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Iterative Multifunctionalization of Unactivated C−H Bonds in Piperidines by Way of Intramolecular Rh(II)-Catalyzed Aminations

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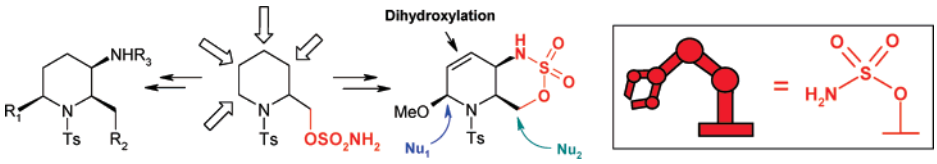

Efficient stereocontrolled synthesis of di-, tri-, tetra-, and pentasubstituted piperidines from simple 2-sulfamoyloxymethyl piperidine derivatives has been performed by way of intramolecular Rh-catalyzed amination of saturated C−H bonds. In this process, the sulfamoyloxymethyl arm was directly or indirectly involved in the functionalization of every saturated methylene group of the piperidine ring at C-3, C-4, C-5, and C-6. Direct application to the total synthesis of iminosugars and related compounds demonstrated the synthetic potential of this strategy.

Introduction

Conquering molecular complexity and diversity using the simplest means is a major challenge in organic chemistry that combines economic with environmental goals.[1] Catalyzed functionalization of unreactive C−H bonds is probably one of the most promising strategies toward this end.[2] The direct and selective introduction of functional groups into saturated hydrocarbons is indeed expected to shorten the syntheses of pharmaceuticals and other relevant targets by reducing the number of steps usually required for protective group manipulation and prefunctionalization via C−X bonds (X = OTf, halogens, etc.). In addition, unlocking the potential of inert C−H bonds offers a major simplification of synthetic sequences and unprecedented chemical possibilities. The importance of nitrogen-based functional groups in natural and synthetic products has stimulated the development of efficient catalytic methods for the amination of unactivated C−H bonds.[3] The major recent advances in this field have involved catalyzed intramolecular C−H insertion reactions using carbamate or sulfamate ester substrates (Figure 1).[4,5] The high regioselectivity usually observed in these processes is mainly controlled by electronic factors. Benzylic, allylic, and tertiary C−H bonds as well as sites adjacent to electron-donating groups are generally favored. Amination reactions performed with sulfamate esters lead generally to the formation of the corresponding six-membered ring insertion product (Figure 1), whereas carbamates afforded only five-membered rings.[3]

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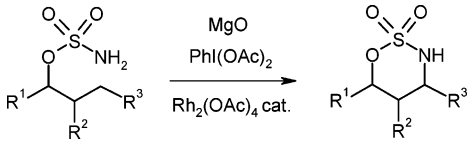
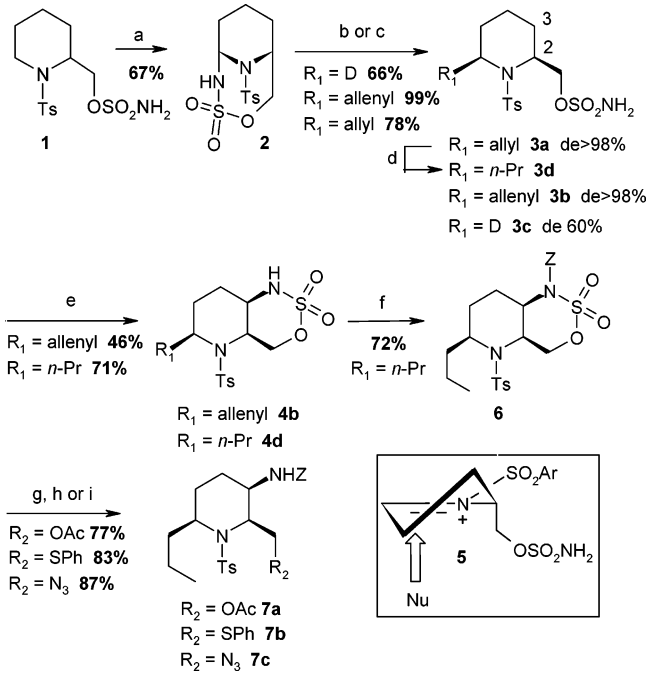


FIGURE 1. Rh-catalyzed oxidative cyclization of sulfamic esters.

SCHEME 1 [a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$ (1.1 equiv), MgO (2.3 equiv), $Rh_2(OAc)_4$ (0.05 equiv), CH_2Cl_2, 40 °C (ref 7); (b) Et_3SiD (3 equiv) or allylTMS (4 equiv), $BF_3{\cdot}OEt_2$ (1 equiv), CH_2Cl_2, −78 °C; (c) propargylTMS (4 equiv), $SnCl_4$ (0.2 equiv), CH_2Cl_2, −78 to 0 °C; (d) H_2, 10% Pd/C, MeOH, rt; (e) $PhI(OAc)_2$ (1.1 equiv), MgO (2.3 equiv), $Rh_2(esp)_2$ (0.02 equiv), CH_2Cl_2, 40 °C; (f) CbzCl (2.5 equiv), *t*-BuOK (1.5 equiv), DME, 0 °C to rt; (g) KOAc (2 equiv), DMF, rt; (h) PhSH (2.4 equiv), K_2CO_3 (2.4 equiv), CH_3CN, −20 °C to rt; (i) NaN_3 (2 equiv), DMSO, 0 °C to rt. [$Rh_2(esp)_2$ = $Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate)$_2$].

In connection with our studies on iminosugars,[6] we have recently reported the first examples of seven- and eight-membered rings generated by way of the intramolecular-catalyzed amination of saturated C−H bonds.[7,8] This reaction, which further expands the synthetic scope of C−H amination, provides access to bicyclic aminals such as **2** (Scheme 1), allowing the functionalization of a C−H bond in a 1,7-relationship with respect to the activating group (Figure 2). It was anticipated that these compounds, as potential precursors of *N*-tosyliminium ions, could react with various reagents to form versatile enamine intermediates or a new bond at C-6 (Figure 2). The major advantage of these processes is the regeneration of the sulfamoyloxy group that may be used again

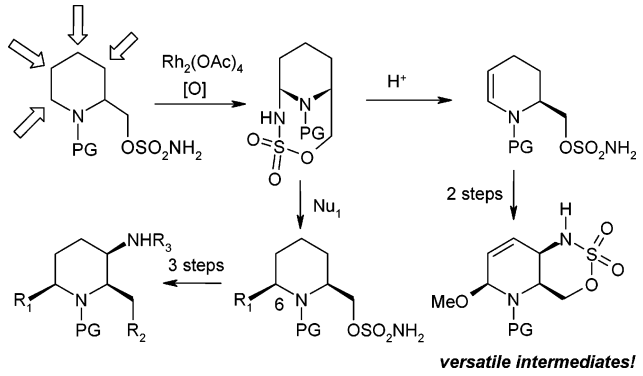


FIGURE 2. Toward multifunctionalization of unactivated C−H bonds in piperidine derivatives.

for further intramolecular C−H amination. Based on this working hypothesis, we have devised molecular systems for selective and iterative multifunctionalization of unactivated C−H bonds in nitrogen-containing heterocycles. In this process, the sulfamoyloxymethyl group is used several times as a "molecular activating arm" allowing the formation of C−C, C−N, or C═C double bonds.[9] The ultimate goal of this strategy would be the diversity-oriented synthesis of bioactive azacycloalkanes by iterative and direct heterocyclic scaffold decoration. We wish to report here our first exploration of the synthetic potential of this new concept in the piperidine series. This major class of biologically active compounds[10] is found in many natural products, glycomimetics (iminosugars),[6d] and drug candidates. Their impact on medicinal science has been superbly highlighted by the fact that, during a recent 10-year period, there were over 12000 piperidine compounds mentioned in clinical and pre-clinical studies.[11]

Results and Discussion

Synthetic Route to 2,6-Disubstituted 3-Aminopiperidines. We first investigated the activating arm concept for the general synthesis of 2,6-disubstituted 3-aminopiperidines (Scheme 1). In contrast to the nucleophilic addition to *N*,*O*-acetals,[12,13] the reactivity of aminals as precursors of *N*-tosyliminium ions has been almost unexplored.[14] To evaluate the synthetic scope of this reaction, a systematic study was performed with aminal **2** over a broad range of conditions (Table 1). We were pleased to find that treatment of aminal **2** with 4 equiv of allylsilane and $BF_3{\cdot}OEt_2$ or $SnCl_4$ afforded the expected 2,6-disubstituted piperidine **3a** in good yields and as a single diastereoisomer.

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(7) Toumieux, S.; Compain, P.; Martin, O. R.; Selkti, M. *Org. Lett.* **2006**, *8*, 4493.

(8) For the first example of a metal-catalyzed amination of pseudo-anomeric C-H bond see: Toumieux, S.; Compain, P.; Martin, O. R. *Tetrahedron Lett.* **2005**, *46*, 4731.

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(11) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.

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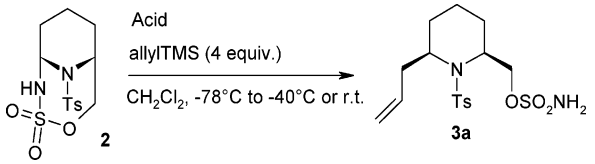
(13) For reviews on the chemistry of *N*-Acyliminiums ions and related intermediates see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311.

(14) Berry, C. R.; Hsung, R. P. *Tetrahedron* **2004**, *60*, 7629.

