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Diastereoselective Synthesis of Substituted Morpholines from *N*-Tethered Alkenols: Total Synthesis of (±)-Chelonin A

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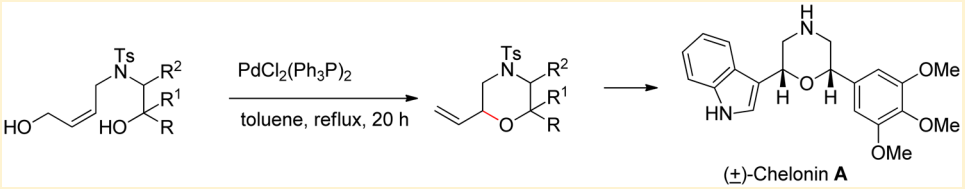
Supporting Information



ABSTRACT: Intramolecular cyclization of nitrogen tethered alkenols catalyzed by palladium chloride leads to substituted morpholines in good yields. The methodology was used for the total synthesis of (±)-chelonin A.

INTRODUCTION

Substituted morpholine derivatives are widely distributed in many naturally occurring and biologically active molecules.[1] For example, viloxazine (**1**), reboxetine (**2**), and edivoxetine (**3**) show antidepressant properties.[2] Similarly, compounds **4** and **5** containing morpholine unit have anti-inflammatory and $GABA_B$ receptor-antagonist properties (Figure 1).[3] Morpholines are

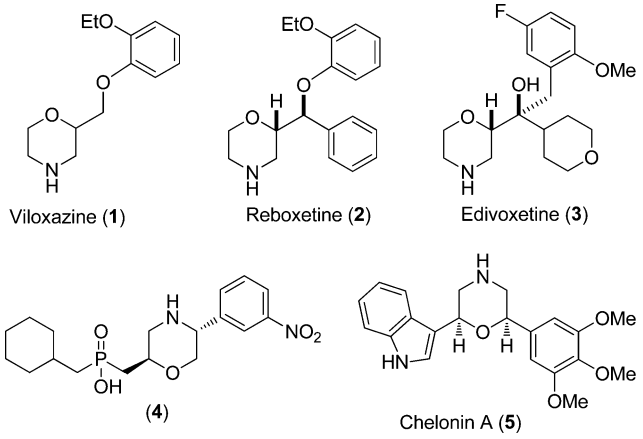


Figure 1. Biologically important morpholines.

used not only in organic synthesis as bases or *N*-alkylating agents[4] but also as versatile synthetic units in organic synthesis particularly for the construction of agrochemicals, fungicides, and bactericides.[5] They are also used as chiral auxiliaries.[6]

Several synthetic approaches have been developed for the preparation of morpholines such as ring closure of amino diols,[7] ring closure of amino alcohols and bromosulphonium salts,[8] double allylic substitution by amino alcohols,[9] cyclization of *N*-tethered haloalcohols,[10] reductive amination of diketones,[11] reductive etherification of *N*-tethered ketoalcohols,[12] cyclization of *O*-protected amino alcohols,[13] oxirane ring opening by tosylamide and subsequent cyclization,[14] ring opening of aziridines,[15] and intramolecular cyclization of *N*-tethered alkene-alkanols.[16] These methods have their own merits and disadvantages. Recently, we have developed a methodology for the synthesis of oxygen and nitrogen heterocyclic compounds via intramolecular C−C bond formation from alkyne-epoxides mediated by boron trifluoride etherate.[17] We now present a methodology for the synthesis of morpholines using intramolecular C−O bond formation of *N*-tethered diols consisting of alkanol and alkenol and catalyzed by palladium(II) in good yields. Palladium(II) salts have been used for the synthesis of oxygen heterocycles via intramolecular oxypalladation.[18] Although gold(I) has been used for the synthesis of 2-vinyl morpholine from *N*-tethered allylic alcohols,[19] the use of palladium(II) in morpholine synthesis is not yet reported.

RESULTS AND DISCUSSION

Considering the ability of palladium(II) compounds to participate in oxypalladation, alkenol **6a** was treated with 5 mol % of preformed $PdCl_2(Ph_3P)_2$ in toluene at 90 °C for 20 h, and 4-tosyl-2-vinylmorpholine **7a** was obtained in 85% yield (Table 1). The reaction was also performed in the absence of PPh_3 with 5 mol % other palladium(II) sources such as $Pd(OAc)_2$ and $PdCl_2$ to give the same product in 20 and 65% yields, respectively. Similarly, reaction with a mixture of $PdCl_2$ (5 mol %) and Ph_3P (10 mol %) gave 85% yields, which suggested that the complex catalyst was formed in situ. To investigate the oxidative addition, cyclization, and reductive elimination process, the reaction was also carried out with $Pd(Ph_3P)_4$ but resulted in no yield (entry 5). This indicates that the reaction proceeds via oxypalladation and elimination processes.

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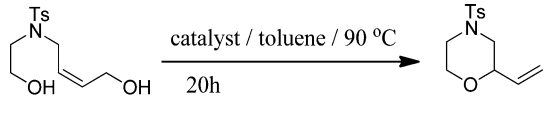
Table 1. Optimization of the Reaction Condition



6a **7a**

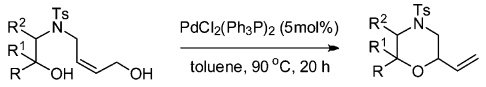
	catalyst (mol %)	7a yield (%)[a]
1	$PdCl_2(Ph_3P)_2$ (5)	85
2	$Pd(OAc)_2$ (5)	20
3	$PdCl_2$ (5)	65
4	$PdCl_2$ (5), Ph_3P (10)	85
5	$Pd(Ph_3P)_4$ (5)	no reaction

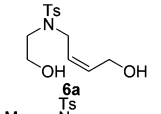
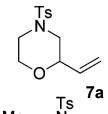
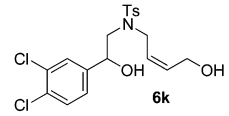
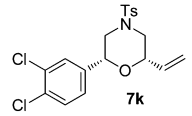
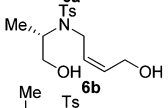
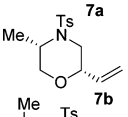
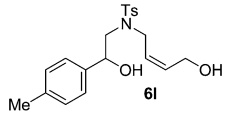
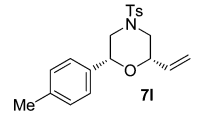
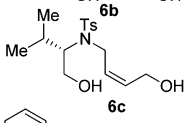
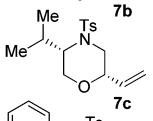
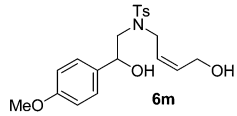
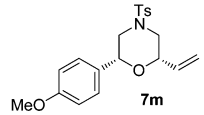
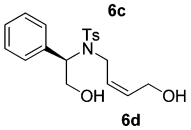
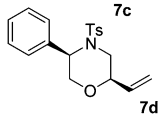
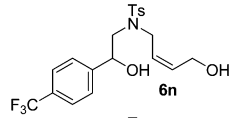
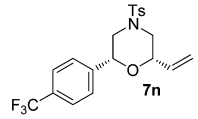
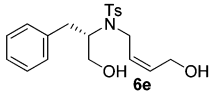
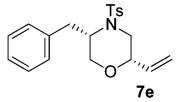
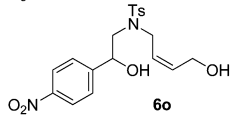
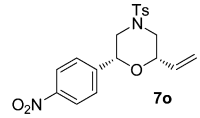
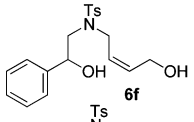
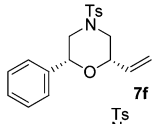
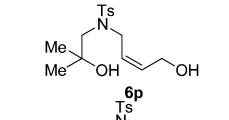
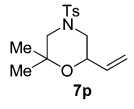
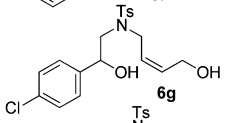
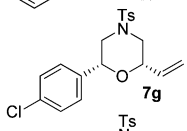
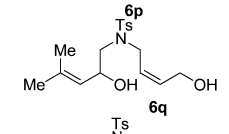
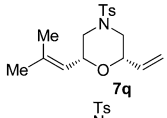
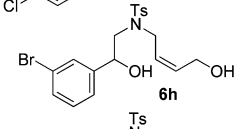
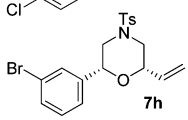
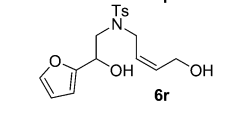
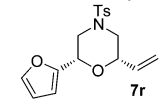
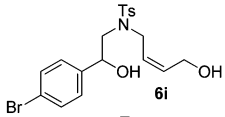
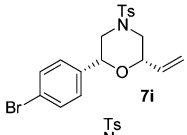
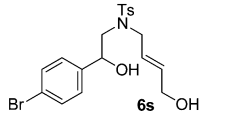
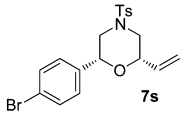
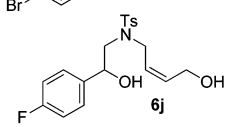
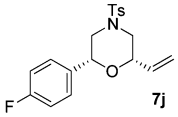
[a]Yield refers to isolated yield.

With the optimized conditions in hand, we further examined the scope of the reaction with a variety of substrates (Table 2).

It was observed from Table 2 that primary (Table 2, **6a**–**e**), secondary, including benzylic or allylic alcohols (Table 2, **6f**–**o**, **q**, **r**, and **s**), and tertiary alcohols (Table 2, **6p**) undergo the reaction smoothly without giving elimination products, indicating those which are crucial for the reaction of secondary and tertiary alcohols, particularly benzylic alcohols, under Lewis acidic or Brönsted acidic conditions. Success in the reaction of substrate **6q**, with its primary and secondary allylic alcohol groups (Table 2, entry 17), indicates that the primary allylic alcohol reacts selectively in its coordination with palladium under these reaction conditions, and this accounts for the observed product **7q**. Sterically hindered tertiary alcohol **6p** (Table 2, entry 16) gave comparatively lower yield (65%), indicating that nucleophilic addition was rate limiting. The reaction worked well for both electron-withdrawing and electron-donating groups on the aromatic ring of benzylic

Table 2. Synthesis of Morpholines



Sl.No.	Substrate **6**	Product **7**	dr[a]	Yield (%)[b]	Sl.No.	Substrate **6**	Product **7**	dr[a]	Yield (%)[b]
1	 **6a**	 **7a**	----	85	11	 **6k**	 **7k**	100:0	74
2	 **6b**	 **7b**	100:0	88	12	 **6l**	 **7l**	93:7	82
3	 **6c**	 **7c**	100:0	72	13	 **6m**	 **7m**	97:3	85
4	 **6d**	 **7d**	97:3	80	14	 **6n**	 **7n**	100:0	82
5	 **6e**	 **7e**	86:14	78	15	 **6o**	 **7o**	93:7	84
6	 **6f**	 **7f**	91:9	90	16	 **6p**	 **7p**	----	65
7	 **6g**	 **7g**	100:0	80	17	 **6q**	 **7q**	91:9	70
8	 **6h**	 **7h**	100:0	85	18	 **6r**	 **7r**	90:10	72
9	 **6i**	 **7i**	91:9	84	19	 **6s**	 **7s**	63:37	70
10	 **6j**	 **7j**	72:28	75					

[a]The ratio was determined by ^1H NMR spectroscopy of crude products. [b]Yield refers to isolated yield. All of the products were characterized by ^1H NMR, ^{13}C NMR, and mass spectrometry.

