5.71 (m, 1H), 5.04 (dd, *J* = 1.6, 10.4 Hz, 1H), 4.84 (dq, *J* = 1.6, 17.2 Hz, 1H), 3.82 (s, 3H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.91 (dt, *J* = 1.6, 5.6 Hz, 2H), 1.68-1.61 (m, 2H), 1.38-1.20 (m, 18H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.62, 146.25, 139.69, 135.78, 132.79, 129.23, 128.92 (2x), 126.89 (2x), 121.73, 116.11, 110.45, 73.59, 55.68, 31.86, 30.06, 29.60, 29.58 (2x), 29.56, 29.52, 29.34, 29.29, 28.78, 25.83, 22.63, 14.07.

N-[4,5-Dimethoxy-2-(3-phenylallyl)phenyl]benzenesulfonamide (6f). Yield 47% (192 mg); Colorless solid; mp 113-115 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{23}H_{24}NO_4S$ 410.1426, found 410.1432; ^{1}H NMR (400 MHz): δ 7.74-7.71 (m, 2H), 7.55-7.51 (m, 1H), 7.42-7.38 (m, 2H), 7.27-7.24 (m, 4H), 7.22-7.17 (m, 1H), 6.76 (s, 1H), 6.73 (s, 1H), 6.61 (s, 1H), 6.24 (dt, *J* = 1.2, 16.0 Hz, 1H), 6.04 (dt, *J* = 6.4, 16.0 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.15 (dt, *J* = 1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz): δ 147.76, 147.52, 139.31, 136.73, 132.74, 131.21, 128.84 (2x), 128.37 (2x), 127.60, 127.37, 127.24, 127.16 (2x), 126.34, 126.05 (2x), 112.46, 110.32, 55.81, 55.75, 34.22.

N-[3,4-Dimethoxy-2-(1-methylallyl)phenyl]benzenesulfonamide (6g). Yield 74% (257 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1270, found 348.1278; ^{1}H NMR (400 MHz): δ

7.78-7.75 (m, 2H), 7.56-7.52 (m, 1H), 7.47-7.43 (m, 2H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.75 (br s, 1H), 6.72 (d, *J* = 9.2 Hz, 1H), 5.98-5.90 (m, 1H), 5.19 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.10 (dd, *J* = 1.2, 17.6 Hz, 1H), 4.02-3.98 (m, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 1.08 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 150.90, 147.21, 141.78, 140.01, 132.81, 131.32, 128.93 (2x), 128.22, 127.16 (2x), 119.25, 114.61, 110.57, 60.96, 55.71, 33.62, 16.88.

N-(2-Allyl-3-hydroxy-4-methoxyphenyl)benzenesulfonamide (6h). For **5b**, Yield 80% (255 mg); For **5g**, Yield 68% (217 mg); For **5h**, Yield=75% (240 mg); For **5i**, Yield 69% (220 mg); Colorless solid; mp 113-115 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{16}H_{18}NO_4S$ 320.0957, found 320.0956; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.69 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.40 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.44 (br s, 1H), 5.81-5.71 (m, 1H), 5.76 (br s, 1H), 5.01 (dq, *J* = 1.6, 10.0 Hz, 1H), 4.87 (dq, *J* = 1.6, 17.2 Hz, 1H), 3.85 (s, 3H), 3.01 (dt, *J* = 1.6, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.04, 143.57, 139.72, 135.19, 132.80, 128.93 (2x), 128.39, 126.98 (2x), 119.87, 117.13, 115.78, 108.65, 55.97, 28.36; Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.49; H, 5.52; N, 4.68. Single-crystal X-Ray diagram: crystal of **6h** was grown by slow diffusion of EtOAc into a solution of **6h** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the orthorhombic crystal system, space group P b c a, *a* = 14.0992(8) Å, *b* = 14.5823(9) Å, *c* = 15.0416(9) Å, *V* = 3092.5(3) Å^3, *Z* = 8, d_{calcd} = 1.376 g/cm^3, *F*(000) = 1352, 2*θ* range 2.42~28.27^o, R indices (all data) R1 = 0.0439, wR2=0.1182.

