Synthesis of *N*-Tosylhomosphinganine and *N*-Tosylsedridine

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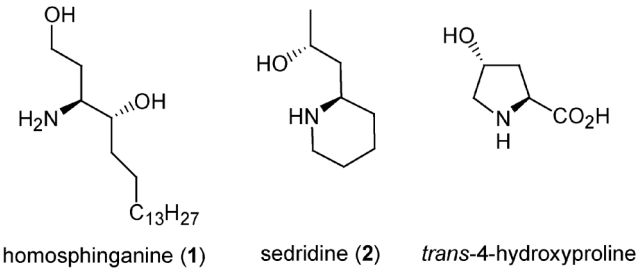
A straightforward synthesis of *N*-tosylhomosphinganine and *N*-tosylsedridine has been achieved from *trans*-4-hydroxyproline by Grignard addition, regioselective Baeyer-Villiger reaction, cross or ring-closing metathesis and hydrogenation as the key steps.

Keywords: *trans*-4-Hydroxyproline; *N*-Tosylhomosphinganine; Sedridine; Allosedridine; Grignard addition; Regioselective Baeyer-Villiger reaction; Cross metathesis; Ring-closing metathesis.

INTRODUCTION

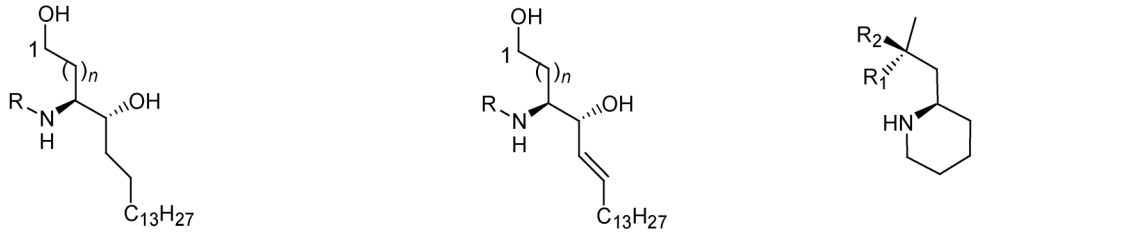
Based on the structural framework of *trans*-4-hydroxyproline, it possesses three functional groups that can be easily modified.[1] The skeleton represents a significant feature for producing a series of different carbon frameworks using an efficient modification technique. Recently we have introduced a straightforward approach to epibatidine,[2a] pancracine,[2b] streptorubin B core,[2c] 4-aryl-3-hydroxyprolinols,[2d] and statine[2e] employing *trans*-4-hydroxyproline as the starting material. In connection with our studies on *trans*-4-hydroxyproline as the chiral material, we are interested in developing a new synthetic route toward homosphinganine (homodihydrosphingosine) and sedridine via Grignard addition, regioselective Baeyer-Villiger reaction, cross or ring-closing metathesis and hydrogenation as the key steps (Fig. 1).

Various sphingolipids with different biological activities are found widely in nature, having been identified and isolated from different organisms.[3] Structurally, this family is composed of three distinct subunits: (1) a polar substitutent (sugar, phosphate or sulfate residue) which is attached to a 1-primary hydroxyl group, (2) a fatty acyl chain which is linked to a 2-amino group by an amide bond, and (3) a sphingoid base with an 2-amino-1,3-diol. In general, this family possesses identical structural features of a sphingoid base except for C4-C5 *trans*-olefin. Basically, some novel synthetic methods for this family and related analogs can be summarized mainly based on asymmetric methodologies (Sharpless dihydroxylation or expoxidation, Henry reaction, or chiral auxiliaries), chiral-pool (serine, galactal, glucose, mannose, lyxose, tartartic acid or aziridine) approaches, and enzymatic resolution.[4] Among this family, the structural characteristics of sphinganine (**1a**) provides the simplest skeleton. Compound **1** and the related analogs **1a**~**1g** are shown in Fig. 2. Here, synthetic studies toward homosphinganine (**1**) with an extra methylene group (-CH_2-) between the C1-C2 position of sphinganine is described. To date, there are only a few reports for synthesizing the homo-analogs.[5] They have also been demonstrated to possess potential apoptotic activities in HL-60 human leukemia cells.[5c] Sedum alkaloids with potential biological activities are a large family of 2-substituted and 2,6-discubstituted piperidines having various hydroxyl functionalities in the side chain, many of which feature the 1,3-aminoalcohol moiety, for example, sedridine (**2**) and allosedridine (**2a**).[6-7] Diverse and elegant synthetic approaches exist toward sedridine (**2**) and allosedridine (**2a**).[8] Sedridine (**2**) and allosedridine (**2a**) have a common structural framework of a piperidine ring and their only difference is the hydroxyl group configuration of the 2-substi-



homosphinganine (**1**) sedridine (**2**) *trans*-4-hydroxyproline

Fig. 1. Structural characteristics of homosphinganine, sedridine, and *trans*-4-hydroxyproline.



R=H, *n*=1, homosphinganine (**1**)
R=H, *n*=0, sphinganine (**1a**)
R=$C_{15}H_{31}CO$, *n*=1, homodihydroceramide (**1b**)
R=$C_{15}H_{31}CO$, *n*=0, dihydroceramide (**1c**)

R=H, *n*=1, homosphingosine (**1d**)
R=H, *n*=0, sphingosine (**1e**)
R=$C_{15}H_{31}CO$, *n*=1, homoceramide (**1f**)
R=$C_{15}H_{31}CO$, *n*=0, ceramide (**1g**)

R_1=OH, R_2=H, sedridine (**2**)
R_1=H, R_2=OH, allosedridine (**2a**)

Fig. 2. Structural characteristics of the sphinganine family, sedridine and allosedridine.

tuted side chain.

