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A synthesis of 5-hydroxysedamine using hydroformylation

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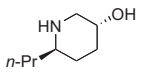
ABSTRACT

A synthesis of 5-hydroxysedamine, a *Sedum* alkaloid, has been completed using *N*,*O*-heterocycle chemistry to establish the aminoalcohol structure, hydroformylation to form the piperidine ring and diastereoselective dihydroxylation to introduce the 5-hydroxy group.

1. Introduction

We have recently shown that the combination of tandem hydroformylation-condensation of *N*-tosyl homoallylic amines, followed by diastereoselective dihydroxylation, provides an efficient route to the synthesis of 3-hydroxypiperidines. This strategy was employed for the synthesis of pseudoconhydrine **1**[1] and azimic acid **2**.[2] We have earlier shown that cyclofunctionalisation of *O*-homoallyl and allenyl hydroxylamine derivatives stereoselectively provides isoxazolidines,[3] which are useful intermediates for the synthesis of 1,3-aminoalcohols and their derivatives, such as monomorine,[4] porantheridine[5] and the *Sedum* alkaloids, sedamine[6] and sedinine.[7]



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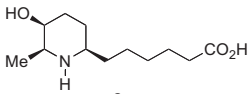

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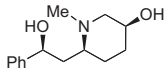

3

We speculated that we could combine both of these methods in the synthesis of 5-hydroxysedamine **3**.[8] Originally isolated from *Sedum acre*, this alkaloid is both a *Sedum* alkaloid,[9] therefore containing a 1,3-aminoalcohol moiety, and a 3-hydroxypiperidine. The use of hydroformylation to construct the piperidine ring would require the synthesis of an allyl isoxazolidine. We have recently shown that these compounds are readily available by Sakurai reaction of the corresponding 3-methoxyisoxazolidines.[10] This reaction favours formation of the *trans* isomer, corresponding to the *anti*-aminoalcohol. As 5-hydroxysedamine possesses *syn* stereochemistry, an inversion of the alcohol group must be included in the synthetic pathway.

2. Results and discussion

The homoallylic alcohol **4**[11] was converted to the *N*-tosyl hydroxylamine **7** through a Mitsunobu reaction[12] with *N*-hydroxyphthalimide, dephthaloylation and reprotection (Scheme 1). While our previous studies of the Sakurai reaction used carbamate protecting groups on nitrogen, we selected a tosyl group due to its greater robustness, the higher possibility of obtaining crystalline intermediates and to avoid issues with rotamer formation. Ozonolysis of hydroxylamine **7** in acidic methanol, followed by a dimethyl sulfide work up, gave 3-methoxyisoxazolidine **8** as an inconsequential 1.5:1 mixture of stereoisomers. Tosic acid monohydrate was used as the acid catalyst as amberlyst-15, which we used previously, did not result in complete conversion to the methoxy compound. Treatment of 3-methoxyisoxazolidine **8** with allyltrimethylsilane in the presence of boron trifluoride at −78 °C with slow warming to room temperature gave the allyl isoxazolidine **9** as a 7.5:1 mixture of stereoisomers. Pleasingly, this ratio is distinctly better than that obtained with carbamate protecting groups (3:1–4:1). The major isomer proved to be crystalline and was confirmed to be the *trans* isomer by X-ray crystallography (Fig. 1).[13] Cleavage of the N–O bond was achieved in the usual way with molybdenum hexacarbonyl in wet acetonitrile[14] to give the protected aminoalcohol **10a**, which would be the intended hydroformylation substrate.[15]

Hydroformylation of aminoalcohol **10a** derivatives can, in principle, give rise to four products (Table 1). Ene-sulfonamide **11a** is the desired product. *N*,*O*-Hemiaminal **12**[16] is the precursor of ene-sulfonamide **11a** by dehydration. Bicyclic *N*,*O*-aminal **13** can arise by cyclisation of the benzylic alcohol group onto the ene-sulfonamide **11a**.[17] The structure of bicyclic *N*,*O*-aminal **13** was also confirmed by X-ray crystallography (Fig. 2).[12] The pyrrolidines **14**, the products of branched hydroformylation, can exist as a mixture of stereoisomers.

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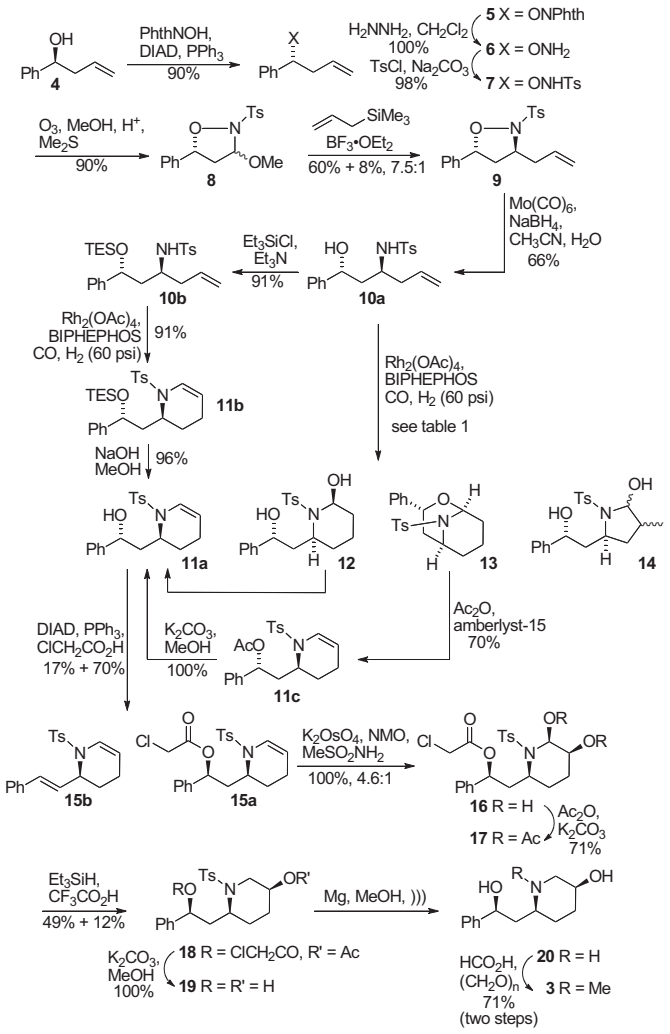

Scheme 1. The synthesis of 5-hydroxysedamine.