A representative synthetic procedure of skeleton (7) is as follows: K_2CO_3 (138 mg, 1.0 mmol) was added to a solution of **6** (0.5 mmol) in acetone (8 mL) at rt. The reaction mixture was stirred at rt for 10 min. Allyl bromide (180 mg, 1.5 mmol) was added to the reaction mixture at rt. The reaction mixture was stirred at reflux for 10 h. The reaction mixture was cooled to rt, concentrated, and partitioned with EtOAc (3 x 30 mL) and water. The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1~8/1) afforded **7a**~**7h**.

N-Allyl-N-(2-allyl-3,4-dimethoxyphenyl)benzenesulfonamide (7a). Yield 90% (168 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{24}NO_4S$ 374.1426, found 374.1433; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.69 (m, 2H), 7.60-7.56 (m, 1H), 7.50-7.45 (m, 2H), 6.62 (d, *J* = 8.8 Hz, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.99-5.89 (m, 1H), 5.76-5.66 (m, 1H), 5.01-4.92 (m, 4H), 4.14 (dd, *J* = 6.4, 14.4 Hz, 1H), 4.02 (dd, *J* = 7.2, 14.4 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.47-3.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.74, 148.04, 139.12, 136.97, 135.41, 132.72, 132.56, 130.55, 128.71 (2x), 127.86 (2x), 124.76, 119.11, 115.14, 109.49, 60.47, 55.50, 55.03, 30.65.

N-Allyl-N-(2-allyl-3-butoxy-4-methoxyphenyl)benzenesulfonamide (7b). Yield 83% (172 mg); Colorless

solid; mp 73-75 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{23}H_{30}NO_4S$ 416.1896, found 416.1897; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.70 (m, 2H), 7.65-7.58 (m, 1H), 7.50-7.45 (m, 2H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 1H), 5.98-5.89 (m, 1H), 5.77-5.67 (m, 1H), 5.00-4.92 (m, 4H), 4.14-4.00 (m, 2H), 3.92-3.86 (m, 2H), 3.81 (s, 3H), 3.45-3.39 (m, 2H), 1.76-1.66 (m, 2H), 1.52-1.42 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.89, 147.38, 139.29, 137.04, 135.56, 133.06, 132.85, 132.54, 128.73 (2x), 127.93 (2x), 124.74, 119.09, 115.08, 109.45, 72.53, 55.54, 55.07, 32.30, 30.81, 19.09, 13.89.

N-Allyl-N-[2-allyl-4-methoxy-3-(3-phenylpropoxy)phenyl]benzenesulfonamide (7c). Yield 84% (200 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{28}H_{32}NO_4S$ 478.2052, found 478.2055; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.72 (m, 2H), 7.65-7.58 (m, 1H), 7.50-7.46 (m, 2H), 7.31-7.21 (m, 5H), 6.63 (d, *J* = 8.8 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 1H), 6.02-5.93 (m, 1H), 5.79-5.69 (m, 1H), 5.03-4.95 (m, 4H), 4.13-3.94 (m, 4H), 3.80 (s, 3H), 3.49-3.48 (m, 2H), 2.82 (dt, *J* = 2.4, 7.6 Hz, 2H), 2.13-2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.74, 147.17, 141.88, 139.12, 136.97, 135.43, 132.76, 132.54, 130.53, 128.69 (2x), 128.38 (2x), 128.22 (2x), 127.85 (2x), 125.70, 124.72, 119.09, 115.11, 109.39, 71.90, 55.43, 55.02, 32.14, 31.88, 30.78.

N-Allyl-N-(2-allyl-4-methoxy-3-octyloxyphenyl)benzenesulfonamide (7d). Yield 87% (205 mg); Colorless solid; mp 60-61 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{27}H_{38}NO_4S$ 472.2522, found 472.2525; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.70 (m, 2H), 7.60-7.57 (m, 1H), 7.50-7.46 (m, 2H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 1H), 5.98-5.89 (m, 1H), 5.77-5.67 (m, 1H), 4.99-4.92 (m, 4H), 4.15-3.85 (m, 4H), 3.80 (s, 3H), 3.44-3.42 (m, 2H), 1.78-1.70 (m, 2H), 1.45-1.39 (m, 2H), 1.35-1.25 (m, 8H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.89, 147.37, 139.26, 137.04, 135.57, 132.84, 132.56, 130.58, 128.74 (2x), 127.93 (2x), 124.72, 119.11, 115.09, 109.41, 72.85, 55.53, 55.08, 31.80, 30.81, 30.20, 29.39, 29.23, 25.86, 22.63, 14.63.