RESULTS AND DISCUSSION

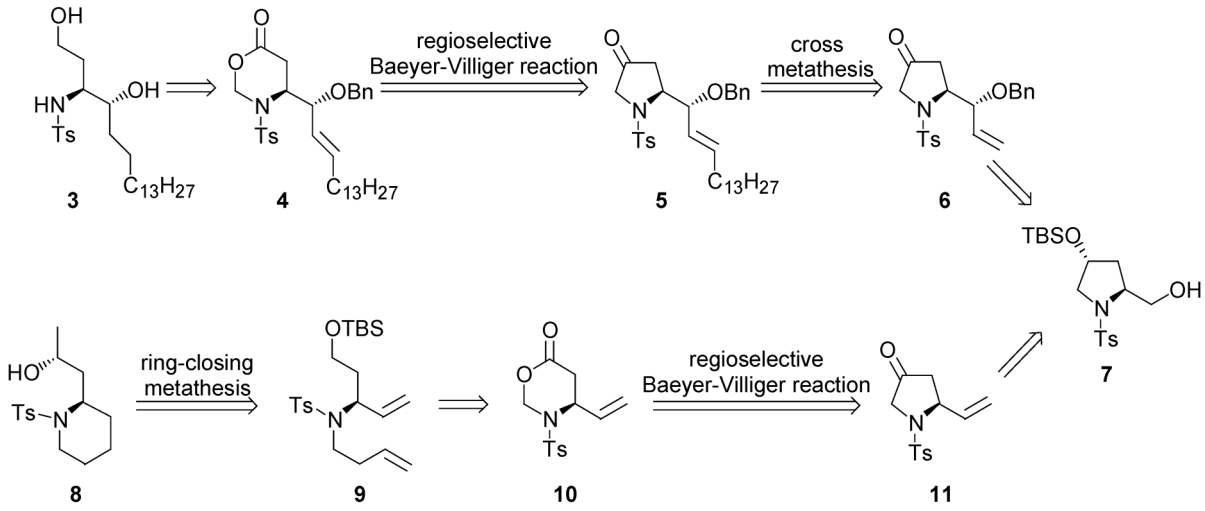
Retrosynthetic analysis of *N*-tosylhomosphinganine and *N*-tosylsedridine

We now wish to describe a novel synthesis of *N*-tosylhomosphinganine (**3**) and *N*-tosylsedridine (**8**) by the remarkable key steps as shown in Scheme I. One is the access to produce the structural framework of tetrahydro-1,3-oxazin-6-ones **4** and **10** by the regioselective Baeyer-Villiger reaction of pyrrolidin-4-ones **5** and **11**. The other is a cross metathesis between ketone **6** and 1-pentadecene and a ring-closing metathesis of diene **9**. Thus, ketones **6** and **11** could be easily synthesized by a series of functional group transformations of prolinol **7**.

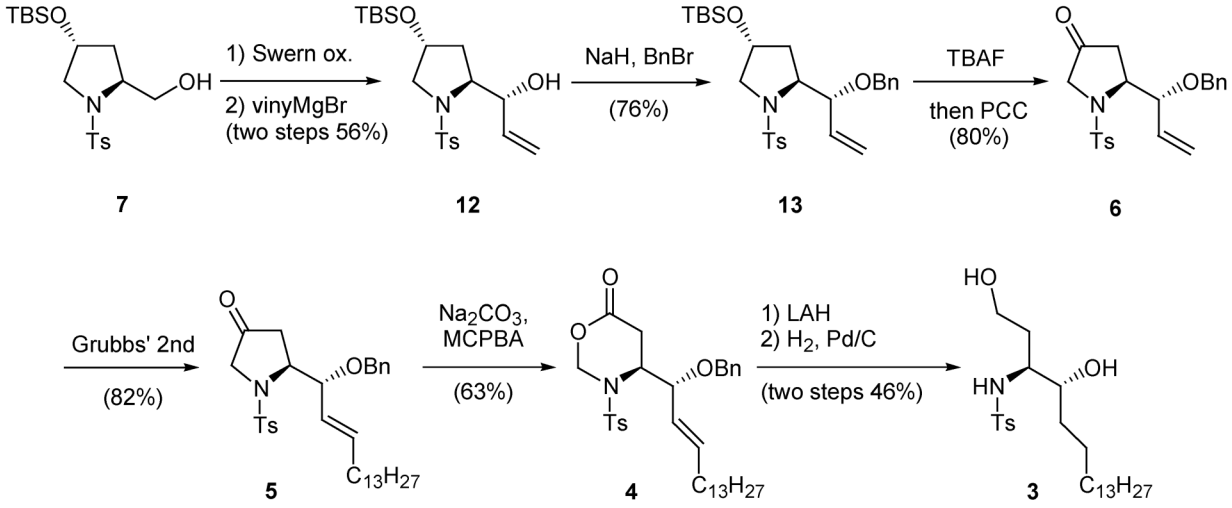
Synthesis of *N*-tosylhomosphinganine (3)

The synthesis of *N*-tosylhomosphinganine (**3**) began from compound **7** as illustrated in Scheme II. According to our preliminary reports,[2a] the four-step preparation of prolinol **7** with 90% overall yield was provided from *trans*-4-hydroxyproline. Initially, prolinol **7** was treated with Swern oxidation and followed by diastereoselective Grignard addition to give compounds **12** and **12a** as a mixture of epimers at -78 °C.[6] The epimeric ratio was nearly 6:1 as determined by the isolated yield. The diastereoselective addition occurred in favor of the *anti* isomer through a chelated intermediate.[9a-b] The structural skeleton of compound **12** was determined by single-crystal X-ray analysis.[10] Then, ketone **6** was provided via *O*-benzylation of allylic alcohol **12** with benzyl bromide and sodium hydride and followed by desilylation of compound **13** with tetra-*n*-butylammo-

