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Stereochemistry of Remote Dianion Addition to Imines. Application to the Synthesis of (1*S*, 8a*S*)-1-Hydroxyindolizidine.[1]

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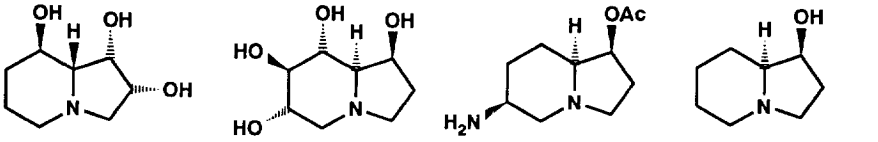
Abstract: A stereoselective route to (1*S*, 8a*S*)-1-hydroxyindolizidine is reported herein that incorporates as a pivotal step the diastereoselective addition of the dianion of 4-(phenylsulfonyl)butanoic acid (4-PSBA) to a chiral α-benzyloxymethyl imine.

(-)-Swainsonine, (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyindolizidine (**1**), is isolable from the fungi *Rhizoctonia leguminicola*[2] or *Metarhizium anisoplia* F3622[3], and several plant species,[4-6] and is a potent inhibitor of mammalian lysosomal α-mannosidase, which functions in the degradation of the oligosaccharide portion of various glycoproteins.[7] In mammals, swainsonine was found to be the causative agent of locoism from ingestion of locoweed.[8] The effects are due to both the lysosomal α-mannosidase inhibition and abnormal glycoprocessing, which results in the storage of abnormally processed asparagine-linked glycans.[9] Swainsonine is also an immunomodulator and could have possible applications in cancer chemotherapy.[10]

Castanospermine (**2**) (1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine, has been isolated from *Castanospermum australe*,[11] a leguminous tree indigenous to Australia. The mature seeds contain the largest concentration (0.3%).[12] Consumption of the seeds results in severe gastroenteritis,[13] presumably due to the inhibition of β-glucosidase.[14] Recent reports indicate that the glycoprotein processing inhibition may enable **2** to find applications as an "antitumor agent,[15] antiviral,[16] and anti-HIV agent.[17]"



1 ***Swainsonine*** **2** ***Castanospermine*** **3** ***Slaframine*** **4** ***1-Hydroxyindolizidine***

Figure 1

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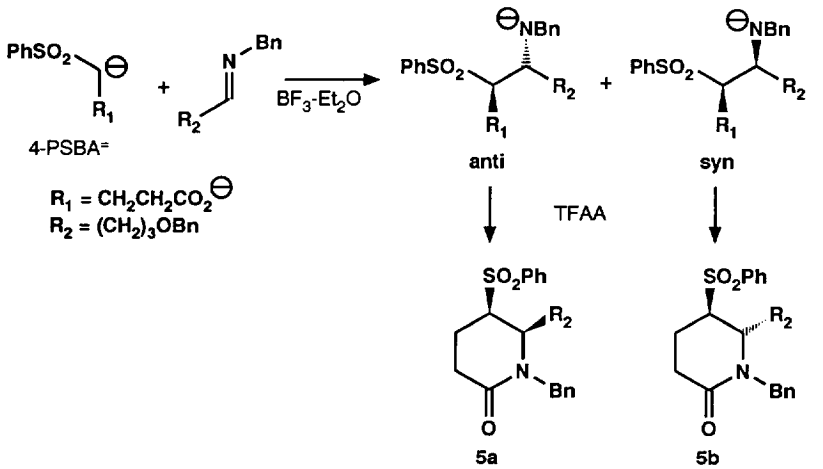
Slaframine (**3**), (1*S*,6*S*,8a*S*)-1-acetoxy-6-aminoindolizidine, is isolated from the fungus *Rhizoctonia leguminicola*,[18] which also produces swainsonine (**1**). Both **1** and **3** are biosynthesized from an intermediate pipecolic acid via (1*S*,8a*S*)-1-hydroxyindolizidine (**4**).[19] Slaframine causes excessive salivation in cattle grazing on fungus-infected red clover hay,[20] but has been cited as a possible therapeutic for the relief of symptoms associated with cystic fibrosis.[21]

With our prior success in the preparation of δ-coniceine[22] and alkylindolizidines,[1] we were encouraged to explore the preparation of a more complex indolizidine natural product. In this endeavor, we first analyzed the stereochemical outcome following the addition of the remote dianion of 4-PSBA to achiral imines to establish any diastereoselectivity. Following this evaluation, we studied the addition of the 4-PSBA dianion to imines that bear an α-asymmetric center in an effort to determine the influence of the chiral auxiliary on the C-C bond-forming reaction. Finally, a total synthesis of enantioenriched (1*S*, 8a*S*)-1-hydroxyindolizidine (**4**) is reported using the 4-PSBA dianion addition to a chiral imine as a pivotal step.