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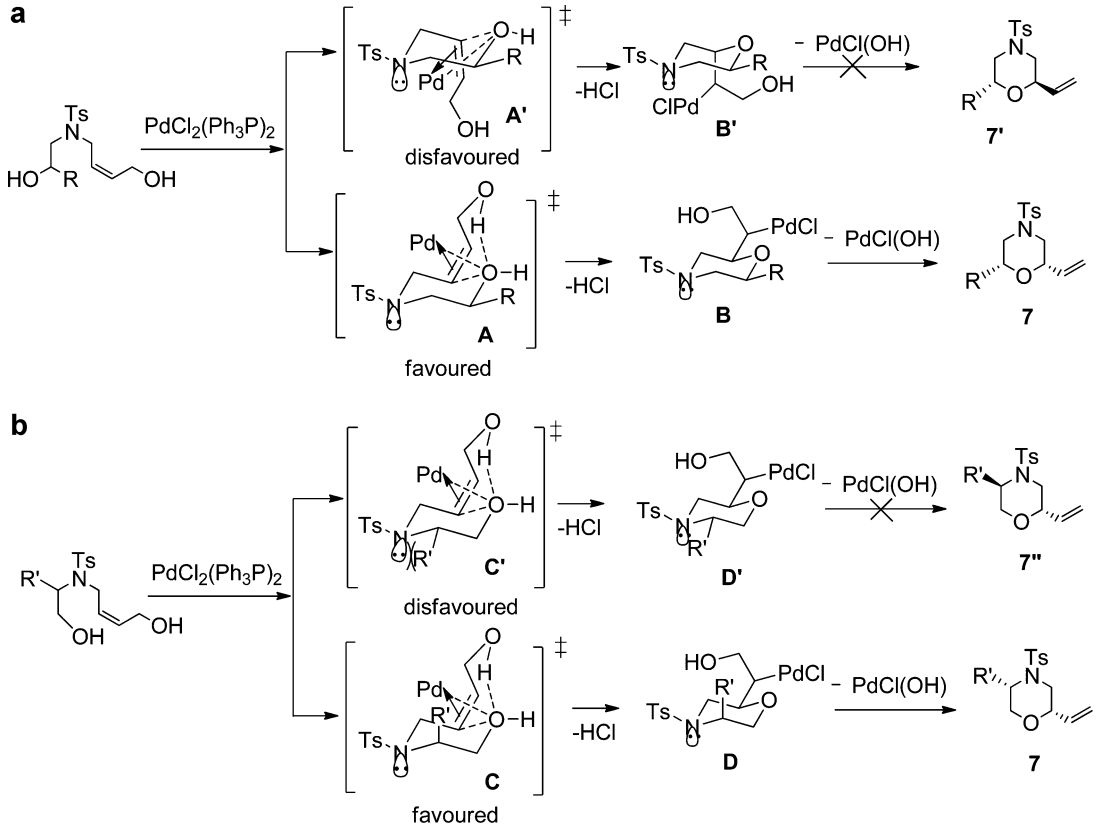
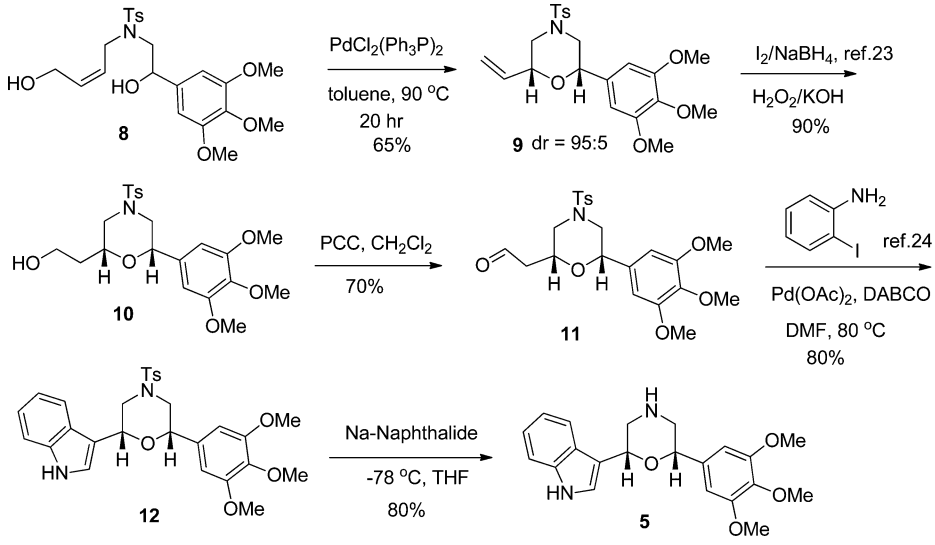
Scheme 1. Plausible Mechanism of the Reaction



Scheme 2. Total Synthesis of (±)-Chelonin A



alcohol substrates, suggesting little influence of the aryl group, and produced the desired morpholines in good yields.

The reaction is highly diastereoselective, which is determined by proton NMR analysis of the crude products. The relative stereochemistry of the preferred substituted morpholines was determined by 2D nuclear Overhauser enhancement spectroscopy (NOESY) of compounds **7o** and **12** and X-ray crystallographic analysis of compounds **7e** and **7o** (see the Supporting Information).[20] The high stereoselectivity may be attributed to the energy differences in the highly coordinated transition states **A**, **A′**, **C**, and **C′** formed by allylic alcohol with palladium(II) species (Scheme 1). The formation of *cis*-2,6-disubstituted morpholine can be attributed to the more stable transition state **A**, where both vinyl and R groups take the equatorial position to minimize the 1,3-diaxial interaction (Scheme 1a). Similarly, selective formation of *cis*-2,5-disubstituted morpholine is due to the favored transition state **C**, where the R′ group takes the axial position to minimize the 1,2-lone pair and bond pair repulsion between the lone pair over nitrogen and C−C bond pair of the R′ group attached to C-5 position. In contrast, the substrate having an *E*- configured

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alkene, alcohol **6s** (Table 2, entry 19), showed poor *cis*/*trans* diastereoselectivity (63:37).[19]

The proposed mechanism of the reaction is similar to that reported by Tragni[19] and others.[18] The reaction proceeds via stepwise oxypalladation and elimination processes.[18d] Palladium(II) chloride forms a π-complex with allylic alcohol in an *anti*-fashion to form transition states **A** and **A′**, of which **A′** is unstable due to the presence of the allylic group in the axial position. The stability of the transition state **A** may be increased by the formation of a second six-membered ring due to the hydrogen bonding between the two hydroxyl groups.[18d] The transition state **A** after nucleophilic attack by the hydroxyl group via an S_N2' pathway forms intermediate **B**. Intermediate **B**, after either *syn*- or *anti*-elimination, forms vinyl substituted morpholines **7a** and **7f**−**7r** (Scheme 1a).[18d] The formation of compounds **7b**−**7e** can be explained as follows. The R′ groups take the axial position in the transition state **C** to minimize the repulsive force between the lone pair over nitrogen and C−C bond pair of R′ group attached to the C-5 position (Scheme 1b).

To investigate the further applicability of the strategy, a total synthesis of (±)-chelonin A was undertaken (Scheme 2). Chelonin A was isolated from marine sponge *Chelonaplysilla* sp.,[21] and its first total synthesis was reported by the Somei group.[22] To start, diol **8** was treated with palladium chloride to give diastereomeric mixture of morpholine **9** with a ratio of 95:5 in 65% yield along with 20% unreacted starting material. Conversion of the olefinic group of the major diastereomer of morpholine **9** into alcohol **10** followed by PCC oxidation gave aldehyde **11** as a single diastereomer in 70% yield. The aldehyde **11** was treated with 2-iodoaniline in the presence of palladium acetate to give tosylated (±)-chelonin A (**12**) in 80% yield. The final compound **5** was obtained by detosylation with sodium naphthalide in 80% yield and 26% overall yield. The spectral data were in good agreement with the literature.[21]

CONCLUSIONS

In conclusion, we developed an efficient method for the synthesis of substituted morpholines via palladium chloride intramolecular cyclization reaction of *N*-tethered diols in good yields. The reaction is compatible with a wide range of functional groups such as ether, -NO_2, chloro, bromo and furan. The major advantage of this reaction is that it regioselectively generates a vinyl group at position 2 of the morpholine ring, which can be used for the synthesis of biologically active molecules (±)-chelonin A.

EXPERIMENTAL SECTION

General Information. All of the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60−120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in ppm and spin−spin coupling constants (J) are given in Hz. HRMS spectra were recorded using Q-TOF mass spectrometer.

General Procedure for the Synthesis of *N*-Tethered Alkenols (6a−6s). To a stirred solution of NaH (2.2 mmol, 60% in mineral oil) in dry DMF (5 mL) was added dropwise a solution of the tosyl amides (2.0 mmol) in dry DMF (10 mL) at 0 °C (N_2 atmosphere). After 20 min, a solution of (*Z*)-4-bromobut-2-en-1-ol (2 mmol) in DMF (5 mL) was added, and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol were added at 0 °C, and the solution was poured into ethyl acetate (50 mL). The organic phase was washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated in vacuo, and column chromatography using ethyl acetate and hexane as eluents gave the *N*-tethered alkenol **6a**−**6s**.

*Preparation of (Z)-N-(4-Hydroxybut-2-en-1-yl)-N-(2-hydroxyethyl)-4-methylbenzene-sulfonamide (**6a**).* To a stirred solution of NaH (88 mg, 2.2 mmol, 60% in mineral oil) in dry DMF (5 mL) was added dropwise a solution of the tosyl amides (2 mmol) in dry DMF (5 mL) at 0 °C (N_2 atmosphere). After 20 min, a solution of (*Z*)-4-bromobut-2-en-1-ol (300 mg, 2 mmol) in DMF (5 mL) was added, and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol were added at 0 °C, and the solution was poured into ethyl acetate (50 mL). The organic phase was washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated in vacuo, and column chromatography (EtOAc:hexane, 3:2) gave the *N*-tethered alkenol **6a**.

White solid; mp 48−50 °C; R_f (hexane:EtOAc 3:2) 0.6; yield 342 mg, 60%; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H, Ts-CH_3), 3.24 (t, J = 5.4 Hz, 2 H, 1′-H), 3.73 (t, J = 5.4 Hz, 2 H, 2′-H), 3.94 (d, J = 7.2 Hz, 2 H, 1-H), 4.13 (d, J = 6.6 Hz, 2 H, 4-H), 5.35−5.38 (m, 1 H, 2-H), 5.74−5.79 (m, 1 H, 3-H), 7.30 (d, J = 8.4 Hz, 2 H, 3″, 5″-H), 7.68 (d, J = 8.4 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.1, 49.9, 57.7, 61.7, 127.0, 127.3, 130.1, 133.0, 136.4, 143.9; IR (KBr, neat) 3579, 2959, 2853, 1923, 1652, 1593, 1449, 1163, 887, 764 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{20}NO_4S$ $(M + H)^+$ 286.1108, found 286.1119.