TABLE 1. Addition of Allylsilane to *N*-Tosyliminium Ions Derived from Aminal 2[a]



entry	acid	equiv	reaction time (h)	*T* (°C)	yield[b] (%)
1	$BF_3{\cdot}OEt_2$	1	16	−78 to −40	78
2	$BF_3{\cdot}OEt_2$	0.5	28	−78 to −40	13
3	$SnCl_4$	1.5	3	−78 to −40	77
4	$SnCl_4$	0.7[c]	24[c]	−78 to rt[c]	86[c]
5	TMSOTf	1	22	−78 to −40	*d*
6	$ZnCl_2$	1.5	16	−78 to rt	*d*
7	*p*-TsOH	0.2	20	0 to rt	*d*

[a] All compounds are racemic. [b] Isolated yield after purification on silica gel. [c] 0.2 equiv of Lewis acid was first introduced in the flask, and then an additional 0.5 equiv of Lewis acid was added after 16 h at 0 °C. [d] Degradation products were observed on TLC and NMR spectra along with various amount of enamine **8**.

The use of other Lewis acids, such as TMSOTf[12f] or $ZnCl_2$[14] (entries 5 and 6), or of a Brønsted acid[12e] (entry 7) led to degradation products and to various amounts of enamine **8**.

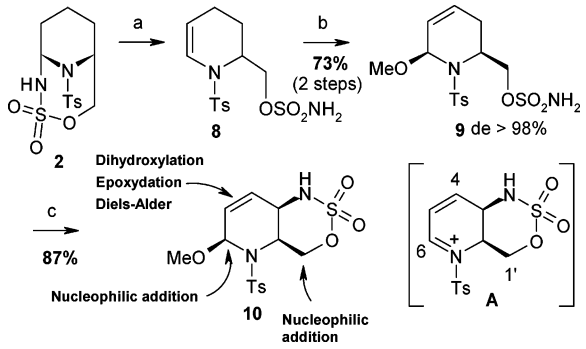
The reaction of aminal **2**[7] with propargyltrimethylsilane or triethylsilane afforded the expected piperidines in good to excellent yield, whereas the addition of 1-phenyl-1-trimethylsilyloxyethylene was unsuccessful. High levels of diastereoselectivity were observed for the addition of propargyltrimethylsilane in favor of the 2,6-cis derivative (Scheme 1). The addition of the less sterically demanding deuteride ion led to piperidine **3c** with a lower degree of diastereoselectivity (60% de). The cis stereoselectivity may be rationalized by preferential axial addition of the nucleophile to a half-chair conformation of the cyclic iminium intermediate **5** in which the substituent at C-2 is pseudoaxial to avoid pseudo A[1,3] strain with the *N*-tosyl group (Scheme 1).[6a,7,15] Delivery of nucleophiles in the axial direction minimizes torsional strain during the transition to the final chair conformation of piperidine ring. The stereochemistry of the newly formed bond was established by extensive NMR analysis and definitively assigned by X-ray crystallographic analysis.[7]

The next key step of our strategy was the second C−H bond amination using the sulfamoyloxymethyl arm regenerated by nucleophilic ring-opening of aminal **2** (Scheme 1).

One of the pivotal issues of this process was the regioselectivity of the insertion reaction at C-2 or C-3, position 6 being at this stage unavailable as a result of the formation of a 2,6-cis isomer. It is indeed known that amination reactions performed with sulfamate esters lead generally to the formation of the corresponding six-membered ring insertion products but that electron-donating groups generally activate the α-C−H bond toward insertion.[3b] The Rh-catalyzed amination was first investigated with 6-propyl piperidine **3d** obtained by hydrogenation of **3a** in the presence of 10% Pd/C in MeOH (Scheme 1). The amination reaction was found to be highly regioselective and afforded the desired oxathiazinane **4d** as a single diastereoisomer. The nature of the Rhodium catalyst was found to be critical since the use of $Rh_2(esp)_2$ provided **4d** in 71% yield whereas the use of $Rh_2(OAc)_4$ led to a much lower yield of 24%. More challenging structures such as **3b** bearing an allenic

(15) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867.

SCHEME 2 [a]



[a] Reagents and conditions: (a) AcOH, 60 °C; (b) (i) I_2 (1.9 equiv), MeONa (2 equiv), MeOH, −78 °C; (ii) DBU (2 equiv), toluene, 60 °C, 20 h; (c) $PhI(OAc)_2$ (1.1 equiv), MgO (2.3 equiv), $Rh_2(esp)_2$ (0.01 equiv), CH_2Cl_2, 40 °C.

group at C-6 afforded the bicyclic piperidine **4b** in 46% yield. Exposure of 6-allyl piperidine **3a** to $PhI(OAc)_2$, MgO, and catalytic $Rh_2(esp)_2$ led to a mixture of unidentifiable products, arising probably from side reactions such as amination of allylic C−H bonds or aziridination. The last step of our strategy, which allowed the introduction of a second diversity point, the creation of a new bond and the removal of the "activating arm", was evaluated on 6-propyl piperidine **4d** to access alkaloids related to coniine.[16] After activation of the oxathiazinane by carbonylation of the NH moiety, ring-opening of compound **6** proceeded in very good yields with various heteroatomic nucleophiles (Scheme 1).[4a,17] It is noteworthy that 3-amino 2,6-disubstituted piperidines are known to display anti-allergic and anti-inflammatory activities.[18]

General Access to Polysubstituted 3-Aminopiperidines. Armed with the first successful results, we further expanded the scope of our iterative strategy with a double objective. First, our aim was to design an approach in which the sulfamoyloxy activating arm would be directly or indirectly involved in the functionalization of every saturated methylene of monosubstituted piperidine **1**. Second, to extend the flexibility of our strategy by avoiding possible chemo- and regioselectivity issues, amination reaction at C-3 was performed before introducing structural diversity at C-6. Our approach exploited the reactivity of enamine **8** which was readily obtained from **2** by reaction in AcOH in 90% yield (Scheme 2).[19,20] The use of a stronger Brønsted acid (TFA) or of Lewis acid conditions ($SnCl_4$ in CH_2Cl_2) led to lower yields.

Iodomethoxylation of α,β-unsaturated *N*-tosylpiperidine **8** using I_2 and MeONa in MeOH, followed by DBU-mediated

(16) See for example: Boto, A.; Hernández, D.; Hernández, R.; Montoya, A.; Suárez, E. *Eur. J. Org. Chem.* **2007**, 325.

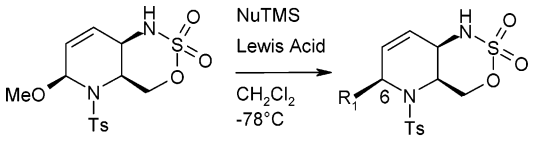
(17) For the synthesis of piperidine derivatives by nucleophilic ring-opening of cyclic sulfamidates see for example: Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 4909.

(18) Takahashi, M.; Miyake, T.; Yamakita, H.; Saito, A.; Asai H. (Tanabe Seiyaku Co., Ltd.), PCT Int. Appl. WO 2002026710, **2002**.

(19) Rossen, K.; Kolarovic, A.; Baskakov, D.; Kiesel, M. *Tetrahedron Lett.* **2004**, *45*, 3023.

(20) *N*-acyl- or *N*-sulfonyl-1,2,3,4-tetrahydropyridine derivatives have been used as versatile intermediates in the general synthesis of polyfunctionalized piperidines, see for example: (a) Comins, D. L.; Sandelier, M. J.; Grillo, T. A. *J. Org. Chem.* **2001**, *66*, 6829. (b) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651. (c) Adelbrecht, J.-C; Craig, D.; Dymock, B. W.; Thorimbert, S. *Synlett* **2000**, 467. (d) Craig, D.; McCague, R.; Potter, G. A.; Williams, R. V. *Synlett* **1998**, 55.

SCHEME 3. Addition of Various Nucleophiles to *N*-Tosyliminium Ions Derived from 10[a]



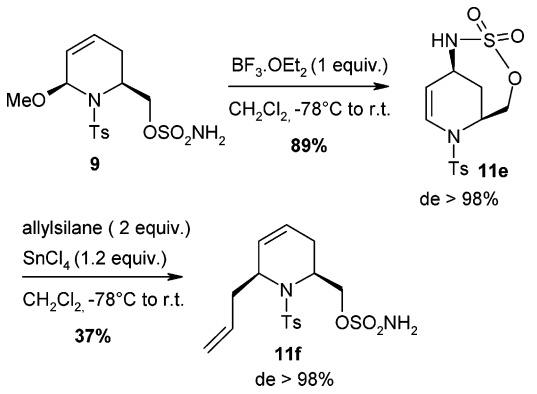
Entry	NuTMS (eq.)	LA (eq.)	Product	Yield[b]	de[c]
1	allylTMS (4)	$SnCl_4$ (1)	**11a**	90%	61%
2	TMSCN (5)	$SnCl_4$ (0.7)	**11b**	97%	>95%
3	CH_2=CH(Ph)OTMS (4)	$SnCl_4$ (1.2)	**11c**	65%	>98%
4	Et_3SiH (4)	$SnCl_4$ (0.7)	**11d**	99%	–

[a] All compounds are racemic. [b]Isolated yield after purification on silica gel. [c]Determined from ^1H and ^{13}C NMR analysis on the crude products.