RESULTS AND DISCUSSION

Our prior work showed that the dianion of 4-PSBA adds to imines (activated by BF_3·Et_2O) to give lactams (Scheme 1).[23] The diastereomeric lactam products resulting from the one-pot, addition-cyclization sequence are related as *cis* **5a** and *trans* **5b**, which are formed from the corresponding *anti* and *syn* addition products, respectively. In order to produce the desired ring junction stereochemistry for **4**, the *anti* addition product is desired, and therefore a preliminary analysis of the diastereoselectivity was deemed necessary before extension to the enantioenriched system was undertaken. When the 4-PSBA dianion is condensed with the 4-benzyloxyimine (Scheme 1; R_2 = $CH_2CH_2CH_2OBn$), a mixture of lactam stereoisomers **5a** and **5b** are isolated in a 2:1 ratio. Unfortunately, we were unable to resolve the stereochemical assignments using proton, and related 2-D spectral methods. As a result, selective deprotection was conducted (10% Pd/C,



Scheme 1. Stereoisomeric lactams resulting from 4-PSBA dianion addition to imines.

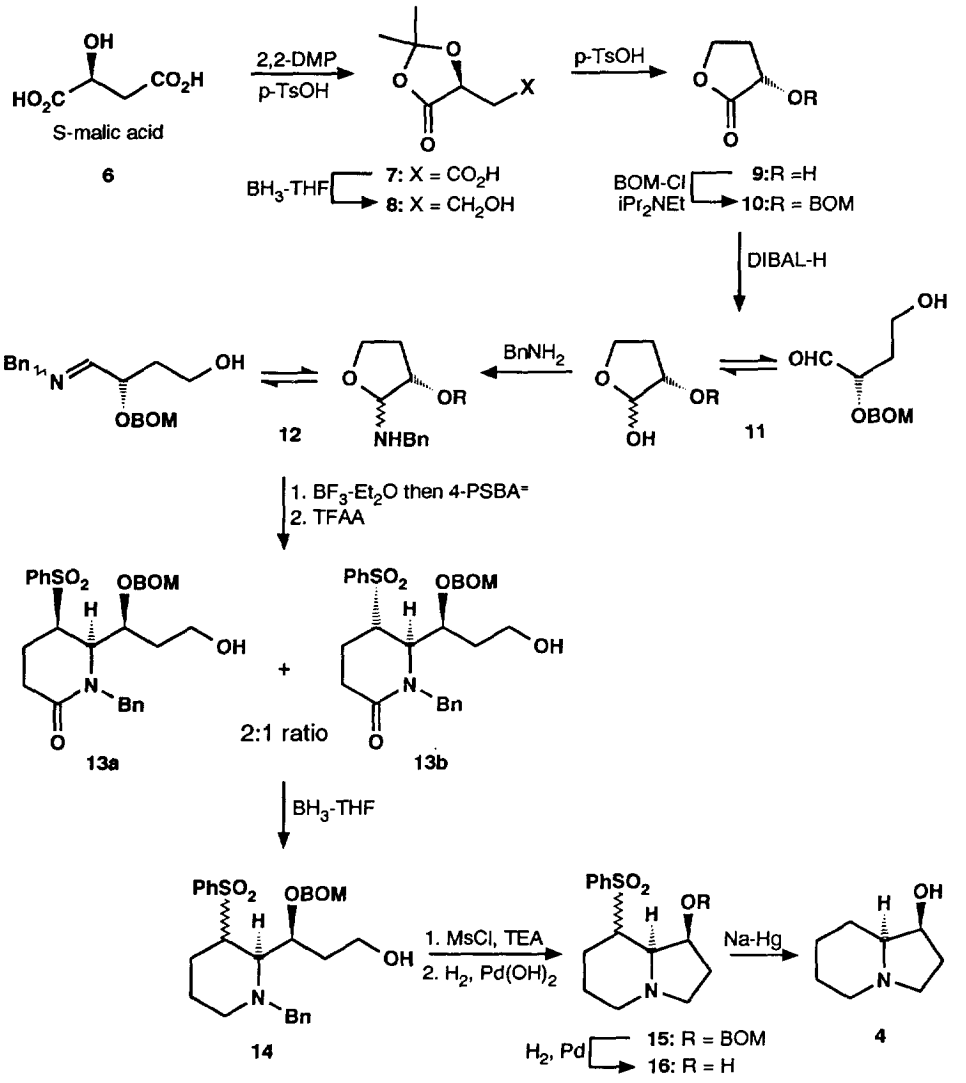
trifluoroacetic acid) to provide the corresponding primary alcohols **5a** and **5b** (R_2 = $CH_2CH_2CH_2OH$) that showed simplified spectra. The predominant stereoisomer **5a** was assigned the *cis* configuration and **5b** the *trans* based upon the coupling constants obtained between the α-phenylsulfonyl methine ($PhSO_2C\underline{H}_a$) and the alkyl side-chain bearing α-methine (R_2-$C\underline{H}_b$-NBn) groups, which were the most clearly resolved absorbencies. When the two ring substituents are *cis*, the angle θ between H_a and H_b is approximately 60° with a predicted J_{HaHb} = 2.5 Hz for a Karplus curve shifted for electronegative substituent.[24] In contrast, the *trans* mixture of conformers should give a more complex spectrum because of two θ values (60° and 180°) of J_{HaHb} = 2.5 and 9.5 Hz, respectively. Indeed, a J_{HaHb} of 2.5 Hz was observed for the major component, while the spectrum acquired from the minor component was too complex to discern a single coupling constant for J_{HaHb}. These spectral signatures led to the assignments of **5a** as *cis* and **5b** as *trans*.

