Diastereoselective Route to Piperidine and Indolizidine Scaffolds From Enantiopure Vinylsulfinyl-Containing Amino Alcohols

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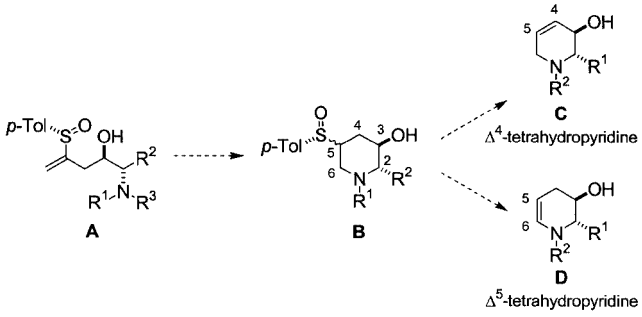
A new route to functionalized piperidine and indolizidine scaffolds, based on the diastereoselective intramolecular Michael cyclization of vinylsulfinyl-containing amino alcohols **1**–**3**, has been developed. Pyrolytic elimination of the resulting cycloadducts resulted in the regioselective formation of the corresponding tetrahydropyridines and indolizidines. The observed regiochemical course of this process can be explained mainly in terms of the steric bias imposed by the disposition of the arylsulfinyl group and the concerted *syn* mechanism accepted for this kind of elimination.

Introduction

Heterocyclic compounds are important structural motifs present both in natural and synthetic compounds.[1] Among the diverse heterocyclic systems, the piperidine ring is specially relevant for its ubiquitous presence in several families of alkaloids,[2] natural peptides,[3−5] and non-proteinogenic amino acids,[6] as well as in many synthetic drugs.[7] Indolizidines share some of the above features, although to a lesser extent, mainly in the field of natural products chemistry.[8,9] Moreover, since indolizidines can also be envisaged as conformationally constrained piperidine analogues, similar synthetic strategies can be planned for both systems.

A few years ago, we started a project addressed towards the development of new building blocks and their application in asymmetric synthesis. As a result, we have recently reported on the preparation of enantiopure 2-sulfinylallyl building blocks and their diastereoselective allylation of aldehydes under Barbier-type conditions[10,11] to afford, inter alia, new polyfunctionalized and versatile (2-sulfinylallyl)-amino alcohols of general structure **A** (Scheme 1).[12] As a result of our ongoing efforts in this field, we now wish to report on a new route to functionalized piperidine and indolizidine scaffolds by suitable chemical manipulation of the above building blocks.



Scheme 1

The general synthetic strategy relies first on an intramolecular 6-*endo*-*trig* conjugate addition of a nitrogen functional group to the vinyl sulfoxide moiety to give sulfinylpiperidines **B**. These synthetic intermediates can be further elaborated by taking advantage of the versatility of the sulfoxide chemistry.[13] In this context, we have explored in this study the pyrolytic elimination from sulfoxides **B** to afford the corresponding tetrahydropyridines **C** or **D** (Scheme 1).

Intramolecular Conjugate Addition of (2-Sulfinylallyl)amino Alcohols 1−3

Although the only literature precedent for a related intramolecular Michael addition of a nitrogen nucleophile to a vinyl sulfoxide requires the use of a trifluoroacetamide to form an "incipient amino anion" as nucleophile,[14,15] we were interested in the exploitation of our *N*-Boc-protected (2-sulfinylallyl)amino alcohols **1**−**3** (Scheme 2) as suitable starting materials for this purpose. We thus designed a "one-pot" procedure based on *N*-Boc removal (HCl/MeOH), followed by neutralization with excess Et_3N and "in situ" cyclization under high-dilution conditions (0.01

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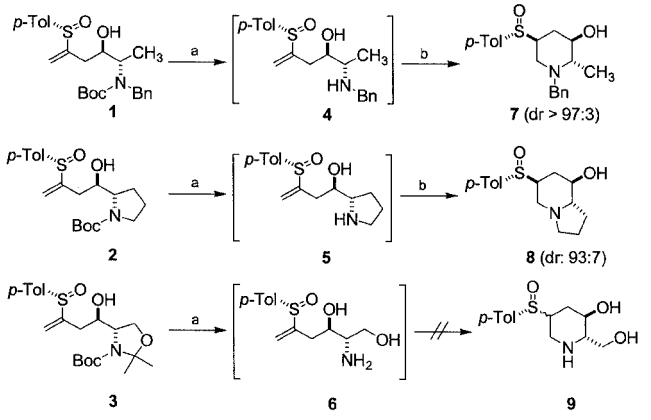
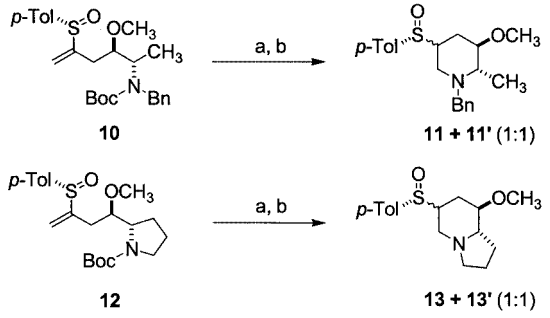
M solution in MeOH) at 50 °C. This procedure afforded sulfinylpiperidine **7** and sulfinylindolizidine **8** in high yields and with high diastereoselectivities from amino alcohols **1** and **2**, respectively. However, amino alcohol **3** failed to react under these conditions, no trace of the expected sulfinylpiperidine **9** being detectable in the complex reaction mixtures obtained[16] (Scheme 2).



Scheme 2. a: AcCl (4 equiv.)/MeOH; b: Et_3N, MeOH (0.01 M solution) (68−70% combined)

The presence of a free homoallylic OH group in the starting amino alcohols **1** and **2** seems to be crucial for the stereochemical outcome of this intramolecular "one-pot" deprotection/conjugate addition process, since the corresponding methoxy derivatives **10** and **12** afforded roughly 1:1 mixtures of cycloadducts (Scheme 3).