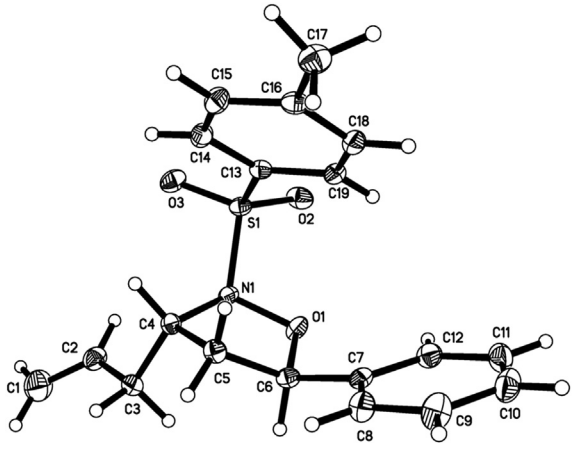

Fig. 1. The X-ray structure of allyl isoxazolidine **9**.

As expected, when triphenylphosphite was used as the ligand, appreciable amounts of the branched isomers **14** were formed. In addition, increasing the amount of this ligand caused an increase in the formation of the desired ene-sulfonamide **11a** at the expense of the *N*,*O*-hemiaminal **12**. At the highest phosphite loading employed, some of the bicyclic *N*,*O*-aminal **13** was also isolated.

Table 1
Hydroformylation of alkene **10a**[a]

Entry	Ligand (L)	L:Rh ratio	Solvent	Yields, %			
				11a	**12**	**13**	**14**
1	$P(OPh)_3$	3:1	THF	2	35	0	29
2	$P(OPh)_3$	10:1	THF	19	27	0	18
3	$P(OPh)_3$	20:1	THF	48	0	18	23
4	BIPHEPHOS	1:1	THF	75	0	12	0
5	BIPHEPHOS	1:1	Toluene	45	0	20	0

[a] All reactions used $Rh_2(OAc)_4$ as the source of rhodium and were run for 22 h at 65 °C under 60 psi of 1:1 CO/H_2.

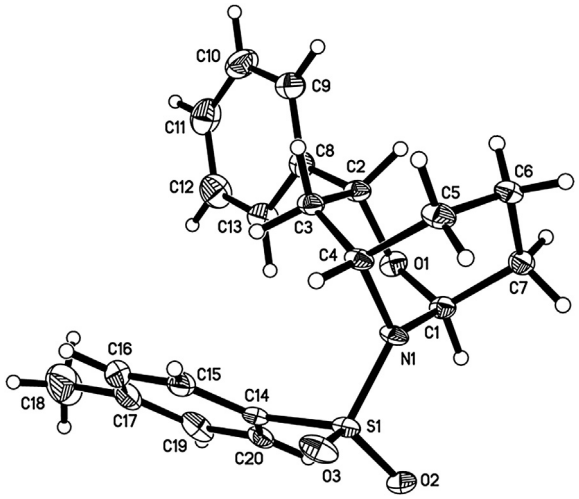

Fig. 2. The X-ray structure of bicyclic *N*,*O*-aminal **13**.

When the bulky, bidentate phosphite ligand BIPHEPHOS[18] was employed, as expected, formation of the branched products **14** was not observed. A somewhat higher yield of the desired ene-sulfonamide **11a** could be obtained in THF. This was accompanied by some formation of the bicyclic *N*,*O*-aminal **13**. We did experience some variability in yield and product distribution depending on the batch of BIPHEPHOS employed. The reaction in toluene proved lower yielding, but more reproducible.

Some of the undesired products could be converted to the desired ene-sulfonamide. Thus, treatment of the bicyclic *N*,*O*-aminal **13** with acetic anhydride in the presence of amberlyst-15 gave acetate **11c**. It is notable that amberlyst-15 proved effective for this ring opening while a series of Lewis acids were ineffective.[19] Acetate **11c** could be converted to ene-sulfonamide **11a** by treatment with methanolic potassium carbonate. *N*,*O*-Hemiaminal **12** could be converted to the desired ene-sulfonamide **11a** by resubjecting this material to the hydroformylation conditions.

The rather complex results of hydroformylation of substrate **10a** stand in contrast to our previous experience. It is apparent that the hydroxy group in the aminoalcohol substrate introduces significant complication and is capable of interfering with the usual smooth running of the hydroformylation reaction. Accordingly, a cleaner hydroformylation was achieved when the original substrate **10a** was protected as its triethylsilyl ether **10b**.[20] With this substrate, hydroformylation proved less complex, however, to ensure that dehydration went to completion, a higher temperature (85 °C) was required. Under these conditions, ene-sulfonamide **11b** was obtained in 90% yield. At 65 °C, only a 30% yield was obtained, accompanied by a 58% yield of the corresponding hemiaminal. Deprotection of ene-sulfonamide **11b** then gave the desired ene-sulfonamide **11a**.

The ene-sulfonamide **11a** represents the opportunity to carry out the necessary inversion of the alcohol to give the *syn* stereochemistry. Disappointingly, a Mitsunobu reaction with acetic acid in THF gave a substantial amount of the eliminated product **15b** (30% yield), alongside the desired acetate (37%) and recovered starting material (16%). The formation of this alkene may be attributed to the steric hindrance around the reaction site. It is known that the balance of reactivity will be tipped in favour of substitution if a more acidic partner is employed.[21] Gratifyingly, the use of chloroacetic acid[22] (pK_a=2.86) in place of acetic acid gave an improved yield, 50%, of the desired substitution product **15a**. A further improvement to 70% was achieved by changing the solvent to toluene. Dihydroxylation of chloroacetate **15a** then gave the diols **16** as an inseparable 4.6:1 mixture of stereoisomers and, based on our previous work, it was assumed that the *cis* isomer was the major product. This was subsequently confirmed by completion of the synthesis. Acetylation then allowed selective removal of the α-acetoxy group under Kursanov–Parnes conditions.[23] Diester **18** could be obtained as a single diastereoisomer after careful column chromatography. Removal of all of the acyl groups and detosylation then gave des-methyl 5-hydroxysedamine **20**. This compound was then methylated to give 5-hydroxysedamine **3** in 71% yield over two steps using the Eschweiler–Clarke reaction: reductive amination with a combination of formaldehyde and formic acid. It was notable that this reaction was much more effective using *para*-formaldehyde rather than formalin as the source of formaldehyde. We attribute this to the higher concentration of formaldehyde being generated in the absence of water, as it will not be lost due to hydrate formation. The spectroscopic data for our synthetic material was in excellent agreement with that reported. In addition, the specific rotation recorded for our material, $[\alpha]_D^{22}$ −55.3 (*c* 0.15, MeOH), is in good agreement with previous reports: $[\alpha]_D^{22}$ −40 (*c* 0.3, MeOH),[8a] $[\alpha]_D^{22}$ −53 (*c* 0.3, MeOH),[8b,d] $[\alpha]_D^{22}$ −51 (*c* 2.5 MeOH),[8c] $[\alpha]_D^{22}$ −53.4 (*c* 0.5, MeOH)[8e] The completion of the synthesis illustrates how these disparate synthetic methods, developed in this laboratory and elsewhere, can be brought together to synthesise complex alkaloids.