*(Z)-N-(4-Hydroxybut-2-en-1-yl)-N-(1-hydroxypropan-2-yl)-4-methylbenzenesulfonamide (**6b**).* Colorless oil; R_f (hexane:EtOAc 3:2) 0.55; yield 400 mg, 67%; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J = 7.2 Hz, 3 H, 2′-CH_3), 2.41 (s, 3 H, Ts-CH_3), 3.49−3.57 (m, 2 H, 1′-H), 3.86 (dd, J = 16.2 and 7.8 Hz, 1 H, 1-H), 3.95−3.98 (m, 2 H, 1-H, 2′-H), 4.21 (d, J = 7.2 Hz, 2 H, 4-H), 5.55−5.60 (m, 1 H, 2-H), 5.71−5.76 (m, 1 H, 3-H), 7.29 (d, J = 8.0 Hz, 2 H, 3″, 5″-H), 7.71 (d, J = 8.0 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.7, 40.3, 55.5, 58.0, 64.8, 127.3, 129.5, 130.0, 131.3, 137.8, 143.7; IR (KBr, neat) 3477, 2980, 2856, 1920, 1647, 1599, 1457, 1324, 1153, 1014, 870, 760 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}NO_4S$ $(M + H)^+$ 300.1264, found 300.1274. $[\alpha]_D^{20}$ +24.9 (c 1.0 $CHCl_3$).

*(Z)-N-(1-Hydroxy-3-methylbutan-2-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6c**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.51; yield 405 mg, 62%; ^1H NMR (600 MHz, $CDCl_3$) δ 0.69 (d, J = 6.6 Hz, 3 H, 3-CH_3), 0.91 (d, J = 6.6 Hz, 3 H, 3-CH_3), 1.79−1.85 (m, 2 H, 3-H, −OH), 2.20 (brs, 1 H, −OH), 2.42 (s, 3 H, Ts-CH_3), 3.44−3.48 (m, 1 H, 2-H), 3.62 (dd, J = 12.0 and 8.4 Hz, 1 H, 1-H), 3.75 (dd, J = 12.0 and 9.6 Hz, 1 H, 1-H), 3.91 (dd, J = 16.2 and 7.2 Hz, 1 H, 1′-H), 4.02 (dd, J = 16.2 and 7.2 Hz, 1 H, 1′-H), 4.21 (d, J = 7.2 Hz, 2 H, 4′-H), 5.60−5.65 (m, 1 H, 2′-H), 5.72−5.77 (m, 1 H, 3′-H), 7.28 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.72 (d, J = 7.8 Hz, 2 H, 2″,6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.3, 20.8, 21.7, 28.2, 41.3, 58.1, 62.4, 66.3, 127.6, 129.5, 129.8, 131.1, 138.2, 143.6; IR (KBr, neat) 3468, 2873, 1920, 1654, 1470, 1290, 1170, 1008, 883, 773 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{26}NO_4S$ $(M + H)^+$ 328.1577, found 328.1598. $[\alpha]_D^{20}$ −5.7 (c 0.8 $CHCl_3$).

*(Z)-N-(2-Hydroxy-1-phenylethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**6d**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.53; yield 404 mg, 56%; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (brs, 1 H, −OH), 2.43 (s, 3 H, Ts-CH_3), 2.57 (brs, 1 H, −OH), 3.75 (dd, J = 16.2 and 7.8 Hz, 1 H, 2-H), 3.91 (dd, J = 16.2 and 6.0 Hz, 1 H, 2-H), 4.00−4.10 (m, 4 H, 1′,4′-H), 5.03 (t, J = 7.2 Hz, 1 H, 1-H), 5.28−5.32 (m, 1 H, 2′-H), 5.60−5.64 (m, 1 H, 3′-H), 6.99 (d, J = 7.2 Hz, 2 H, 2‴, 6‴-H), 7.22−7.26 (m, 3 H, 3‴, 4‴, 5‴-H), 7.28 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.72 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 41.7, 57.9, 62.1, 62.4, 127.6, 128.3, 128.5, 128.9, 129.0, 129.9, 131.3, 136.0, 137.9, 143.8; IR (KBr, neat) 3528, 2924, 1598, 1496, 1305, 1164, 1017, 891, 739 cm^{-1}; HRMS (ESI)

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calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 362.1431. $[\alpha]_D^{20}$ −28.4 (c 0.8 $CHCl_3$).

*(Z)-N-(1-Hydroxy-3-phenylpropan-2-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6e**).* White solid, mp 108−110 °C; R_f (hexane:EtOAc 3:2) 0.50; yield 450 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3 H, Ts-CH_3), 2.64 (dd, J = 13.8 and 6.0 Hz, 1 H, 3-H), 2.78 (dd, J = 13.8 and 8.4 Hz, 1 H, 3-H), 2.92 (brs, 1 H, −OH), 3.58−3.65 (m, 2 H, 1-H), 4.00 (d, J = 6.6 Hz, 2 H, 1′-H), 4.04−4.09 (m, 1 H, 2-H), 4.21 (d, J = 6.6 Hz, 2 H, 4′-H), 5.54−5.59 (m, 1 H, 2′-H), 5.70−5.73 (m, 1 H, 3′-H), 7.03 (d, J = 7.2 Hz, 2 H, 2‴, 6‴-H), 7.18−7.20 (m, 5 H, 3‴, 4‴, 5‴-H, 3″, 5″-H), 7.58 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 36.2, 41.3, 58.0, 61.7, 62.6, 126.7, 127.3, 128.7, 129.1, 129.4, 129.8, 131.2, 137.6, 137.8, 143.6; IR (KBr, neat) 3479, 2967, 1658, 1598, 1496, 1289, 1158, 872, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_4S$ $(M + H)^+$ 376.1577, found 376.1576. $[\alpha]_D^{20}$ −28.0 (c 0.9 $CHCl_3$).

*(Z)-N-(2-Hydroxy-2-phenylethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**6f**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.52; yield 397 mg, 55%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H, Ts-CH_3), 3.29 (d, J = 6.0 Hz, 2 H, 1-H) 3.98 (dd, J = 15.6 and 7.2 Hz, 1 H, 1′-H), 4.02 (dd, J = 15.6 and 7.8 Hz, 1 H, 1′-H), 4.11 (dd, J = 12.6 and 6.6 Hz, 1 H, 4′-H), 4.19 (dd, J = 12.6 and 6.6 Hz, 1 H, 4′-H), 4.98 (t, J = 6.0 Hz, 1 H, 2-H), 5.34−5.39 (m, 1 H, 2′-H), 5.78−5.83 (m, 1 H, 3′-H), 7.29 (d, J = 7.8 Hz, 3 H, 3″, 5″, 4‴-H), 7.30−7.36 (m, 4 H, 2‴, 3‴, 5‴, 6‴-H), 7.69 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.5, 55.6, 58.0, 73.8, 126.1, 127.1, 127.5, 128.3, 128.8, 130.1, 133.1, 136.6, 141.5, 143.9; IR (KBr, neat) 3400, 2924, 1640, 1448, 1331, 1155, 1087, 816, 656 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{24}NO_4S$ $(M + H)^+$ 362.1421, found 362.1405.

*(Z)-N-(2-(4-Chlorophenyl)-2-hydroxyethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6g**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.48; yield 482 mg, 61%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.23 (brs, 1 H, −OH), 2.42 (s, 3 H, Ts-CH_3), 3.23 (d, J = 5.4 Hz, 2 H, 1-H), 3.38 (brs, 1 H, −OH), 3.95−4.03 (m, 2 H, 1′-H), 4.13 (dd, J = 13.2 and 7.2 Hz, 1 H, 4′-H), 4.19 (dd, J = 13.2 and 6.6 Hz, 1 H, 4′-H), 4.96 (t, J = 6.0 Hz, 1 H, 2-H), 5.33−5.38 (m, 1 H, 2′-H), 5.78−5.83 (m, 1 H, 3′-H), 7.26−7.30 (m, 6 H, 2‴,3‴,5‴,6‴-H, 3″, 5″-H), 7.67 (d, J = 8.4 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.5, 55.5, 57.9, 73.1, 126.9, 127.4, 127.5, 128.9, 130.1, 133.2, 133.9, 136.4, 140.0, 144.1; IR (KBr, neat) 3500, 2924, 2870, 1597, 1492, 1334, 1159, 1090, 817, 658 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}ClNO_4S$ $(M + H)^+$ 396.1031, found 396.1038.

*(Z)-N-(2-(3-Bromophenyl)-2-hydroxyethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6h**).* White solid, mp 108−110 °C; R_f (hexane:EtOAc 3:2) 0.50; yield 570 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H, Ts-CH_3), 2.60 (brs, 1 H, −OH), 3.24 (d, J = 6.0 Hz, 2 H, 1-H), 3.73 (brs, 1 H, −OH), 3.94−4.03 (m, 2 H, 1′-H), 4.11 (dd, J = 12.6 and 5.4 Hz, 1 H, 4′-H), 4.17 (dd, J = 12.6 and 7.2 Hz, 1 H, 4′-H), 4.93 (t, J = 6.0 Hz, 1 H, 2-H), 5.30−5.35 (m, 1 H, 2′-H), 5.76−5.81 (m, 1 H, 3′-H), 7.19 (t, J = 7.8 Hz, 1 H, 5‴-H), 7.27−7.30 (m, 3 H, 4‴-H, 3″, 5″-H), 7.39 (d, J = 8.4 Hz, 1 H, 6‴-H), 7.49 (s, 1 H, 2‴-H), 7.67 (t, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.4, 55.3, 57.8, 73.0, 122.8, 124.8, 126.8, 127.4, 129.2, 130.1, 130.3, 131.1, 133.2, 136.3, 143.9, 144.0; IR (KBr, neat) 3521, 2922, 2856, 1919, 1596, 1473, 1332, 1161, 889, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0532.

*(Z)-N-(2-(4-Bromophenyl)-2-hydroxyethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6i**).* White solid, mp 111−113 °C; R_f (hexane:EtOAc 3:2) 0.53; yield 570 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H, Ts-CH_3), 3.22 (d, J = 6.0 Hz, 2 H, 1-H), 3.96 (dd, J = 15.6 and 7.2 Hz, 1 H, 1′-H), 4.00 (dd, J = 15.6 and 7.8 Hz, 1 H, 1′-H), 4.10 (dd, J = 13.2 and 6.6 Hz, 1 H, 4′-H), 4.16 (dd, J = 13.2 and 7.2 Hz, 1 H, 4′ -H), 4.92 (t, J = 6.0 Hz, 1 H, 2-H), 5.29−5.33 (m, 1 H, 2′-H), 5.76−5.80 (m, 1 H, 3′-H), 7.21 (d, J = 7.8 Hz, 2 H, 2‴, 6‴-H), 7.28 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.43 (d, J = 7.8 Hz, 2 H, 3‴, 5‴-H), 7.65 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.3, 55.1, 57.7, 73.1, 121.9, 126.7, 127.3, 127.8, 130.1, 131.8, 133.2, 136.3, 140.5, 144.0; IR (KBr, neat) 3530, 2925, 2850, 1925, 1590, 1480, 1356, 1156, 878, 755 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ $(M + H)^+$ 440.0526, found 440.0529.