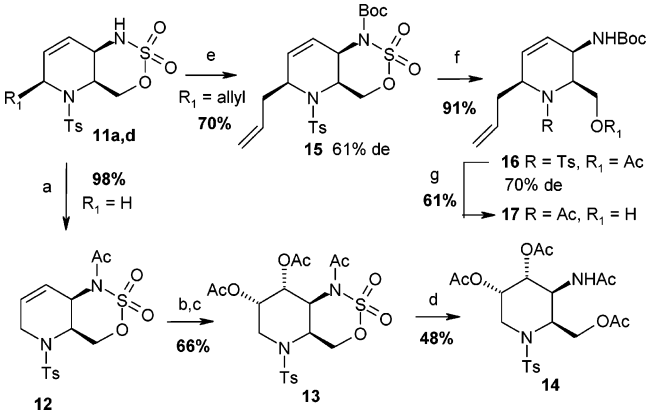
dehydroiodination, provided the desired 6-methoxytetrahydropyridine **9** with a double bond tactically positioned at C(4)−C(5).[21] Remarkably, this three-step process can be performed without purification of the intermediates providing compound **9** in 73% yield from **2**. Rh-catalyzed amination of allylic C−H bond at C-3 was then favored and provided in 87% yield oxathiazinane **10** as an advanced intermediate for the general synthesis of pentasubstituted piperidines. As a potential precursor of the α,β-unsaturated iminium ion **A** with three electrophilic sites of orthogonal reactivity at C-4, C-6, and C-1′, bicyclic compound **10** displays a unique reactivity pattern. The different reactivity of the three electrophilic sites was confirmed by treatment of **10** with $SnCl_4$ and various silylated nucleophiles according to conditions described for ring opening of **2** (Scheme 3).[21,22]

This process provided piperidines **11a**−**d**, corresponding to the 1,2-adducts, with good to high diastereoselectivity and with complete regioselectivity. It was established by 2D COSY and NOESY NMR experiments that the relative configurations of the major epimers obtained are cis,cis. For example, the definite NOE interactions in **11a** between −C*H*$_2$SO$_2$− and −C*H*$_2$CH═CH$_2$, and between H-2 and H-3, indicated that these substituents were on the same side of the piperidine rings. Contrary to results obtained with aminal **2**, addition of silylated enol ethers, such as 1-phenyl-1-trimethylsilyloxyethylene, could be performed successfully. The diastereoselectivity observed in favor of the cis products may be explained as a result of a strong stereoelectronic preference for a pseudoaxial attack of the nucleophile on the intermediate iminium ion **A** (Scheme 2) with a pseudoaxial sulfamoyloxymethyl substituent.[22d] Equatorial attack would indeed generate torsional and pseudo A^{1,3} strain during the transition from a sp^2 to a sp^3 carbon at C-6. Also, the versatile synthon **11e**[21,23] was obtained in 89% yield by way of an S_N2' (or S_N1')-like reaction at C-4 upon treatment of **9** with BF_3·OEt_2 (Scheme 4). Addition of allylsilane onto **11e** in the presence of $SnCl_4$ afforded the 2,6-disubstituted piperidine **11f** in modest yield (not optimized) but as a single cis diastereoisomer, demonstrating the synthetic potential of such an intermediate. The stereochemistry of **11f** was determined by its conversion to piperidine **3d** via hydrogenation in the presence of 10% Pd/C in MeOH.

SCHEME 4



SCHEME 5 [a]



[a] Reagents and conditions: (a) Ac_2O (5 equiv), DMAP (0.1 equiv), *t*-BuOK (1.1 equiv), CH_2Cl_2, −20 °C; (b) OsO_4 (0.2 equiv), NMO (4 equiv), acetone/water (9/1), rt; (c) Ac_2O (15 equiv), DMAP (0.3 equiv), CH_2Cl_2, rt; (d) KOAc (2 equiv), DMF, 40 °C; (e) Boc_2O (2 equiv), DMAP (0.2 equiv), pyridine (14 equiv), CH_2Cl_2, 0 °C, 70% (two steps from **10**); (f) KOAc (2 equiv), DMF, 40 °C; (g) Na/naphthalene (9 equiv), THF, −78 °C.

To further probe the versatility of bicyclic intermediate **10**, stepwise functionalization into more complex structures related to iminosugars was then performed with compounds **11a** (R_1 = allyl) and **11d** (R_1 = H) (Scheme 5). The electrophilic activity of the oxathiazinane was enhanced by the addition of an *N*-acyl substituent. Formation of **15**, the *N*-Boc derivatives of sulfamate **11a**, followed by ring-opening with potassium acetate provided **16** in good yield. Deprotection of the *N*-tosylpiperidines with sodium naphthalenide afforded the advanced intermediates **17** which resulted from *O* → *N*-acetyl group migration.

Synthesis of the fully protected amino iminosugar **14** (in racemic form) began with the *N*-acetylation of oxathiazinane **11d**, and the highly diastereoselective dihydroxylation of the endocyclic double bond of **12**, which occurred anti to the oxathiazinane ring under Upjohn reaction conditions.[24] It is noteworthy that the same reaction performed with the unacylated

(21) Shono, T.; Terauchi, J.; Ohki, Y.; Matsumura, Y. *Tetrahedron Lett.* **1990**, *31*, 6385.

(22) For a related process see: (a) Torii, S.; Inokuchi, T.; Takagishi, S.; Akahoshi, F.; Uneyama, K. *Chem. Lett.* **1987**, 639. (b) Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Chem. Commun.* **2000**, 699. (c) Kinderman, S. S.; Doodeman, R.; Van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; Van Maarseveen, J. H.; Hiemstra, H.; Shoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736. (d) Kennedy, A.; Nelson, A.; Perry, A. *Belstein J. Org. Chem.* **200**5, *1:2*, doi:10.1186/1860−5397-1−2.

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(24) Kennedy, A.; Nelson, A.; Perry, A. *Chem. Commun.* **2005**, 1646.

analog of **12**, compound **11d**, led only to degradation products. Direct acetylation of the resulting product followed by nucleophilic ring-opening with potassium acetate afforded the expected protected iminosugar **14**.

Conclusion

In conclusion, these preliminary studies demonstrate that the iterative multifunctionalization of unactivated C−H bonds is an attractive strategy for the general synthesis of polyfunctionalized piperidines. Efficient stereocontrolled preparations of di-, tri-, tetra-, and penta-substituted piperidines from simple 2-sulfamoyloxymethyl piperidine derivatives have been performed. In this process, the "sulfamoyloxymethyl activating arm" was directly or indirectly involved in the functionalization of every saturated methylene of the piperidine ring at C-3, C-4, C-5, and C-6. Direct application to the total synthesis of iminosugars and related compounds demonstrates the synthetic potential of this strategy which should become a useful tool for the diversity-oriented synthesis of various bioactive azacycloalkanes by iterative and direct heterocyclic scaffold decoration. Recent studies have for example shown the interest of grafting pharmacophore groups at selected positions on piperidine scaffolds.[25] Following these lines, we are currently devising various nitrogen-containing systems (cyclic or acyclic) to further expand the synthetic scope of this chemistry.

Experimental Section

(2*S,6*R**)-6-Propadienyl-2-sulfamoyloxymethyl-1-(toluene-4-sulfonyl)piperidine (3b).** To a 0.1 M solution of **2**[7] (50 mg, 0.144 mmol) in CH_2Cl_2 were added at −78 °C propargyltrimethylsilane (0.086 mL, 0.576 mmol, 4 equiv) and $SnCl_4$ (1M in CH_2Cl_2) (0.028 mL, 0.028 mmol, 0.2 equiv). The solution was rapidly warmed to 0 °C and stirred for 6 h at this temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (PE/AcOEt 6:4) gave **3b** as a colorless oil (54 mg, 99%, de ≥ 98%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22−1.42 (m, 3H, H_{3A}, $2H_5$), 1.56−1.89 (m, 3H, H_{3B}, $2H_4$), 2.44 (s, 3H, Me), 4.35−4.42 (m, 3H, CH_2OSO_2, H_2), 4.64 (m, 1H, H_6), 4.86 (dd, 2H, $J \approx 4.4$, 6.4 Hz, CH═C═CH_2), 5.04 (s, 2H, NH_2), 5.25−5.31 (m, 1H, CH═C═CH_2), 7.31 (d, 2H, $J \approx 8.0$ Hz, H_{Ar}), 7.72 (d, 2H, $J \approx 8.3$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 14.1 (C_4), 21.6 (Me), 24.2 (C_3 or C_5), 26.0 (C_3 or C_5), 49.4 (C_6), 50.8 (C_2), 69.7 (CH_2OSO_2), 78.4 (*C*H_2═C═CH), 93.8 (CH_2═C═*C*H), 127.0 (CH_{Ar}), 130.0 (CH_{Ar}), 137.9 (Cq), 143.8 (Cq), 207.0 (CH_2═*C*═CH). IR (neat) 3268, 1952 cm^{-1}. HRMS: calcd for $C_{16}H_{23}N_2O_5S_2$ $[M + H]^+$ 387.10484, found 387.1040 (2 ppm).