3. Experimental section

3.1. General

Unless otherwise indicated, all starting materials were obtained from commercial suppliers, and were used without further purification. Each reaction with air- and moisture-sensitive components was carried out under a nitrogen atmosphere unless otherwise indicated. Tetrahydrofuran was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was performed on Merck DC pre coated TLC plates with 0.25 mm Kieselgel 60 F_{254}. Visualization was performed with a 254 nm UV lamp, or stained with ammonium molybdate or potassium permanganate solution. Flash chromatography was performed using silica gel 60 (particle size 0.040–0.063) purchased from Merck. All melting points were measured on a Stanford Research Systems OptiMelt apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1030 polarimeter using a 10 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 400 MHz or JEOL 396 MHz spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) with solvent (δ 7.26 for ^{1}H, δ 77.0 for ^{13}C) or Me_4Si (δ=0.00 ppm) as internal standards. Coupling constants (*J*) are reported in Hertz. IR spectra were obtained on a Jasco FT/IR-4100 spectrometer or Shimadzu IR Prestige-21 spectrometer and are reported in frequency of absorption (cm^{-1}). Low resolution mass spectrometry was obtained on a Waters Acquity UPLC PDA with ZQ2000 system. High-resolution mass spectra (HRMS) were acquired on a Waters Q-ToF Premier mass spectrometer in positive ion mode.

*3.1.1. (R)-2-((1-Phenylbut-3-en-1-yl)oxy)isoindoline-1,3-dione (**5**).* A stirred mixture of homoallylic alcohol **4** (8.00 g, 54.0 mmol), PPh_3 (17.0 g, 64.8 mmol) and *N*-hydroxyphthalimide (10.6 g, 64.8 mmol) in anhydrous THF (100 mL) was cooled to 0 °C in an ice-water bath. A solution of DIAD (12.8 mL, 64.8 mmol) in anhydrous THF (20 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and then stirred at room temperature overnight. The mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and absorbed onto silica. The residue was purified by flash chromatography with gradual elution (5–20% Ethyl Acetate/Hexane) to give the desired *N*-hydroxyphthalimide **5** derivative as a colourless solid (14.2 g, 90%); mp 85–86 °C; R_f 0.35 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ +197.1 (*c* 0.11, CH_2Cl_2); ν_{max} (Nujol) 3404, 1728, 1643, 698 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.59–7.78 (4H, m), 7.46 (2H, dd, *J* 7.5, 2.0 Hz), 7.26–7.39 (3H, m), 5.78 (1H, ddt, *J* 17.0, 10.3, 7.0 Hz), 5.39 (1H, t, *J* 7.0 Hz), 4.99–5.22 (2H, m), 2.95 (1H, dt, *J* 14.4, 7.1 Hz), 2.72 (1H, dt, *J* 14.3, 6.9 Hz); δ_C (100 MHz, $CDCl_3$): 163.6, 137.4, 134.2, 133.0, 129.1, 128.8, 128.3, 128.1, 123.3, 118.0, 88.3, 39.2; MS (ESI +ve) *m/z* 131.5 ($M^+-C_8H_4NO_3$, 100); HRMS (ESI) *m/z* calculated for $C_{18}H_{16}O$ $[M+H]^+$ 294.1130, found 294.1128.

*3.1.2. (R)-O-(1-Phenylbut-3-en-1-yl)hydroxylamine (**6**).* Hydrazine monohydrate (8.6 mL, 177 mmol) was added dropwise to a stirred solution of *N*-hydroxyphthalimide **5** (13.0 g, 44.3 mmol) in CH_2Cl_2 (350 mL) at room temperature. The mixture was stirred for 2 h, then filtered through a pad of Celite, washing with Et_2O (100 mL). The filtrate was concentrated *in vacuo* to give the desired hydroxylamine **6** (7.41 g, 100%) as a clear oil that was used without further purification; R_f 0.15 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ +68.3 (*c* 0.13, CH_2Cl_2); ν_{max} (neat) 3420, 3317, 3075, 3030, 2905, 1641, 1585, 1454, 1184 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.27–7.41 (5H, m), 5.76 (1H, ddt, *J* 17.0, 10.1, 7.0 Hz), 5.24 (2H, br s), 4.99–5.13 (2H, m), 4.56 (1H, t, *J* 6.9 Hz), 2.59 (1H, dt, *J* 14.6, 7.3 Hz), 2.42 (1H, dt, *J* 14.0, 7.0 Hz); δ_C (100 MHz, $CDCl_3$): 141.3, 134.4, 128.4, 127.8, 126.7, 117.0, 86.6, 40.5; MS (ESI −ve) *m/z* 163.4 (M^-, 100); HRMS (ESI) *m/z* calculated for $C_{10}H_{14}O$ $[M+H]^+$ 164.1075, found 164.1075.

*3.1.3. (R)-4-Methyl-N-((1-phenylbut-3-en-1-yl)oxy)benzenesulfonamide (**7**).* Anhydrous sodium carbonate (4.88 g, 46.0 mmol) and tosyl chloride (8.77 g, 46.0 mmol) were added sequentially to a stirred solution of hydroxylamine **6** (5.00 g, 30.6 mmol) in CH_2Cl_2 (50 mL) and water (50 mL) at room temperature. The mixture was stirred overnight. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography with gradual elution (5–20% Ethyl Acetate/Hexane) to give the desired *N*-tosyl hydroxylamine **7** (9.48 g, 98%) as a clear oil; R_f 0.32 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ +102.8 (*c* 0.34, CH_2Cl_2); ν_{max} (neat) 3435, 3225, 3066, 3032, 2924, 1714, 1643, 1597, 1454, 1339, 1183 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.82 (2H, d, *J* 8.2 Hz), 7.23–7.40 (7H, m), 6.67 (1H, s), 5.77 (1H, ddt, *J* 17.2, 9.9, 7.0 Hz), 4.98–5.15 (3H, m), 2.65 (1H, dt, *J* 14.8, 7.5 Hz), 2.41–2.54 (4H, m); δ_C (100 MHz, $CDCl_3$) 144.8, 139.6, 133.8, 133.7, 129.6, 128.7, 128.4, 128.3, 127.1, 117.6, 88.0, 39.6, 21.7; MS (ESI +ve) *m/z* 131.5 ($M^+-C_7H_8NO_3S$, 100), 148.6 ($M^+-C_7H_7NO_2S$, 10); HRMS (ESI) *m/z* calculated for $C_{17}H_{20}NO_3S$ $[M+H]^+$ 318.1164, found 318.1185.