Scheme I Retrosynthetic analysis of *N*-tosylhomosphinganine and *N*-tosylsedridine



Scheme II Synthesis of *N*-tosylhomosphinganine (**3**)



nium fluoride and subsequent oxidation of the corresponding secondary alcohol with pyridinium chlorochromate and Celite. To elongate the side arm, ketone **6** was subjected to cross metathesis reaction. Intermolecular olefin cross metathesis reaction has been established as a powerful method for the synthesis of carbohydrates, heterocycles, and alkaloids.[11] While pondering over the related literature reports,[12] we investigated the olefin cross metathesis reaction between ketone **6** and 1-pentadecene. When ketone **6** was subjected to cross metathesis reaction with 1-pentadecene employing first generation Grubbs' catalyst [$Cl_2(PCy_3)_2Ru$=CHPh], the expected compound **5** was only generated in nearly 20~26% yields under a number of conditions (prolonged reaction time, elevated temperature, and different solvents). Therefore, we next turned our attention to examine the second generation Grubbs' catalyst, which has higher thermal stability and lower sensitivity to double bond migration. Using similar reaction conditions, ketone **5** was obtained in 82% yield.

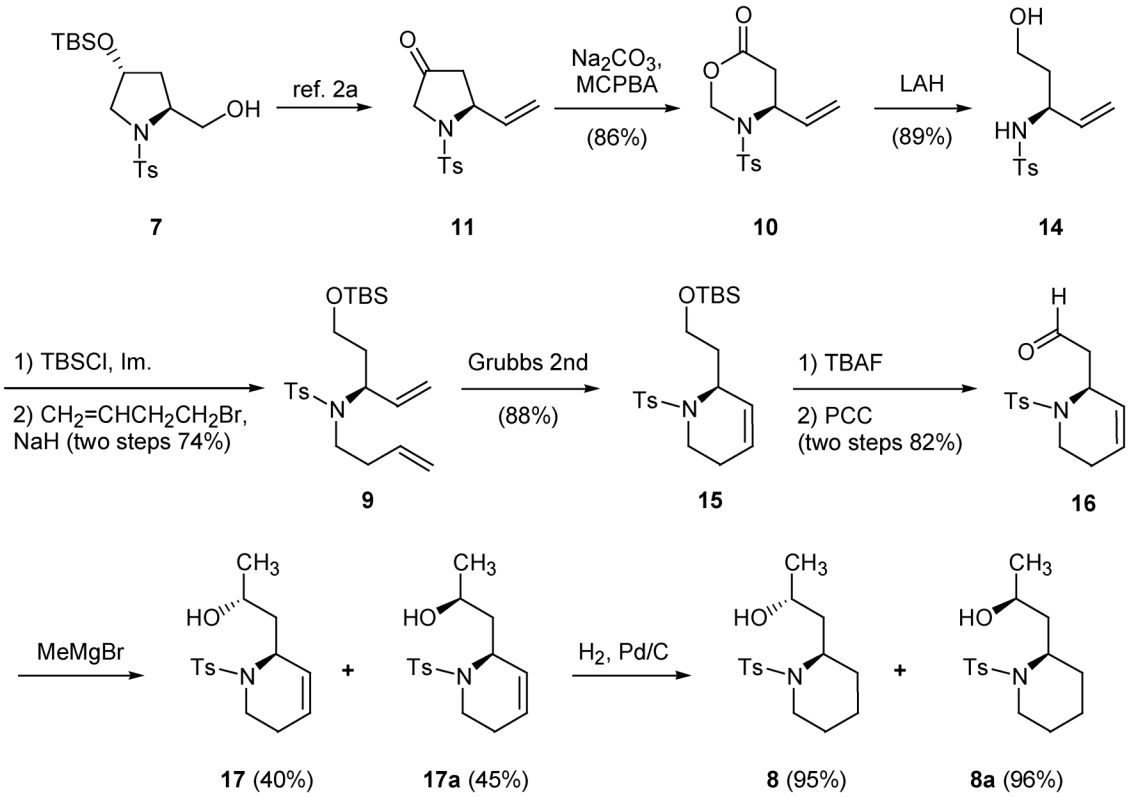
With compound **5** in hand, regioselective Baeyer-Villiger reaction of compound **5** was next examined. According to the our preliminary experiences and Young's group reports,[13] compound **5** was successfully treated with sodium carbonate and *m*-chloroperoxybenzoic acid to afford the tetrahydro-1,3-oxazin-6-one **4** in 63% yield via the regiospecific ring expansion by the nitrogen lone pair of ketone **5**. Finally, synthesis of *N*-tosylhomosphinganine (**3**) was accomplished via reduction with lithium aluminum hydride and hydrogenation with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon.

Synthesis of *N*-tosylsedridine (8)

As shown in Scheme III, we studied the approach to sedridine (**2**) from ketone **11**, which was prepared from prolinol **7** as in our preliminary report.[2a] Regioselective Baeyer-Villiger lactonization[13] of ketone **11** was carried out by treating with *m*-chloroperoxybenzoic acid and sodium carbonate to afford sole tetrahydro-1,3-oxazin-6-one **10**. During the lactonization process, the other ring-expanded framework was not observed. Reduction of the regioisomer **10** with lithium aluminum hydride provided 1,3-aminoalcohol **14**. Compound **9** was synthesized in 74% yield over two steps via silylation of compound **14** with *t*-butyldimethylsilyl chloride and imidazole and followed by *N*-alkylation of the resultant product with 4-bromo-1-butene and sodium hydride at room temperature. The key ring-closing metathesis was examined in the following step.[14] To build up the piperidine skeleton, diene **9** was subjected to a ring-closing metathesis employing Grubbs' 2nd catalyst; the expected 2-substituted piperidine ring **15** was generated in 88% yield. Compound **15** was further transformed to aldehyde **16** in 82% yield over two steps by desilylation with tetra-*n*-butylammonium fluoride and subsequent pyridinium chlorochromate-mediated oxidation under the standard conditions. When olefinic compound **15** was hydrogenated to yield saturated compound **15a**, we found that Singh and co-workers[8m] had developed the key intermediate **15a** toward the synthetic applications of various analogs of sedamine and tetraponerine.