(2*S,6*S**)-6-Propyl-2-sulfamoyloxymethyl-1-(toluene-4-sulfonyl)piperidine (3d).** To **3a**[7] (920 mg, 2.37 mmol) in MeOH (20 mL) was added 10% Pd/C (0.2 equiv). The flask was purged three times with Ar and then filled with H_2. The reaction mixture was stirred at rt. After 15 h, the solids were removed by filtration and washed with MeOH. The filtrate was concentrated under reduced pressure. Purification on silica gel (PE/AcOEt 7/3) gave **3d** as a colorless oil (763 mg, 72%, de ≥ 98%): ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.92 (t, 3H, $J \approx 7.2$ Hz, CH_3CH_2CH_2), 1.16−1.71 (m, 10H, $2H_3$, $2H_4$, $2H_5$, $CH_3CH_2CH_2$), 2.42 (s, 3H, Me), 3.91 (q, 1H, $J \approx 5.6$ Hz, H_6), 4.40 (br s, 3H, CH_2OSO_2, H_2), 5.37 (s, 2H, NH_2), 7.30 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}), 7.72 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 13.7 (C_4), 13.9 ($CH_2CH_2CH_3$), 20.4 ($CH_2CH_2CH_3$), 21.6 (Me), 24.0 (C_3 or C_5), 26.6 (C_3 or C_5), 37.7 ($CH_2CH_2CH_3$), 50.5 (C_2), 52.5 (C_6), 70.7 (CH_2OSO_2), 126.9 (CH_{Ar}), 129.9 (CH_{Ar}), 137.9 (Cq_{Ar}), 143.5 (Cq_{Ar}). IR (neat) 3281, 1377, 1163 cm^{-1}. HRMS: calcd for $C_{16}H_{26}N_2O_5S_2Na$ $[M + Na]^+$ 413.1181, found 413.1182 (0 ppm).

General Cyclization Procedure. To a ∼0.04 M solution of sulfamate ester dissolved in degassed dichloromethane were successively added MgO (2.3 equiv), $PhI(OAc)_2$ (1.1 equiv), and $Rh_2(esp)_2$ or $Rh_2(OAc)_4$ (0.02−0.05 equiv). The solution was stirred at 40 °C until TLC indicated total conversion of starting material (4−24 h). After cooling at room temperature, the solution was filtered through a pad of Celite and washed three times with dichloromethane and acetone. The filtrate was evaporated to dryness under reduced pressure. The crude mixture was purified by chromatography on silica gel.

(4a*S,6*R**,8a*R**)-6-Propadienyl-5-(toluene-4-sulfonyl)octahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (4b).** Compound **3b** (50 mg, 0.134 mmol) was treated as described in the general cyclization procedure using MgO (13 mg, 0.309 mmol, 2.3 equiv), $PhI(OAc)_2$ (49 mg, 0.148 mmol, 1.1 equiv), and $Rh_2(esp)_2$ (2 mg, 0.003 mmol, 0.02 equiv). The resulting crude product was purified by silica gel chromatography (PE/AcOEt 7/3) to provide **4b** (24 mg, 46%, de ≥ 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.38 (m, 1H, H_5), 1.77 (m, 1H, H_{4eq}), 2.01 (br d, 1H, H_{5eq}), 2.44 (s, 3H, Me), 2.66 (dq, 1H, $J \approx 3.5$ Hz, $J \approx 3 \times 14.0$ Hz, H_{4ax}), 3.16 (m, 1H, H_3), 4.34 (ddd, 1H, $J \approx 1.5$ Hz, $J \approx 6.5$ Hz, $J \approx 11.3$ Hz, CH_AOSO_2), 4.49 (dt, 1H, $J \approx 2 \times 5.4$ Hz, $J \approx 11.0$ Hz, H_2), 4.68 (narrow m, 1H, H_6), 4.96 (m, 3H, CH_2═C═CH, NH), 5.10−5.18 (m, 2H, CH_BOSO_2, CH_2═C═CH), 7.32 (d, 2H, $J \approx 8.0$ Hz, H_{Ar}), 7.72 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 20.2 (C_4), 21.7 (Me), 26.6 (C_5), 48.6 (C_6), 48.7 (C_2), 53.6 (C_3), 69.2 (CH_2OSO_2), 79.12 (*C*H_2═C═CH), 93.1 (CH_2═C═*C*H), 126.9 (CH_{Ar}), 130.3 (CH_{Ar}), 137.3 (Cq), 144.4 (Cq), 207.3 (CH_2═*C*═CH). IR (neat) 3273, 1956, 1161 cm^{-1}. HRMS: calcd for $C_{16}H_{20}N_2O_5NaS_2$ $[M + Na]^+$ 407.07114, found 407.0702 (2 ppm).

(4a*S,6*S**,8a*R**)-6-Propyl-5-(toluene-4-sulfonyl)octahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (4d).** Compound **3d** (71 mg, 0.182 mmol) was treated as described in the general cyclization procedure using MgO (16.7 mg, 0.419 mmol, 2.3 equiv), $PhI(OAc)_2$ (64.6 mg, 0.20 mmol, 1.1 equiv), and $Rh_2(esp)_2$ (6.84 mg, 0.009 mmol, 0.02 equiv). The resulting crude product was purified by silica gel chromatography (PE/AcOEt 7/3) to provide **4d** (50 mg, 71%, de ≥ 98%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.95 (t, 3H, $J \approx 7.25$ Hz, CH_3CH_2CH_2), 1.15−1.45 (m, 3H), 1.53−1.58 (m, 2H), 1.66−1.73 (m, 2H) ($CH_3CH_2CH_2$, H_{4eq}, $2H_5$), 2.42 (s, 3H, Me), 2.51 (br q, 1H, $J \approx 13.0$ Hz, H_{4ax}), 3.01 (m, 1H, H_3), 3.91 (q, 1H, $J \approx 6.5$ Hz, H_6), 4.44 (dd, 1H, $J \approx 4.0$ Hz, $J \approx 11.0$ Hz, CH_AOSO_2), 4.50 (dt, 1H, $J \approx 2 \times 5.5$, 11.6 Hz, H_2), 4.88 (t, 1H, $J \approx 11.3$ Hz, CH_BOSO_2), 5.35 (d, 1H, $J \approx 6.0$ Hz, NH), 7.31 (d, 2H, $J \approx 8.0$ Hz, H_{Ar}), 7.71 (d, 2H, $J \approx 8.0$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 13.9 ($CH_2CH_2CH_3$), 19.8 ($CH_2CH_2CH_3$), 20.5 (C_4), 21.7 (Me), 27.0 (C_5), 37.5 ($CH_2CH_2CH_3$), 48.2 (C_2), 51.8 (C_6), 53.45 (C_3), 70.1 (CH_2OSO_2), 126.8 (CHAr), 130.3 (CHAr), 137.4 (CqAr), 144.2 (CqAr). IR (neat) 1265, 1163 cm^{-1}. HRMS: calcd for $C_{16}H_{25}N_2O_5S_2$ $[M + H]^+$ 389.1205, found 389.1221 (4 ppm).

(4a*S,6*S**,8a*R**)-1-Benzyloxycarbonyl-6-propyl-5-(toluene-4-sulfonyl)octahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (6).** To a solution of **4d** (290 mg, 0.747 mmol) in DME (15 mL) was added *t*-BuOK (127 mg, 1.12 mmol, 1.5 equiv) at 0 °C. The mixture was stirred during 1.5 h at this temperature. CbzCl (0.266 mL, 1.868 mmol, 2.5 equiv) was added, and the reaction was stirred overnight at rt. The reaction mixture was quenched with H_2O, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (PE/AcOEt 8/2) gave **6** as a colorless oil (280 mg, 72%, de ≥ 98%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.96 (t, 3H, $J \approx 7.2$ Hz, $CH_2CH_2CH_3$), 1.20−1.48 (m, 3H, H_{5A}, $CH_2CH_2CH_3$), 1.52−1.76 (m, 4H, H_{4eq}, H_{5B}, $CH_2CH_2CH_3$), 2.21 (m, 1H, H_{4ax}), 2.43 (s, 3H, Me), 3.97 (q, 1H, $J \approx 6.6$ Hz, H_6), 4.19 (m, 1H, H_3), 4.56 (q, 1H, $J \approx 6.9$ Hz, H_2), 4.65−4.83 (m, 2H, CH_2OSO_2), 5.29 (AB, 2H, $J \approx 12.2$ Hz, OCH_2Ph),

(25) Murphy, P. V.; Dunne, J. L. *Curr. Org. Synth.* **2006**, *3*, 403.

7.25−7.40 (m, 7H, H_{Ar}), 7.67 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 13.9 ($CH_2CH_2CH_3$), 20.4 (C_4, CH_2CH_2-CH_3), 21.7 (Me), 26.3 (C_5), 36.0 ($CH_2CH_2CH_3$), 48.2 (C_2), 51.8 (C_6), 55.9 (C_3), 69.9 (OCH_2Ph), 73.4 (CH_2OSO_2), 126.0 (CH_{Ar}), 126.7 (CH_{Ar}), 127.8 (CH_{Ar}), 128.8 (CH_{Ar}), 130.3 (CH_{Ar}), 134.5 (Cq), 137.3 (Cq), 144.3 (Cq), 151.6 (C═O). IR (neat) 2960, 1740, 1291, 1165 cm^{-1}. HRMS: calcd for $C_{24}H_{31}N_2O_7NaS_2$ $[M + Na]^+$ 545.13921, found 545.1394 (0 ppm).