*3.1.4. (5R)-3-Methoxy-5-phenyl-2-tosylisoxazolidine (**8**).* *p*-Toluenesulfonic acid monohydrate (230 mg, 1.2 mmol) was added to a solution of *N*-tosyl hydroxylamine **7** (7.66 g, 24.1 mmol) in MeOH (100 mL). The mixture was cooled to −78 °C and a stream of O_3/O_2 was passed through the mixture until the solution turned blue in colour. The flask was then purged with O_2 until the blue colour dissipated. Me_2S (2.4 mL, 28.9 mmol) was added and the reaction

mixture was warmed to room temperature and stirred for a further 48 h. The reaction solvent was removed with a rotary evaporator and the residue was taken up in CH_2Cl_2 (100 mL) and washed with water (2×50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography with gradual elution (5–25% Ethyl Acetate/Hexane) to give methoxyisoxazolidine **8** (7.22 g, 90%) as a mixture of diastereomers (ratio=1.5:1) and as a clear oil; R_f 0.38, 0.33 (20% Ethyl Acetate/Hexane); ν_{max} (neat) 3500, 2957, 1635, 1597, 1456, 1368, 1333, 1224, 1183 cm^{-1}; MS (ESI +ve) *m/z* 302.9 (M^+-OCH_3, 28); HRMS (ESI) *m/z* calculated for $C_{17}H_{19}NO_4SNa$ $[M+Na]^+$ 356.0932, found 356.0930.

Minor diastereomer: δ_H (400 MHz, $CDCl_3$): 7.89 (2H, d, *J* 8.2 Hz), 7.22–7.44 (7H, m), 5.71 (1H, dd, *J* 6.8, 2.7 Hz), 5.46 (1H, t, *J* 8.2 Hz), 3.54 (3H, s), 2.98 (1H, ddd, *J* 13.4, 8.4, 6.8 Hz), 2.42 (3H, s), 2.33 (1H, ddd, *J* 13.1, 8.2, 2.7 Hz); δ_C (100 MHz, $CDCl_3$): 145.1, 137.6, 133.6, 129.7, 129.0, 128.7, 128.6, 127.5, 91.7, 84.7, 56.6, 44.0, 21.7.

Major diastereomer: δ_H (400 MHz, $CDCl_3$): 7.82 (2H, d, *J* 8.2 Hz), 7.22–7.44 (7H, m), 5.51 (1H, d, *J* 5.4 Hz), 5.30 (1H, dd, *J* 11.9, 5.0 Hz), 3.54 (3H, s), 2.40–2.50 (4H, m), 2.08 (1H, ddd, *J* 12.3, 5.2 Hz); δ_C (100 MHz, $CDCl_3$): 145.2, 136.4, 132.6, 129.6, 129.4, 128.8, 128.5, 127.4, 91.9, 83.2, 55.7, 43.0, 21.7.

*3.1.5. (3S,5R)-3-Allyl-5-phenyl-2-tosylisoxazolidine (**9**).* $BF_3 \cdot Et_2O$ (4.4 mL, 36.0 mmol) was added dropwise to a stirred solution of methoxyisoxazolidine **8** (6.00 g, 18.0 mmol) and allyltrimethylsilane (11.4 mL, 72.0 mmol) in anhydrous CH_2Cl_2 (60 mL) at −78 °C. The mixture was gradually warmed to room temperature and stirred until the reaction was shown to be complete by TLC analysis. The reaction mixture was cooled to −78 °C and quenched with Et_3N (2.5 mL, 18.0 mmol). The mixture was allowed to warm to room temperature and was washed with water (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5–20% Ethyl Acetate/Hexane) to give the *trans* isomer **9** (3.73 g, 60%) as a crystalline solid and the *cis* isomer (517 mg, 8%) as a pale yellow oil.

Major diastereomer: mp 72–77 °C; R_f 0.40 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ +85.7 (*c* 0.25, CH_2Cl_2); ν_{max} (neat) 3439, 2922, 2852, 1636, 1456, 1377 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.80 (2H, d, *J* 8.2 Hz), 7.23–7.37 (7H, m), 5.90 (1H, ddt, *J* 17.1, 10.1, 7.0 Hz), 5.13–5.25 (3H, m), 4.39 (1H, q, *J* 7.0 Hz), 2.63 (1H, dt, *J* 14.2, 6.4 Hz), 2.39–2.48 (4H, m), 2.29–2.38 (1H, m), 2.19 (1H, td, *J* 11.8, 8.0 Hz); δ_C (100 MHz, $CDCl_3$): 144.9, 137.1, 133.7, 132.1, 129.6, 129.5, 128.5, 128.4, 127.2, 118.3, 82.9, 61.1, 40.5, 39.1, 21.7; MS (ESI +ve) *m/z*, 345.0 (M^++H, 100), 367.0 (M^++Na, 10); HRMS (ESI) *m/z* calculated for $C_{19}H_{22}NO_3S$ $[M+H]^+$ 344.1320, found 344.1311.

Minor diastereomer: R_f 0.46 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −68.0 (*c* 0.20, CH_2Cl_2); ν_{max} (film) 3065, 2981, 2852, 1598, 1357, 1332 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.90 (2H, d, *J* 8.2 Hz), 7.27–7.41 (7H, m), 5.89 (1H, ddt, *J* 17.2, 10.2, 6.9 Hz), 5.13–5.21 (3H, m), 4.45 (1H, qd, *J* 7.8, 5.5 Hz), 2.64–2.83 (2H, m), 2.42–2.55 (4H, m), 2.08 (1H, ddd, *J* 12.5, 10.2, 7.5 Hz); δ_C (100 MHz, $CDCl_3$): 144.9, 136.9, 133.7, 133.2, 129.7, 129.2, 128.6, 128.5, 127.8, 126.8, 118.2, 83.2, 60.0, 42.4, 40.4, 21.7; MS (ESI +ve) *m/z*, 345.0 (M^++H, 100), 240.8 (40), 173.6 (64), 155.5 (70); HRMS (ESI) *m/z* calculated for $C_{19}H_{22}NO_3S$ $[M+H]^+$ 344.1320, found 344.1319.