N-Allyl-N-(2-allyl-3-dodecyloxy-4-methoxyphenyl)benzenesulfonamide (7e). Yield 82% (216 mg); Colorless solid; mp 66-67 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{31}H_{46}NO_4S$ 528.3148, found 528.3152; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.70 (m, 2H), 7.60-7.56 (m, 1H), 7.52-7.46 (m, 2H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.99-5.89 (m, 1H), 5.78-5.67 (m, 1H), 5.01-4.92 (m, 4H), 4.15-3.85 (m, 4H), 3.80 (s, 3H), 3.45-3.43 (m, 2H), 1.77-1.68 (m, 2H), 1.45-1.27 (m, 18H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.86, 147.35, 139.23, 137.02, 135.53, 132.81, 132.53, 130.57, 128.70 (2x), 127.89 (2x), 124.67, 119.06, 115.05, 109.39, 72.81, 55.50, 55.05, 31.84, 30.79, 30.18, 29.61, 29.56 (2x), 29.41 (2x), 29.28, 25.84, 22.61, 14.05; Anal. Calcd for $C_{31}H_{45}NO_4S$: C, 70.55; H, 8.59; N, 2.65. Found: C, 70.68; H, 8.81; N, 2.49.

N-Allyl-N-[4,5-dimethoxy-2-(3-phenylallyl)phenyl]benzenesulfonamide (7f). Yield 40% (90 mg);

Colorless solid; mp 130-132 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{26}H_{28}NO_4S$ 450.1739, found 450.1742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.73 (m, 2H), 7.64-7.59 (m, 1H), 7.54-7.49 (m, 2H), 7.38-7.35 (m, 2H), 7.32-7.28 (m, 2H), 7.23-7.19 (m, 1H), 6.76 (s, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.26 (dt, *J* = 7.2, 15.6 Hz, 1H), 5.99 (s, 1H), 5.84-5.74 (m, 1H), 5.06-4.98 (m, 2H), 4.39 (dd, *J* = 6.0, 13.6 Hz, 1H), 3.88 (dd, *J* = 7.6, 13.6 Hz, 1H), 3.83 (s, 3H), 3.68 (dd, *J* = 1.2, 7.2 Hz, 1H), 3.56 (dd, *J* = 1.2, 7.2 Hz, 1H), 3.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.91, 146.97, 138.93, 137.49, 134.28, 132.70, 132.56 (2x), 131.46, 129.01, 128.84 (2x), 128.49 (2x), 128.06 (2x), 127.07, 126.10 (2x), 119.49, 112.30, 111.32, 55.83, 55.66, 55.12, 34.15; Anal. Calcd for $C_{26}H_{28}NO_4S$: C, 69.46; H, 6.05; N, 3.12. Found: C, 69.66; H, 6.29; N, 3.29.

N-Allyl-N-[3,4-dimethoxy-2-(1-methylallyl)phenyl]benzenesulfonamide (7g). Yield 81% (157 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{21}H_{26}NO_4S$ 388.1583, found 388.1587; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78-7.73 (m, 2H), 7.57-7.50 (m, 3H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.30 (d, *J* = 8.4 Hz, 1H), 6.28-6.05 (m, 1H), 5.85-5.62 (m, 1H), 5.00-4.92 (m, 4H), 4.25-4.20 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.80-3.77 (m, 2H), 1.41 (d, *J* = 7.2 Hz, 3H).

N-Allyl-N-(2-allyl-3-allyloxy-4-methoxyphenyl)benzenesulfonamide (7h). Yield 85% (170 mg); Colorless solid; mp 60-62 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{22}H_{26}NO_4S$ 400.1583, found 400.1584; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.69 (m, 2H), 7.60-7.56 (m, 1H), 7.50-7.46 (m, 2H), 6.62 (d, *J* = 8.8 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 1H), 6.10-6.02 (m, 1H), 6.01-5.89 (m, 1H), 5.77-5.66 (m, 1H), 5.35 (dq, *J* = 1.6, 17.2 Hz, 1H), 5.20 (dq, *J* = 1.6, 10.4 Hz, 1H), 5.00-4.92 (m, 4H), 4.54-4.43 (m, 2H), 4.13 (dd, *J* = 6.4, 14.4 Hz, 1H), 4.03 (dd, *J* = 7.2, 14.4 Hz, 1H), 3.80 (s, 3H), 3.44 (dt, *J* = 1.6, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.76, 146.85, 139.14, 136.85, 135.57, 134.18, 132.73, 132.56, 130.55, 128.71 (2x), 127.84 (2x), 124.92, 119.10, 116.89, 115.14, 109.43, 73.32, 55.51, 55.02, 30.84; Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.35; H, 6.18; N, 3.72.