This assignment suggests that the *anti* addition product is the major isomer formed from the addition of the dianion of 4-PSBA to imines assuming no equilibration occurs following the addition. Subsequent experiments showed that the reaction time, cyclization reagent, and added base (to deprotonate the α-$PhSO_2C\underline{H}$ group) had no effect on the isolated stereoisomer composition. This interesting preference for *anti* diastereoselection does not parallel organometallic additions to aldimines, which normally favor the *syn* addition products.[25] However, the influence of the Lewis acid activation and the nature of the carbanion species complicate predictions of the operative transition state. Importantly, the major product of the dianion addition is the *cis* lactam product, which is the desired stereochemistry for the synthesis of **4**.

Synthesis of (1*S*, 8a*S*)-1-hydroxyindolizidine

Having completed our stereochemical analysis, we turned our attention to the preparation of (1*S*, 8a*S*)-1-hydroxyindolizidine (**4**). We hoped to expand further our stereochemical knowledge of dianion additions to cases when the imine contains an asymmetric center (Scheme 2). The synthesis of the target enantioenriched 1-hydroxyindolizidine requires an imine similar to that shown in Scheme 1 modified to contain a chiral, alpha-hydroxyl group. (S)-Malic acid was chosen as the starting material to prepare the imine **12**.

The synthesis of the imine precursor benzyloxymethyl-protected lactone **9** is based on a procedure developed by Still et al.[26] (*S*)-Malic acid was protected as the acetonide **7** (2,2-dimethoxypropane, *p*-TsOH), and the carboxylic acid was reduced to the alcohol using BH_3·THF. This unstable product immediately rearranged to (S)-3-hydroxybutyrolactone (**9**) upon heating in the presence of *p*-TsOH. The hydroxyl group was protected as the benzyloxymethyl (BOM) ether to provide the known lactone **10** in 33% overall yield (lit. [26] 52%). Reduction of the ester with diisobutyl aluminum hydride (DIBAL-H) provided an equilibrium mixture of lactol and hydroxy aldehyde **11** accompanied with overreduction to the alcohol. The ^{13}C NMR spectrum of **11** was complicated by the presence of diastereomers yet sufficiently similar to sugars bearing anomeric centers.[27] A ^1H NMR and IR study of **11** in several different solvents (CD_3CN, diethyl ether, acetone, methanol, THF, $CDCl_3$) was undertaken in order to evaluate the optimum solvent for obtaining the desired aldehyde form. As expected, the lactol form dominates in most solvents, with only THF showing the presence of aldehyde. This information was used to optimize the yield for the DIBAL-H reduction. Using ether in place of THF as the solvent decreased overreduction of the lactone to the diol.



Scheme 2

Since the equilibrium in THF showed some of the aldehyde form of **11**, we hoped to capture the open chain form by selectively blocking the primary hydroxyl group. Reaction of **11** with *tert*-butyldimethylsilyl chloride gave a 3:1 ratio of TBDMS-lactol and TBDMS-aldehyde, respectively. The diphenylmethylsilyl ether also was prepared, yielding only protected lactol. Interestingly, the *tert*-butyldiphenylsilyl (TBDPS) ether provided primarily the desired aldehyde. This aldehyde was converted to the imine ($PhCH_2NH_2$, $-H_2O$), activated with $BF_3{\cdot}Et_2O$, and reacted with the dianion of 4-PSBA. Although

the addition products could be isolated, no cyclization to the corresponding lactam was observed. This difficulty presumably arises because of the bulkiness of the side chain with both BOM and TBDPS ether appendages. In continuation of the protecting group strategy for **11**, reaction with BnBr yielded only protected lactol and reaction of **11** with triphenylmethyl chloride resulted in no reaction.

It was decided that condensation of the lactol **11** with benzylamine to from the imine would be attempted followed by protection of the alcohol. The imine **12** could be formed although the product was very unstable and not amenable to subsequent alcohol protection steps. Attempted protection as the TBDMS and benzyl ethers resulted in some product formation although workup procedures were accompanied by significant hydrolysis of the imine. The imine product **12** showed spectroscopic evidence that it existed in equilibrium with the hemi-aminal form. Since the open chain form is likely to dominate the equilibrium following deprotonation, the dianion addition reaction was performed directly on **12** in the hope that deprotonation by the first equivalent of dianion would lead to formation of the open-chain, alkoxide form of the imine *in situ*.