Next, Grignard addition of aldehyde **16** with methyl magnesium bromide yielded a mixture of alcohols **17** and

Scheme III Synthesis of *N*-tosylsedridine (**8**)



17a with a nearly 1:1 ratio. Finally, known compounds **8** and **8a** were afforded via hydrogenation of compounds **17** and **17a** with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon. The NMR spectral data of *N*-tosylsedridine (**8**) and *N*-tosylallosedridine (**8a**) were in accordance with those reported in the literature.[8h]

CONCLUSION

In summary, we succeeded in accomplishing the synthesis of *N*-tosylhomosphinganine (**3**) and *N*-tosylsedridine (**8**) and *N*-tosylallosedridine (**8a**) from *trans*-4-hydroxyproline via the Grignard addition, regioselective Baeyer-Villiger reaction, cross or ring-closing metathesis and hydrogenation as the key steps.

EXPERIMENTAL

General

Tetrahydrofuran (THF) was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. All reported melting temperatures are uncorrected.

2-(1-Hydroxy-2-propenyl)-4-(*t*-butyldimethylsilanyloxy)-1-(4-methylphenylsulfonyl)-pyrrolidine (12)

A stirred solution of oxalyl chloride (400 mg, 3.15 mmol) in CH_2Cl_2 (20 mL) was mixed with dimethyl sulfoxide (400 mg, 5.1 mmol) at –78 °C. The solution was warmed to –40 °C for 15 min and recooled to –78 °C, and then a solution of compound **7** (385 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise for 90 min followed by excess triethylamine (4 mL, 28.5 mmol) for 30 min. The reaction mixture was warmed to rt and poured into $NH_4Cl_{(aq)}$ solution (15%, 2 mL) and concentrated. The residue was diluted with water (15 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine and water, dried, filtered and evaporated to produce crude product. Without further purification, a solution of vinylmagnesium bromide (1.0 M in THF, 1.5 mmol, 1.5 mL) was added to a stirred solution of resulting product in THF (20 mL) at -78 °C. The reaction mixture was stirred at

rt for 2 h. Saturated $NaHCO_{3(aq)}$ (1 mL) was added to the reaction mixture and the solvent was concentrated. Water (3 mL) and EtOAc (10 mL) was added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was evaporated to afford the residue. The residue was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 4/1) afforded compound **12** (230 mg, 56% of two steps) and compound **12a** (37 mg, 9% of two steps). Compound **12**: $[\alpha]_D^{28}$ -64.2° (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 3482, 1923, 1341, 1159, 836 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{20}H_{34}NO_4SSi$ 412.1978, found 412.1980; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.81 (ddd, *J* = 5.4, 10.5, 17.1 Hz, 1H), 5.35 (dt, *J* = 2.5, 17.1 Hz, 1H), 5.21 (dt, *J* = 2.5, 10.5 Hz, 1H), 4.64 (br s, 1H), 4.28-4.23 (m, 1H), 3.71 (dt, *J* = 2.1, 7.8 Hz, 1H), 3.58 (dd, *J* = 4.2, 11.1 Hz, 1H), 3.24 (ddd, *J* = 1.8, 2.4, 11.1 Hz, 1H), 2.99 (br s, 1H), 2.41 (s, 3H), 2.00 (ddd, *J* = 4.8, 8.1, 12.9 Hz, 1H), 1.64-1.56 (m, 1H), 0.71 (s, 9H), -0.10 (s, 3H), -0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.90, 136.33, 134.11, 129.95 (2x), 128.09 (2x), 116.93, 73.37, 69.96, 63.78, 58.80, 36.21, 25.90 (3x), 21.74, 18.20, -4.71, -4.84. Compound **12a**: mp 172-173 °C; $[\alpha]_D^{29}$ +81.6° (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 3434, 2954, 1636, 1347, 1159 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{20}H_{34}NO_4SSi$ 412.1978, found 412.1978; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.81 (ddd, *J* = 4.8, 10.8, 17.1 Hz, 1H), 5.40 (dt, *J* = 1.2, 17.1 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H), 4.60 (br s, 1H), 4.02-3.96 (m, 1H), 3.88-3.83 (m, 1H), 3.71 (d, *J* = 5.4 Hz, 1H), 3.38 (dd, *J* = 5.1, 10.8 Hz, 1H), 3.24 (dd, *J* = 3.3, 10.8 Hz, 1H), 2.42 (s, 3H), 1.87-1.81 (m, 2H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.04, 137.91, 134.85, 130.02 (2x), 127.76 (2x), 116.18, 73.37, 70.31, 63.55, 57.20, 34.49, 25.83 (3x), 21.76, 18.19, -4.78, -4.91; Anal. Calcd for $C_{20}H_{33}NO_4SSi$: C, 58.36; H, 8.08; N, 3.40. Found: C, 58.62; H, 8.29; N, 3.56.