A representative synthetic procedure of skeleton (8) and compound (9) is as follows: Grubbs 2nd catalyst (24 mg, 2.83 mmol%) was added to a solution of **7** (0.3 mmol) in CH_2Cl_2 (10 mL) at rt for 1 h. The reaction mixture was concentrated and partitioned with EtOAc (3 x 20 mL) and water. The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc=10/1~8/1) afforded **8a**~**8h** and **9**.

1-Benzenesulfonyl-6,7-dimethoxy-2,5-dihydro-1H-benzo[b]azepine (8a). Yield 93% (96 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{20}NO_4S$ 346.1131, found 346.1137; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.57-7.53 (m, 1H), 7.47-7.42 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* =8 .8 Hz, 1H), 5.67-5.61 (m, 1H), 5.45-5.40 (m, 1H), 4.38-4.36 (br m, 2H), 3.84 (s, 3H), 3.68 (s, 3H), 2.98 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.83, 145.62, 141.47, 135.63, 132.41, 131.81, 128.84 (2x), 126.99

(2x), 126.16, 125.60, 125.24, 109.70, 60.90, 55.72, 49.46, 22.90.

1-Benzenesulfonyl-6-butoxy-7-methoxy-2,5-dihydro-1H-benzo[b]azepine (8b). Yield 84% (98 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{21}H_{26}NO_4S$ 388.1583, found 388.1584; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.72 (m, 2H), 7.56-7.49 (m, 1H), 7.45-7.41 (m, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 5.65-5.59 (m, 1H), 5.44-5.39 (m, 1H), 4.36 (br s, 2H), 3.84 (s, 3H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.94 (br s, 2H), 1.69-1.61 (m, 2H), 1.48-1.39 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.88, 141.46, 135.72, 132.36, 128.97, 128.80 (2x), 126.95 (2x), 126.83, 126.10, 125.36, 125.28, 109.71, 73.27, 55.70, 49.43, 32.06, 23.03, 19.08, 13.78.

1-Benzenesulfonyl-7-methoxy-6-(3-phenylpropoxy)-2,5-dihydro-1H-benzo[b]azepine (8c). Yield 88% (119 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{26}H_{28}NO_4S$ 450.1739, found 450.1742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (m, 2H), 7.55-7.51 (m, 1H), 7.44-7.40 (m, 2H), 7.32-7.26 (m, 2H), 7.22-7.18 (m, 3H), 7.04 (dd, *J* = 0.8, 8.8 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 5.63-5.58 (m, 1H), 5.44-5.41 (m, 1H), 4.38 (br s, 2H), 3.84 (t, *J* = 6.4 Hz, 2H), 3.82 (s, 3H), 2.95 (br s, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.06-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.77, 144.69, 141.61, 141.38, 135.64, 132.36, 131.65, 128.79 (2x), 128.34 (2x), 128.27 (2x), 126.90 (2x), 126.11, 125.78, 125.46, 125.16, 109.66, 72.69, 55.63, 49.39, 32.10, 31.59, 23.04.

1-Benzenesulfonyl-7-methoxy-6-octyloxy-2,5-dihydro-1H-benzo[b]azepine (8d). Yield 90% (120 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{25}H_{34}NO_4S$ 444.2209, found 444.2213; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.72 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 5.66-5.59 (m, 1H), 5.44-5.39 (m, 1H), 4.37 (br s, 2H), 3.82 (s, 3H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.94 (br s, 2H), 1.70-1.63 (m, 2H), 1.41-1.35 (m, 2H), 1.31-1.28 (m, 8H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.86, 144.84, 141.43, 135.69, 132.35, 131.64, 128.80 (2x), 126.93 (2x), 126.08, 125.36, 125.26, 109.65, 73.59, 55.67, 49.42, 31.75, 29.98, 29.28, 29.17, 25.84, 23.02, 22.57, 14.03.