Scheme 3. a: AcCl (4 equiv.)/MeOH; b: Et_3N (10 equiv.), MeOH (0.01 M solution) (80−90% combined)

The mainly or exclusively *syn* relationship between *p*-tolylsulfinyl and hydroxy groups found in **7** and **8** can be explained in terms of complete π-facial diastereoselectivity in the conjugate addition step followed by a fast protonation of the carbanion developing at C-5 (Figure 1). This scenario can be set up by assuming a stabilizing intramolecular S=O/OH hydrogen bonding in the most reactive conformation of the putative intermediates (conformation **A**, Figure 1).[17] This stabilization would not be operative in methoxy derivatives **10** and **12**, in which alternative conformations **B** and **C** (Figure 1) would also demand consideration.[18] Conjugated addition in each of these conformations would take place from opposite faces of the vinyl sulfoxide double bond, this explaining the observed lack of diastereoselectivity in the resulting cycloadducts. Apparently, none of these scenarios would be operative from amino diol **6** (Scheme 2), in which different competing intramolecular hydrogen bonding would divert the expected reaction course.

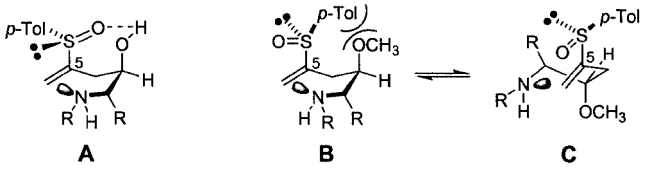
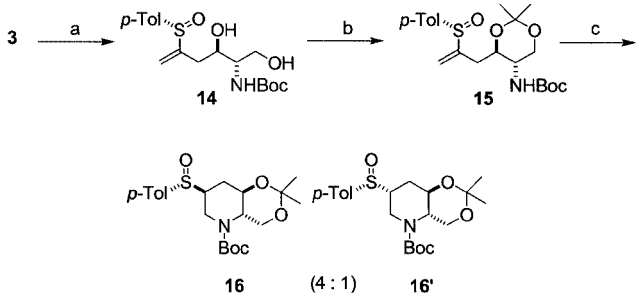


Figure 1. Proposed reactive conformations for intramolecular conjugate additions

It was possible to carry out intramolecular conjugate addition from amino alcohol **3** by an alternative strategy, as shown in Scheme 4. This approach required conversion of **3** into carbamate **14**, and selective ketalization to afford **15**, followed by cyclization under basic conditions to give a 4:1 mixture of easily separable (flash chromatography) diastereomeric piperidines **16** and **16′**.

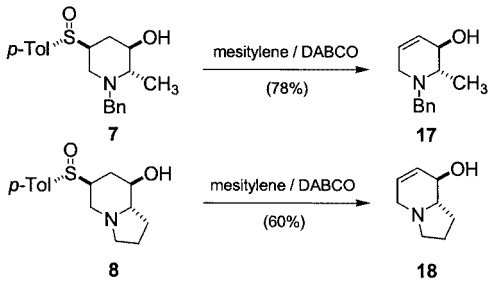


Scheme 4. a: *p*TsOH, MeOH (85%); b: 2,2-DMP, *p*TsOH, acetone (90%); c: NaH, DMF (0 °C) (93%)

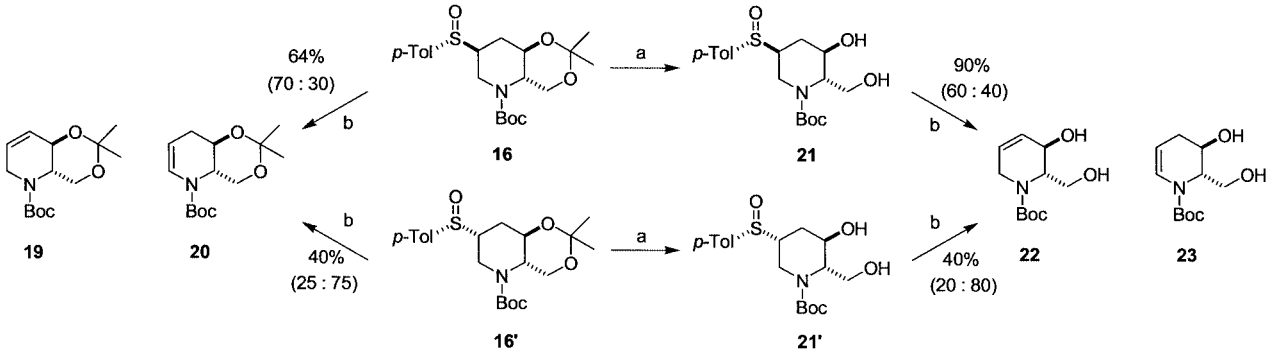
Pyrolytic Elimination of the Sulfoxide Group

Pyrolytic elimination of sulfoxides has considerable precedent in the literature.[19] In general, a concerted *syn* elimination process takes place at moderate to high temperatures in a variety of solvents, usually in the presence of a base, to afford the corresponding olefins in good overall yields.

Initial experiments with sulfinylpiperidines **7** and **8** with DABCO as a base in refluxing toluene resulted in the recovery of unchanged starting material. However, the use of a higher boiling solvent, such as mesitylene, afforded the corresponding Δ^4-tetrahydropyridines **17** and **18** as single regioisomers in acceptable yields (Scheme 5).