*(Z)-N-(2-(4-Fluorophenyl)-2-hydroxyethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6j**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.50; yield 500 mg, 66%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H, Ts-CH_3), 3.20−3.26 (m, 2 H, 1-H), 3.94 (dd, J = 15.6 and 6.6 Hz, 1 H, 1′-H), 4.01 (dd, J = 15.6 and 7.8 Hz, 1 H, 1′-H), 4.09 (dd, J = 12.6 and 7.2 Hz, 1 H, 4′-H), 4.15 (dd, J = 12.6 and 6.6 Hz, 1 H, 4′-H), 4.94 (t, J = 7.8 Hz, 1 H, 2-H), 5.27−5.32 (m, 1 H, 2′-H), 5.74−5.78 (m, 1 H, 3′-H), 7.00 (t, J = 7.2 Hz, 2 H, 2‴, 6‴-H), 7.27−7.31 (m, 4 H, 3″, 5″-H, 3‴, 5‴-H), 7.66 (d, J = 7.2 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.3, 55.2, 57.7, 73.0, 115.5 (d, J = 22.5 Hz), 126.7, 127.3, 127.7 (d, J = 9.0 Hz), 130.1, 133.2, 136.4, 137.3, 144.0, 162.5 (d, J = 244.5 Hz, C−F); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 38.05; IR (KBr, neat) 3500, 2926, 2857, 1600, 1450, 1338, 1222, 737 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}FNO_4S$ $(M + H)^+$ 380.1326, found 380.1332.

*(Z)-N-(2-(3,4-Dichlorophenyl)-2-hydroxyethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**6k**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.48; yield 549 mg, 64%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3 H, Ts-CH_3), 2.55 (brs, 1 H, −OH), 3.22 (d, J = 6.0 Hz, 2 H, 1-H), 3.79 (brs, 1 H, −OH), 3.96−4.03 (m, 2 H, 1′-H), 4.09−4.20 (m, 2 H, 4′-H), 4.90−4.94 (m, 1 H, 2-H), 5.32−5.36 (m, 1 H, 2′-H), 5.78−5.82 (m, 1 H, 3′-H), 7.18 (d, J = 7.8 Hz, 1 H, 6‴-H), 7.29 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.37 (dd, J = 8.4 and 3.6 Hz, 1 H, 5‴-H), 7.44 (s, 1 H, 2‴-H), 7.65 (dd, J = 7.8 and 1.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.5, 55.2, 57.8, 72.5, 125.6, 126.8, 127.3, 128.1, 130.1, 130.7, 131.9, 132.8, 133.2, 136.2, 141.8, 144.2; IR (KBr, neat) 3419, 2925, 2854, 1641, 1470, 1337, 1159, 1089, 820, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}Cl_2NO_4S$ $(M + H)^+$ 430.0641, found 430.0643.

*(Z)-N-(2-Hydroxy-2-(p-tolyl)ethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**6l**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.51; yield 435 mg, 58%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3 H, Tol-CH_3), 2.40 (s, 3 H, Ts-CH_3), 2.83 (brs, 1 H, −OH), 3.25 (d, J = 6.0 Hz, 2 H, 1-H), 3.54 (brs, 1 H, −OH), 3.94 (dd, J = 15.6 and 6.6 Hz, 1 H, 1′-H), 4.03 (dd, J = 15.6 and 7.8 Hz, 1 H, 1′-H), 4.09 (dd, J = 12.6 and 6.6 Hz, 1 H, 4′-H), 4.15 (dd, J = 12.6 and 7.2 Hz, 1 H, 4′-H), 4.90 (t, J = 5.4 Hz, 1 H, 2-H), 5.30 (dd, J = 17.4 and 7.8 Hz, 1 H, 2′-H), 5.76 (dd, J = 17.4 and 6.6 Hz, 1 H, 3′-H), 7.12 (d, J = 7.8 Hz, 2 H, 2‴, 6‴-H), 7.21 (d, J = 7.8 Hz, 2 H, 3‴, 5‴-H), 7.26 (d, J = 8.4 Hz, 2 H, 3″, 5″-H), 7.66 (d, J = 8.4 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.7, 46.2, 55.2, 57.7, 73.6, 126.0, 126.8, 127.3, 129.4, 130.0, 133.1, 136.6, 137.8, 138.5, 143.8; IR (KBr, neat) 3498, 2923, 1640, 1330, 1153, 1086, 939, 816, 754 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_4S$ $(M + H)^+$ 376.1577, found 376.1594.

*(Z)-N-(2-Hydroxy-2-(4-methoxyphenyl)ethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6m**).* White solid, mp 79−81 °C; R_f (hexane:EtOAc 3:2) 0.45; yield 523 mg, 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H, Ts-CH_3), 2.69 (brs, 1 H, −OH), 3.25 (d, J = 6.0 Hz, 2 H, 1-H), 3.43 (brs, 1 H, −OH), 3.78 (s, 3 H, -OCH_3), 3.94 (dd, J = 15.6 and 6.0 Hz, 1 H, 1′-H), 4.03 (dd, J = 15.6 and 7.8 Hz, 1 H, 1′-H), 4.07 (dd, J = 12.6 and 6.0 Hz, 1 H, 4′-H), 4.16 (dd, J = 12.6 and 6.0 Hz, 1 H, 4′-H), 4.90 (t, J = 5.4 Hz, 1 H, 2-H), 5.31 (dd, J = 16.2 and 7.8 Hz, 1 H, 2′-H), 5.76 (dd, J = 16.2 and 6.0 Hz, 1 H, 3′-H), 6.86 (d, J = 8.4 Hz, 2 H, 2‴, 6‴-H), 7.24−7.29 (m, 4 H, 3″, 5″-H, 3‴, 5‴-H), 7.67 (d, J = 8.4 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.2, 55.2, 55.5 57.7, 73.4, 114.1, 126.9, 127.3, 127.4, 130.0, 133.1, 133.6, 136.6, 143.8, 159.5; IR (KBr, neat) 3503, 2925, 2839, 1612, 1447, 1334, 1249, 1156, 1032, 835, 745 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{26}NO_5S$ $(M + H)^+$ 392.1526, found 392.1530.

*(Z)-N-(2-Hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**6n**).* White solid, mp 78−79 °C; R_f (hexane:EtOAc 3:2) 0.52; yield 506 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H, Ts-CH_3), 3.25 (d, J = 6.0 Hz, 2 H, 1-H), 3.95−4.07 (m, 2 H, 1′-H), 4.11−4.22 (m, 2 H, 4′-H), 5.03−5.06 (m, 1 H, 2-H), 5.34 (dd, J = 17.6 and 7.2 Hz, 1 H, 2′-H), 5.77−583 (m, 1 H, 3′-H), 7.28 (d, J = 8.0 Hz, 2 H, 3″, 5″-H), 7.47 (d, J = 8.0 Hz, 2 H, 3‴, 5‴-H), 7.57 (d, J = 8.0 Hz, 2 H, 2″, 6″-H), 7.66 (d, J = 8.0 Hz, 2 H, 2‴, 6‴-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7,

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46.5, 55.4, 57.8, 73.2, 122.9, 125.7 (q, J = 3.8 Hz), 126.46, 126.5, 126.8, 127.4, 127.5, 130.1, 134.7 (q, J = 294.4 Hz), 144.2, 145.5; ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 13.4; IR (KBr, neat) 3508, 2926, 2873, 1621, 1599, 1449, 1320, 1169, 1014, 851, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{23}F_3NO_4S$ (M + H)$^+$ 430.1294, found 430.1308.

*(Z)-N-(2-Hydroxy-2-(4-nitrophenyl)ethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6o**).* White solid, mp 75−77 °C; R_f (hexane:EtOAc 3:2) 0.40; yield 416 mg, 51%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.41 (s, 3 H, Ts-CH_3), 2.50 (brs, 1 H, −OH), 3.25 (d, J = 7.8 Hz, 2 H, 1-H), 3.96 (brs, 1 H, −OH), 4.00 (d, J = 7.2 Hz, 2 H, 1′-H), 4.12−4.21 (m, 2 H, 4′-H), 5.08−5.10 (m, 1 H, 2-H), 5.33 (dd, J = 18.0 and 7.8 Hz, 1 H, 2′-H), 5.80 (m, 1 H, 3′-H), 7.29 (d, J = 8.4 Hz, 2 H, 3″, 5″-H), 7.54 (d, J = 8.4 Hz, 2 H, 3‴, 5‴-H), 7.65 (d, J = 8.4 Hz, 2 H, 2″, 6″-H), 8.16 (d, J = 8.4 Hz, 2 H, 2‴, 6‴-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.4, 54.9, 57.7, 72.8, 123.8, 126.6, 127.0, 127.3, 130.1, 133.3, 136.0, 144.3, 147.5, 148.9; IR (KBr, neat) 3558, 2923, 2858, 1602, 1529, 1449, 1309, 1160, 1089, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}N_2O_6S$ (M + H)$^+$ 407.1271, found 407.1279.

*(Z)-N-(2-Hydroxy-2-methylpropyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (**6p**).* White solid, mp 97−99 °C; R_f (hexane:EtOAc 3:2) 0.50; yield 375 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.23 (s, 6 H, 2−2CH_3), 2.15 (brs, 1 H, −OH), 2.42 (s, 3 H, Ts-CH_3), 2.80 (brs, 1 H, −OH), 3.66 (s, 2 H, 1-H), 4.13 (d, J = 6.0 Hz, 2 H, 1′-H), 4.21 (d, J = 6.0 Hz, 2 H, 4′-H), 5.67−5.75 (m, 2 H, 2″,3′-H) 7.29 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.74 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 25.0, 43.7, 58.3, 63.8, 69.8, 127.3, 129.9, 130.0, 131.3, 140.0, 143.6; IR (KBr, neat) 3505, 2926, 2880, 1646, 1472, 1310, 1147, 1090, 879, 736, 660 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{24}NO_4S$ (M + H)$^+$ 314.1421, found 314.1443.

*(Z)-N-(2-Hydroxy-4-methylpent-3-en-1-yl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6q**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.55; yield 325 mg, 48%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.66 (s, 3 H, 5-CH_3), 1.69 (s, 3 H, 4′-CH_3), 2.41 (s, 3 H, Ts-CH_3), 2.80 (brs, 2 H, −2OH), 3.07 (d, J = 4.2 Hz, 2 H, 1-H), 3.97 (dd, J = 15.6 and 6.0 Hz, 1 H, 1′-H), 4.03 (dd, J = 15.6 and 7.8 Hz, 1 H, 1′-H), 4.09 (dd, J = 12.6 and 6.0 Hz, 1 H, 4′-H), 4.15 (dd, J = 12.6 and 7.2 Hz, 1 H, 4′-H), 4.56−4.61 (m, 1 H, 2-H), 5.07 (d, J = 7.2 Hz, 1 H, 3-H), 5.32−5.39 (m, 1 H, 2′-H), 5.75−5.80 (m, 1 H, 3′-H), 7.29 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.68 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.6, 21.7, 25.9, 46.4, 53.4, 57.7, 68.6, 124.5, 127.1, 127.4, 130.0, 133.0, 136.6, 137.3, 143.8; IR (KBr, neat) 3418, 2922, 1648, 1447, 1335, 1158, 1019, 817, 769 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{26}NO_4S$ (M + H)$^+$ 340.1577, found 340.1598.