(2*S,3*R**,6*S**)-2-Acetoxymethyl-3-benzyloxycarbonylamino-6-propyl-1-(toluene-4-sulfonyl)piperidine (7a).** To a solution of **6** (50 mg, 0.0957 mmol) in DMF (1 mL) was added KOAc (19 mg, 0.192 mmol, 2 equiv) at rt. The mixture was stirred for 15 h, and aqueous HCl 1 N solution was then added; the mixture was stirred for 1 h at rt, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (PE/AcOEt 7/3) gave **7a** as a colorless oil (37 mg, 77%). ^{1}H NMR (DMSO-d_6, 80 °C, 250 MHz): δ 0.88 (t, 3H, $J \approx 7.0$ Hz, CH_2-CH_2CH_3), 1.09−1.75 (m, 8H, $2H_4$, $2H_5$, $CH_2CH_2CH_3$, CH_2CH_2-CH_3), 1.95 (s, 3H, CH_3), 2.39 (s, 3H, Me), 3.37 (m, 1H, H_3), 3.81 (q, 1H, $J \approx 6.2$ Hz, H_6), 3.98 (dd, 1H, $J \approx 7.2$ Hz, $J \approx 11.5$ Hz, CH_AOSO_2), 4.32 (dd, 1H, $J \approx 6.0$ Hz, $J \approx 11.5$ Hz, CH_BOSO_2), 4.55 (q, 1H, $J \approx 6.2$ Hz, H_2), 5.07 (s, 2H, OCH_2Ph), 7.14 (br s, 1H, NH), 7.34−7.38 (m, 7H, H_{Ar}), 7.69 (d, 2H, $J \approx 7.75$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 14.0 ($CH_2CH_2CH_3$), 20.4 (C_4 or $CH_2CH_2CH_3$), 20.9 (CH_3), 21.2 (C_4 or $CH_2CH_2CH_3$), 21.7 (Me), 26.9 (C_5), 36.8 ($CH_2CH_2CH_3$), 49.1 (C_3), 51.5 (C_6), 52.6 (C_2), 63.2 (CH_2OAc), 67.0 (OCH_2Ph), 126.7 (CH_{Ar}), 128.3 (CH_{Ar}), 128.4 (CH_{Ar}), 128.7 (CH_{Ar}), 136.2 (Cq), 138.5 (Cq), 143.3 (Cq), 151.6 (C═O), 170.9 (C═O). IR (neat) 3359, 1735, 1715, 1520, 1165 cm^{-1}. HRMS: calcd for $C_{26}H_{34}N_2O_6NaS$ $[M + Na]^+$ 525.2035, found 525.2046 (2 ppm).

(2*S,3*R**,6*S**)-2-Phenylthiomethyl-3-benzyloxycarbonylamino-6-propyl-1-(toluene-4-sulfonyl)piperidine (7b).** To a solution of **6** (50 mg, 0.0957 mmol) in CH_3CN (5 mL) were added K_2CO_3 (32 mg, 0.229 mmol, 2.4 equiv) and thiophenol (0.023 mL, 0.229 mmol, 2.4 equiv) at −20 °C to rt over 24 h. The mixture was then stirred for 15 h at rt. Aqueous 1 N HCl solution (10 mL) and AcOEt (10 mL) were added to the reaction mixture, which was stirred for 1 h at rt and then extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (PE/AcOEt 7/3) gave **7b** as colorless oil (44 mg, 83%). ^{1}H NMR (DMSO-d_6, 80 °C, 250 MHz): δ 0.86 (m, 3H, $CH_2CH_2CH_3$), 1.13−1.42 (m, 5H, H_{4A}, $CH_2CH_2CH_3$, $CH_2CH_2CH_3$), 1.46−1.80 (m, 3H, H_{4B}, H_5), 2.38 (s, 3H, Me), 2.94−3.09 (m, 1H, CH_ASPh), 3.27−3.41 (m, 2H, H_3, CH_BSPh), 3.81 (m, 1H, H_6), 4.60 (m, 1H, H_2), 5.07 (m, 2H, OCH_2Ph), 7.20 (m, 2H, CH_{ar}, NH), 7.29−7.40 (m, 11H, H_{Ar}), 7.65−7.73 (m, 2H, H_{Ar}). ^{13}C NMR (DMSO-d_6, 80 °C, 100 MHz): δ 12.9 ($CH_2CH_2CH_3$), 19.4 (C_4 or $CH_2CH_2CH_3$), 19.3 (C_4 or $CH_2CH_2CH_3$), 20.3 (Me), 26.2 (C_5), 33.4 (CH_2S), 35.7 (CH_2-CH_2CH_3), 49.5 (C_3), 50.9 (C_6), 53.8 (C_2), 65.1 (OCH_2Ph), 125.2 (CH_{Ar}), 126.2 (CH_{Ar}), 127.1 (CH_{Ar}), 127.2 (CH_{Ar}), 127.7 (CH_{Ar}), 128.1 (CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 129.1 (CH_{Ar}), 136.6 (Cq), 137.9 (Cq), 142.4 (Cq), 154.3 (C═O). IR (neat) 3366, 1714, 1158 cm^{-1}. HRMS: calcd for $C_{30}H_{36}N_2O_4NaS_2$ $[M + Na]^+$ 575.20142, found 575.2005 (2 ppm).

(2*S,3*R**,6*S**)-2-Azidomethyl-3-benzyloxycarbonylamino-6-propyl-1-(toluene-4-sulfonyl)piperidine (7c).** To a solution of **6** (50 mg, 0.0957 mmol) in DMSO (2 mL) was added NaN_3 (12.5 mg, 0.191 mmol, 2 equiv) at 0 °C to rt over 8 h. Aqueous 1 N HCl (2 mL) solution and Et_2O (2 mL) were added to the reaction mixture, which was stirred for 1 h at rt, extracted with Et_2O, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (PE/AcOEt 8/2) gave **7c** as colorless oil (40 mg, 87%). ^{1}H NMR (DMSO-d_6, 80 °C, 250 MHz): δ 0.90 (t, 3H, CH_2-CH_2CH_3), 1.10−1.69 (m, 8H, $2H_4$, $2H_5$, $CH_2CH_2CH_3$), 2.40 (s, 3H Me), 3.23 (m, 1H, H_3), 3.39 (dd, 1H, $J \approx 7.0$ Hz, $J \approx 13.0$ Hz, CH_AN_3), 3.60 (dd, 1H, $J \approx 6.0$ Hz, $J \approx 13.0$ Hz, CH_BN_3), 3.81 (q, 1H, $J \approx 6.5$ Hz, H_6), 4.46 (q, 1H, $J \approx 6.3$ Hz, H_2), 5.06 (AB, 2H, $J \approx 12.7$ Hz, OCH_2Ph), 7.14 (br d, 1H, $J \approx 6.0$ Hz, NH), 7.28−7.45 (m, 7H, H_{Ar}), 7.71 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}). ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 14.0 ($CH_2CH_2CH_3$), 19.2 (C_4 or $CH_2CH_2CH_3$), 19.5 (C_4 or $CH_2CH_2CH_3$), 20.4 (Me), 26.0 (C_5), 35.7 (CH_2CH_2-CH_3), 48.6 (C_3), 50.3 (C_6 or C_2), 50.8 (C_6 or C_2), 53.3 (CH_2N_3), 65.2 (OCH_2Ph), 126.3 (CH_{Ar}), 127.2 (CH_{Ar}), 127.3 (CH_{Ar}), 127.8-(CH_{Ar}), 129.3 (CH_{Ar}), 136.6 (Cq), 137.8 (Cq), 142.5 (Cq). IR (neat) 3365, 2101, 1715, 1162 cm^{-1}. HRMS: calcd for $C_{24}H_{31}N_5O_4NaS$ $[M + Na]^+$ 508.1994, found 508.1994 (0 ppm).

2-Sulfamoyloxymethyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydropyridine (8). A solution of **2** (3.89 g, 11.2 mmol) in AcOH (80 mL) was stirred for 6 h at 60 °C. The solvent was removed by coevaporation with toluene. The crude product was used directly in the next steps. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.98 (m, 1H, H_{4A}), 1.71−2.07 (m, 3H, $2H_3$, H_{4B}), 2.41 (s, 3H, Me), 4.10 (dd, 1H, $J \approx 7.7$ Hz, $J \approx 10.0$ Hz, CH_AOSO_2), 4.24−4.30 (m, 3H, CH_B-OSO_2, H_2), 5.07 (m, 1H, H_5), 5.39 (s, 2H, NH_2), 6.58 (d, 1H, $J \approx 8.2$ Hz, H_6), 7.31 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}), 7.67 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 17.0 (C_3), 20.3 (C_4), 21.7 (Me), 51.0 (C_2), 68.3 (CH_2OSO_2), 109.3 (C_5), 123.3 (C_6), 127.1 (CH_{Ar}), 130.1 (CH_{Ar}), 135.3 (Cq), 144.2 (Cq). MS−IS *m*/*z* 369.0 $[M + Na]^+$, 347.0 $[M + H]^+$. IR (neat) 3281, 1346, 1162 cm^{-1}.

(2*S,6*S**)-6-Methoxy-2-sulfamoyloxymethyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (9).** To a solution of crude **8** (3.890 g, 11.2 mmol) in MeOH (130 mL) was added NaOMe (1.17 g, 22.480 mmol, 2 equiv). The mixture was cooled to −78 °C, and I_2 (5.425 g, 21.36 mmol, 1.9 equiv) was added. The mixture was stirred for 1.25 h at this temperature. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, extracted with AcOEt, dried over $MgSO_4$, and concentrated under reduced pressure to afford the iodomethoxylation product as a single diastereoisomer which was used directly in the next step with no further treatment. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.60−1.85 (m, 3H, $2H_3$, H_{4A}), 2.14 (m, 1H, H_{4B}), 2.44 (s, 3H, Me), 3.46 (s, 3H, OMe), 3.92 (m, 1H, H_2), 4.40−4.52 (m, 3H, CH_2OSO_2, H_5), 5.15 (s, 2H, NH_2), 5.30 (s, 1H, H_6), 7.32 (d, 2H, $J \approx 8.2$ Hz, H_{ar}), 7.90 (d, 2H, $J \approx 8.2$ Hz, H_{ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 20.4 (C_3), 21.7 (Me), 22.7 (C_4), 27.2 (C_5), 50.3 (C_2), 56.5 (OMe), 68.9 (CH_2OSO_2), 88.3 (C_6), 128.6 (CH_{Ar}), 129.6 (CH_{Ar}), 135.6 (Cq), 144.4 (Cq).