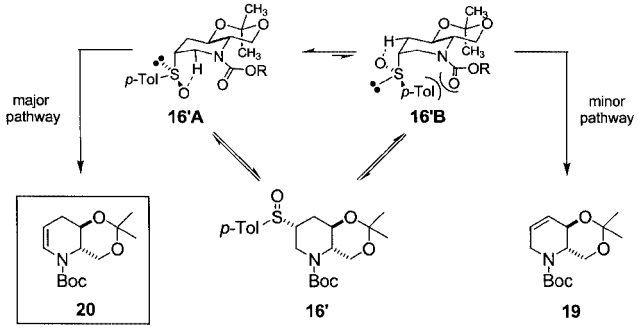
Scheme 5



Scheme 6. a: *p*TsOH/MeOH (80−85%); b: toluene, DABCO, reflux

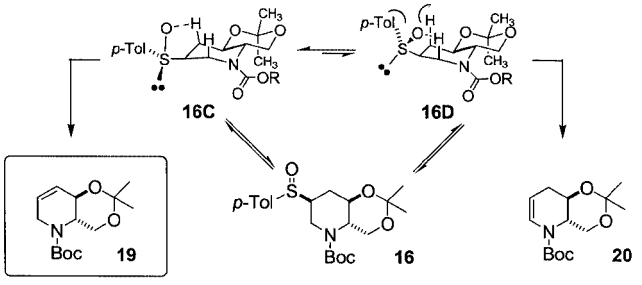
The rigidity of the system does not seem to play a significant role for the regioisomeric ratio, since both piperidine **7** and its conformationally constrained analogue indolizidine **8** afforded a single regioisomer (Scheme 5). Similarly, a comparable regioisomeric distribution was observed between the rigid *N*-Boc-piperidine **16** and its flexible counterpart **21**, as well as between **16′** and **21′** after pyrolytic elimination in refluxing toluene in the presence of DABCO (Scheme 6).

Interestingly, the regioselectivity of this process depends on the configuration of the carbon atom bearing the arylsulfinyl group. The observed regioselectivity towards Δ^5-tetrahydropyridines from α-sulfinyl derivatives **16′** and **21′**[20] can be satisfactorily explained on steric grounds.[21,22] Thus, as demonstrated in Scheme 7 for sulfinylpiperidine **16′**, two limit conformations **16′A** and **16′B** can be postulated to account for the required *syn* elimination processes. According to this model, the dominant formation of Δ^5-tetrahydropyridine **20** would be consistent with the operation of the sterically less hindered conformation **16′A**. The same argument is also valid to account for the dominant formation of Δ^5-tetrahydropyridine **23** from pyrolytic elimination of sulfinylpiperidine **21′**.



Scheme 7. Pyrolytic elimination pathways from **16′**; only hydrogen atoms *syn* to the S=O bond are indicated for clarity

Similarly, the regioselective formation of Δ^4-tetrahydropyridines from β-sulfinyl derivatives **7**, **8**, **16**, and **21** is also consistent with the above arguments. Thus, as shown in Scheme 8 for sulfinylpiperidine **16**, the less hindered conformation **16C** would account for the dominant formation of tetrahydropyridine **19**. Nevertheless, the electronic properties of the nitrogen functional group should also be considered. Thus, while tertiary amines **7** and **8** each afforded the corresponding Δ^4-tetrahydropyridine, **17** and **18**, respectively, as single regioadducts (Scheme 5), carbamates **16** and **21** afforded regioisomeric mixtures of Δ^4- and Δ^5-tetrahydropyridines (Scheme 6). In all cases, however, the observed regiochemistry is as expected, due to the well-known preference of sulfoxides to eliminate away from the heteroatom.[23]



Scheme 8. Pyrolytic elimination pathways from **16**; only hydrogen atoms *syn* to the S=O bond are indicated for clarity

In summary, we have developed a new route to functionalized piperidine and indolizidine scaffolds, based on the diastereoselective intramolecular Michael cyclization of amino alcohols **1**−**3**. In addition, pyrolytic elimination of the resulting cycloadducts resulted in the regioselective formation of the corresponding tetrahydropyridines and indolizidines. The observed regiochemical course of this process can be explained mainly in terms of the steric bias imposed by the disposition of the arylsulfinyl group and the concerted *syn* mechanism accepted for this kind of elimination.

Experimental Section

General Methods: Solvents were distilled prior to use and dried by standard methods.[24] Melting points are uncorrected. FT-IR spectra are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions at 300 MHz (for ^1H) and 75 MHz (for ^{13}C), respectively, unless otherwise indicated. Chemical shifts are reported in δ units [ppm] relative to the singlet at δ = 7.24 ppm of $CDCl_3$ for ^1H and relative to the center line of the triplet at δ =

77.0 ppm of $CDCl_3$ for ^{13}C. Electrospray mass spectra in positive mode were obtained by HPLC-MS, with a mixture of 10 mM ammonium formate/acetonitrile (25:75) at 0.5 mL/min as mobile phase. Samples were analyzed by FIA (flow inject analysis). EIHRMS were carried out at SCSIE, University of Valencia.

Starting Materials: Amino alcohols **1**−**3** were obtained as described in a previous publication.[12]

(2*S*,3*R*,*R*$_S$)-2-Amino-5-[(4-methylphenyl)sulfinyl]-5-hexene-1,3-diol (6): A solution of **3** (170 mg, 0.4 mmol) in MeOH (2 mL) was added at 5 °C to a solution of acetyl chloride (50 μL, 0.7 mmol) in MeOH (1 mL). After stirring for 8 h at room temp., the reaction mixture was treated with 0.5 mL of 2 N HCl in Et_2O and the solvent was removed. The remaining solid was washed with Et_2O (3 × 2 mL), taken up in MeOH, and treated with 80 mg of $NaHCO_3$. After the mixture had been stirred for 1 h at room temp., the solvent was removed and the remaining solid was washed with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried and the solvents were evaporated to give amino diol **6** (98 mg, 91%), which was used without further purification. IR: $\tilde{\nu}$ = 3408, 2923, 1492, 1041 cm^{-1}. ^1H NMR: δ = 1.92 (m, 1 H), 1.93 (s, 3 H), 2.32 (m, 2 H), 2.53 (m, 1 H), 3.53 (m, 4 H), 5.47 (s, 1 H), 5.71 (s, 1 H), 6.84 (AA′ of AA′BB′, *J* = 8.4, 2 H), 7.40 (BB′ of AA′BB′, *J* = 8.4, 2 H) ppm. ^{13}C NMR: δ = 21.3, 33.1, 55.6, 64.2, 72.1, 122.4, 124.9, 129.9, 138.0, 141.7, 151.3 ppm. MS: *m*/*z* = 270 [M + 1].