1-Benzenesulfonyl-6-dodecyloxy-7-methoxy-2,5-dihydro-1H-benzo[b]azepine (8e). Yield 88% (132 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{29}H_{42}NO_4S$ 500.2835, found 500.2839; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.72 (m, 2H), 7.57-7.51 (m, 1H), 7.46-7.42 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 5.65-5.59 (m, 1H), 5.44-5.40 (m, 1H), 4.42 (br s, 2H), 3.83 (s, 3H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.93 (br s, 2H), 1.71-1.60 (m, 2H), 1.41-1.26 (m, 18H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.92, 144.92, 141.51, 135.76, 132.39, 131.71, 128.84 (2x), 127.01 (2x), 126.13, 125.43, 125.33, 109.72, 73.67, 55.74, 49.47, 31.89, 30.05, 29.64, 29.60, 29.57, 29.40, 29.33, 25.91, 23.09, 23.09, 22.66, 14.10.

1-Benzenesulfonyl-7,8-dimethoxy-2,5-dihydro-1H-benzo[b]azepine (8f). Yield 80% (83 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{20}NO_4S$ 346.1113, found 346.1115; ^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.76-7.72 (m, 2H), 7.56-7.52 (m, 1H), 7.45-7.43 (m, 2H), 6.77 (s, 1H), 6.49 (s, 1H), 5.62-5.55 (m, 1H), 5.46-5.41 (m, 1H), 4.19 (br s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 2.75 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.51, 147.41, 141.34, 133.17, 132.39, 130.58, 128.76 (2x), 127.09 (2x), 125.68, 125.35, 113.33, 111.70, 55.92, 55.84, 48.99, 31.98.

1-Benzenesulfonyl-6,7-dimethoxy-5-methyl-2,5-dihydro-1H-benzo[b]azepine (8g). Yield 82% (88 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1274; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.63-7.54 (m, 3H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.91-5.85 (m, 1H), 5.54-5.50 (m, 1H), 4.68 (dd, *J* = 4.8, 17.2 Hz, 1H), 4.13-4.06 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.71 (d, *J* = 17.2 Hz, 1H), 1.51 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.45, 146.07, 142.28, 138.95, 132.54, 132.47, 132.31, 129.20 (2x), 127.05 (2x), 124.70, 122.19, 109.85, 61.07, 55.75, 49.45, 31.12, 21.73.

6-Allyloxy-1-benzenesulfonyl-7-methoxy-2,5-dihydro-1H-benzo[b]azepine (8h). Yield 62% (69 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{22}NO_4S$ 372.1270, found 372.1277; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.74 (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.42 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.02-5.92 (m, 1H), 5.64-5.59 (m, 1H), 5.44-5.40 (m, 1H), 5.28 (dq, *J* = 1.2, 17.2 Hz, 1H), 5.18 (dq, *J* = 1.2, 10.4 Hz, 1H), 4.36 (br s, 2H), 4.34 (dt, *J* = 1.2, 6.0 Hz, 2H), 3.84 (s, 3H), 2.94 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.88, 144.34, 141.51, 135.91, 133.86, 132.40, 131.74, 128.84 (2x), 127.01 (2x), 126.09, 125.73, 125.29, 117.84, 109.70, 74.20, 55.75, 49.45, 23.25.

N-Allyl-N-(9-methoxy-2,5-dihydrobenzo[b]oxepin-6-yl)benzenesulfonamide (9). Yield 30% (33 mg); Colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{22}NO_4S$ 372.1270, found 372.1273; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.68 (m, 2H), 7.60-7.56 (m, 1H), 7.50-7.46 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.77-5.67 (m, 2H), 5.41-5.37 (m, 1H), 5.03-4.96 (m, 2H), 4.64-4.53 (m, 2H), 4.26 (ddt, *J* = 1.2, 6.0, 14.0 Hz, 1H), 3.88 (dd, *J* = 7.2, 14.0 Hz, 1H), 3.83 (s, 3H), 3.48-3.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.30, 147.19, 140.56, 139.17, 132.56, 132.44, 128.83 (2x), 128.57, 127.71 (2x), 127.20, 125.45, 124.92, 119.27, 109.42, 70.37, 55.76, 55.09, 25.44.

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SUPPLEMENTARY MATERIAL

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