2-(1-Benzyloxy-2-propenyl)-1-(4-methylphenylsulfonyl)-pyrrolidin-4-one (6)

A solution of compound **12** (410 mg, 1.0 mmol) in THF (5 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in THF (10 mL). After the reaction mixture was stirred at rt for 10 min, a solution of benzyl bromide (200 mg, 1.16 mmol) in THF (2 mL) was added. The reaction mixture was stirred at rt for 20 h, poured into $NH_4Cl_{(aq)}$ (15%, 2 mL), and evaporated to afford the residue. The residue was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 10/1) afforded compound **13** (380 mg, 76%) as a viscous oil. $[\alpha]_D^{29}$ -20.3° (*c* 0.01, $CHCl_3$); HRMS (ESI, M^++1) calcd for $C_{27}H_{40}NO_4SSi$ 502.2447, found 502.2449; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.37-7.23 (m, 7H), 5.70 (ddd, *J* = 6.0, 10.5, 17.1 Hz, 1H), 5.39 (d, *J* = 17.1 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.63-4.42 (m, 4H), 3.75-3.70 (m, 1H), 3.60 (dd, *J* = 5.4, 9.9 Hz, 1H), 3.04 (dd, *J* = 4.8, 9.9 Hz, 1H), 2.41 (s, 3H), 2.19 (dt, *J* = 5.4, 12.6 Hz, 1H), 1.50-1.41 (m, 1H), 0.74 (s, 9H), -0.10 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.48, 139.05, 136.03, 135.07, 129.85 (2x), 128.47 (2x), 127.85 (2x), 127.73 (2x), 127.60, 117.96, 82.28, 72.16, 70.63, 62.94, 56.71, 34.92, 25.96 (3x), 21.73, 18.29, -4.78, -4.85; Anal. Calcd for $C_{27}H_{39}NO_4SSi$: C, 64.63; H, 7.83; N, 2.79. Found: C, 64.46; H, 8.01; N, 2.51. A solution of tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) in THF (2 mL) was added to a solution of compound **13** (350 mg, 0.7 mmol) in THF (5 mL) at rt. The reaction mixture was stirred at rt for 2 h, poured into $NH_4Cl_{(aq)}$ (15%, 2 mL), and evaporated to afford the residue. The residue was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, a solution of the resultant product in CH_2Cl_2 (5 mL) was added to a mixture of pyridinium chlorochromate (431 mg, 2.0 mmol) and Celite (1.0 g) in CH_2Cl_2 (20 mL). After being stirred at rt for 20 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/EtOAc = 5/1) afforded compound **6** (215 mg, 80% of two steps). mp 83-84 °C; $[\alpha]_D^{28}$ +123.2° (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2953, 1759, 1625, 1152 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{21}H_{24}NO_4S$ 386.1426, found 386.1423; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.34-7.26 (m, 5H), 7.15 (d, *J* = 8.1 Hz, 2H), 5.67 (ddd, *J* = 6.0, 10.5, 17.1 Hz, 1H), 5.39 (dt, *J* = 2.0, 17.1 Hz, 1H), 5.29 (dt, *J* = 2.0, 10.5 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.36-4.27 (m, 2H), 4.22 (d, *J* = 11.7 Hz, 1H), 3.76 (d, *J* = 17.7 Hz, 1H), 3.69 (d, *J* = 17.7 Hz, 1H), 2.50 (d, *J* = 18.0 Hz, 1H), 2.42 (s, 3H), 2.10 (dd, *J* = 9.6, 18.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.30, 144.36, 137.94, 135.86, 134.24, 130.33 (2x), 128.63 (2x), 127.82, 127.28 (2x), 127.24 (2x), 119.71, 83.36, 71.42, 60.84, 53.95, 37.29,

21.77; Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found: C, 65.27; H, 6.33; N, 3.96.

2-(1-Benzyloxy-2-pentadecenyl)-1-(4-methylphenylsulfonyl)-pyrrolidin-4-one (5)

Grubbs' 2nd generation catalyst (30 mg) was added to a solution of compound **6** (200 mg, 0.52 mmol) in CH_2Cl_2 (50 mL) at rt. The reaction mixture was refluxed under nitrogen atmosphere for 2 h. The mixture was evaporated and purified by flash column chromatography (hexane/EtOAc = 4/1) to yield compound **5** (242 mg, 82%). mp 50-51 °C; $[\alpha]_D^{28}$ +2.3° (*c* 0.01, $CHCl_3$); IR ($CHCl_3$) 2924, 2853, 1766, 1455, 1351, 1159, 1093 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{34}H_{50}NO_4S$ 568.3461, found 568.3464; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.31-7.22 (m, 5H), 7.12 (d, *J* = 8.1 Hz, 2H), 5.79 (dt, *J* = 6.6, 15.3 Hz, 1H), 5.22 (dd, *J* = 7.2, 15.3 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.27 (br s, 1H), 4.25 (br s, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.76 (d, *J* = 17.7 Hz, 1H), 3.69 (d, *J* = 17.7 Hz, 1H), 2.51 (d, *J* = 17.7 Hz, 1H), 2.42 (s, 3H), 2.11 (dd, *J* = 9.6, 17.7 Hz, 1H), 2.05 (q, *J* = 7.2 Hz, 2H), 1.26 (br s, 22H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.59, 144.23, 138.22, 137.22, 136.01, 130.27 (2x), 128.57 (2x), 127.68, 127.26 (2x), 127.18 (2x), 125.63, 83.17, 70.83, 61.36, 53.99, 37.51, 32.59, 32.15, 29.92 (3x), 29.85 (2x), 29.67, 29.59, 29.42, 29.19, 22.92, 21.76, 14.35; Anal. Calcd for $C_{34}H_{49}NO_4S$: C, 71.92; H, 8.70; N, 2.47. Found: C, 72.30; H, 8.41; N, 2.78.