(2*S*,3*R*,5*S*,*R*$_S$)-1-Benzyl-2-methyl-5-[(4-methylphenyl)sulfinyl]-piperidin-3-ol (7): A solution of sulfinylamino alcohol **1** (250 mg, 0.56 mmol) in MeOH (4 mL) was treated at 0 °C with a solution of AcCl in MeOH (1 mL, prepared from 0.8 mL of acetyl chloride in 10 mL of MeOH). After stirring for 24 h at room temp., the reaction mixture was diluted with 50 mL of MeOH, treated with Et_3N (0.85 mL, 6 mmol) and stirred for an additional 20 h at 50 °C. The reaction solvents were evaporated to dryness and the residue was taken up in Et_2O and washed with satd. aqueous $NaHCO_3$ and brine. After conventional workup, the crude mixture was flash-chromatographed with CH_2Cl_2/MeOH (95:5) to afford 190 mg (70%) of piperidine **7**. R_f = 0.27 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D$ = +100.6 (*c* = 0.15, CH_2Cl_2). IR: $\tilde{\nu}$ = 3391, 3029, 1034 cm^{-1}. ^1H NMR (200 MHz): δ = 1.18 (d, *J* = 6.2 Hz, 3 H), 1.88 (m, 2 H), 2.36 (s, 3 H), 2.40 (m, 1 H), 2.59 (m, 2 H), 2.89 (dd, J_1 = 12.0, J_2 = 4.5, 1 H), 3.38 (m, 2 H), 3.80 (d, *J* = 13.4 Hz, 1 H), 7.17−7.34 (m, 9 H) ppm. ^{13}C NMR: δ = 12.6, 21.4, 27.4, 48.5, 58.1, 59.7, 61.8, 70.4, 124.3−129.7, 138.6, 141.4 ppm. MS: *m*/z = 344 [M + 1]. $C_{20}H_{25}NO_2S$: calcd. C 69.93, H 7.34, N 4.08, S 9.34; found C 70.21, H 7.58, N 4.16.

(6*S*,8*R*,8a*S*,*R*$_S$)-6-[(4-Methylphenyl)sulfinyl]octahydroindolizin-8-ol (8): Treatment of amino alcohol **2** (130 mg, 0.34 mmol) by the procedure described for compound **7** afforded a 93:7 diastereomeric mixture of indolizidines **8** and **8′** (as determined by ^1H NMR of the crude reaction mixture). Isolated yields after flash chromatography with CH_2Cl_2/MeOH (95:5): indolizidine **8** (61 mg, 63%); indolizidine **8′** (4.5 mg, 5%). Mixture of isomers: MS: *m*/*z* = 280 [M + 1]. $C_{15}H_{21}NO_2S$: calcd. C 64.48, H 7.58, N 5.01, S 11.48; found C 64.62, H 7.74, N 5.19.

Compound 8: R_f = 0.20 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D$ = +110.0 (*c* = 0.31, CH_2Cl_2). IR: $\tilde{\nu}$ = 3385, 2953−2799, 1035 cm^{-1}. ^1H NMR: δ = 1.48−1.56 (m, 2 H), 1.74−1.84 (m, 3 H), 1.97−2.15 (m, 2 H), 2.21−2.32 (m, 3 H), 2.42 (s, 3 H), 2.88 (m, 1 H), 3.05 (m, 1 H), 3.14 (m, 1 H), 3.38 (m, 1 H), 7.20−7.45 (m, 4 H) ppm. ^{13}C NMR: δ = 21.0, 21.4, 27.9, 30.4, 51.2, 53.8, 59.6, 69.3, 72.2, 124.5, 129.8, 137.9, 141.7 ppm.

Compound 8′: R_f = 0.25 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_D$ = −60 (*c* = 0.06, CH_2Cl_2). IR: $\tilde{\nu}$ = 3300, 2925, 1031 cm^{-1}. ^1H NMR (200 MHz): δ = 1.45−2.15 (m, 6 H), 2.30 (d, *J* = 13.4 Hz, 2 H), 2.42 (s, 3 H), 2.51 (dd, J_1 = 12.6 J_2 = 6.2, 1 H), 2.77 (broad, 1 H), 3.13 (dd, J_1 = 10.6, J_2 = 6.6, 1 H), 3.48 (d, *J* = 12.6 Hz, 1 H), 3.74 (broad, 1 H), 4.41 (d, *J* = 10.2 Hz, 1 H), 7.32−7.52 (4 H, arom.) ppm. ^{13}C NMR: δ = 20.8, 21.4, 24.7, 30.1, 54.9, 55.0, 61.6, 63.2, 67.9, 124.8, 129.8, 135.2, 141.6 ppm.

***tert*-Butyl (1′*S*,2′*R*,*R*$_S$)-*N*-Benzyl-2-methoxy-1-methyl-4-[(4-methylphenyl)sulfinyl]pent-4-enylcarbamate (10):** A solution of sulfinylamino alcohol **1** (360 mg, 0.81 mmol) in THF (5 mL) was treated under argon with CH_3I (0.5 mL, 1.15 g, 0.81 mmol). The reaction mixture was cooled to 5 °C (ice/water bath), and NaH (210 mg, 0.89 mmol from a 60% mineral oil dispersion) was added portionwise. After stirring for 1 h at room temp., the reaction mixture was quenched with 6 mL of a saturated aqueous NH_4Cl solution. Conventional workup, followed by flash chromatography (hexanes/EtOAc 60:40), afforded carbamate **10** (305 mg, 80%). ^1H NMR: (200 MHz): δ = 1.06 (d, *J* = 6.8 Hz, 3 H), 1.32 and 1.43 (s, 9 H, rotamers), 2.20 (dd, J_1 = 4.0 Hz; J_2 = 15.4 Hz, 1 H), 2.40 (s, 3 H), 3.25 (s, 3 H), 3.44 (broad, 1 H), 3.67 and 3.96 (broad, 1 H, rotamers), 4.32 (m, 2 H), 5.60 and 5.77 (broad, 1 H), 6.13 (s, 1 H), 7.10−7.29 (m, 7 H), 7.51 (2 H) ppm. MS: *m*/*z* = 458 [M + 1].