*3.1.6. N-((1R,3S)-1-Hydroxy-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (**10a**).* $Mo(CO)_6$ (692 mg, 2.62 mmol) was added to a solution of isoxazolidine **9** (3.01 g, 8.76 mmol) in acetonitrile (28 mL) and water (4 mL). The mixture was stirred at room temperature for 15 min, and $NaBH_4$ (758 mg, 13.1 mmol) was added in one portion. The reaction mixture was heated at 90 °C overnight. The mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with Et_2O (20 mL) and the resulting mixture was filtered through a pad of Celite, washing with Et_2O (2×20 mL). The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography with gradual elution (5–30% Ethyl Acetate/Hexane) to give the desired 1,3-aminoalcohol **10a** (2.00 g, 66%) as a colourless solid; mp 92–93 °C; R_f 0.13 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ +30.6 (*c* 0.12, CH_2Cl_2); ν_{max} (Nujol mull) 3446, 1638, 1597, 1317, 1155 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.70–7.91 (2H, m), 7.11–7.45 (7H, m), 5.40–5.54 (1H, m), 4.71–5.07 (4H, m), 3.61–3.72 (1H, m), 2.87 (1H, br s), 2.45 (3H, s), 1.97–2.18 (2H, m), 1.70–1.82 (1H, m), 1.54–1.68 (1H, m); δ_C (100 MHz, $CDCl_3$): 144.1, 143.5, 137.7, 132.9, 129.7, 128.4, 127.3, 127.2, 125.5, 119.1, 70.0, 50.5, 43.9, 39.4, 21.5; MS (ESI −ve) *m/z*, 345.00 (M^-−H, 100); HRMS (ESI) *m/z* calculated for $C_{19}H_{24}NO_3S$ $[M+H]^+$ 346.1477, found 346.1468.

*3.1.7. 4-Methyl-N-((1R,3S)-1-phenyl-1-((triethylsilyl)oxy)hex-5-en-3-yl)benzenesulfonamide (**10b**).* Triethylamine (380 μL, 4.1 mmol) was added dropwise to a solution of aminoalcohol **10a** (1.00 g, 2.9 mmol) and chlorotriethylsilane (420 μL, 3.5 mmol) in CH_2Cl_2 (15 mL) at 0 °C. Once addition was complete, the mixture was warmed to room temperature and stirred overnight. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NH_4Cl (20 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10% Ethyl Acetate/Hexane) to give the desired silyl ether **10b** (1.22 g, 91%) as a clear oil; R_f 0.43 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ +28.7 (*c* 0.25, CH_2Cl_2); ν_{max} (film) 3284, 2954, 2911, 2876, 1454, 1415, 1329, 1160, 1092 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.72 (2H, d, *J* 8.2 Hz), 7.29 (2H, d, *J* 8.2 Hz), 7.18–7.23 (3H, m), 7.03–7.09 (2H, m), 5.51–5.69 (2H, m), 4.93–5.07 (2H, m), 4.87 (1H, dd, *J* 7.7, 4.1 Hz), 3.28–3.38 (1H, m), 2.44 (3H, s), 2.18–2.38 (2H, m), 1.58–1.79 (2H, m), 0.83–0.92 (9H, m), 0.42–0.60 (6H, m); δ_C (100 MHz, $CDCl_3$): 143.9, 143.1, 138.2, 133.8, 129.6, 128.2, 127.4, 127.2, 125.7, 118.2, 73.0, 51.2, 42.8, 38.9, 21.5, 6.7, 4.7; MS (ESI −ve) *m/z* 459.1 (M^-−H, 88), 345.0 (30), 171.6 (44), 117.3 (100); HRMS (ESI) *m/z* calculated for $C_{25}H_{38}NO_3SSi$ $[M+H]^+$ 460.2342, found 460.2328.

*3.1.8. (S)-2-((R)-2-Phenyl-2-((triethylsilyl)oxy)ethyl)-1-tosyl-1,2,3,4-tetrahydropyridine (**11b**).* In a Fisher–Porter tube, silyl ether **10b** (500 mg, 1.09 mmol), $Rh_2(OAc)_4$ (4 mg, 0.01 mmol) and BIPHEPHOS (17 mg, 0.02 mmol) were dissolved in anhydrous toluene (20 mL). The mixture was purged with H_2/CO (1:1) three times and then charged with H_2 (30 psi) and CO (30 psi). The mixture was stirred at 85 °C for 22 h. The mixture was allowed to cool to room temperature, the pressure was vented and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography with gradual elution (5–15% Ethyl Acetate/Hexane) to give the desired ene-sulfonamide **11b** (466 mg, 91%) as a clear oil; R_f 0.58 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −218.8 (*c* 0.18, CH_2Cl_2); ν_{max} (film) 2952, 2912, 2875, 1643, 1449, 1358, 1166, 1095 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.64 (2H, d, *J* 8.2 Hz), 7.20–7.34 (7H, m), 6.58 (1H, d, *J* 8.2 Hz), 4.99–5.05 (1H, m), 4.96 (1H, dd, *J* 9.1, 3.2 Hz), 4.12 (1H, m), 2.42 (3H, s), 1.61–1.94 (5H, m), 1.39–1.53 (1H, m), 0.85–0.92 (9H, m), 0.37–0.73 (6H, m); δ_C (100 MHz, $CDCl_3$): 145.5, 143.3, 136.0, 129.6, 128.1, 127.2, 127.0, 126.0, 123.7, 110.0, 72.3, 50.6, 44.1, 24.2, 21.5, 17.3, 6.9, 4.9; MS (ESI −ve) *m/z* 341.0 (M^-−OTES, 100), 236.8 (95); HRMS (ESI) *m/z* calculated for $C_{26}H_{38}NO_3SSiNa$ $[M+Na]^+$ 494.2161, found 494.2165.