Thus, imine **12** was pretreated with $BF_3{\cdot}Et_2O$ (3 eq.) and reacted with the dianion of 4-PSBA (2 eq.) to give the diasteromeric lactams **13a** (tentative ring substituent assignment trans; non-polar chromatographic fraction) and **13b** (tentative ring substituent assignment cis; polar chromatographic fraction) in modest yield (29% after purification) again in a 2:1 ratio as in the case of achiral lactam (Scheme 1). The low yield is both due to insufficient conversion of **11** to the imine **12**, and poor interconversion to the open-chain alkoxy imine. As mentioned, the addition reaction requires two equivalents of dianion; one to deprotonate the unprotected terminal hydroxyl group, and the second dianion equivalent is delivered to the imine. Excess 4-PSBA was readily removed and recovered through basic workup. The remainder of the reaction mass balance was the N-benzyl amide of 4-PSBA and the product of addition of the 4-PSBA dianion to unconverted lactol **11**. It is surprising that the α-benzyloxymethyl ether moiety does not alter the diastereoselection of the addition reaction. Conversion of **13a** and **13b** into the desired (1*S*, 8a*S*)-1-hydroxyindolizidine **4** is conducted in a manner similar to that reported for alkyl-substituted indolizidines[1] and a δ-coniceine synthesis.[22]

To make stereochemical assignment, lactams **13a** (non-polar) and **13b** (polar) were separated and brought through the following sequence as individual stereoisomers and as a mixture. Lactam **13a** or **13b** was reduced to the corresponding piperidines **14a** or **14b** in 84% yield with borane-THF. The hydroxyl group was converted to a mesylate resulting in spontaneous quarternization to the bicyclic indolizidine mesylate, which is directly subjected to hydrogenolysis over Pearlman's catalyst giving the BOM-protected 1-hydroxy-8-(phenylsulfonyl)indolizidines **15a** or **15b** (98%). If the hydrogenolysis was carried out under slightly acidic conditions (0.010 mL TFA), cleavage of the BOM protecting group could also be achieved concurrently with N-benzyl cleavage providing a direct synthetic route to **16a** or **16b**. Alternatively, compound **15** may be purified and resubjected to the hydrogenolysis in slightly reduced overall yield. Last, desulfonylation of **16a** or **16b** with sodium amalgam provides (1*S*, 8a*S*)-1-hydroxyindolizidine **4** in 67% yield. The rotation of synthetic **4** obtained from **16a** gave α_D^{22} = +16.4° (0.28, $CDCl_3$) and from **16b** gave α_D^{22} = +18.1° (0.42, $CDCl_3$). These rotations are consistent with enantioenriched (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine [lit α_D^{22}=20.2° (1.03, EtOH)] prepared by an alternative path.[28] These results indicate that lactam stereoisomers **13a** and **13b** were isomeric at the phenylsulfonyl-CH position since desulfonylation led to the same 1-hydroxyindolizidine product.

The 1-hydroxyindolizidine isolated by the two parallel sequences were derivatized with (*S*)-1-napthylethyl isocyanate and analyzed by HPLC (D-phenylglycine; 70:30 hexane/isopropanol) and showed them to be greater than 95% optically pure and chromatographically identical.

This investigation showed that the "remote" dianion addition-cyclization procedure can be extended to include the preparation of enantioenriched indolizidines from imines. Moreover, the highly functionalized, asymmetric lactams **13a** and **13b** may be envisioned as versatile intermediates in the preparation of more complex indolizidine natural products.

EXPERIMENTAL

***(S)-(2,2-Dimethyl-1,3-dioxolan-4-one)-5-ethanoic acid* (7).** To a room temperature suspension of S-malic acid (10 g, 75 mmol) in 25 mL 2,2-dimethoxypropane was added p-TsOH (200 mg, 1.05 mmol) with stirring. After 30 min, the reaction mixture was partitioned between water and CH_2Cl_2, and the aqueous layer extracted twice more with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 7.47 g of a white solid (57%). Colorless needles (6.16 g, 50%) were obtained from recrystallization with 1:1 $CHCl_3/CCl_4$. R_f = 0.42 (ethyl acetate). mp 115-117°C (lit[26]. mp 107-108°C) $[\alpha]_D^{22}$ = +6.9° (0.94, $CHCl_3$). IR 1720 cm^{-1} (COOH), 1790 cm^{-1} (COOR). ^1H NMR: δ 9.98 (br s, 1H), 4.70 (m, 1H), 2.91 (m, 2H), 1.58 (d, 6H, J = 15.3 Hz). ^{13}C NMR: δ 175.1, 172.1, 111.6, 70.6, 36.2, 27.0, 26.0.