(2*S*,3*R*,5*RS*,*R*$_S$)-1-Benzyl-3-methoxy-2-methyl-5-[(4-methylphenyl)-sulfinyl]piperidine (11 and 11′): Treatment of compound **10** (51 mg, 0.11 mmol) by the procedure described for compound **7** afforded 32 mg (82%) of a 1:1 mixture of piperidines **11** and **11′**. $C_{21}H_{27}NO_2S$: calcd. C 70.55, H 7.61, N 3.92, S 8.97; found C 70.33, H 7.55, N 4.18. Selected signals of the mixture of isomers: ^1H NMR (200 MHz): δ = 1.25 (d, *J* = 6.2 Hz, 3 H), 1.85 (m, 2 H), 2.30 (s, 3 H), 2.39 (m, 1 H), 2.71 (m, 2 H), 2.82 (dd, 1 H), 3.35 (m, 1 H), 3.40 (m, 1 H), 3.62 (s, 3 H), 3.85 (d, 1 H), 7.2−7.4 (m, 9 H) ppm. ^{13}C NMR: δ = 14.6, 22.5, 26.3, 45.5, 56.3, 55.7, 62.5, 68.4, 76.3, 123.7−131.5, 140.2, 144.4 ppm. MS: *m*/*z* = 358 [M + 1].

***tert*-Butyl (1′*R*,2*S*,*R*$_S$)-2-{1-Methoxy-3-[(4-methylphenyl)sulfinyl]-but-3-enyl}pyrrolidine-1-carboxylate (12):** Treatment of compound **2** (370 mg, 0.97 mmol) by the procedure described for compound **10** afforded 250 mg (65%) of pyrrolidine **12** after flash chromatography with hexanes/EtOAc (60:40). R_f = 0.25 (hexanes/EtOAc, 60:40). $[\alpha]_D$ = +12.56 (*c* = 1.17, acetone). IR: $\tilde{\nu}$ = 2973, 2929, 1691, 1052 cm^{-1}. ^1H NMR (C_6D_6, 60 °C): δ = 1.21−1.77 (m, 4 H), 1.48 (s, 9 H), 1.98 (s, 3 H), 1.98−2.05 (m, 1 H), 2.17 (dd, J_1 = 6.0, J_2 = 15.0, 1 H), 3.15 (m, 4 H), 3.32 (broad, 1 H), 3.72 (broad, 1 H), 4.04 (broad, 1 H), 5.66 (broad, 1 H), 6.12 (broad, 1 H), 6. 90 (AA′, *J* = 8.0 Hz, 2 H), 7.51 (BB′, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (C_6D_6): δ = 21.0, 24.5, 25.0, 28.7, 30.9, 47.3, 59.1, 60.5, 78.8, 80.4, 117.9, 125.7, 129.8, 141.0, 141.8, 154.0, 154.5 ppm. MS: *m*/*z* = 394 [M + 1].

(6*RS*,8*R*,8a*S*,*R*$_S$)-8-Methoxy-6-[(4-methylphenyl)sulfinyl]octahydroindolizine (13 and 13′): Treatment of pyrrolidine **12** (120 mg, 0.42 mmol) by the procedure described for compound **7** afforded 110 mg (90%) of a 1:1 mixture of indolizidines **13** after flash chromatography with EtOAc. HRMS: calcd. for $C_{16}H_{24}NO_2S$ [M^+ + 1] 294.152776; found 294.154161.

Compound 13 [(6*R*) Isomer]: $[\alpha]_D$ = +53.7 (*c* = 0.89, acetone); m.p. 110−112 °C. IR: $\tilde{\nu}$ = 2945, 2786, 1492, 1043 cm^{-1}. ^1H NMR: δ = 1.33 (ddd, J_1 = 5.0, J_2 = 11.1, J_3 = 14.7 Hz, 1 H), 1.55−1.91 (m, 5 H), 2.02−2.1 (m, 1 H), 2.19 (dd, J_1 = 8.7, J_2 = 17.4 Hz, 1 H),

2.32 (dd, J_1 = 2.7, J_2 = 12.6, 1 H), 2.40 (s, 3 H), 2.89 (m, 1 H), 3.12−3.25 (m, 2 H), 3.28 (s, 3 H), 3.76 (d, J = 12.6 Hz, 1 H), 7.31 (AA′, J = 8.4 Hz, 2 H), 7.58 (BB′, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR: δ = 21.1, 21.5, 29.0, 29.9, 49.7, 53.6, 56.9, 64.4, 68.6, 79.0, 125.5, 129.9, 140.4, 142.3 ppm.

Compound 13′ [(6*S*) Isomer]: $[\alpha]_D$ = +64.3 (c = 0.87, acetone); m.p. 78−80 °C. IR: $\tilde{\nu}$ = 2950; 2929, 1492, 1095 cm^{-1}. ^{1}H NMR: δ = 1.39, (dt, J_1 = 12.6, J_2 = 10.8, 1 H), 1.42−1.51 (m, 1 H), 1.60−1.86 (m, 4 H), 2.00−2.23 (m, 2 H), 2.30 (ddt, J_1 = 12.6, J_2 = 4.5, J_3 = 1.2 Hz, 1 H), 2.42 (s, 3 H), 2.82−2.93 (m, 1 H), 2.95−3.04 (m, 3 H), 3.33 (s, 3 H), 7.32 (AA′, J = 8.4, 2 H), 7.78 (BB′, J = 8.4, 2 H) ppm. ^{13}C NMR: δ = 21.2, 21.4, 27.7, 28.4, 51.0, 53.6, 56.8, 60.0, 67.7, 81.3, 124.7, 129.9, 138.2, 141.8 ppm.