*3.1.9. (R)-1-Phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl) ethanol (**11a**) by desilylation.* A solution of ene-sulfonamide **11b** (465 mg, 0.99 mmol) in 10% methanolic NaOH (10 mL) was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2×10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The residue was purified by flash chromatography (20% Ethyl Acetate/Hexane) to give the desired alcohol **11a** (340 mg, 96%) as a colourless solid; mp 117–119 °C; R_f 0.24 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −213.7 (*c* 0.35, CH_2Cl_2); ν_{max} (film) 3443, 1645, 1597, 1338, 1163, 1101, 922 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.71 (2H, d, *J* 8.6 Hz), 7.23–7.42 (7H, m), 6.66 (1H, d, *J* 8.2 Hz), 5.12 (1H, t, *J* 5.9 Hz), 5.02 (1H, dd, *J* 11.1, 2.0 Hz), 4.30 (1H, d, *J* 10.9 Hz), 3.63 (1H, d, *J* 4.5 Hz), 2.44 (3H, s), 1.73–1.98 (3H, m), 1.37–1.53 (1H, m), 0.80–0.99 (2H, m); δ_C (100 MHz, $CDCl_3$): 144.2, 143.8, 135.1, 129.8, 128.3, 127.2, 127.1, 125.7, 123.1, 110.9, 69.2, 49.7, 41.6, 23.8, 21.6, 17.5; MS (ESI +ve) *m*/*z* 381.0 (M^+ +Na, 10), 341.0 (M^+−OH, 100); HRMS (ESI) *m*/*z* calculated for $C_{20}H_{24}NO_3S$ $[M+H]^+$ 358.1477, found 358.1461.

*3.1.10. (R)-1-Phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl) ethanol (**11a**) by saponification.* K_2CO_3 (21 mg, 0.15 mmol) was added to a solution of acetate **11c** (50 mg, 0.13 mmol) in MeOH (5 mL) and CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 2 h, then concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (5 mL) and washed with water (3 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the desired alcohol **11a** (46 mg, 100%) as a colourless solid, identical to that described above.

*3.1.11. (R)-1-Phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl) ethanol (**11a**) and (1S,3S,5S)-3-phenyl-9-tosyl-2-oxa-9-azabicyclo [3.3.1]nonane (**13**) by hydroformylation.* In a Fisher–Porter tube, aminoalcohol **10a** (100 mg, 0.29 mmol), $Rh_2(OAc)_4$ (1 mg, 0.03 mmol) and BIPHEPHOS (5 mg, 0.06 mmol) was dissolved in anhydrous toluene (5 mL). The mixture was purged with H_2/CO (1:1) three times and then charged with H_2 (30 psi) and CO (30 psi). The reaction mixture was heated to 65 °C and stirred for 22 h. The reaction mixture was allowed to cool to room temperature, the pressure was vented and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography with gradual elution (5–25% Ethyl Acetate/Hexane) to give two products, the desired ene-sulfonamide **11a** (47 mg, 46%), identical to that described above, and bicyclic acetal **13** (36 mg, 35%).

Bicyclic acetal **13**: mp 138–142 °C; R_f 0.31 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ +3.83 (*c* 0.37, CH_2Cl_2); ν_{max} (film) 2921, 1704, 1643, 1598, 1347, 1163 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.86 (2H, d, *J* 8.2 Hz), 7.33 (2H, d, *J* 8.2 Hz), 7.12–7.20 (3H, m), 6.72 (2H, dd, *J* 7.5, 2.1 Hz), 5.74 (1H, m), 5.38 (1H, dd, *J* 12.4, 4.1 Hz), 4.26 (1H, m), 2.46 (3H, s), 2.13–2.33 (4H, m), 1.87–1.99 (2H, m), 1.77 (1H, td, *J* 12.8, 5.9 Hz), 1.17–1.26 (1H, m); δ_C (100 MHz, $CDCl_3$): 143.3, 142.6, 138.7, 129.8, 128.1, 127.9, 127.6, 125.6, 79.0, 73.2, 47.6, 35.6, 30.7, 30.3, 21.5, 20.2; MS (ESI +ve) *m*/*z* 381.0 (M^+ +Na, 10), 341.0 (40), 254.8 (100), 236.8 (58); HRMS (ESI) *m*/*z* calculated for $C_{20}H_{23}NO_3S$ $[M+H]^+$ 358.1477, found 358.1493.

*3.1.12. (S)-1-Phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl) ethyl acetate (**11c**).* Amberlyst-A15 (12 mg) and Ac_2O (120 μL, 1.21 mmol) were added to a solution of the bicyclic acetal (289 mg, 0.81 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight. The mixture was filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10–20% Ethyl Acetate/Hexane) to give acetate **11c** as a colourless powder in (224 mg, 70%); mp 171–175 °C; R_f 0.27 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −169 (*c* 0.11, CH_2Cl_2); ν_{max} (Nujol) 3422, 2361, 1738, 1647, 1597, 1365, 1337, 1231, 1161 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.62 (2H, d, *J* 8.2 Hz), 7.35 (4H, m), 7.28–7.31 (3H, m), 6.60 (1H, d, *J* 8.6 Hz), 5.82 (1H, dd, *J* 9.5, 4.5 Hz), 4.95–5.20 (1H, m), 4.10 (1H, dd, *J* 7.7, 3.6 Hz), 2.42 (3H, s), 2.08–2.25 (3H, s), 1.76–2.05 (4H, m), 1.40–1.52 (1H, m), 0.83–0.98 (1H, m); δ_C (100 MHz, $CDCl_3$): 170.1, 143.4, 140.6, 135.8, 129.6, 128.5, 127.9, 127.1, 126.5, 123.5, 109.9, 72.9, 49.5, 38.2, 23.3, 21.5, 21.2, 17.3; MS (ESI +ve) *m*/*z* 340.1 (M^+−OAc, 30); HRMS (ESI) *m*/*z* calculated for $C_{22}H_{26}NO_4S$ $[M+H]^+$ 400.1583, found 400.1592.

*3.1.13. (S)-1-Phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl) ethyl 2-chloroacetate (**15a**).* DIAD (710 μL, 3.57 mmol) was added dropwise to a solution of ene-sulfonamide **11a** (639 mg, 1.79 mmol), PPh_3 (939 mg, 3.57 mmol) and chloroacetic acid (338 mg, 3.57 mmol) in toluene at 0 °C. The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred overnight. The mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and absorbed onto silica, then purified by flash chromatography with gradual elution (5–15% Ethyl Acetate/Hexane) to give chloroacetate **15a** (540 mg, 70%) as a clear oil and alkene **15b** (100 mg, 17%) as a colourless powder.