This crude product (5.17 g, 10.25 mmol) was dissolved in toluene (200 mL). DBU (3.05 mL, 20.5 mmol, 2 equiv) was added and the solution was stirred 20 h at 60 °C. The reaction mixture was quenched with 5% aqueous $NaHCO_3$, extracted with AcOEt, dried over Na_2SO_4, and concentrated under reduced pressure. Purification on silica gel (CH_2Cl_2/Acetone 95/5) gave **9** as a colorless oil (3.070 g, 73%, three steps from **2**, de ≥ 98%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.70 (m, 1H, H_{3A}), 1.91 (dd, 1H, $J \approx 5.5$ Hz, $J \approx 18.7$ Hz, H_{3B}), 2.43 (s, 3H, Me), 3.50 (s, 3H, OMe), 4.29 (m, 3H, CH_2OSO_2, H_2), 5.17 (s, 2H, NH_2), 5.35 (br s, 1H, H_6), 5.64−5.87 (m, 2H, H_4, H_5), 7.30 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}), 7.67 (d, 2H, $J \approx 8.2$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 21.7 (Me), 23.2 (C_3), 48.2 (C_2), 56.0 (OMe), 70.2 (CH_2OSO_2), 80.9 (C_6), 123.9 (C_4 or C_5), 125.6 (C_4 or C_5), 127.0 (CH_{Ar}), 130.0 (CH_{Ar}), 137.4 (Cq), 144.2 (Cq). IR (neat) 3285, 1361, 1162, 958 cm^{-1}. HRMS: calcd for $C_{14}H_{20}N_2O_6NaS_2$ $[M + Na]^+$ 399.0660, found 399.0663 (1 ppm).

(4a*S,6*S**,8a*R**)-6-Methoxy-5-(toluene-4-sulfonyl)-1,4,4a,5,6,-8a-hexahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (10).** Compound **9** (1.008 g, 2.681 mmol) was treated as described in the general cyclization procedure using MgO (246 mg, 4.756 mmol, 2.3 equiv), $PhI(OAc)_2$ (952 mg, 2.274 mmol, 1.1 equiv), and Rh_2-$(esp)_2$ (20.1 mg, 0.020 mmol, 0.01 equiv). The resulting crude product was purified by silica gel chromatography (EP/AcOEt 7/3) to provide **10** (863 mg, 87%, de ≥ 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.43 (s, 3H, Me), 3.48 (s, 3H, OMe), 3.67 (t, 1H, $J \approx 6.0$ Hz, H_3), 4.20 (dt, 1H, $J \approx 2 \times 5.0$ Hz, $J \approx 10.0$ Hz, H_2), 4.26 (dd, 1H, $J \approx 4.8$ Hz, $J \approx 11.6$ Hz, CH_AOSO_2), 5.13 (d, 1H, $J \approx 6.4$ Hz, NH), 5.19 (dd, 1H, $J \approx 10.5$ Hz, $J \approx 11.6$ Hz, CH_BOSO_2), 5.33 (d, 1H, $J \approx 2.8$ Hz, H_6), 5.99 (narrow AB,

2H, H_4, H_5), 7.32 (d, 2H, $J \approx 8.4$ Hz, H_{Ar}), 7.70 (d, 2H, $J \approx 8.4$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7 (Me), 45.2 (C_2), 50.5 (C_3), 56.4 (OMe), 69.5 (CH_2OSO_2), 80.3 (C_6), 126.3 (C_4 or C_5), 127.2 (CH_{Ar}), 127.9 (C_4 or C_5), 130.4 (CH_{Ar}), 136.5 (Cq), 145.0 (Cq). IR (neat) 3269, 1351, 1190, 1166 cm^{-1}. HRMS: calcd for $C_{14}H_{18}N_2O_6NaS_2$ [M + Na]$^+$ 397.05040, found 397.0499 (1 ppm).

(4a*S,6*R***S**,8a*R**)-6-Allyl-5-(toluene-4-sulfonyl)-1,4,4a,5,6,-8a-hexahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxides (11a).** To a solution of **10** (50 mg, 0.134 mmol) in CH_2Cl_2 (3 mL) were added at −78 °C allyltrimethylsilane (0.087 mL, 0.535 mmol, 4 equiv) and $SnCl_4$ (1M in CH_2Cl_2, 0.134 mL, 0.134 mmol, 1 equiv). The solution was stirred for 1.5 h at this temperature and was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (PE/AcOEt 8/2) gave **11a** as a mixture of epimers (colorless oil, 46 mg, 90%, de 61%). NMR analysis given for a 2:1 cis/trans mixture of epimers **11a**. ^{1}H NMR (acetone-d_6, 400 MHz): δ 2.35−2.47 (s and m, 5.5H, Me, CH_{cis}CH=CH$_2$), 2.47−2.57 (m, 1H, CH_{2trans}CH=CH$_2$), 2.57−2.67 (m, 1H, CH_{cis}-CH=CH$_2$), 3.54 (m, 1H, H_{3cis}), 4.23−4.38 (m, 2.5H, $CH_{Acis}OSO_2$, H_{3trans}, H_{6cis}), 4.42−4.50 (m, 1H, H_{6trans}, H_{2trans}), 4.56 (dt, 1H, $J \approx$ 5.6 Hz, $J \approx 11.2$ Hz, H_{2cis}), 4.64 (ddd, 0.5H, $J \approx 1.2$ Hz, $J \approx 3 \times$ 4.4 Hz, $CH_{Atrans}OSO_2$), 4.76 (t, 1H, $J \approx 11.2$ Hz, $CH_{Bcis}OSO_2$), 4.86−4.98 (m, 1.5H, CH_2CH=CH_{2trans}, $CH_{Btrans}OSO_2$), 5.11−5.24 (m, 2H, CH_2CH=CH_{2cis}), 5.57 (m, 0.5H, CH_2CH_{trans}=CH$_2$), 5.80−6.02 (m, 4H, H_{4cis}, H_{4trans}, H_{5cis}, H_{5trans}, CH_2CH_{cis}=CH$_2$), 6.22 (d, 0.5H, $J \approx 6.4$ Hz, NH_{trans}), 6.92 (d, 1H, $J \approx 5.6$ Hz, NH_{cis}), 7.39−7.46 (m, 3H, H_{Ar}), 7.77−7.86 (m, 3H, H_{Ar}). ^{13}C NMR (acetone-d_6, 100 MHz): δ 21.4 (Me), 38.7 (CH_{2trans}CH=CH$_2$), 43.3 (CH_{2cis}-CH=CH$_2$), 46.2 (C_{2cis}), 49.6 (C_{2trans}), 50.4 (C_{3cis}), 53.0 (C_{6cis}), 53.9 (C_{3trans}), 54.5 (C_{6trans}), 70.1 ($CH_{2cis}OSO_2$), 70.3 ($CH_{2trans}OSO_2$), 118.6 (CH_2CH=CH_{2trans}), 118.8 (CH_2CH=CH_{2cis}), 125.2 (C_{4trans} or C_{5trans}), 125.8 (C_{4cis} or C_{5cis}), 127.3 (C_{4cis} or C_{5cis}), 127.7 (CH_2−CH_{cis}=CH$_2$), 127.8 (CH_{Arcis}), 130.5 (C_{4trans} or C_{5trans}), 130.7 ($CH_{Artrans}$), 131.1 (CH_{Arcis}), 133.8 (CH_2−CH_{trans}=CH$_2$), 135.0 ($CH_{Artrans}$), 137.9 (Cq_{cis}), 140.0 (Cq_{trans}), 144.7 Cq_{trans}, 145.2 (Cq_{cis}). IR (neat) 3271, 1352, 1191, 1163 cm^{-1}. ESI: calcd for $C_{16}H_{20}N_2O_5S_2Na$ [M + Na]$^+$ 407.4, found 407.5.

(4a*S,6*R**,8a*R**)-6-Cyano-5-(toluene-4-sulfonyl)-1,4,4a,5,6,8a-hexahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (11b).** To a solution of **10** (100 mg, 0.268 mmol) in CH_2Cl_2 (2 mL) were added at −78 °C trimethylsilyl cyanide (0.142 mL, 1.33 mmol, 5 equiv) and $SnCl_4$ (1M in CH_2Cl_2, 0.187 mL, 0.187 mmol, 0.7 equiv). The solution was stirred for 2.5 h at this temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at −78 °C, allowed to warm to rt, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure to afford **11b** as a colorless oil (96 mg, 97%, de ≥ 95%). It is important to note that partial degradation occurred during purification on silica gel. ^{1}H NMR (acetone-d_6, 250 MHz): δ 2.45 (s, 3H, Me), 3.94 (br s, 1H, H_3), 4.40 (ddd, 1H, $J \approx 1.2$ Hz, $J \approx 5.2$ Hz, $J \approx 11.2$ Hz, CH_AOSO_2), 4.68 (m, 1H, H_2), 4.91 (t, 1H, $J \approx 11.0$ Hz, CH_BOSO_2), 5.62 (m, 1H, H_6), 6.00 (dt, 1H, $J \approx 2 \times 3.5$ Hz, $J \approx 10.5$ Hz, H_4), 6.20 (br d, 1H, $J \approx 10.4$ Hz, H_5), 7.10 (br d, 1H, $J \approx 5.6$ Hz, NH), 7.48 (d, 2H, $J \approx 8.4$ Hz, H_{Ar}), 7.86 (d, 2H H_{Ar}). ^{13}C NMR (acetone-d_6, 62.5 MHz): δ 21.5 (Me), 42.0 (C_6), 45.7 (C_2), 50.6 (C_3), 67.8 (CH_2OSO_2), 117.8 (CN), 120.6 (C_4 or C_5), 128.0 (CH_{Ar}), 130.2 (C_4 or C_5), 131.3 (CH_{Ar}), 136.6 (Cq), 146.2 (Cq). IR (neat) 3323, 2245, 1350, 1190, 1163 cm^{-1}. HRMS calcd for $C_{14}H_{15}N_3O_5S_2Na$ [M + Na]$^+$ 392.03508, found 392.0341 (2 ppm).