*(Z)-N-(2-(Furan-2-yl)-2-hydroxyethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6r**).* Pale yellow oil; R_f (hexane:EtOAc 3:2) 0.50; yield 414 mg, 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3 H, Ts-CH_3), 3.44 (d, J = 5.2 Hz, 2 H, 1-H), 3.90 (dd, J = 15.6 and 10.2 Hz, 1 H, 1′-H), 4.00 (dd, J = 15.6 and 12.0 Hz, 1 H, 1′-H), 4.08 (dd, J = 13.2 and 6.8 Hz, 1 H, 4′-H), 4.15 (dd, J = 13.2 and 7.6 Hz, 1 H, 4′-H), 4.95 (t, J = 6.0 Hz, 1 H, 2-H), 5.29 (dd, J = 17.6 and 7.2 Hz, 1 H, 2′-H), 5.72−5.79 (m, 1 H, 3′-H), 6.29−6.32 (m, 2 H, 3‴, 4‴-H), 7.30 (d, J = 8.4 Hz, 2 H, 3″, 5″-H), 7.35 (m, 1 H, 5‴-H), 7.69 (d, J = 8.4 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.3, 52.1, 57.7, 67.5, 107.4, 110.6, 126.6, 127.4, 130.1, 133.2, 136.5, 142.4, 143.9, 153.8; IR (KBr, neat) 3585, 2923, 2870, 1632, 1598, 1449, 1330, 1160, 1094, 917, 749 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{22}NO_5S$ (M + H)$^+$ 352.1213, found 352.1211.

*(E)-N-(2-(4-Bromophenyl)-2-hydroxyethyl)-N-(4-hydroxybut-2-en-1-yl)-4-methylbenzene-sulfonamide (**6s**).* Pale yellow oil; Rf (hexane:EtOAc 3:2) 0.50; yield 518 mg, 59%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3 H, Ts-CH_3), 3.06 (dt, J = 15.6 and 2.4 Hz, 1 H, 1-H), 3.16−3.26 (m, 1 H, 1-H), 3.64−3.69 (m, 1 H, 1′-H), 3.74−3.76 (m, 1 H, 1′-H), 3.96 (brs, 2 H, 4′-H), 4.81−4.86 (m, 1 H, 2-H), 5.40−5.45 (m, 1 H, 2′-H), 5.62−5.65 (m, 1 H, 3′-H), 7.12−7.14 (m, 1 H), 7.19−7.22 (m, 2 H), 7.25−7.37 (m, 2 H), 7.34−7.37 (m, 1 H), 7.57−7.60 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 51.7, 55.7, 62.6, 72.9, 121.8, 126.2, 127.5, 128.7, 130.0, 131.7, 134.5, 136.0, 141.5, 143.9; IR (KBr, neat) 3604, 2922, 2865, 1597, 1457, 1377, 1164, 1096, 973, 747 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{23}BrNO_4S$ (M + H)$^+$ 440.0526, found 440.0529.

General Procedure for the Synthesis of Vinylmorpholine (7a−s). A solution of *N*-tethered alkenol (0.50 mmol) and $PdCl_2(PPh_3)_2$ (0.025 mmol) in 10 mL of toluene was heated at 90 °C for 20 h. The reaction was monitored by TLC. After completion of the reaction, ethyl acetate (15 mL) was poured into the reaction mixture and passed through Celite. The filtrate was concentrated in vacuo and purified by column chromatography using ethyl acetate and hexane as eluents to give the morpholine derivatives.

*Synthesis of 4-Tosyl-2-vinylmorpholine (**7a**).* A solution of *N*-tethered alkenol (143 mg, 0.50 mmol) and $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol) in 10 mL of toluene was heated at 90 °C for 20 h. The reaction was monitored by TLC. After completion of the reaction, ethyl acetate (15 mL) was poured into the reaction mixture and passed through Celite. The filtrate was concentrated in vacuo and purified by column chromatography (EtOAc:hexane, 1:4) to give **7a**.

*4-Tosyl-2-vinylmorpholine (**7a**).*[19] White solid; mp 126−128 °C (reported mp 126−128 °C); R_f (hexane:EtOAc 4:1) 0.55; yield 114 mg, 85%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.12 (dd, J = 11.4 and 10.8 Hz, 1 H, 3-Ha), 2.40 (dd, J = 11.4 and 3.0 Hz, 1 H, 3-He), 2.44 (s, 3 H, Ts-CH_3), 3.52 (d, J = 11.4 Hz, 1 H, 5-Ha), 3.60 (d, J = 11.4 Hz, 1 H, 5-He), 3.72 (dd, J = 11.4 and 10.8 Hz, 1 H, 6-Ha), 3.95 (d, J = 11.4 Hz, 1 H, 6-He), 4.04−4.06 (m, 1 H, 2-H), 5.21 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.33 (d, J = 16.8 Hz, 1 H, 8-H_{trans}), 5.69−5.75 (m, 1 H, 7-H), 7.34 (d, J = 7.8 Hz, 2 H, 3′,5′-H), 7.63 (d, J = 7.8 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 45.5, 50.2, 65.9, 75.9, 117.9, 128.0, 130.0, 132.3, 134.8, 144.2; IR (KBr, neat) 2923, 2856, 1651, 1451, 1267, 1163, 1095, 938, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{18}NO_3S$ (M + H)$^+$ 268.1002, found 268.1023.

(2S,5S*)-5-Methyl-4-tosyl-2-vinylmorpholine (**7b**).*[19] Colorless oil; R_f (hexane:EtOAc 4:1) 0.52; yield 124 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 7.2 Hz, 3 H, 5-CH_3), 2.43 (s, 3 H, Ts-CH_3), 2.87 (dd, J = 12.8 and 10.8 Hz, 1 H, 3-Ha), 3.60 (dd, J = 12.8 and 2.4 Hz, 1 H, 3-He), 3.67 (d, J = 1.2 Hz, 2 H, 6-H), 3.83−3.88 (m, 1 H, 2-H), 3.98 (q, J = 6.8 Hz, 1 H, 5-H), 5.24 (d, J = 10.8 Hz, 1 H, 9-H_{cis}), 5.35 (d, J = 17.6 Hz, 1 H, 9-H_{trans}), 5.72−5.80 (m, 1 H, 8-H), 7.31 (d, J = 8.0 Hz, 2 H, 3′,5′-H), 7.70 (d, J = 8.0 Hz, 2 H, 2′,6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.7, 44.4, 48.4, 71.4, 76.4, 117.9, 127.3, 130.0, 134.9, 137.6, 143.6; IR (KBr, neat) 2982, 2857, 1648, 1598, 1457, 1258, 1183, 927, 764 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{20}NO_3S$ (M + H)$^+$ 282.1158, found 282.1179. $[\alpha]_D^{20}$ +22.9 (c 0.9 $CHCl_3$).

(2S,5S*)-5-Isopropyl-4-tosyl-2-vinylmorpholine (**7c**).*[19] White solid, mp 100−102 °C (reported liquid); R_f (hexane:EtOAc 4:1) 0.55; yield 111 mg, 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (d, J = 7.2 Hz, 3 H, 7-CH_3), 0.96 (d, J = 7.2 Hz, 3 H, 7-CH_3), 2.19−2.26 (m, 1 H, 7-H), 2.43 (s, 3 H, Ts-CH_3), 2.92 (dd, J = 15.0 and 11.4 Hz, 1 H, 3-Ha), 3.28−3.30 (m, 2 H, 3-He, 6-Ha), 3.54−3.58 (m, 1 H, 2-H), 3.67 (dd, J = 15.0 and 4.2 Hz, 1 H, 6-He), 3.88 (d, J = 11.4 Hz, 1 H, 5-H), 5.17 (d, J = 10.8 Hz, 1 H, 11-H_{cis}), 5.24 (d, J = 17.4 Hz, 1 H, 11-H_{trans}), 5.63−5.69 (m, 1 H, 10-H), 7.30 (d, J = 7.8 Hz, 2 H, 3′,5′-H), 7.71 (d, J = 7.8 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.9, 20.1, 21.7, 25.5, 45.5, 59.1, 66.2, 75.0, 117.8, 127.1, 130.0, 135.0, 138.8, 143.5; IR (KBr, neat) 2980, 2857, 1649, 1598, 1466, 1277, 1179, 1088, 929, 818, 680 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{24}NO_3S$ (M + H)$^+$ 310.1471, found 310.1460. $[\alpha]_D^{20}$ +3.2 (c 0.9 $CHCl_3$).

(2R,5R*)-5-Phenyl-4-tosyl-2-vinylmorpholine (**7d, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer**).*[19] Colorless oil; R_f (hexane:EtOAc 4:1) 0.54; yield 137 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3 H, Ts-CH_3), 2.91 (dd, J = 14.0 and 11.2 Hz, 1 H, 3-Ha), 3.65 (dd, J = 14.0 and 2.4 Hz, 1 H, 3-He), 3.82 (dd, J = 12.0 and 4.0 Hz, 1 H, 6-Ha), 3.85−3.90 (m, 1 H, 2-H), 4.32 (d, J = 12.0 Hz, 1 H, 6-He), 4.93 (d, J = 3.2 Hz, 1 H, 5-H), 5.20 (d, J = 10.4 Hz, 1 H, 8-H_{cis}), 5.31 (d, J = 17.6 Hz, 1 H, 8-H_{trans}), 5.67−5.76 (m, 1 H, 7-H), 7.22 (d, J = 8.4 Hz, 2 H, 3′,5′-H), 7.24−7.30 (m, 3 H, 3″, 4″, 5″-H), 7.45−7.48 (m, 2 H, 2″, 6″-H), 7.59 (d, J = 8.4 Hz, 2 H, C-2′,6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 45.5, 54.5, 68.7, 75.7, 117.9, 127.2, 127.8, 128.4, 128.5, 129.8, 134.8, 137.6, 137.9, 143.6; IR (KBr, neat) 2918, 2859, 1649, 1598, 1495, 1338, 1165, 1096, 937, 817, 737 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ (M + H)$^+$ 344.1315, found 344.1313. $[\alpha]_D^{20}$ −17.4 (c 0.8 $CHCl_3$).

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(2S,5S*)-5-Benzyl-4-tosyl-2-vinylmorpholine (**7e**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).*[19] White solid, mp 118−120 °C (reported 120−123 °C); R_f (hexane:EtOAc 4:1) 0.50; yield 139 mg, 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H, Ts-CH_3), 2.68 (dd, J = 13.2 and 4.8 Hz, 1 H, 3-Ha), 2.96−3.05 (m, 2 H, 7-H), 3.47 (dd, J = 12.0 and 2.0 Hz, 1 H, 6-Ha), 3.65 (dd, J = 13.2 and 2.8 Hz, 1 H, 3-He), 3.69 (d, J = 12.0 Hz, 1 H, 6-He), 3.86−3.91 (m, 1 H, 2-H), 3.97−4.02 (m, 1 H, 5-H), 5.27 (d, J = 10.8 Hz, 1 H, 9-H_{cis}), 5.31 (d, J = 16.0 Hz, 1 H, 9-H_{trans}), 5.76−5.85 (m, 1 H, 8-H), 7.16−7.20 (m, 2 H, 3′,5′-H), 7.22−7.30 (m, 5 H, Ph-H), 7.63 (d, J = 8.0 Hz, 2 H, 2′,6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 34.1, 45.1, 54.3, 67.3, 76.2, 118.1, 126.8, 127.3, 128.9, 129.7, 130.1, 135.0, 137.7, 138.0, 143.7; IR (KBr, neat) 2921, 2857, 1599, 1495, 1344, 1164, 1090, 1057, 816, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_3S$ (M + H)$^+$ 358.1471, found 358.1483. $[\alpha]_D^{20}$ −7.6 (c 0.6 $CHCl_3$).