***(S)-(2,2-Dimethyl-1,3-dioxolan-4-one)-5-ethanol* (8).** Acid **7** (5.57 g, 32 mmol) was dissolved in 32 mL THF under an Ar blanket and cooled to -78°C. A solution of BH_3·THF (35 mL, 1 M in THF, 35 mmol) was added over 40 min, and allowed to warm to ambient temperature overnight. The solvent was removed in vacuo and the crude mixture purified directly by flash chromatography (100% acetone) to yield 5.49 g of a light yellow oil (>100%). This unstable material was subjected to the next reaction without further purification. R_f = 0.52 (ethyl acetate). $[\alpha]_D^{22}$ = +3.7° (0.76, $CHCl_3$). ^1H NMR: δ 4.65 (m, 1H), 3.85 (t, 2H, J = 6.0 Hz), 3.20 (s, 1H), 2.15 (m, 2H), 1.65 (d, 6H, J = 15.3 Hz). ^{13}C NMR: δ 173.6, 111.0, 72.1, 58.7, 34.0, 27.1, 25.6.

***(S)-3-(Hydroxy)butyrolactone* (9).** Alcohol **8** (5.49 g, 34 mmol) and p-TsOH (50 mg) were dissolved in 100 mL toluene and the mixture heated to 65°C for 1 h. After cooling to room temperature, 75 uL pyridine was added, the mixture filtered, and the solvent removed in vacuo to yield 4.23 g of a yellow oil. The product was purified by flash chromatography (70 g silica, 40% acetone/petroleum ether elution) to provide 2.92 g of a colorless oil (83%). R_f = 0.31 (ethyl acetate). $[\alpha]_D^{22}$ = -20.3° (2.2, methanol). IR 1775 cm^{-1} (C=O). ^1H NMR: δ 4.51 (dd, 1H, J = 8.4, 10.1 Hz), 4.42 (dt, 1H, J = 2.0, 9.0 Hz), 4.20 (m, 1H), 3.70 (bs, 1H), 2.58 (m, 1H), 2.28 (m, 1H). ^{13}C NMR: δ 178.1, 67.4, 65.2, 30.8.

***(S)-3-Hydroxybutyrolactone, benzyloxy methyl ether* (10).** (S)-3-(Hydroxy)butyrolactone **9** (1.68 g, 16.4 mmol) was dissolved in 13 mL 1,2-dimethoxyethane (DME) under N_2, followed by sequential addition of iPr_2NEt (3.37 mL, 19.3 mmol) and benzyl chloromethyl ether (3.6 mL, 25.9 mmol). The reaction mixture was heated at 65°C for 2 h, cooled to 0°C, diluted with water, and extracted thrice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. Removal of solvent provided a yellow oil that was

chromatographed (60 g silica, 30% ethyl acetate/petroleum ether elution) to yield 2.87 g of a clear, colorless oil (79%). R_f = 0.42 (diethyl ether). $[\alpha]_D^{22}$ = -81.67° (1.86, $CHCl_3$). ^1H NMR: δ 7.32 (m, 5H), 5.07 (d, 1H, J = 7.1 Hz), 4.68 (d, 2H, J = 2.3 Hz), 4.87 (d, 1H, J = 7.1 Hz), 4.47 (dd, 1H, J = 8.1, 9.1 Hz), 4.40 (dt, 1H, J = 3.0, 8.8 Hz), 4.20 (dt, 1H, J = 6.5, 9.3 Hz), 2.51 (m, 1H), 2.25 (m, 1H). ^{13}C NMR: δ 174.85, 128.5, 128.4, 128.0, 127.9, 94.0, 70.4, 70.15, 65.1, 29.9.

3-(S)-Hydroxybutyrolactol, 3-benzyloxy methyl ether **(11)**. To a solution of lactone **10** (2.20 g, 9.9 mmol) in 100 mL diethyl ether at -78°C was added 10.0 mL 1.0 M DIBAL-H. The -78°C bath was exchanged for a 0°C bath, and after 4 h, 100 mL 1% NaOH was added and the mixture was extracted thrice with diethyl ether. Removal of solvent followed by column purification (1:1 CH_2Cl_2/petroleum ether) yielded 1.61 g of a clear, colorless oil (73%). R_f = 0.34 (diethyl ether). $[\alpha]_D^{22}$ = +33.7° (2.3, $CHCl_3$). IR 3420 cm-1 (OH), 1785 cm^{-1} (C=O). Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.71; H, 7.35. ^1H NMR: δ 7.30 (m, 5H), 5.36 (m, 1H), 4.83 (m, 2H), 4.63 (m, 2H), 4.21 (m, 1H), 4.07 (m, 2H), 3.04 (s, 1H), 2.10 (m, 2H). ^{13}C NMR: δ 137.6, 128.5, 128.4, 127.9, 127.8, 127.7, 101.05, 96.4, 94.3, 93.7, 81.3, 76.65, 70.1, 69.7, 66.9, 64.8, 29.9, 29.8. (Mixture of α- and β- anomers).