4-(1-Benzyloxy-2-pentadecenyl)-3-(4-methylphenylsulfonyl)-[1,3]oxazinan-6-one (4)

A solution of *m*-chloroperoxybenzoic acid (138 mg, 75%, 0.6 mmol) in CH_2Cl_2 (10 mL) was added to a solution of ketone **5** (210 mg, 0.37 mmol) and Na_2CO_3 (106 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at rt for 20 h. Saturated $Na_2CO_{3(aq)}$ (10 mL) was added to the reaction mixture and the solvent was evaporated to afford the residue. The residue was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 4/1~2/1) afforded compound **4** (136 mg, 63%) as a viscous oil. $[\alpha]_D^{26}$ -3.8° (*c* 0.01, $CHCl_3$); HRMS (ESI, M^++1) calcd for $C_{34}H_{50}NO_5S$ 584.3410, found 584.3410; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.39-7.24 (m, 7H), 5.90-5.80 (m, 1H), 5.80 (d, *J* = 12.0 Hz, 1H), 5.29 (d, *J* = 12.0 Hz, 1H), 5.24 (dd, *J* = 7.5, 15.6 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.36 (d, *J* = 7.5 Hz, 1H), 3.72-3.66 (m, 1H), 3.00 (dd, *J* = 10.5, 16.2 Hz, 1H), 2.47-2.39 (m, 1H), 2.41 (s, 3H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.26 (br s, 22H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.28, 145.06, 138.17, 137.48, 135.15, 130.34 (2x), 128.73 (2x), 128.08 (3x), 127.90 (2x), 124.92, 82.56, 76.17, 71.48, 55.42, 32.56, 32.16, 29.92 (5x), 29.69, 29.59, 29.44, 29.19, 28.51, 22.92, 21.87, 14.36; Anal. Calcd for $C_{34}H_{49}NO_5S$: C, 69.95; H, 8.46; N, 2.40. Found: C, 70.28; H, 8.32; N, 2.68.

3-(4-Methylphenylsulfonylamino)-nonadecan-1,4-diol (3)

A solution of the compound **4** (115 mg, 0.2 mmol) in THF (10 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. $NH_4Cl_{(aq)}$ (15%, 2 mL) was added to the reaction mixture. The residue was filtered through a short plug of Celite and washed with EtOAc (2 × 10 mL). The combined organic layers were evaporated to yield the crude product. Without further purification, the resultant compound was dissolved in MeOH (20 mL) and 10% palladium on activated carbon (10 mg) as catalyst was added. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 10 h. The catalyst was filtered through a short plug of Celite and washed with MeOH (2 × 10 mL). The combined organic layers were evaporated under reduced pressure to yield the crude product. Purification on silica gel (hexane/EtOAc = 5/1) afforded compound **3** (43 mg, 46%). mp 76-77 °C; HRMS (ESI, M^++1) calcd for $C_{26}H_{48}NO_4S$ 470.3304, found 470.3306; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 5.32 (br d, *J* = 7.5 Hz, 1H), 3.85-3.78 (m, 1H), 3.70-3.63 (m, 1H), 3.41-3.33 (m, 1H), 3.31-3.26 (m, 1H), 2.43 (s, 3H), 1.95 (br s, 2H), 1.73-1.58 (m, 2H), 1.25 (br s, 28H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.84, 137.80, 130.03 (2x), 127.18 (2x), 73.32, 58.54, 55.06, 33.92, 32.16, 30.46, 29.94 (5x), 29.82 (2x), 29.70, 29.60, 29.53, 25.94, 22.93, 21.80, 14.37.

3-(4-Methylphenylsulfonyl)-4-vinyl-[1,3]oxazinan-6-one (10)

To a solution of *m*-chloroperoxybenzoic acid (600 mg, 75%, 2.6 mmol) in CH_2Cl_2 (10 mL) was added a solution of ketone **11** (265 mg, 1.0 mmol) and Na_2CO_3 (420 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at rt for 40 h. Saturated aqueous Na_2CO_3 (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 × 20 mL). The combined organic

layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 4/1~2/1) afforded compound **10** (242 mg, 86%). $[\alpha]_D^{31.4}$ -174.31° (*c* 0.025, $CHCl_3$); HRMS (ESI, M^++1) calcd for $C_{13}H_{16}NO_4S$ 282.0800, found 282.0803; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.83 (ddd, *J* = 5.0, 10.5, 17.0 Hz, 1H), 5.77 (dd, *J* = 1.0, 11.5 Hz, 1H), 5.29 (dd, *J* = 1.5, 17.0 Hz, 1H), 5.25 (dd, *J* = 1.5, 10.5 Hz, 1H), 5.12 (d, *J* = 11.5 Hz, 1H), 4.35-4.31 (m, 1H), 2.58 (dd, *J* = 7.5, 16.5 Hz, 1H), 2.50 (dd, *J* = 9.0, 16.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.57, 144.72, 135.07, 134.79, 129.91 (2x), 127.58 (2x), 117.18, 74.00, 52.50, 33.72, 21.36; Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98. Found: C, 55.69; H, 5.60; N, 5.12.

N-[1-(2-Hydroxyethyl)allyl]-4-methylbenzenesulfonamide (14)

A solution of compound **10** (200 mg, 0.71 mmol) in THF (10 mL) was added to a rapidly stirred suspension of lithium aluminum hydride (76 mg, 2.0 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h. $NH_4Cl_{(aq)}$ (15%, 2 mL) was added to the reaction mixture and filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude compound. Purification on silica gel (hexane/EtOAc = 2/1) afforded aminoalcohol **14** (162 mg, 89%). $[\alpha]_D^{31.2}$ +22.94° (*c* 0.017, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}NO_3S$ (M^++1) 256.1007 found 256.1010; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.57 (ddd, *J* = 6.0, 9.5, 16.5 Hz, 1H), 5.24 (d, *J* = 8.0 Hz, 1H), 4.97 (d, *J* = 16.5 Hz, 1H), 4.95 (d, *J* = 9.5 Hz, 1H), 3.99 (br s, 1H), 3.86 (dt, *J* = 3.5, 12.5 Hz, 1H), 3.69-3.65 (m, 1H), 2.42 (s, 3H), 2.37 (br s, 1H), 1.84-1.78 (m, 1H), 1.61-1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.39, 137.61, 137.22, 129.58 (2x), 127.12 (2x), 115.78, 58.82, 53.48, 37.22, 21.50; Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49. Found: C, 56.59; H, 6.54.; N, 5.85.