Chloroacetate **15a**: R_f 0.32 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −221.2 (*c* 0.14, CH_2Cl_2); ν_{max} (film) 2961, 2926, 1759, 1644, 1340, 1165 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.63 (2H, d, *J* 8.2 Hz), 7.23–7.44 (7H, m), 6.62 (1H, d, *J* 7.8 Hz), 5.94 (1H, dd, *J* 9.1, 4.6 Hz), 4.98–5.10 (1H, m), 3.96–4.21 (3H, m), 2.29–2.49 (4H, m), 1.77–1.97 (3H, m), 1.55 (1H, m), 0.82–1.00 (1H, m); δ_C (100 MHz, $CDCl_3$): 166.6, 143.5, 139.4, 135.8, 129.7, 128.6, 128.5, 126.9, 126.8, 123.6, 109.1, 75.4, 49.8, 41.1, 38.3, 22.8, 21.5, 17.1; MS (ESI +ve) *m*/*z* 236.8 (100), 341.0 ($M^+-C_2H_2O_2Cl$, 90), 435.0/437.0 (M^++H, 23), 457.0/459 (M^++Na, 23); HRMS (ESI) *m*/*z* calculated for $C_{22}H_{25}NO_4S^{35}Cl$ $[M+H]^+$ 434.1193, found 434.1189.

Alkene **15b**: mp 108–110 °C; R_f 0.45 (20% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −188.1 (*c* 0.09, CH_2Cl_2); ν_{max} (film) 2927, 2193, 2021, 1648, 1596, 1494, 1359, 1339, 1163, 1098 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.68 (2H, d, *J* 7.8 Hz), 7.17–7.32 (7H, m), 6.73 (1H, d, *J* 8.2 Hz), 6.48 (1H, d, *J* 16.0 Hz), 5.93 (1H, dd, *J* 15.8, 5.7 Hz), 5.02 (1H, t, *J* 6.9 Hz), 4.74 (1H, m), 2.36 (3H, s), 1.69–2.09 (4H, m), 1.31–1.47 (2H, m); δ_C (100 MHz, $CDCl_3$): 143.4, 136.5, 136.4, 131.4, 129.6, 128.4, 127.5, 127.1, 126.4, 126.2, 123.7, 108.2, 54.4, 25.5, 21.5, 17.5; MS (ESI +ve) *m*/*z* 341.0 (M^+ +H, 30), 169.7 (45), 143.6 (100); HRMS (ESI) *m*/*z* calculated for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.1371, found 340.1377.

*3.1.14. (2S,3S,6S)-6-((S)-2-(2-Chloroacetoxy)-2-phenylethyl)-1-tosylpiperidine-2,3-diyl diacetat (**17**).* $MeSO_2NH_2$ (166 mg, 1.74 mmol) was added to a solution of ene-sulfonamide **15a** (250 mg, 0.58 mmol) in THF (18 mL) with stirring. When the $MeSO_2NH_2$ had completely dissolved, NMO (410 μL of a 50% aqueous solution, 1.74 mmol), H_2O (2 mL) and $K_2OsO_4 \cdot 2H_2O$ (21 mg, 0.06 mmol) were added. The mixture was stirred at room temperature for 48 h. The reaction mixture was taken up in EtOAc (30 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give diols **16** (271 mg, 0.58 mmol) as a mixture of diastereomers (ratio=4.6:1) that was used without further purification.

Ac_2O (120 μL, 1.28 mmol), triethylamine (210 μL, 1.45 mmol) and DMAP (1 mg, 0.01 mmol) were added to the solution of the crude diols in anhydrous CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 3 h. The mixture was diluted with saturated aqueous NH_4Cl (15 mL) and CH_2Cl_2 (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (25% Ethyl Acetate/Hexane) to give the desired diacetates **17** (268 mg, 83%) as a crystalline solid and as an inseparable mixture of diastereomers (ratio=4.6:1); mp 135–140 °C; R_f 0.27 (40% Ethyl Acetate/Hexane); ν_{max} (film) 2952, 2373, 2364, 1747, 1362, 1240, 1165 cm^{-1}.

Major diastereomer: δ_H (396 MHz, $CDCl_3$): 7.72 (2H, d, *J* 8.6 Hz), 7.27–7.40 (7H, m), 6.82 (1H, d, *J* 3.6 Hz), 5.82 (1H, dd, *J* 10.4, 3.6 Hz), 4.66 (1H, dt, *J* 11.9, 4.2 Hz), 3.98–4.26 (3H, m), 2.44 (3H, s), 2.29–2.41 (1H, m), 2.12–2.28 (1H, m), 1.96 (3H, s), 1.95 (3H, s), 1.78–1.89 (2H, m), 1.59–1.71 (2H, m); δ_C (100 MHz, $CDCl_3$): 169.8, 168.9, 166.9, 144.1, 139.1, 137.2, 129.9, 128.8, 128.6, 127.3, 126.4, 75.8,

75.4, 69.4, 48.9, 41.0, 39.6, 26.0, 21.6, 21.0, 20.7, 19.0; MS (ESI +ve) *m/z* 575.1/577.1 (M^++Na, 14), 493.0/495.0 (M^+−OAc, 44), 399.0 ($M^+-C_4H_4O_4^{35}Cl$, 100), 351.0 (45), 294.9 (90); HRMS (ESI) *m/z* calculated for $C_{26}H_{30}NO_8S^{35}Cl$ $[M+H]^+$ 552.1459, found 552.1474.

*3.1.15. (S)-2-((2S,5S)-5-Acetoxy-1-tosylpiperidin-2-yl)-1-phenylethyl 2-chloroacetate (**18**).* Et_3SiH (580 μL, 3.63 mmol) and trifluoroacetic acid (30 μL, 0.36 mmol) were added to a solution of diacetates **17** (200 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (10 mL). The mixture was stirred at room temperature overnight. The mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (10–20% Ethyl Acetate/Hexane) to give the two isomers as clear oils: major isomer **18** (75 mg, 42%), minor isomer (33 mg, 18%).

Major isomer: R_f 0.36 (40% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −44.5 (*c* 0.38, CH_2Cl_2); ν_{max} (film) 3449, 2594, 1759, 1732, 1597, 1494, 1454, 1342, 1242, 1161 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.67 (2H, d, *J* 8.2 Hz), 7.21–7.32 (7H, m), 5.77 (1H, dd, *J* 8.6, 5.0 Hz), 4.31 (1H, tt, *J* 10.3, 4.9 Hz), 3.89–4.13 (4H, m), 2.86 (1H, dd, *J* 14.0, 11.3 Hz), 2.36 (3H, s), 2.24–2.33 (1H, m), 1.94 (3H, s), 1.87 (1H, ddd, *J* 14.5, 6.8, 5.0 Hz), 1.69–1.79 (1H, m), 1.34–1.45 (3H, m); δ_C (100 MHz, $CDCl_3$): 169.9, 166.6, 143.6, 139.0, 137.9, 129.9, 128.7, 128.6, 127.0, 126.7, 76.0, 67.4, 49.1, 43.3, 41.1, 36.3, 26.1, 24.5, 21.5, 21.0; MS (ESI +ve) *m/z* 399.0 ($M^+-C_2H_2O_2Cl$, 15), 269.9 (100), 236.8 (15); HRMS (ESI) *m/z* calculated for $C_{24}H_{29}NO_6S^{35}Cl$ $[M+H]^+$ 494.1404, found 494.1397.