N-benzylidene, 2-(S)-benzyloxymethylether-4-hydroxybutanal **(12)**. A solution of lactol **11** (0.625 g, 2.8 mmol) in 1 mL toluene was added to a stirred solution of benzylamine (0.38 g,1.25 eq) in 2 mL toluene at room temperature for 10 h. The solvent was removed in vacuo and the unreacted benzylamine was removed at 60-80°C (0.5 mm) yielding 0.869 g of a yellow oil (99.5%). This product was not stable and used in the next reaction without purification. R_f = 0.5 (diethyl ether). IR 1660 cm^{-1} (C=N). ^1H NMR (60 MHz): δ 7.35 (d, 10H), 4.85 (s, 2H), 4.65 (s, 2H), 3.5-4.2 (m, 4H), 2.45 (s, 2H), 1.6-2.3 (m, 2H).

1-Benzyl-5-(phenylsulfonyl)-6-[1-benzyloxymethyl-3-hydroxypropyl]-2-piperidone **(13a and 13b).** Imine **12** (0.869 g, 2.8 mmol) was dissolved in 5 mL THF at -78°C and 1.0 mL boron trifluoride etherate (3.0 eq) was added. In a separate flask, 4-PSBA (1.28 g, 5.6 mmol) was dissolved in 75 mL THF at -78°C, and n-BuLi (4.5 mL, 2.5 M, 11.2 mmol) was added dropwise to give a clear, yellow solution. After the imine solution had stirred for 0.5 h, it was transferred to the dianion solution, which discharged the color. The mixture was allowed to equilibrate to 0°C whereupon 1.5 mL TFAA was added. After 0.5 h, the reaction was partitioned between ethyl acetate and saturated Na_2CO_3. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases were dried over Na_2SO_4. Removal of the solvent yielded 1.543 g of a yellow oil (>100%). Column purification (ethyl acetate elution) provided two products of R_f = 0.21 and 0.11 designated as non-polar and polar bands, respectively, in a total yield of 0.395 g (27%). Anal calcd. for $C_{29}H_{33}NO_6S.^1/_2H_2O$: C, 65.39; H, 6.43; N, 2.63. Found: C, 65.68; H, 6.29; N, 2.68. **13a** (non-polar): $[\alpha]_D^{22}$ = -5.3° (0.34, $CHCl_3$). IR 3500 cm^{-1} (OH), 1640 cm^{-1} (C=O, strong). ^1H NMR: δ 7.58 (m, 3H), 7.44 (m, 2H), 7.29 (m, 10H), 5.3 (d, 1H, J = 14.7 Hz), 4.73 (d, 1H, J = 6.8 Hz), 4.56 (d, 1H, J = 6.8 Hz), 4.52 (d, 2H, J = 3.9 Hz), 4.06 (m, 2H), 4.04 (d, 1H, J = 14.8 Hz), 3.53 (m, 3H), 2.53 (m, 2H), 2.13 (m, 2H), 1.54 (m, 2H). ^{13}C NMR: δ 171.0, 136.95, 136.7, 136.6, 136.3, 133.9, 129.3, 129.2, 129.1, 128.9, 128.75, 128.6, 128.5, 128.4, 127.9, 127.7, 127.6, 127.5, 94.7, 76.5, 70.4, 58.8, 58.5, 56.5, 48.3, 33.8, 29.5, 21.1. (Some aromatic resonances unresolved). **13b** (polar): $[\alpha]_D^{22}$ = -63.46° (0.26, $CHCl_3$). White crystals from $CHCl_3$/diethyl ether; mp 153.5-154.5°C. IR 3500 cm^{-1} (OH), 1640 cm^{-1} (C=O, strong). ^1H

NMR: δ 7.44 (m, 15H), 5.61 (d, 1H, J = 14.9 Hz), 4.58 (d, 1H, J = 12.1 Hz), 4.40 (d, 1H, J = 12.0 Hz), 4.19 (m, 1H), 3.99 (d, 1H, J = 14.9 Hz), 3.94 (m, 3H), 3.66 (m, 3H), 2.93 (m, 1H), 2.57 (m, 2H), 2.18 (m, 2H), 1.75 (m, 1H), 1.52 (m, 1H). ^{13}C NMR: δ 170.0, 137.05, 136.95, 136.2, 133.8, 129.3, 129.2, 128.8, 128.7, 128.5, 128.0, 127.8, 127.6, 93.2, 72.8, 70.1, 58.75, 56.5, 53.9, 48.1, 32.5, 28.5, 18.9. (Some aromatic resonances unresolved).