***N*-1-Butenyl-*N*-[1-(2-*t*-butyldimethylsilyloxyethyl)allyl]-4-methylbenzenesulfonamide (9)**

t-Butyldimethylsilyl chloride (150 mg, 1.0 mmol) and imidazole (136 mg, 2.0 mmol) were added to a stirred solution of compound **14** (150 mg, 0.59 mmol) in DMF (3 mL) at rt. The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to yield crude product. Without further purification, a solution of the resultant product in DMF (2 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in DMF (3 mL). After the reaction mixture was stirred at 0 °C for 5 min, 4-bromo-1-butene (110 mg, 0.82 mmol) was added at 0 °C. The resultant mixture was stirred at rt for 3 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (15%, 2 mL) and the mixture was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/EtOAc = 10/1) afforded compound **9** (185 mg, 74% yield of two steps). $[\alpha]_D^{30}$ +40.2° (*c* 0.005, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{38}NO_3SSi$ (M^++1) 424.2342, found 424.2344; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 5.75-5.57 (m, 2H), 5.12-5.01 (m, 4H), 4.46-4.41 (m, 1H), 3.62-3.53 (m, 2H), 3.17 (ddd, *J* = 5.0, 10.5, 15.0 Hz, 1H), 3.06 (ddd, *J* = 5.5, 10.5, 16.0 Hz, 1H), 2.48-2.41 (m, 1H), 2.42 (s, 3H), 2.36-2.28 (m, 1H), 1.84-1.76 (m, 2H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.96, 138.10, 136.14, 134.95, 129.49 (2x), 127.33, 127.30 (2x), 117.72, 116.77, 59.83, 56.89, 44.33, 35.53, 25.91 (3x), 21.49, 18.24, -5.38 (2x); Anal. Calcd for $C_{22}H_{37}NO_3SSi$: C, 62.37; H, 8.80; N, 3.31. Found: C, 62.67; H, 8.59; N, 3.66.

2-(1-*t*-Butyldimethylsilyloxyethyl)-1-(4-methylphenylsulfonyl)-1,2,3,6-tetrahydropyridine (15)

Grubbs' 2nd catalyst (17 mg, 0.02 mmol) was added to a solution of compound **9** (150 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) and the reaction mixture was refluxed under nitrogen atmosphere for 2 h. The mixture was concentrated to yield crude product. Purification on silica gel (hexane/EtOAc = 8/1) afforded compound **15** (123 mg, 88%). $[\alpha]_D^{25}$ +26.3° (*c* 0.005, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{20}H_{34}NO_3SSi$ (M^++1) 396.2029, found 396.2032; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.66-5.58 (m, 2H), 4.41 (br s, 1H), 3.88 (dd, *J* = 6.0, 14.5 Hz, 1H), 3.74-3.67 (m, 2H), 3.14 (ddd, *J* = 4.5, 11.5, 14.5 Hz, 1H), 2.41 (s, 3H), 1.87-1.81 (m, 2H), 1.79-1.70 (m, 2H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.93, 138.50, 129.47 (2x), 128.00, 127.01 (2x), 124.77, 60.14, 50.93, 38.31, 37.94, 25.92 (3x), 23.03, 21.49, 18.24, -5.29, -5.41; Anal. Calcd for $C_{20}H_{33}NO_3SSi$: C, 60.72; H, 8.41; N, 3.54.

Found: C, 60.59; H, 8.16; N, 3.92.

2-(1-*t*-Butyldimethylsilyloxyethyl)-1-(4-methylphenyl-sulfonyl)-piperidine (15a)[8m]

10% Palladium on activated carbon (10 mg) was added to the solution of compounds **15** (20 mg, 0.05 mmol) in MeOH (10 mL). Then hydrogen was bubbled into the mixture for 10 min, and the reaction mixture was stirred for 3 h at rt. The catalyst was filtered through a short plug of Celite and washed with MeOH (2 × 10 mL). The combined organic layers were evaporated to yield crude compound. Purification on silica gel (hexane/EtOAc = 10/1) afforded compound **15a** (19 mg, 95%). HRMS (ESI) *m/z* calcd for $C_{20}H_{36}NO_3SSi$ (M^++1) 398.2185, found 398.2184; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.16-4.12 (m, 1H), 3.80 (dd, *J* = 4.0, 14.0 Hz, 1H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.98 (dt, *J* = 2.5, 14.0 Hz, 1H), 2.42 (s, 3H), 1.84-1.77 (m, 1H), 1.71-1.64 (m, 1H), 1.57-1.46 (m, 2H), 1.30-1.22 (m, 4H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.71, 138.85, 129.56 (2x), 126.99 (2x), 60.62, 50.20, 40.73, 32.59, 29.69, 27.73, 25.91 (3x), 24.68, 21.48, 18.54, -5.36, -5.43.