(4a*S,6*S**,8a*R**)-6-Benzoylmethyl-5-(toluene-4-sulfonyl)-1,4,-4a,5,6,8a-hexahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (11c).** To a solution of **10** (134 mg, 0.358 mmol) in CH_2Cl_2 (3 mL) were added at −78 °C 1-phenyl-1-trimethylsiloxyethylene (0.293 mL, 1.43 mmol, 4 equiv) and $SnCl_4$ (1M in CH_2Cl_2, 0.429 mL, 0.429 mmol, 1.2 equiv). The solution was stirred for 20 h at this temperature, quenched with saturated aqueous $NaHCO_3$ at −78 °C, warmed to rt, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel with pure CH_2Cl_2 followed by PE/AcOEt 9/1 to 7/3 gave **11c** as a colorless oil (105 mg, 65%, de ≥ 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H, Me), 3.26 (dd, 1H, $J \approx 10.8$ Hz, $J \approx 17.2$ Hz, CH_AC=O), 3.56 (br s, 1H, H_3), 3.65 (dd, 1H, $J \approx 2.8$ Hz, $J \approx$ 17.2 Hz, CH_BC=O), 4.48 (dd, 1H, $J \approx 5.2$ Hz, $J \approx 10.8$ Hz, CH_A-OSO_2), 4.66 (q, 1H, $J \approx 5.6$ Hz, H_2), 4.83 (t, 1H, $J \approx 10.8$ Hz, CH_BOSO_2), 4.89 (m, 1H, H_6), 5.32 (d, 1H, $J \approx 6.0$ Hz, NH), 5.92 (m, 2H, H_4, H_5), 7.31 (d, 1H, $J \approx 8.0$ Hz, H_{Ar}), 7.48 (t, 2H, $J \approx$ 8.0 Hz, H_{Ar}), 7.60 (t, 1H, $J \approx 7.6$ Hz, H_{Ar}), 7.73 (d, 1H, $J \approx 8.0$ Hz, H_{Ar}), 7.96 (d, 2H, $J \approx 7.6$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7 (Me), 45.3 (C_2), 46.8 (*C*H$_2$C=O), 48.5 (C_6), 50.1 (C_3), 69.5 (CH_2OSO_2), 124.5 (C_4 or C_5), 126.8 (CH_{Ar}), 127.7 (C_4 or C_5), 128.2 (CH_{Ar}), 128.9 (CH_{Ar}), 130.6 (CH_{Ar}), 133.8 (CH_{Ar}), 136.2 (Cq), 144.8 (Cq), 196.8 (C=O). IR (neat) 3282, 1681, 1353, 1191, 1162 cm^{-1}. HRMS: calcd for $C_{21}H_{22}N_2O_6NaS_2$ [M + Na]$^+$ 485.0817, found 485.0819 (0 ppm).

(1*S,6*S**)-4-Oxa-7-(toluene-4-sulfonyl)-3-thia-2,7-diazabicyclo-[4.3.1]dec-8-ene 3,3-Dioxide (11e).** To a solution of **9** (54 mg, 0.144 mmol) in CH_2Cl_2 (3 mL), was added at −78 °C BF_3·OEt_2 (0.028 mL, 0.144 mmol, 1 equiv). The solution was allowed to return slowly to rt to complete conversion of starting material (nearly 1 h) and was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by filtration on a pad of silica gel (CH_2Cl_2/acetone 9/1) gave **11e** as a colorless oil (44 mg, 89%, de ≥ 98%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.68 (dt, 1H, $J \approx 2 \times 4.3$ Hz, $J \approx 14.8$ Hz, H_{3A}), 2.39−2.47 (m, 4H, Me, H_{3B}), 3.73 (t, 1H, $J \approx 4.3$ Hz, H_4), 4.28−4.44 (m, 2H, H_2, CH_AOSO_2), 4.51 (dd, 1H, $J \approx 2.5$ Hz, $J \approx 12.5$ Hz, CH_BOSO_2), 4.98 (s, 1H, NH), 5.10 (m, 1H, H_5), 7.03 (d, 1H, $J \approx 8.4$ Hz, H_6), 7.33 (d, 2H, $J \approx 8.4$ Hz, H_{Ar}), 7.67 (d, 2H, $J \approx 8.4$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7 (Me), 29.3 (C_3), 42.6 (C_4), 51.5 (C_2), 74.5 (CH_2OSO_2), 104.6 (C_5), 126.9 (CH_{Ar}), 128.7 (C_6), 130.3 (CH_{Ar}), 135.7 (Cq), 144.8 (Cq). IR (neat) 3286, 1355, 1215, 1169 cm^{-1}. HRMS: calcd for $C_{13}H_{16}N_2O_5NaS_2$ [M + Na]$^+$ 367.03984, found 367.0408 (3 ppm).

(2*S,6*S**)-6-Allyl-2-sulfamoyloxymethyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (11f).** To a solution of compound **11e** (72 mg, 0.209 mmol) in CH_2Cl_2 at −78 °C were added allyltrimethylsilane (66 μL, 0.418 mmol, 2 equiv) and $SnCl_4$ (1 M in CH_2Cl_2) (209 μL, 0.209 mmol, 1 equiv). The solution was stirred for 3 h at −78 °C and then 16 h at −35 °C. $SnCl_4$ (42 μL, 0.042 mmol, 0.2 equiv) was added at −35 °C, and the reaction mixture was stirred another 24 h at room temperature. The solution was then quenched with $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification on silica gel (CH_2Cl_2/acetone 9/1) gave **11f** as a colorless oil (30 mg, 37%, de ≥ 98%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.72 (m, 1H, H_{3A}), 1.88 (m, 1H, H_{3B}), 2.29 (ddd, 1H, $J \approx 2 \times 8.7$ Hz, $J \approx 17.2$ Hz, CH_2CH=CH$_2$), 2.42 (s, 3H, Me), 2.65 (m, 1H, CH_2CH=CH$_2$), 4.16 (m, 2H, CH_2OSO_2), 4.29 (m, 1H, H_6), 4.38 (m, 1H, H_2), 5.15 (m, 2H, CH_2CH=CH_2), 5.29 (s, 2H, NH_2), 5.60 (m, 1H, H_4), 5.71 (m, 1H, H_5), 5.88 (m, 1H, CH_2CH=CH$_2$), 7.29 (d, 2H, $J \approx 8.0$ Hz, H_{Ar}), 7.29 (d, 2H, $J \approx 8.4$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.7 (Me), 23.1 (C_3), 43.0 (*C*H$_2$CH=CH$_2$), 48.6 (C_2), 52.9 (C_6), 70.4 (CH_2OSO_2), 118.5 (CH_2CH=CH_2), 121.7 (C_4), 125.9 (C_5), 126.9 (CH_{Ar}), 130.1 (CH_{Ar}), 134.2 (CH_2CH=CH$_2$), 137.3 (Cq_{Ar}), 143.9 (Cq_{Ar}). IR (neat) 3279, 1375, 1184, 1163 cm^{-1}. HRMS: calcd for $C_{12}H_{22}N_2O_5NaS_2$ [M + Na]$^+$ 409.08679, found 409.0866 (0 ppm).

(4a*S,7*S**,8*R**,8a*S**)-1-Acetyl-7,8-diacetoxy-5-(toluene-4-sulfonyl)-1,4,4a,5,6,8a-hexahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (13).** To a solution of **12** (280 mg, 0.725 mmol) in acetone/water 9/1 (10 mL), were added at room temperature NMO (543 mg, 2.901 mmol, 4 equiv), a 2.5% solution of of OsO_4 in *t*-BuOH (1.8 mL, 0.145 mmol, 0.2 equiv). The solution was stirred 18 h at this temperature and was quenched with saturated aqueous $Na_2S_2O_5$, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. To the crude mixture in CH_2Cl_2 (7 mL) were added at room-temperature acetic anhydride (1.05

mL, 10.88 mmol, 15 equiv) and DMAP (26.5 mg, 0.217 mmol, 0.3 equiv). The solution was stirred for 4 h at this temperature. The reaction was quenched with water; the mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (CH_2Cl_2/acetone 95/5) gave **13** as a colorless oil (225 mg, 66%, de ≥ 98%, two steps from **12**). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89 (s, 3H, COMe), 1.95 (s, 3H, COMe), 2.45 (s, 3H, Me), 2.50 (s, 3H, Me), 3.31 (d, 1H, $J \approx 15.0$ Hz, H_6), 4.03 (dd, 1H, $J \approx 2.0$ Hz, $J \approx 15.0$ Hz, H_6), 4.59−4.79 (m, 3H, H_2, CH_2OSO_2), 5.34 (s, 1H, H_5), 5.48−5.59 (m, 2H, H_4, H_3), 7.35 (d, 1H, $J \approx 8.0$ Hz, H_{Ar}), 7.71 (d, 1H, $J \approx 8.0$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 20.6 (Me), 20.7 (Me), 21.7 (Me), 24.8 (Me), 43.6 (C_6), 49.4 (C_2), 50.3 (C_3), 66.4 (C_4 or C_5), 68.4 (C_4 or C_5), 70.3 (CH_2OSO_2), 127.3 (CH_{Ar}), 130.3 (CH_{Ar}), 136.6 (Cq), 144.6 (Cq), 168.1 (C═O), 169.6 (C═O), 169.9 (C═O). IR (neat) 1751, 1713, 1178 cm^{-1}. HRMS: calcd for $C_{19}H_{24}N_2O_{10}NaS_2$ $[M + Na]^+$ 527.0770, found 527.0774 (1 ppm).