***tert*-Butyl (1′*S*,2′*R*,R_S)-2-Hydroxy-1-(hydroxymethyl)-4-[(4-methylphenyl)sulfinyl]pent-4-enylcarbamate (14):** A solution of sulfinylamino alcohol **3** (380 mg, 0.9 mmol) in MeOH (10 mL) was treated at room temp. with *p*TsOH (40 mg, 0.22 mmol). After the mixture had been stirred for 3 h at room temp., the reaction solvents were evaporated to dryness and the residue was taken up in EtOAc and washed with satd. aqueous $NaHCO_3$. Conventional workup, followed by flash chromatography (CH_2Cl_2/MeOH, 97:3), afforded 290 mg (85%) of carbamate **14**. $[\alpha]_D$ = +26.7 (c = 1.20, acetone). IR: $\tilde{\nu}$ = 3382, 2978, 1691, 1043 cm^{-1}. ^{1}H NMR: δ = 1.38 (s, 9 H), 2.28 (dd, J_1 = 7.2, J_2 = 15.0, 1 H), 2.36−2.42 (m, 1 H), 3.21 (broad, 1 H), 3.48 (broad, 1 H), 3.55−3.61 (m, 1 H), 3.73−3.81 (m, 1 H), 3.92 (d, J = 11.4, 1 H), 4.61 (d, J = 6.3 Hz, 1 H), 5.23 (broad, 1 H), 5.89 (s, 1 H), 6.10 (s, 1 H), 7.28 (AA′, J = 8.1, 2 H), 7.43 (BB′, J = 8.1, 2 H) ppm. ^{13}C NMR: δ = 21.4, 28.3, 33.5, 54.7, 62.7, 70.5, 79.5, 124.5, 124.8, 130.0, 137.7, 141.7, 150.5, 155.9 ppm. MS: m/z = 370 [M + 1].

***tert*-Butyl (4*R*,5*S*,R_S)-2,2-Dimethyl-4-{2-[(4-methylphenyl)sulfinyl]-2-propenyl}-1,3-dioxan-5-ylcarbamate (15):** A solution of **14** (120 mg, 310 mmol) in 2,2-dimethoxypropane (5 mL) was treated with *p*TsOH (10 mg, 0.06 mmol) and stirred for 30 min at room temp. The reaction mixture was then concentrated to dryness and the remaining residue was taken up with EtOAc and washed with satd. aqueous $NaHCO_3$. Conventional workup, followed by flash chromatography (CH_2Cl_2/MeOH, 98:2), afforded 110 mg (90%) of compound **15**. $[\alpha]_D$ = +85.9 (c = 0.74, acetone). IR: $\tilde{\nu}$ = 3382, 1691, 1045 cm^{-1}. ^{1}H NMR: δ = 1.36 (s, 3 H), 1.37 (s, 3 H), 1.42 (s, 9 H), 2.00 (dd, J_1 = 9.0, J_2 = 15.3, 1 H), 3.38 (s, 3 H), 2.49 (d, J = 15.3 Hz, 1 H), 3.34−3.42 (m, 1 H), 3.48 (dd, J_1 = 9.0, J_2 = 11.1, 1 H), 3.61 (t, J = 9.0 Hz, 1 H), 3.85 (dd, J_1 = 5.1, J_2 = 11.1, 1 H), 4.77 (d, J = 7.8 Hz, 1 H), 5.72 (s, 1 H), 6.04 (s, 1 H), 7.27 (AA′, J = 8.0, 2 H), 7.48 (BB′, J = 8.0, 2 H) ppm. ^{13}C NMR: δ = 19.4, 21.3, 28.3, 31.6, 49.1, 63.2, 72.5, 79.6, 98.8, 119.4, 125.2, 129.8, 139.0, 141.6, 151.2, 155.2 ppm. MS: m/z = 410 [M + 1].

***tert*-Butyl (4a*S*,7*RS*,8a*R*,R_S)-2,2-Dimethyl-7-[(4-methylphenyl)sulfinyl]hexahydro-5*H*-[1,3]dioxino[5,4-*b*]pyridine-5-carboxylate (16 and 16′):** A solution of compound **15** (70 mg, 0.18 mmol) in DMF (7 mL) was treated at 0 °C with NaH (7 mg of a 60% dispersion in mineral oil, equivalent to 4.2 mg, 0.18 mmol). The mixture was allowed to react at room temp. for 30 min, cooled to 0 °C, quenched with 1 mL of satd. aqueous NH_4Cl solution, and diluted with H_2O (50 mL). Extraction with Et_2O, followed by conventional workup and flash chromatography (hexanes/EtOAc 70:30), afforded 70 mg (93%) of a 4:1 mixture of **16** and **16′**. HRMS (mixture of diastereomers): calcd. for $C_{21}H_{32}NO_5S$ [M$^+$ + 1] 410.200120; found 410.201110.

Compound 16 [(7*S*), Major Diastereomer]: $[\alpha]_D$ = +143.4 (c = 0.94, acetone); m.p. 175−177 °C. IR: $\tilde{\nu}$ = 2979, 1699 (C=O st.), 1380, 1043 (SO st.) cm^{-1}. ^{1}H NMR: δ = 1.35 (s, 3 H), 1.41 (s, 9 H), 1.44 (s, 3 H), 1.70−1.80 (m, 2 H), 2.41 (s, 3 H), 2.66−2.77 (m, 1 H), 2.91−2.98 (m, 1 H), 3.00 (dd, J_1 = 10.8, J_2 = 13.5, 1 H), 3.69 (m, 1 H), 4.22 (dd, J_1 = 5.0, J_2 = 12.0, 1 H), 4.10−4.28 (m, 2 H), 7.32 (AA′, J = 8.0, 2 H), 7.45 (BB′, J = 8.0, 2 H) ppm. ^{13}C NMR: δ = 19.1, 21.4, 26.8, 28.3, 29.3, 49.1, 57.8, 58.3, 62.3, 69.3, 81.1, 98.8, 124.5, 129.9, 137.5, 141.7, 154.2 ppm.