(2R,6S*)-2-Phenyl-4-tosyl-6-vinylmorpholine (**7f**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* White solid, mp 102−104 °C; R_f (hexane:EtOAc 4:1) 0.51; yield 154 mg, 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.12−2.19 (m, 2 H, 3-Ha, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.73 (d, J = 11.4 Hz, 1 H, 5-He), 3.78 (d, J = 10.8 Hz, 1 H, 3-He), 4.28−4.31 (m, 1 H, 6-H), 4.71 (dd, J = 10.8 and 2.4 Hz, 1 H, 2-H), 5.24 (d, J = 10.2 Hz, 1 H, 8-H_{cis}), 5.42 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.79−5.85 (m, 1 H, 7-H), 7.29−7.34 (m, 7 H, Ph-H, 3′,5′-H), 7.60 (d, J = 7.8 Hz, 2 H, 2′,6′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 49.6, 51.5, 71.2, 76.0, 117.7, 126.1, 127.8, 128.3, 128.5, 129.9, 132.2, 134.6, 138.7, 144.0; IR (KBr, neat) 2925, 2847, 1648, 1598, 1495, 1230, 1170, 1091, 930, 765 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{22}NO_3S$ (M + H)$^+$ 344.1315, found 344.1293.

(2R,6S*)-2-(4-Chlorophenyl)-4-tosyl-6-vinylmorpholine (**7g**).* White solid, mp 141−143 °C; R_f (hexane:EtOAc 4:1) 0.50; yield 151 mg, 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.08−2.15 (m, 2 H, 3-Ha, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.72−3.77 (m, 2 H, 3-He, 5-He), 4.27−4.30 (m, 1 H, 6-H), 4.68 (dd, J = 11.4 and 1.8 Hz, 1 H, 2-H), 5.25 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.41 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.77−5.83 (m, 1 H, 7-H), 7.27 (d, J = 8.4 Hz, 2 H, 3′,5′-H), 7.30−7.33 (m, 4 H, 2″, 3″, 5″, 6″-H), 7.60 (d, J = 7.8 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.7, 51.6, 76.5, 76.7, 118.0, 127.6, 128.0, 128.9, 130.1, 132.3, 134.3, 134.6, 137.3, 144.3; IR (KBr, neat) 2987, 2852, 1648, 1598, 1491, 1349, 1166, 1087, 1017, 975, 776, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}ClNO_3S$ (M + H)$^+$ 378.0925, found 378.0927.

(2R,6S*)-2-(3-Bromophenyl)-4-tosyl-6-vinylmorpholine (**7h**).* White solid, mp 115−117 °C; R_f (hexane:EtOAc 4:1) 0.56; yield 179 mg, 85%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.09−2.15 (m, 2 H, 3-Ha, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.73 (d, J = 11.4 Hz, 1 H, 5-He), 3.76 (d, J = 11.4 Hz, 1 H, 3-He), 4.26−4.29 (m, 1 H, 6-H), 4.68 (dd, J = 10.2 and 1.8 Hz, 1 H, 2-H), 5.26 (d, J = 10.2 Hz, 1 H, 8-H_{cis}), 5.41 (d, J = 16.8 Hz, 1 H, 8-H_{trans}), 5.78−5.84 (m, 1 H, 7-H), 7.20 (t, J = 7.8 Hz, 1 H, 5″-H), 7.25 (d, J = 7.8 Hz, 1 H, 6″-H), 7.32 (d, J = 7.8 Hz, 2 H, 3′, 5′-H), 7.42 (d, J = 7.8 Hz, 1 H, 4″-H), 7.50 (s, 1 H, 2″-H), 7.60 (d, J = 7.8 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 49.6, 51.5, 76.3, 76.6, 118.1, 122.8, 124.9, 127.9, 129.3, 130.1, 130.2, 131.5, 132.2, 134.5, 141.0, 144.3; IR (KBr, neat) 2923, 2849, 1597, 1570, 1451, 1345, 1169, 1092, 1025, 972, 737, 662 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}BrNO_3S$ (M + H)$^+$ 422.0420, found 422.0414.

(2R,6S*)-2-(4-Bromophenyl)-4-tosyl-6-vinylmorpholine (**7i**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* White solid, mp 149−151 °C; R_f (hexane:EtOAc 4:1) 0.60; yield 177 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.07−2.14 (m, 2 H, 3-Ha, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.71−3.76 (m, 2 H, 3-He, 5-He), 4.26−4.32 (m, 1 H, 6-H), 4.67 (d, J = 10.8 Hz, 1 H, 2-H), 5.25 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.40 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.77−5.83 (m, 1 H, 7-H), 7.21 (d, J = 7.8 Hz, 2 H, 2″,6″-H), 7.32 (d, J = 7.8 Hz, 2 H, 3′,5′-H), 7.46 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.60 (d, J = 7.8 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.6, 51.5, 76.2, 76.7, 118.1, 122.4, 126.3, 128.0, 130.1, 131.8, 132.2, 134.5, 137.8, 144.3; IR (KBr, neat) 2923, 2849, 1597, 1491, 1348, 1168, 1090, 1012, 975, 818, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}BrNO_3S$ (M + H)$^+$ 422.0420, found 422.0433.

(2R,6S*)-2-(4-Fluorophenyl)-4-tosyl-6-vinylmorpholine (**7j**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* White solid, mp 130−132 °C; R_f (hexane:EtOAc 4:1) 0.52; yield 136 mg, 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11−2.16 (m, 2 H, 3-Ha, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.72−3.77 (m, 2 H, 3-He, 5-He), 4.27−4.27−4−30 (m, 1 H, 6-H), 4.68 (d, J = 13.2 Hz, 1 H, 2-H), 5.25 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.41 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.77−5.83 (m, 1 H, 7-H), 7.02 (t, J = 8.4 Hz, 2 H, 2″,6″-H), 7.28−7.34 (m, 4 H, 3′,5′-H, 3″,5″-H), 7.60 (d, J = 8.4 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 49.7, 51.7, 76.3, 76.8, 115.6 (d, J = 21.0 Hz), 118.0, 127.9, 128.0, 128.1, 130.1, 132.4, 134.6, 144.3, 162.8 (d, J = 246.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 47.99 (t, J = 5.26 Hz); IR (KBr, neat) 2850, 1604, 1511, 1348, 1228, 1166, 1088, 975, 762, 667 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}FNO_3S$ (M + H)$^+$ 362.1221, found 362.1252.

(2R,6S*)-2-(3,4-Dichlorophenyl)-4-tosyl-6-vinylmorpholine (**7k**).* White solid, mp 117−119 °C; R_f (hexane:EtOAc, 4:1) 0.48; yield 152 mg, 74%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.08 (t, J = 10.8 Hz, 1 H, 3-Ha), 2.12 (t, J = 10.8 Hz, 1 H, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.71−3.77 (m, 2 H, 3, 5-He), 4.25−4.28 (m, 1 H, 6-H), 4.67 (d, J = 10.8 Hz, 1 H, 2-H), 5.26 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.40 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.77−5.83 (m, 1 H, 7-H), 7.16 (d, J = 7.8 Hz, 1 H, 6″-H), 7.32 (d, J = 7.8 Hz, 2 H, 3′,5′-H), 7.40 (d, J = 7.8 Hz, 1 H, 5″-H), 7.44 (s, 1 H, 2″-H), 7.60 (d, J = 7.8 Hz, 2 H, 2′, 6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.6, 51.4, 76.1, 76.3, 118.2, 125.6, 127.9, 128.2, 130.1, 130.7, 132.2, 132.4, 133.0, 134.4, 139.0, 144.4; IR (KBr, neat) 2923, 2850, 1646, 1598, 1471, 1350, 1168, 1090, 1030, 977, 820, 704, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{20}Cl_2NO_3S$ (M + H)$^+$ 412.0535, found 412.0547.

(2R,6S*)-2-(p-Tolyl)-4-tosyl-6-vinylmorpholine (**7l**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* White solid, mp 104−106 °C; R_f (hexane:EtOAc 4:1) 0.55; yield 147 mg, 82%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.10−2.17 (m, 2 H, 3-Ha, 5-Ha), 2.33 (s, 3 H, Tol-CH_3), 2.43 (s, 3 H, Ts-CH_3), 3.71−3.77 (m, 2 H, 3-He, 5-He), 4.26−4.29 (m, 1 H, 6-H), 4.66 (d, J = 11.4 Hz, 1 H, 2-H), 5.23 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.41 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.78−5.84 (m, 1 H, 7-H), 7.14 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.21 (d, J = 7.8 Hz, 2 H, 2″, 6″-H), 7.30 (d, J = 7.8 Hz, 2 H, 3′, 5″-H), 7.60 (d, J = 7.8 Hz, 2 H, 2′, 6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 21.7, 49.7, 51.7, 76.2, 77.0, 117.8, 126.2, 128.0, 129.3, 130.0, 132.4, 134.8, 135.9, 138.2, 144.1; IR (KBr, neat) 2924, 2846, 1598, 1353, 1231, 1168, 1087, 818, 758 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_3S$ (M + H)$^+$ 358.1471, found 358.1497.

(2R,6S*)-2-(4-Methoxyphenyl)-4-tosyl-6-vinylmorpholine (**7m**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* White solid, mp 109−111 °C; R_f (hexane:EtOAc 4:1) 0.45; yield 158 mg, 85%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11−2.17 (m, 2 H, 3-Ha, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.71−3.75 (m, 2 H, 3-He, 5-He), 3.79 (s, 3 H, -OCH_3), 4.25−4.30 (m, 1 H, 6-H), 4.65 (d, J = 10.8 Hz, 1 H, 2-H), 5.24 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.41 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.77−5.84 (m, 1 H, 7-H), 6.86 (d, J = 8.4 Hz, 2 H, 3″, 5″-H), 7.25 (d, J = 8.4 Hz, 2 H, 2″, 6″-H), 7.32 (d, J = 8.4 Hz, 2 H, 3′, 5′-H), 7.61 (d, J = 8.4 Hz, 2 H, 2′, 6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 49.7, 51.7, 55.5, 76.2, 77.0, 114.1, 117.9, 127.6, 128.0, 130.0, 131.0, 132.4, 134.8, 144.2, 159.8; IR (KBr, neat) 2926, 1612, 1515, 1447, 1250, 1167, 1087, 1031, 831, 757 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{24}NO_4S$ (M + H)$^+$ 374.1421, found 374.1400.

(2R,6S*)-4-Tosyl-2-(4-(trifluoromethyl)phenyl)-6-vinylmorpholine (**7n**).* White solid, mp 115−117 °C; R_f (hexane:EtOAc 4:1) 0.55; yield 169 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08−2.18 (m, 2 H, 3-Ha, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.75 (dt, J = 11.4 and 2.4 Hz, 1 H, 5-He), 3.80 (dt, J = 11.6 and 2.4 Hz, 1 H, 3-He), 4.29−4.34 (m, 1 H, 6-H), 4.78 (dd, J = 11.6 and 2.4 Hz, 1 H, 2-H), 5.27 (dt, J = 11.2 and 1.6 Hz, 1 H, 8-H_{cis}), 5.43 (dt, J = 17.6 and 1.2 Hz, 1 H, 8-H_{trans}), 5.78−5.87 (m, 1 H, 7-H), 7.32 (d, J = 8.4 Hz, 2 H, 3′, 5′-H), 7.47 (d, J = 8.4 Hz, 2 H, 2″, 6″-H), 7.60 (d, J = 8.4 Hz, 4 H, 2′, 6′-H, 3″, 5″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.7, 51.5, 76.3, 76.7, 118.1, 124.2 (q, J = 271.5 Hz), 125.7, 126.6, 128.0, 130.1, 130.6 (q, J = 33.0 Hz), 132.3, 134.4, 142.7, 144.4; ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 99.10; IR (KBr, neat) 2924, 2850, 1622, 1598, 1452, 1356, 1171, 1020,

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972, 857, 738, 668 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}F_3NO_3S$ (M + H)$^+$ 412.1189, found 412.1198.