2-(1-Benzyloxymethyl-3-hydroxypropyl)-3-(phenylsulfonyl)-N-benzyl-piperidine **(14a and 14b).** Piperidone **13a** or **13b** (0.105 g, 0.2 mmol) was dissolved in 5 mL THF at 0°C and 0.6 mL of 1M BH_3.THF (3.0 eq) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of 0.25 mL of 5% NaOH and partitioned between equal volumes of CH_2Cl_2 and saturated Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and dried over Na_2SO_4. Removal of solvent in vacuo yielded 95.1 mg of a pale yellow oil. The product was purified on florisil (ethyl acetate with 1% TEA elution) to yield 84.5 mg of a clear, colorless oil (84%). **14a** (non-polar): R_f = 0.34 (diethyl ether). $[\alpha]_D22$ = +13.0° (0.52, $CHCl_3$). HRMS m/z calcd for $C_{29}H_{35}NO_5S$ 509.2236, found 509.2316. ^{1}H NMR: δ 7.99 (d, 2H, J = 7.1 Hz), 7.62 (m, 3H), 7.36 (m, 8H), 7.19 (m, 2H), 4.84 (d, 1H, J = 14.7 Hz), 4.82 (d, 1H, J = 14.7 Hz), 4.56 (d, 1H, J = 11.9 Hz), 4.52 (d, 1H, J = 11.9 Hz), 4.17 (m, 1H), 4.11 (s, 2H), 3.65 (m, 4H), 2.82 (bs, 1H), 2.70 (m, 2H), 1.98 (m, 5H), 1.25 (m, 1H). ^{13}C NMR: δ 139.25 139.1, 137.1, 133.4, 129.1, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 127.8, 127.4, 127.0, 94.5, 76.0, 70.4, 59.2, 58.2, 57.7, 46.25, 45.1, 35.3, 20.95, 16.6. (Some aromatic resonances unresolved). **14b** (polar): R_f = 0.29 (diethyl ether). $[\alpha]_D^{22}$ = -46.5° (0.16, $CHCl_3$). ^{1}H NMR: δ 7.89 (m, 2H), 7.63 (m, 1H), 7.53 (m, 2H), 7.37 (m, 10H), 4.64 (d, 1H, J = 11.9 Hz),4.58 (s, 2H), 4.53 (d, 1H, J = 11.9 Hz), 4.18 (q, 1H, J = 6.0 Hz), 4.09 (d, 1H, J = 13.7 Hz),3.98 (d, 1H, J = 13.7 Hz), 3.70 (m, 2H), 3.58 (t, 1H, J = 4.2 Hz), 3.50 (m, 2H), 2.92 (m, 1H), 2.74 (m, 1H), 2.01 (m, 5H), 1.50 (m, 1H). ^{13}C NMR: δ 138.9, 138.35, 137.4, 133.4, 129.1, 129.0, 128.7, 128.4, 128.3, 127.8, 127.6, 127.1, 94.8, 78.6, 70.3, 59.0, 58.6, 58.5, 57.25, 45.95, 35.0, 21.8, 17.6. (Some aromatic resonances unresolved).

1-(Benzyloxymethyl)-8-(phenylsulfonyl)indolizidine **(15a and 15b).** A general procedure is presented. Piperidine **14a** or **14b** was dissolved in CH_2Cl_2 (approximately 25 mg/mL) at room temperature and K_2CO_3 (2 g), TEA (0.25 mL), and 1 eq. methanesulfonyl chloride were added sequentially. After 2 h, the mixture was filtered and the solvent was removed. The residue was dissolved in methanol (1-2 mL) and hydrogenolyzed (100 mg Pearlman's catalyst, 39 psi H_2). The solution was filtered and the solvent was removed in vacuo. Column purification (florisil, ethyl acetate with 1% TEA elution) provided the products as lightly yellow oils. **15a** (non-polar): 85.4 mg piperidine reacted, 146.1 mg crude mesylate obtained, 69.1 mg crude indolizidine obtained (98%), 27.5 mg pure indolizidine recovered (40%). R_f = 0.31 (ethyl acetate). $[\alpha]_{D23}$ = -65.8° (0.16, $CHCl_3$). HRMS m/z calcd for $C_{22}H_{27}NO_4S$ 401.1661, found 401.1608. ^{1}H NMR: δ 8.00 (m, 2H), 7.65 (m, 3H), 7.38 (m, 5H), 5.08 (d, 1H, J = 7.0 Hz), 5.02 (d, 1H, J = 7.0 Hz), 4.87 (d, 1H, J = 11.9 Hz), 4.69 (d, 1H, J = 11.8 Hz), 4.57 (dt, 1H, J = 2.0, 6.0 Hz), 3.03 (m, 3H), 2.47 (m, 1H), 2.33 (dd, 1H, J = 5.4, 9.9 Hz), 2.16 (m, 2H), 1.95 (m, 2H), 1.64 (m, 2H), 1.32 (dq, 1H, J = 4.5, 12.7 Hz). ^{13}C NMR: δ 138.1 137.6, 133.55, 129.3, 129.2, 128.9, 128.4, 127.7, 127.5, 96.3, 81.6, 70.1, 68.8, 64.7, 52.1, 51.5, 31.6, 27.1, 24.15. (Some aromatic resonances unresolved). **15b** (polar): 171.1 mg piperidine reacted, 234.2 mg crude mesylate obtained, 141 mg crude indolizidine obtained (100%), 72.8 mg pure indolizidine