Compound 16′ [(7*R*), Minor Diastereomer]: $[\alpha]_D$ = +80.2 (c = 0.47, $CHCl_3$); m.p. 128−130 °C. IR: $\tilde{\nu}$ = 2977, 1699, 1045 cm^{-1}. ^{1}H NMR: δ = 1.37 (s, 3 H), 1.46 (s, 9 H), 1.51 (s, 3 H), 1.67−1.81 (m, 1 H), 1.89−1.97 (m, 1 H), 2.41 (s, 3 H), 2.91−2.99 (m, 1 H), 3.10 (dt, J_1 = 10.0, J_2 = 5.0, 1 H), 3.40 (dd, J_1 = 4.5, J_2 = 14.4, 1 H), 3.99 (ddd, J_1 = 4.8, J_2 = 10.5, J_3 = 11.7, 1 H), 4.18−4.42 (m, 3 H), 7.33 (AA′, J = 8.0, 2 H), 7.53 (BB′, J = 8.0, 2 H) ppm. ^{13}C NMR: δ = 19.4, 21.5, 28.3, 29.3, 29.8, 40.6, 57.4, 59.9, 62.6, 66.6, 81.0, 99.2, 125.0, 130.1, 138.3, 142.3, 154.6 ppm.

(2*S*,3*R*)-1-Benzyl-2-methyl-1,2,3,6-tetrahydropyridin-3-ol (17): A solution of sulfinylpiperidine **7** (278 mg, 0.81 mmol) and DABCO (95 mg, 0.82 mmol) in mesitylene (80 mL) was heated at 130 °C for 24 h. The reaction solvents were evaporated to dryness and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 96:4) to afford 130 mg (78%) of dehydropiperidine **17**[25] as a brown oil. R_f = 0.2 (CH_2Cl_2/MeOH, 96:4). $[\alpha]_D$ = −12.5 (c = 0.08, CH_2Cl_2). IR: $\tilde{\nu}$ = 3356, 3031, 1666 cm^{-1}. ^{1}H NMR: δ = 0.94 (d, J = 6.8 Hz, 3 H), 2.87−2.93 (m., 1 H), 3.00 (m, 1 H), 3.07 (broad, 1 H), 3.64 (m, 2 H), 3.67 (m, 1 H), 5.81−5.83 (m, 2 H), 7.23−7.35 (m, 5 H) ppm. ^{13}C NMR: δ = 7.7, 47.3, 57.8, 58.6, 68.7, 126.0, 127.3, 128.4, 128.5, 128.8, 129.1 ppm. MS: m/z = 204 [M + 1].

(8*R*,8a*S*)-1,2,3,5,8,8a-Hexahydroindolizin-8-ol (18): Treatment of sulfinylindolizidine **8** (50 mg, 0.18 mmol) according to the experimental procedure described for compound **17** afforded 15 mg (60%) of compound **18**[26] after flash chromatography with CH_2Cl_2/MeOH (90:10). R_f = 0.1 (CH_2Cl_2/MeOH, 90:10). $[\alpha]_D$ = −11.8 (c = 0.28, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3300, 1457, 1417 cm^{-1}. ^{1}H NMR: δ = 1.86−2.36 (m, 6 H), 2.84 (d, J = 15.2, 1 H), 3.21 (m, 1 H), 3.45 (d, J = 14.4 Hz, 1 H), 4.18 (m, 1 H), 5.76 (m, 2 H) ppm. ^{13}C NMR: δ = 28.6, 33.5, 51.8, 54.1, 66.7, 72.0, 126.3, 129.6 ppm. MS: m/z = 140 [M + 1].

***tert*-Butyl (4a*S*,8a*R*)-2,2-Dimethyl-4,4a,6,8a-tetrahydro-5*H*-[1,3]dioxino[5,4-*b*]pyridine-5-carboxylate (19) and *tert*-Butyl (4a*S*,8a*R*)-2,2-Dimethyl-4,4a,8,8a-tetrahydro-5*H*-[1,3]dioxino[5,4-*b*]pyridine-5-carboxylate (20):** A solution of **16** (50 mg, 0.12 mmol) and DABCO (13.8 mg, 0.12 mmol) in toluene (13 mL) was heated at 110 °C for 24 h. The reaction mixture was then concentrated to dryness and the residue was taken up in CH_2Cl_2 and washed with satd. aqueous $NaHCO_3$. Conventional workup afforded 21 mg (64%) of a mixture of **19** and **20**. Flash chromatography (CH_2Cl_2/MeOH, 95.5:0.5) gave 14.7 mg (45%) of **19** (R_f = 0.45) as a colorless oil and 6.3 mg (19%) of **20** (R_f = 0.35) as a colorless oil. Starting from **16′**, a 25:75 mixture of **19** and **20** was obtained in a combined 40% yield.

Compound 19: $[\alpha]_D$ = +74.2 (c = 0.36, CH_2Cl_2). IR: $\tilde{\nu}$ = 2989, 1714, 1655, 1368, 1354 cm^{-1}. ^{1}H NMR (40 °C): δ = 3.02 (m, 1 H), 3.62 (m, 1 H), 4.2 (m, 1 H), 4.31 (m, 2 H), 4.53 (1 H), 5.70 (2 H) ppm. ^{13}C NMR (40 °C): δ = 18.9, 28.4, 29.6, 46.1, 56.0, 62.9, 67.9, 80.5, 125.8, 127.8, 154.3 ppm. MS: m/z = 270 [M + 1]. HRMS: calcd. for $C_{14}H_{23}NO_4$ 269.16271; found 269.16349.