(2R,6S*)-2-(4-Nitrophenyl)-4-tosyl-6-vinylmorpholine (**7o**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* White solid, mp 128−130 °C; R_f (hexane:EtOAc 4:1) 0.40; yield 163 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11 (dd, J = 11.4 and 10.2 Hz, 1 H, 3-Ha), 2.15 (dd, J = 11.4 and 10.8 Hz, 1 H, 5-Ha), 2.43 (s, 3 H, Ts-CH_3), 3.76 (dd, J = 11.4 and 3.0 Hz, 1 H, 5-He), 3.83 (dd, J = 11.4 and 2.4 Hz, 1 H, 3-He), 4.30−4.34 (m, 1 H, 6-H), 4.82 (dd, J = 10.2 and 2.4 Hz, 1 H, 2-H), 5.29 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.45 (d, J = 16.2 Hz, 1 H, 8-H_{trans}), 5.80−5.85 (m, 1 H, 7-H), 7.32 (d, J = 8.4 Hz, 2 H, 3′,5′-H), 7.53 (d, J = 8.4 Hz, 2 H, 2″,6″-H), 7.60 (d, J = 8.4 Hz, 2 H, 2′, 6′-H), 8.21 (d, J = 8.4 Hz, 2 H, 3″,5″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8, 49.6, 51.3, 76.3, 76.4, 118.3, 123.9, 127.1, 127.9, 130.1, 132.2, 134.3, 144.4, 145.8, 148.0; IR (KBr, neat) 3082, 2849, 1603, 1522, 1452, 1351, 1168, 1092, 862, 774, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}N_2O_5S$ (M + H)$^+$ 389.1166, found 389.1178.

*2,2-Dimethyl-4-tosyl-6-vinylmorpholine (**7p**).* White solid, mp 92−94 °C; R_f (hexane:EtOAc 4:1) 0.50; yield 96 mg, 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (s, 3 H, 2-CH_3), 1.33 (s, 3 H, 2-CH_3), 2.43 (s, 3 H, Ts-CH_3), 2.96 (t, J = 12.0 Hz, 1 H, 5-Ha), 3.38 (s, 2 H, 3-H), 3.77 (d, J = 12.0 Hz, 1 H, 5-He), 4.00−4.10 (m, 1 H, 6-H), 5.39 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.41 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.79−5.85 (m, 1 H, 7-H), 7.29 (d, J = 7.8 Hz, 2 H, 3′,5′-H), 7.69 (d, J = 7.8 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.1, 21.7, 24.8, 47.2, 56.9, 77.4, 77.9, 118.0, 127.4, 129.9, 134.9, 139.3, 143.5; IR (KBr, neat) 2978, 2854, 1646, 1599, 1454, 1330, 1160, 1093, 940, 818, 668 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{22}NO_3S$ (M + H)$^+$ 296.1315, found 296.1338.

(2R,6S*)-2-(2-Methylprop-1-en-1-yl)-4-tosyl-6-vinylmorpholine (**7q**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* Colorless oil; R_f (hexane:EtOAc 4:1) 0.60; yield 112 mg, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 6 H, 2′-2CH_3), 2.00−2.06 (m, 2 H, 3-Ha, 5-Ha), 2.44 (s, 3 H, Ts-CH_3), 2.96 (dt, J = 12.0 and 1.6 Hz, 1 H, 5-He), 3.62 (dt, J = 12.0 and 2.0 Hz, 1 H, 3-He), 4.12−4.16 (m, 1 H, 6-H), 4.31−4.37 (m, 1 H, 2-H), 5.02 (d, J = 10.0 Hz, 1 H, 1′-H), 5.20 (d, J = 10.4 Hz, 1 H, 8-H_{cis}), 5.33 (d, J = 17.6 Hz, 1 H, 8-H_{trans}), 5.68−5.77 (m, 1 H, 7-H), 7.34 (d, J = 8.0 Hz, 2 H, 3″,5″-H), 7.62 (d, J = 8.0 Hz, 2 H, 2″,6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.9, 21.8, 26.0, 49.4, 49.5, 72.9, 75.9, 118.1, 121.6, 128.0, 130.0, 132.3, 135.0, 139.1, 144.1; IR (KBr, neat) 2924, 2854, 1598, 1453, 1378, 1167, 1078, 971, 818, 778 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{24}NO_3S$ (M + H)$^+$ 322.1471, found 322.1457.

(2S,6S*)-2-(Furan-2-yl)-4-tosyl-6-vinylmorpholine (**7r**, Diastereomeric Mixture with a Ratio of 97:3; Data Only for Major Isomer).* Colorless oil; R_f (hexane:EtOAc 4:1) 0.60; yield 120 mg, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (dd, J = 11.2 and 10.8 Hz, 1 H, 5-Ha), 2.45 (s, 3 H, Ts-CH_3), 2.53 (dd, J = 11.2 and 11.2 Hz, 1 H, 5-He), 3.70 (dt, J = 11.2 and 2.0 Hz, 1 H, 3-Ha), 3.81 (dt, J = 11.2 and 2.4 Hz, 1 H, 3-He), 4.23−4.28 (m, 1 H, 6-H), 4.74 (dd, J = 10.8 and 2.8 Hz, 1 H, 2-H), 5.24 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.37 (d, J = 17.6 Hz, 1 H, 8-H_{trans}), 5.71−5.80 (m, 1 H, 7-H), 6.31 (d, J = 3.6 Hz, 1 H, 3″-H), 6.34 (dd, J = 3.2 and 1.6 Hz, 1 H, 4″-H), 7.33−7.37 (m, 3 H, 3′, 5′, and 5″-H), 7.64 (d, J = 8.4 Hz, 2 H, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 48.2, 49.5, 71.2, 76.5, 108.3, 110.5, 118.6, 128.0, 130.1, 132.2, 134.4, 142.9, 144.3, 151.1; IR (KBr, neat) 2922, 2853, 1648, 1598, 1454, 1344, 1168, 1095, 934, 819, 664 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{20}NO_4S$ (M + H)$^+$ 334.1108, found 334.1111.

(2R,6S*)-2-(4-Bromophenyl)-4-tosyl-6-vinylmorpholine and (2S*,6S*)-2-(4-Bromophenyl)-4-tosyl-6-vinylmorpholine (**7s**:**7s′** 63:37).* Colorless solid, mp (mixed) 150−152 °C; R_f (hexane:EtOAc 4:1) 0.60; yield mg, 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96−2.11 (m, 2 H, 3,5-Ha), 2.35 (s, 3 H, Ts-CH_3), 3.66 (m, 2 H, major, 3,5-He), 3.70 (m, 2 H, minor, 5-He), 4.19−4.23 (m, 1 H, 6-H), 4.59 (dd, J = 10.8 and 2.4 Hz, 1 H, major, 2-H), 4.63 (dd, J = 10.8 and 3.0 Hz, 1 H, minor, 2-H), 5.17 (dd, J = 10.8 and 3.0 Hz, 1 H, 8-H_{cis}), 5.33 (d, J = 17.4 Hz, 1 H, major, 8-H_{trans}), 5.35 (d, J = 16.8 Hz, 1 H, minor, 8-H_{trans}), 5.70−5.77 (m, 1 H, 7-H), 7.13 (d, J = 8.4 Hz, 2 H, major, 2″,6″-H), 7.22−7.26 (m, 2 H, major and minor, 3′, 5′ and 2″, 6″-H), 7.39 (d, J = 7.8 Hz, 2 H, major, 3″, 5″-H), 7.52 (d, J = 7.8 Hz, 2 H, major, 2′,6′-H), 7.53 (d, J = 7.8 Hz, 2 H, minor, 2′,6′-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 49.6, 49.7, 51.5, 51.7, 76.2, 76.3, 76.7, 77.4, 117.9, 118.0, 122.4, 126.3, 127.9, 128.0, 128.4, 128.7, 130.0, 130.1, 131.8, 132.3, 134.6, 134.8, 137.8, 138.8, 144.2, 144.3; IR (KBr, neat) 3090, 3063, 2847, 1650, 1598, 1492, 1268, 1176, 1097, 929, 852, 775 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}BrNO_3S$ (M + H)$^+$ 422.0420, found 422.0430.

Preparation of (*Z*)-*N*-(2-Hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide (8). To a stirred solution of NaH (176 mg, 4.4 mmol, 60% in a mineral oil) in dry DMF (10 mL) was added dropwise a solution of the *N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-4-methylbenzenesulfonamide (1.524 g, 4 mmol) in dry DMF (15 mL) at 0 °C (N_2 atmosphere). After 20 min, DMF (5 mL) solution of (*Z*)-4-bromobut-2-en-1-ol (600 mg, 4 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, a few drops of methanol were added at 0 °C, and the solution was poured in ethyl acetate (60 mL). The organic phase was washed with brine (3 × 40 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (EtOAc:hexane, 3:2) to give 1.074 g (60%) of (*Z*)-*N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide **8** as light yellow solid, mp 92−93 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.92 (brs, 2H, −2OH), 2.41 (s, 3 H, Ts-CH_3), 3.24−3.31 (m, 2 H, 1-H), 3.81 (s, 3 H, 4‴-OCH_3), 3.84 (s, 6 H, 3‴, 5‴-2CH_3), 3.93 (dd, J = 16.2 and 6.6 Hz, 1 H, 1′-H), 3.98 (dd, J = 16.2 and 7.8 Hz, 1 H, 1′-H), 4.10 (dd, J = 12.6 and 6.6 Hz, 1 H, 4′-H), 4.16 (dd, J = 12.6 and 7.2 Hz, 1 H, 4′-H), 4.90 (dd, J = 7.2 and 3.6 Hz, 1 H, 2-H), 5.31 (dd, J = 10.8 and 7.8 Hz, 1 H, 2′-H), 5.78 (dd, J = 10.8 and 4.8 Hz, 1 H, 3′-H), 6.58 (s, 2 H, 2‴, 6‴-H), 7.29 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.68 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 46.3, 55.5, 56.3, 57.8, 61.0, 73.8, 102.9, 126.8, 127.4, 130.1, 133.2, 136.5, 137.3, 144.0, 153.5; IR (KBr, neat) 3475, 2939, 2835, 1596, 1462, 1332, 1232, 1160, 1002, 916, 839, 772 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{30}NO_7S$ (M + H)$^+$ 452.1737, found 452.1733. Anal. Calcd for $C_{22}H_{29}NO_7S$: C, 58.52; H, 6.47; N, 3.10. Found: C, 58.45; H, 6.43; N, 3.07.