(2*S,3*S**,4*R**,5*S**)-4,5-Diacetoxy-2-acetoxymethyl-3-acetylamino-1-(toluene-4-sulfonyl)piperidine (14).** To a solution of **13** (26 mg, 0.0515 mmol) in dry DMF (1 mL) was added potassium acetate (10.8 mg, 0.130 mmol, 2 equiv). The solution was warmed at 40 °C during 2.5 h. THF (1 mL), H_2SO_4 98% (150 μL), and water (50 μL) were then added at rt. The mixture was then stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (pH ∼5). The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (CH_2Cl_2/acetone 85/15) gave **14** as a colorless oil (12 mg, 48%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.79 (s, 3H, Me), 1.97 (s, 3H, Me), 2.01 (s, 3H, Me), 2.4 (s, 3H, Me), 2.34 (s, 3H, Me), 3.50 (d, 1H, $J \approx 15.5$ Hz, H_6), 4.00 (d, 1H, $J \approx 15.2$ Hz, H_6), 4.16 (dd, 1H, $J \approx 3.0$ Hz, $J \approx 12.0$ Hz, CH_AOAc), 4.42−4.62 (m, 2H, H_3, CH_BOAc), 4.74 (m, 1H, H_2), 5.10−5.20 (m, 2H, H_4, H_5), 5.91 (d, 1H, $J \approx 7.7$ Hz, NH), 7.31 (d, 1H, $J \approx 8.5$ Hz, H_{Ar}), 7.77 (d, 1H, $J \approx 8.2$ Hz, H_{Ar}). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7 (Me), 20.9 (Me), 21.1 (Me), 21.6 (Me), 23.3 (Me), 44.4 (C_6), 47.9 (C_3), 53.9 (C_2), 61.6 (CH_2OAc), 67.1 (C_4 or C_5), 68.3 (C_4 or C_5), 127.4 (CH_{Ar}), 129.8 (CH_{Ar}), 138.0 (Cq), 143.6 (Cq), 170.2 (C═O), 170.6 (C═O), 170.9 (C═O), 171.9 (C═O). IR (neat) 3280, 1744, 1667, 1155 cm^{-1}. HRMS: calcd for $C_{21}H_{28}N_2O_9NaS$ $[M + Na]^+$ 507.14132, found 507.1414 (0 ppm).

(4a*S,6*R***S**,8a*R**)-6-Allyl-5-(toluene-4-sulfonyl)-1-(*tert*-butyloxycarbonyl)-4,4a,5,6,8ahexahydro-3-oxa-2-thia-1,5-diazanaphthalene 2,2-Dioxide (15).** To the mixture of diastereoisomers **11a** (335 mg, 0.872 mmol) in CH_2Cl_2 were added at 0 °C Boc_2O (380 mg, 1.74 mmol, 2 equiv), pyridine (1 mL), and DMAP (22 mg, 0.174 mmol, 0.2 equiv). After 1 h at this temperature, the solvents were removed under reduced pressure, and pyridine was coevaporated with toluene. The crude mixture was taken up with CH_2Cl_2, and the solution was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (AcOEt/PE 2/8) gave **15** as a mixture of epimers (colorless oil, 298 mg, 70%, de 61%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (s, 9H, $(CH_3)_3$), 2.35−2.47 (m, 3.8H, Me, C*H*$_{cis}$CH═CH_2), 2.52−2.58 (m, 0.4H, C*H*$_{2trans}$CH═CH_2), 2.68 (m, 0.8H, C*H*$_{cis}$CH═CH_2), 4.30 (m, 0.8H, H_{3cis}), 4.37−4.47 (m, 0.4H, H_{4trans}, $CH_{2trans}OSO_2$), 4.55−4.72 (m, 3.8H, H_{2cis}, $CH_{2cis}OSO_2$, H_{3cis}, H_{2trans}, H_{3trans}, $CH_{trans}OSO_2$), 4.82−5.02 (m, 0.6H, CH_2CH═C*H*$_{2trans}$, $CHOSO_{2trans}$), 5.08−5.22 (m, 1.8H, H_{4trans}, CH_2CH═C*H*$_{2cis}$), 5.44 (m, 0.2H, CH_2C*H*$_{trans}$═CH_2), 5.64 (d, 0.8H, $J \approx 10.8$ Hz, H_{4cis}), 5.77−5.92 (m, 1.8H, H_{5trans}, H_{5cis}, CH_2C*H*$_{cis}$═CH_2), 7.33 (m, 2H, H_{Ar}), 7.62−7.77 (m, 2H, H_{Ar}). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 21.6 (CH_3), 27.8 (*t*-Bu$_{cis}$), 27.9 (*t*-Bu$_{trans}$), 38.2 (*C*H$_{2trans}$CH═CH_2), 41.4 (*C*H$_{2cis}$CH═CH_2), 46.9 (C_{2cis} + C_{2trans}), 50.8 (C_{3trans} or C_{6trans}), 51.5 (C_{6cis}), 52.2 (C_{3cis}), 54.9 (C_{3trans} or C_{6trans}), 71.7 ($CH_{2trans}OSO_2$), 72.1 ($CH_{2cis}OSO_2$), 86.1 (*t*-Bu$_{cis}$), 86.3 (*t*-Bu$_{trans}$), 119.1 (CH_2CH═*C*H$_{2cis}$), 119.3 (CH_2CH═*C*H$_{2trans}$), 124.4 (C_{4cis} + C_{4trans}), 126.0 (C_{5trans} or CH_2*C*H$_{trans}$═CH_2), 126.8 (CH_{Arcis}), 127.0 ($CH_{Artrans}$), 127.7 (C_{5cis} or CH_2*C*H$_{cis}$═CH_2), 128.7 (C_{4trans}), 130.0 ($CH_{Artrans}$), 130.3 (CH_{Arcis}), 131.7 (C_{5trans} or CH_2*C*H$_{trans}$═CH_2), 133.5 (C_{5cis} or CH_2*C*H$_{cis}$═CH_2), 136.4 (Cq_{cis}), 137.7 (Cq_{trans}), 144.5 (Cq), 150.0 (C═O). IR (neat) 1734, 1355, 1215, 1146 cm^{-1}. HRMS: calcd for $C_{21}H_{28}N_2O_7NaS_2$ $[M + Na]^+$ 507.12356, found 507.1225 (2 ppm).

(2*S,3*R**,6*R***S**)-*N*-Acetyl-6-allyl-3-*tert*-butyloxycarbonylamino-1,2,3,6-tetrahydropyridine (17).** To a solution of naphthalene (0.64 mg, 5 mmol, 1 equiv) in THF (10 mL) was added sodium (115 mg, 5 mmol, 1 equiv) at rt. The solution turned to dark green and was stirred 4 h. To a solution of diastereoisomers **16** (44 mg, 0.0948 mmol) in THF (3 mL) at −78 °C was added the 0.5 M sodium/naphthalenide solution (900 μL, 9 equiv). The mixture was stirred for 20 min at −78 °C. The reaction was quenched with methanol (2 mL) and water (2 mL) at −78 °C. The reaction mixture was then allowed to warm to rt. The solution was then extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification on silica gel (CH_2Cl_2/acetone 8/2) gave **17** as a colorless oil (18 mg, 61%). ^{1}H NMR (DMSO-d_6, 90 °C, 250 MHz) (mixture of rotamers): δ 1.43 (s, 9H, *t*-Bu), 2.01−2.22 (m, 4H, C*H*CH═CH_2, CH_3), 2.50 (m partially masked by the signal of solvent residual peak, 1H, C*H*CH═CH_2), 3.43 (m, 1H, CH_AOAc), 3.65 (m, 1H, CH_BOAc), 4.06 (br s, 1H, OH), 4.13−4.56 (m, 3H, H_2, H_3, H_6), 5.06 (m, 2H, CH_2CH═C*H*$_2$), 5.59 (d, 1H, $J \approx 10.5$ Hz, H_4), 5.67−5.94 (m, 2H, CH_2C*H*═CH_2, H_5), 6.55 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) (mixture of rotamers): 22.4 (Me), 23.3 (Me), 28.2 (Me), 29.6 (Me), 36.6 (CH_2), 38.5 (CH_2), 47.9 (CH), 48.4 (CH), 49.2 (CH), 50.5 (CH), 52.5 (CH), 55.0 (CH), 57.3 (CH), 57.8 (CH_2), 59.6 (CH_2), 78.3 (Cq), 117.1 (CH_2), 117.4 (CH_2), 124.8 (CH), 126.0 (CH), 126.9 (CH), 127.0 (CH), 129.2 (CH), 134.1 (CH), 135.6 (CH), 155.1 (C═O), 155.2 (C═O), 169.6 (C═O), 171.5 (C═O). HRMS: calcd for $C_{16}H_{26}N_2O_4$-Na $[M + Na]^+$ 333.17903, found 333.1790 (0 ppm). IR (neat): 3442, 1707, 1628 cm^{-1}.

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Supporting Information Available: Additional procedures and characterization data for new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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