Compound 20: $[\alpha]_D$ = +6.25 (*c* = 0.32, CH_2Cl_2). IR: $\tilde{\nu}$ = 3020, 2900, 1680, 1380 cm^{-1}. ^1H NMR(40 °C): δ = 1.27−1.55 (m, 15 H), 2.01−2.28 (m, 2 H), 3.38 (m, 1 H); 3.85 (m, 1 H), 3.95 (m, 1 H), 4.81 (1 H), 4.85 (m, 1 H), 6.70 (m, 1 H) ppm. ^{13}C NMR (40 °C): δ = 19.3, 28.1, 28.2, 29.1, 102.0, 127.1, 152.8 ppm. MS: *m*/*z* = 270 [M + 1]. HRMS: calcd. for $C_{14}H_{23}NO_4$ 269.16271; found 269.16351.

***tert*-Butyl (2*S*,3*R*,5*S*,R_S)-3-Hydroxy-2-(hydroxymethyl)-5-[(4-methylphenyl)sulfinyl]piperidin-1-carboxylate (21):** A solution of **16** (150 mg, 0.37 mmol) in MeOH (7 mL) was treated at room temp. with a catalytic amount of *p*TsOH. After 1 h, the reaction solvents were evaporated to dryness and the residue was taken up in CH_2Cl_2 and washed with satd. aqueous $NaHCO_3$ and brine. Conventional workup, followed by flash chromatography of the resulting crude product, afforded 110 mg (81%) of piperidine **21**. $[\alpha]_D$ = +136.0 (*c* = 0.12, $CHCl_3$); m.p. 155−157 °C (white solid). IR: $\tilde{\nu}$ = 3413, 2982−2932, 1981, 1025 cm^{-1}. ^1H NMR: δ = 1.48 (s, 9 H), 2.04 (1 H), 2.33 (1 H), 2.40 (s, 3 H), 2.71 (1 H), 3.00 (1 H), 3.41 (1 H), 3.66 (2 H), 3.84 (1 H), 4.25 (1 H), 4.42 (1 H), 5.29 (1 H), 7.24−7.60 (m, 4 H) ppm. ^{13}C NMR: δ = 21.3, 26.3, 28.3, 58.6, 59.6, 60.4, 62.2, 64.4, 80.9, 124.3, 124.7, 129.8, 129.9, 138.1, 141.9, 155.6 ppm. MS: *m*/*z* = 370 [M + 1]. HRMS: calcd. for $C_{18}H_{27}NO_5S$ 369.16099; found 369.16194.

***tert*-Butyl (2*S*,3*R*,5*R*,R_S)-3-Hydroxy-2-(hydroxymethyl)-5-[(4-methylphenyl)sulfinyl]piperidin-1-carboxylate (21′):** Treatment of compound **16′** (90 mg, 0.22 mmol) by the procedure described for **21** afforded 68 mg (84%) of piperidine **21′**. $[\alpha]_D$ = +120.7 (*c* = 0.14, MeOH); m.p. 182−185 C. IR: $\tilde{\nu}$ = 3390, 2949−2830, 1685, 1030 cm^{-1}. ^1H NMR: δ = 1.29 (s, 9 H), 2.08 (2 H), 2.40 (s, 3 H), 2.60−3.15 (m, 3 H), 3.59−3.90 (m, 3 H), 4.15 (m, 2 H), 5.25 (broad, 1 H), 7.20−7.55 (m, 4 H) ppm. ^{13}C NMR: δ = 21.3, 28.3, 53.8, 58.4, 59.7, 62.1, 64.8, 80.6, 124.3, 124.6, 141.6, 141.8, 156.1 ppm. MS: *m*/*z* = 370 [M + 1]. HRMS: calcd. for $C_{18}H_{27}NO_5S$ 369.16099; found 369.16188.

***tert*-Butyl (2*S*,3*R*)-3-Hydroxy-2-(hydroxymethyl)-1,2,3,6-tetrahydropyridin-1-carboxylate (22) and *tert*-Butyl (2*S*,3*R*)-3-Hydroxy-2-(hydroxymethyl)-1,2,3,4-tetrahydropyridin-1-carboxylate (23):** Treatment of sulfinylpiperidine **21** (46 mg, 0.12 mmol) according to the procedure described for compound **16** afforded 25 mg (90% combined yield) of a 60:40 mixture of dehydropiperidines **22** and **23**. In a similar way, sulfinylpiperidine **21′** (75 mg, 0.20 mmol) provided 18 mg (40% combined yield) of a 20:80 mixture of dehydropiperidines **22** and **23**. Flash chromatography ($CHCl_3$/MeOH, 95:5) afforded pure diastereomers:

Compound 22: R_f = 0.25 ($CHCl_3$/MeOH, 95:5). $[\alpha]_D$ = −41.5 (*c* = 0.78, CH_2Cl_2). IR: $\tilde{\nu}$ = 3413, 3000, 1677, 1417, 1007 cm^{-1}. ^1H NMR: δ = 1.25−1.69 (m, 9 H), 2.52−3.62 (m, 3 H), 4.11 (m, 1 H), 4.19−4.40 (m, 1 H), 4.49 (m, 1 H), 5.95 (m, 2 H) ppm. ^{13}C NMR: δ = 28.3, 40.8, 58.1, 61.1, 63.3, 80.5, 124.8, 127.7, 155.2 ppm. MS: *m*/*z* = 230 [M + 1]. HRMS: calcd. for $C_{11}H_{19}NO_4$ 229.13141; found 229.13088.

Compound 23: R_f = 0.35 ($CHCl_3$/MeOH, 95:5). $[\alpha]_D$ = +35.3 (*c* = 0.25, CH_2Cl_2). IR: $\tilde{\nu}$ = 3422, 2975, 1682, 1370 cm^{-1}. ^1H NMR: δ = 1.20−1.70 (broad, 9 H), 1.95 (m, 1 H); 2.05−2.40 (m, 2 H), 3.59 (m, 2 H), 4.19 (m, 1 H), 4.39 (broad, 1 H), 4.78 (m. 1 H), 6.80 (m, 1 H) ppm. ^{13}C NMR: δ = 26.5, 28.2, 31.5, 58.3, 62.8, 81.8, 100.2, 124.1, 156.4 ppm. MS: *m*/*z* = 230 [M + 1]. HRMS: calcd. for $C_{11}H_{19}NO_4$ 229.13141; found 229.13166.

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