Minor isomer: R_f 0.40 (40% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −87.33 (*c* 0.21, CH_2Cl_2); ν_{max} (film) 2962, 1758, 1347, 1213, 1163 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.64 (2H, d, *J* 8.2 Hz), 7.28–7.45 (7H, m), 6.62 (1H, s), 5.95 (1H, dd, *J* 8.6, 5.0 Hz), 4.16 (1H, d, *J* 16.0 Hz), 4.05 (1H, d, *J* 12.0 Hz), 3.91–4.00 (1H, m), 2.36–2.48 (4H, m), 2.10–2.29 (4H, m), 1.82–1.96 (2H, m), 1.51 (1H, dd, *J* 13.8, 6.6 Hz), 0.80–1.00 (3H, m); δ_C (100 MHz, $CDCl_3$): 169.5, 166.5, 143.9, 139.1, 137.0, 135.0, 129.8, 128.6, 128.5, 127.1, 126.8, 115.9, 75.4, 49.6, 41.1, 37.9, 22.5, 21.5, 20.7, 20.4; MS (ESI +ve) *m/z* 399.0 ($M^+-C_2H_2O_2^{35}Cl$, 100), 357.0 (36), 294.9 (42); HRMS (ESI) *m/z* calculated for $C_{24}H_{29}NO_6S^{35}Cl$ $[M+H]^+$ 494.1404, found 494.1409.

*3.1.16. (3S,6S)-6-((S)-2-Hydroxy-2-phenylethyl)-1-tosylpiperidin-3-ol (**19**).* K_2CO_3 (31 mg, 0.23 mmol) was added to a stirred solution of piperidine **18** (45 mg, 0.09 mmol) in methanol (5 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was taken up in EtOAc (5 mL) and washed with water (3 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give piperidinol **19** as a colourless oil (34 mg, 100%), which was used without further purification; R_f 0.06 (40% Ethyl Acetate/Hexane); $[\alpha]_D^{22}$ −56.2 (*c* 0.10, CH_2Cl_2); ν_{max} (film) 3451, 2925, 2854, 1598, 1454, 1330, 1154 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.73 (2H, d, *J* 8.2 Hz), 7.26–7.37 (7H, m), 4.71 (1H, dd, *J* 8.9, 4.3 Hz), 4.20–4.30 (1H, m), 3.92 (1H, ddd, *J* 14.0, 4.3, 0.9 Hz), 3.36–3.54 (1H, m), 2.77 (1H, dd, *J* 13.7, 11.0 Hz), 2.42 (3H, s), 2.27 (1H, d, *J* 5.5 Hz), 1.93–2.03 (1H, m), 1.75–1.90 (2H, m), 1.30–1.51 (3H, m); δ_C (100 MHz, $CDCl_3$): 144.2, 143.4, 137.9, 129.8, 128.6, 127.7, 127.1, 125.8, 72.3, 66.1, 49.6, 46.6, 38.9, 28.2, 26.5, 21.5; MS (ESI +ve) *m/z* 399.0 (M^++Na, 10), 254.8 (100), 114.3 (68); HRMS (ESI) *m/z* calculated for $C_{20}H_{25}NO_4SNa$ $[M+Na]^+$ 398.1402, found 398.1430.

*3.1.17. (−)-5-Hydroxysedamine (**3**).* Activated Mg turnings (24 mg, 1.00 mmol) were added in 5 mg portions every hour to a solution of *N*-tosylpiperidinol **19** (19 mg, 0.05 mmol) in anhydrous MeOH (4 mL) as the mixture was being sonicated in an ultrasonic cleaning bath. Once the reaction was complete as determined by TLC analysis, the reaction mixture was acidified with 2 M HCl and washed with CH_2Cl_2 (5 mL). The aqueous layer was neutralized with 2 M NaOH and extracted with CH_2Cl_2 (2×5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give piperidinol **20** as a pale yellow oil, which was used without further purification.

Formic acid (20 μL, 0.50 mmol) and paraformaldehyde (15 mg, 0.50 mmol) were added to a solution of piperidinol **20** (11 mg, 0.05 mmol) in dioxane (3 mL). The reaction mixture was heated and stirred at 100 °C overnight. The mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (5 mL) and Et_3N (110 μL, 0.80 mmol) was added. The mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography (10% MeOH/$CHCl_3$ with 1% Et_3N) to give 5-hydroxysedamine **3** as a yellow oil (8.3 mg, 71%); R_f 0.04 (10% MeOH/$CHCl_3$ with 1% Et_3N); $[\alpha]_D^{22}$ −55.3 (*c* 0.15, MeOH); ν_{max} (film) 3343, 2934, 2802, 1600, 1451, 1253, 1058 cm^{-1}; δ_H (396 MHz, $CDCl_3$): 7.19–7.43 (5H, m), 4.87 (1H, dd, *J* 10.4, 2.3 Hz), 3.88 (1H, tt, *J* 7.5, 3.6 Hz), 2.88 (1H, dd, *J* 12.7, 7.7 Hz), 2.66–2.74 (1H, m), 2.59 (1H, dd, *J* 13.1, 3.6 Hz), 2.48 (3H, s), 2.17 (1H, ddd, *J* 14.2, 10.3, 8.2 Hz), 1.91 (1H, ddt, *J* 13.4, 8.9, 4.5 Hz), 1.67–1.76 (1H, m), 1.53–1.66 (2H, m), 1.49 (1H, ddd, *J* 14.2, 5.5, 2.8 Hz); δ_C (100 MHz, $CDCl_3$): 145.0, 128.2, 127.2, 125.4, 73.3, 63.6, 59.7, 57.5, 42.4, 39.6, 30.1, 24.0; MS (ESI +ve) *m/z* 236.9 (M^++H, 80), 114.4 (100); HRMS (ESI) *m/z* calculated for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1651, found 236.1642.

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