2-[1-(4-Methylphenylsulfonyl)-3,4-dihydro-*1H*-pyridin-2-yl]-acetaldehyde (16)

A solution of tetra-*n*-butylammonium fluoride (0.5 mL, 1.0 M in THF, 0.5 mmol) in THF (1 mL) was added to a solution of compound **15** (100 mg, 0.25 mmol) in THF (3 mL) at rt for 1 h. A mixture of pyridinium chlorochromate (216 g, 1.0 mmol), Celite (0.5 g) and CH_2Cl_2 (10 mL) was added to the stirred reaction. After being stirred at rt for 10 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/EtOAc = 8/1) afforded compound **16** (58 mg, 82% yield of two steps). $[\alpha]_D^{28}$ -18.2° (*c* 0.005, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{18}NO_3S$ (M^++1) 280.1007, found 280.1008; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.0 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 5.72-5.66 (m, 2H), 4.84 (br s, 1H), 3.87 (dd, *J* = 5.5, 14.5 Hz, 1H), 3.11 (ddd, *J* = 5.0, 11.0, 19.0 Hz, 1H), 2.81 (ddd, *J* = 2.5, 6.5, 17.0 Hz, 1H), 2.74 (ddd, *J* = 2.0, 7.5, 17.0 Hz, 1H), 2.42 (s, 3H), 1.87-1.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.08, 143.48, 137.69, 129.71 (2x), 127.01 (2x), 126.59, 126.10, 48.96, 38.57, 29.69, 22.93, 21.53.

1-[1-(4-Methylphenylsulfonyl)-3,4-dihydro-*1H*-pyridin-2-yl]-propan-2-ol (17) and (17a)

A solution of methylmagnesium bromide (1.0 M in THF, 0.5 mL, 0.5 mmol) was added to a stirred solution of compound **16** (50 mg, 0.18 mmol) in THF (5 mL) at -78 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (15%, 1 mL) and the mixture was concentrated. The residue was diluted with water (5 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to yield crude product. Purification on silica gel (hexane/EtOAc = 4/1) afforded two compounds **17** (21 mg, 40%) and **17a** (24 mg, 45%). For compound **17**: $[\alpha]_D^{26}$ +16.8° (*c* 0.005, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_3S$ (M^++1) 296.1320, found 296.1322; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 5.64-5.56 (m, 2H), 4.40-4.15 (m, 1H), 4.06-4.01 (m, 1H), 3.90 (dd, *J* = 6.0, 15.0 Hz, 1H), 3.20 (ddd, *J* = 5.0, 11.5, 19.5 Hz, 1H), 2.41 (s, 3H), 2.20 (br s, 1H), 1.85-1.61 (m, 4H), 1.26 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.30, 137.94, 129.57 (2x), 127.71, 127.07 (2x), 125.00, 66.30, 52.05, 43.64, 38.28, 23.72, 22.60, 21.52. For compound **17a**: $[\alpha]_D^{28}$ -12.8° (*c* 0.005, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_3S$ (M^++1) 296.1320, found 296.1325; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 5.58-5.51 (m, 2H), 4.51 (dd, *J* = 2.5, 11.5 Hz, 1H), 4.16-4.10 (m, 1H), 3.90 (dt, *J* = 3.0, 15.0 Hz, 1H), 3.57 (br s, 1H), 3.11 (ddd, *J* = 7.0, 9.0, 14.5 Hz, 1H), 2.42 (s, 3H), 1.66-1.49 (m, 4H), 1.24 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.43, 137.94, 129.67 (2x), 128.10, 126.83 (2x), 124.72, 62.87, 50.99, 43.20, 38.06, 22.46, 22.21, 21.52.

1-[1-(4-Methylphenylsulfonyl)-piperidin-2-yl]-propan-2-ol (8) and (8a)[8h,8m]

10% Palladium on activated carbon (10 mg) was added to the solution of compounds **17a** (15 mg, 0.05 mmol) or **17b** (15 mg, 0.05 mmol) in MeOH (10 mL). Then hydrogen was bubbled into the mixture for 10 min, and the reaction mixture continued to be stirred for 3 h at rt. The catalyst was filtered through a short plug of Celite and washed with MeOH (2 × 10 mL). The combined organic layers were evaporated to yield crude compound. Purification on silica gel (hexane/EtOAc = 4/1) afforded compound **8** (14.3 mg, 95%) or **8a** (14.5 mg, 96%). For compound **8**: $[\alpha]_D^{26}$ +21.3° (*c* 0.005, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NO_3S$ (M^++1) 298.1477, found 298.1478; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 4.25-4.21 (m, 1H), 4.03-3.97 (m, 1H), 3.91 (dd, *J* = 4.0, 15.0 Hz, 1H), 3.49 (br s, 1H), 3.02 (dt, *J* = 2.5,

15.0 Hz, 1H), 2.44 (s, 3H), 2.02 (ddd, J = 2.5, 12.5, 14.5 Hz, 1H), 1.48-1.38 (m, 3H), 1.33-1.16 (m, 4H), 1.24 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.16, 138.67, 129.85 (2x), 126.70 (2x), 63.12, 49.64, 40.81, 39.31, 27.76, 23.87, 22.66, 21.52, 18.67. For compound **8a**: $[\alpha]_D^{28}$ +36.5° (*c* 0.005, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NO_3S$ (M^++1) 298.1477, found 298.1479; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 4.23-4.19 (m, 1H), 3.93-3.87 (m, 1H), 3.81 (dd, J = 4.5, 14.5 Hz, 1H), 3.08 (dt, J = 3.0, 14.0 Hz, 1H), 2.43 (s, 3H), 1.90 (dt, J = 8.0, 14.0 Hz, 1H), 1.55-1.32 (m, 6H), 1.26-1.17 (m, 2H), 1.23 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.07, 138.41, 129.69 (2x), 126.08 (2x), 66.38, 50.95, 40.87, 39.15, 27.79, 24.15, 23.75, 21.50, 18.47. The desulfonated procedure from compounds **8** and **8a** to sedridine (**2**) and allosedridine (**2a**) is shown in references 8h and 8m.

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