Preparation of 4-Tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine (9). To a solution of (*Z*)-*N*-(2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl)-*N*-(4-hydroxybut-2-en-1-yl)-4-methylbenzenesulfonamide **8** (902 mg, 2 mmol) in toluene was added $PdCl_2(PPh_3)_2$ (70 mg, 5 mol %) and the solution was refluxed for 20 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite, and the filtrate was purified by column chromatography (EtOAc:hexane, 1:3) to give 4-tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine (0.56 g, 65% yield). R_f = 0.50 (hexane:EtOAc 4:1 (v/v). White solid, mp 142−144 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.13−2.17 (m, 2 H, 3-Ha, 5-Ha), 2.42 (s, 3 H, Ts-CH_3), 3.72 (d, J = 11.4 Hz, 1 H, 5-He), 3.77 (d, J = 11.4 Hz, 1 H, 3-He), 3.81 (s, 3 H, 4′-OCH_3), 3.84 (s, 6 H, 3′,5′-2OCH_3), 4.27−4.30 (m, 1 H, 6-H), 4.63 (d, J = 11.4 Hz, 1 H, 2-H), 5.24 (d, J = 10.8 Hz, 1 H, 8-H_{cis}), 5.40 (d, J = 17.4 Hz, 1 H, 8-H_{trans}), 5.79−5.85 (m, 1 H, 7-H), 6.54 (s, 2 H, 2′, 6′-H), 7.32 (d, J = 7.8 Hz, 2 H, 3″, 5″-H), 7.61 (d, J = 7.8 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 49.6, 51.8, 56.4, 61.0, 76.4, 77.6, 103.3, 118.0, 128.0, 130.1, 132.5, 134.4, 134.7, 138.0, 144.2, 153.5; IR (KBr, neat) 3446, 2938, 2844, 1592, 1461, 1341, 1237, 1169, 1089, 973, 839, 776 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{28}NO_6S$ (M + H)$^+$ 434.1632, found 434.1635. Anal. Calcd for $C_{22}H_{27}NO_6S$: C, 60.95; H, 6.28; N, 3.23. Found: C, 60.87; H, 6.22; N, 3.21.

Preparation of 2-(4-Tosyl-6-(3,4,5-trimethoxyphenyl)-morpholin-2-yl)ethanol (10). In a two-neck septum-capped round-bottom flask, $NaBH_4$ (87 mg, 2.3 mmol) was added to dry THF (25 mL). Iodine (292 mg, 1.15 mmol) in dry THF (10 mL) was added under nitrogen atmosphere over 2.5 h at 0 °C. A THF solution of 4-tosyl-2-(3,4,5-trimethoxyphenyl)-6-vinylmorpholine (500 mg, 1.15 mmol) was added, and the reaction mixture was stirred for 6 h at 25 °C. It was quenched with water (2 mL), THF (10 mL) was added and oxidized using H_2O_2 (30%, 10 mL)/NaOH (3N, 10 mL).

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The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extract was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by column chromatography (EtOAc:hexane, 1:1) gives 468 mg (90%) of 2-(4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)ethanol as a colorless solid, mp 93−95 °C. R_f = 0.45 (hexane:EtOAc 3:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.27 (m, 2 H, 7-H), 2.16 (dd, J = 11.2 and 10.8 Hz, 1 H, 3-Ha), 2.24 (dd, J = 11.2 and 10.8 Hz, 1 H, 5-Ha), 2.44 (s, 3 H, Ts-CH_3), 3.57−3.79 (m, 3 He, 5-He, 6-H, 8-H), 3.83 (s, 3 H, 4′-OCH_3), 3.85 (s, 6 H, 3′, 5′-2OCH_3), 4.62 (t, J = 9.6 Hz, 1 H, 2-H), 6.51 (s, 2 H, 2′, 6′-H), 7.34 (d, J = 7.6 Hz, 2 H, 3″, 5″-H), 7.62 (d, J = 7.6 Hz, 2 H, 2″, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 35.4, 49.8, 51.9, 56.4 (2C), 60.3, 61.0, 75.4, 77.9, 103.1, 127.9, 130.0, 132.4, 134.3, 137.9, 144.2, 153.5; IR (KBr, neat) 3519, 2936, 2842, 1594, 1461, 1342, 1268, 1166, 1091, 977, 739 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{30}NO_7S$ (M + H)$^+$ 452.1737, found 452.1735. Anal. Calcd for $C_{22}H_{29}NO_7S$: C, 58.52; H, 6.47; N, 3.10. Found: C, 58.41; H, 6.42; N, 3.12.

Preparation of 2-(4-Tosyl-6-(3,4,5-trimethoxyphenyl)-morpholin-2-yl)acetaldehyde (11). Pyridinium chlorochromate (286 mg, 1.33 mmol) was suspended in DCM (10 mL), and the alcohol (400 mg, 0.89 mmol) in 10 mL of DCM was rapidly added at room temperature. The reaction mixture was stirred for another 2 h. The black reaction mixture was diluted with 5 volumes of anhydrous ether and filtered through a short Celite pad. Evaporation of the solvent at reduced pressure followed by purification by column chromatography (EtOAc:hexane, 1:1) gives 280 mg (70%) of 2-(4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholin-2-yl)acetaldehyde as a colorless solid, mp 115−117 °C. R_f = 0.50 (hexane:EtOAc 6:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13−2.25 (m, 2 H, 3-Ha, 5-Ha), 2.44 (s, 3 H, Ts-CH_3), 2.59 (dd, J = 16.8 and 6.6 Hz, 1 H, 7-H), 2.69 (dd, J = 16.8 and 6.8 Hz, 1 H, 7-H), 3.65−3.78 (m, 2 H, 3-He, 5-He), 3.82 (s, 3 H, 4′-OCH_3), 3.84 (s, 6 H, 3′, 5′-2OCH_3), 4.29−4.36 (m, 1 H, 6-H), 4.65 (t, J = 9.2 Hz, 1 H, 2-H), 6.50 (s, 2 H, 2′, 6′-H), 7.34 (d, J = 8.0 Hz, 2 H, 3″, 5″-H), 7.63 (d, J = 8.0 Hz, 2 H, 2″, 6″-H), 9.78 (s, 1 H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 46.7, 49.3, 51.6, 56.4, 61.0, 78.0, 79.3, 103.1, 127.9, 130.1, 132.4, 134.0, 138.0, 144.3, 153.5, 199.2; IR (KBr, neat) 3517, 2844, 1727, 1594, 1462, 1340, 1272, 1121, 1011, 977, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{28}NO_7S$ (M + H)$^+$ 450.1581, found 450.1583. Anal. Calcd for $C_{22}H_{27}NO_7S$: C, 58.78; H, 6.05; N, 3.12. Found: C, 58.68; H, 6.00; N, 3.08.

Preparation of 2-(1*H*-Indol-2-yl)-4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholine (12). A mixture of *o*-iodoaniline (107 mg, 0.49 mmol), aldehyde (200 mg, 0.45 mmol), and DABCO (151.2 mg, 1.35 mmol) in dry DMF (7 mL) was degassed for 20 min. $Pd(OAc)_2$ (5.2 mg, 0.0225 mmol) was added to the reaction, and the resulting reaction mixture was heated at 80 °C until the reaction was complete (12 h). The reaction mixture was cooled to room temperature and diluted with water. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Purification of the crude product by column chromatography (EtOAc:hexane, 2:3) gives 188 mg (80%) of 2-(1*H*-indol-2-yl)-4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholine. Rf = 0.45 (hexane:EtOAc, 7:3). Colorless solid, mp 137−139 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (dd, J = 11.2 and 10.8 Hz, 1 H, 5-Ha), 2.42 (s, 3 H, Ts-CH_3), 2.63 (dd, J = 11.2 and 10.8 Hz, 1 H, 3-Ha), 3.82 (s, 3 H, 10-OCH_3), 3.84 (s, 6 H, 9, 11−2OCH_3), 3.90−3.98 (m, 2 H, 3-He, 5-He), 4.85 (d, J = 10.0 Hz, 1 H, 6-H), 5.17 (d, J = 10.8 Hz, 1 H, 2-H), 6.64 (s, 2 H, 8, 12-H), 7.11 (t, J = 8.0 Hz, 1 H, 5′-H), 7.18−7.22 (m, 2 H, 2′, 6′-H), 7.30 (d, J = 8.0 Hz, 2 H, 3″, 5″-H), 7.38 (d, J = 8.0 Hz, 1 H, 7′-H), 7.61 (d, J = 8.0 Hz, 2 H, 2″, 6″-H), 7.73 (d, J = 8.0 Hz, 1 H, 4′-H), 8.29 (brs, 1 H, -NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 50.8, 52.1, 56.4, 61.0, 73.3, 77.9, 103.3, 111.7, 114.1, 119.9, 120.0, 122.2, 122.6, 125.7, 127.9, 130.1, 134.8, 136.5, 144.1, 153.5; IR (KBr, neat) 3374, 2927, 2852, 1594, 1461, 1342, 1267, 1166, 1090, 976, 743 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{31}N_2O_6S$ (M + H)$^+$ 523.1897, found 523.1901. Anal. Calcd for $C_{28}H_{30}N_2O_6S$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.31; H, 6.71; N, 5.32.

Preparation of Chelonin A. To the solution of 2-(1*H*-indol-2-yl)-4-tosyl-6-(3,4,5-trimethoxyphenyl)morpholine (100 mg, 0.19 mmol) in dry THF (10 mL) at −78 °C was added freshly prepared sodium naphthalenide solution [obtained by addition of naphthalene (245 mg, 1.9 mmol) to the vigorously stirred solution of Na (45.6 mg, 1.9 mmol) in dry THF (4 mL) at room temperature for 2 h] and the resulting solution was stirred at the same temperature for another 1 h. The reaction mixture was quenched by the addition of saturated NH_4Cl solution at −78 °C and slowly warmed to room temperature. Then, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the combined organic layer was treated with dil. HCl (3 × 5 mL). The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4, and the solvent was evaporated in vacuo followed by purification by column chromatography (CH_2Cl_2:MeOH, 19:1), which gives chelonin A (56 mg, 80%) as a colorless solid, mp 180−182 °C (reported 180−182 °C). R_f = 0.35 (DCM:MeOH 9.5:0.5).[21]

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.90 (dd, J = 11.4 and 10.8 Hz, 1 H, 5-Ha), 3.15−3.26 (m, 3 H, 3, 5-H), 3.82 3.82 (s, 3 H, 10-OCH_3), 3.85 (s, 6 H, 9, 11-2OCH_3), 4.74 (d, J = 10.8 Hz, 1 H, 6-H), 5.06 (d, J = 9.0 Hz, 1 H, 2-H), 6.68 (s, 2 H, 8, 12-H), 7.12 (t, J = 7.2 Hz, 1 H, 5′-H), 7.16−7.20 (m, 2 H, 2′, 6′-H), 7.35 (d, J = 7.2 Hz, 1 H, 7′-H), 7.84 (d, J = 7.2 Hz, 1 H, 4′-H), 8.30 (brs, 1 H, -NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.1, 52.6, 56.3 (2C), 61.0, 74.5, 79.6, 103.4 (2C), 111.5, 115.6, 119.8, 120.0, 121.9, 122.4, 126.1, 136.3, 136.6, 137.6, 153.4 (2C); IR (KBr, neat) 3371, 2923, 2852, 1593, 1462, 1335, 1235, 1127, 1003, 908, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{25}N_2O_4$ (M + H)$^+$ 369.1803, found 369.1818.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02260.

HRMS spectra of all new compounds (PDF)
^{1}H, ^{13}C, and ^{19}F NMR spectra and additional spectra (PDF)
X-ray crystallographic data of compound **7e** (CIF)
X-ray crystallographic data of compound **7o** (CIF)

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Notes

The authors declare no competing financial interest.

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