recovered (52%). R_f = 0.29 (ethyl acetate). $[\alpha]_D^{23}$ = -5.1° (0.22, $CHCl_3$). HRMS m/z calcd for $C_{22}H_{27}NO_4S$ 401.1661, found 401.1663. ^1H NMR: δ 7.95 (m, 2H), 7.62 (m, 3H), 7.37 (m, 5H), 5.09 (d, 1H, J = 7.1 Hz), 5.03 (d, 1H, J = 7.1 Hz), 4.86 (d, 1H, J = 11.8 Hz), 4.72 (d, 1H, J = 11.8 Hz), 4.67 (m, 1H), 3.61 (m, 1H), 3.11 (m, 3H), 2.19 (m, 2H), 1.77 (m, 5H), 1.30 (t, 1H, J = 7.3 Hz). ^{13}C NMR: δ 138.2, 137.9, 133.6, 129.3, 129.05, 128.9, 128.7, 128.3, 128.15, 127.7, 127.6, 127.5, 95.8, 78.4, 70.0, 64.9, 60.1, 52.0, 51.6, 30.4, 25.3, 23.9.

***1-Hydroxy-8-(phenylsulfonyl)-indolizidine* (16a and 16b).** A solution of indolizidine **15a** or **15b** (65.8 mg, 0.16 mmol) in MeOH (3 mL), 20 mg of 10% Pd/C, and 10 uL TFA were stirred under 10-20 psi H_2 at ambient temperature for 10 h. The solution was filtered and the solvent was removed in vacuo to yield 49.3 mg of a brown oil. The product was purified on florisil (ethyl acetate) to give 27.3 mg (54%) of a clear, colorless oil. **16a** (non-polar): R_f = 0.21 (ethyl acetate). $[\alpha]_D^{23}$ = -13.7° (0.8, methanol). HRMS m/z calcd for $C_{14}H_{19}NO_3S$ 281.1086, found 281.1108. ^1H NMR: δ 7.90 (m, 2H), 7.62 (m, 3H), 4.39 (m, 1H), 4.09 (d, 1H, J = 2.8 Hz), 2.95 (m, 3H), 2.42 (q, 1H, J = 8.9 Hz), 2.31 (m, 1H), 2.11 (dd, 1H, J = 6.6, 10.0 Hz), 1.97 (dt, 1H, J = 2.9, 11.6 Hz), 1.83 (m, 1H), 1.69 (m, 2H), 1.45 (m, 1H), 1.28 (dq, 1H, J = 4.4, 12.8 Hz). ^{13}C NMR: δ 134.05, 129.2, 129.1, 75.0, 69.2, 66.3, 52.15, 51.6, 30.3, 26.3, 24.3. (Some aromatic resonances unresolved). **16b** (polar): R_f = 0.14 (ethyl acetate), $[\alpha]_D^{23}$ = + 35.2° (1.1, methanol). HRMS m/z calcd for $C_{14}H_{19}NO_3S$ 281.1086, found 281.1097. ^1H NMR: δ 7.85 (m, 2H), 7.60 (m, 3H), 3.19 (m, 3H), 3.16 (dt, 1H, J = 1.7, 8.9 Hz), 1.82 (m, 10H). ^{13}C NMR: δ 134.05, 129.3, 129.2, 129.1, 128.8, 128.4, 71.3, 67.3, 61.2, 52.9, 51.9, 31.0, 25.6, 24.1.

***(+)-(1S, 8aS)-1-hydroxyindolizidine* (4).** A solution of indolizidine **16a** or **16b** (16.4 mg, 0.058 mmol) in MeOH (2 mL) was reacted with 1 g portions of 6% Na/Hg at room temperature until TLC showed consumption of the starting material. The solution was filtered into a flask containing 1.5 mL methanolic HCL, and the solvent removed in vacuo to provide a yellow solid. The residue was dissolved in water (2 mL) and KOH (0.10 g) was added followed by extraction with diethyl ether (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo to yield 6.8 mg of a light yellow oil (83%). Filtration through florisil to remove the color provided 5.5 mg clear oil (67%). From non-polar **16a**: $[\alpha]_D^{22}$ = +16.4° (0.28, $CDCl_3$); HRMS m/z calcd for $C_8H_{15}NO$ 141.1154, found 141.1157. From polar **16b**: $[\alpha]_D^{22}$ = +18.1° (0.42, $CDCl_3$); HRMS m/z calcd for $C_8H_{15}NO$ 141.1154, found 141.1150. IR 2800 cm^{-1} (Bohlmann band). ^1H NMR: δ 4.00 (m, 1H), 3.47 (s, 1H), 3.00 (m, 2H), 1.77 (m, 10H). ^{13}C NMR: δ 76.4, 71.1, 53.3, 52.5, 31.8, 28.8, 25.0, 24.1.

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