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The Intramolecular Schmidt Reaction of Azides with Tertiary Alcohols: Synthesis of 5-(α-Naphthyl)- and 5-(β-Naphthyl)indolizidines as Potential Dopamine Analogs and Non-Opiate Antinociceptive Agents

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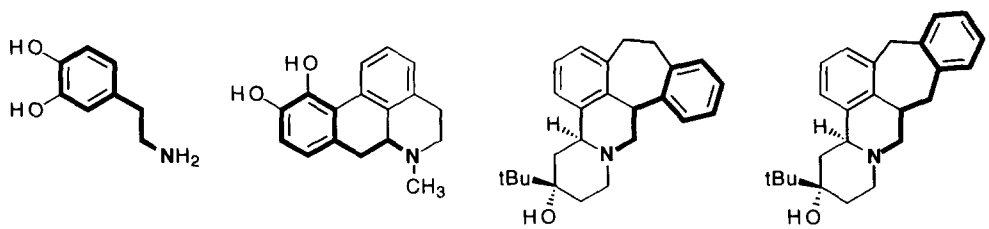
Abstract: Intramolecular Schmidt reaction of the azido alcohols **9**, **11**, and **12** afforded the 5-naphthylindolizidines **10**, **13**, and **14**, respectively. The naphthylmethylamine subunit present in each has an amine and a π-system oriented in a fashion similar to the β-phenethylamine subunit of dopamine and many of its agonists and antagonists. These analogs also closely resemble the bicyclic tertiary amines **8**, which have recently been found to exhibit non-opiate analgesic activity. Testing of **10**, **13**, and **14** for dopaminergic activity is described. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Since dopamine (**1**) was identified as a neurotransmitter in 1958,[1] an enormous amount of research has been carried out on its function and the disorders associated with it, such as Parkinson's disease, Huntington's disease, Tourette's syndrome, and schizophrenia.[2] The development of agonists (e.g. **2**[3]) and antagonists (e.g. **3**,[4,5] **4**[6,7]) which are selective for dopamine receptors continues to be an active area of research, providing compounds that are useful as biochemical probes and as potential therapeutic agents. There is also a need for new compounds that will help to define the structural units which make compounds selective for one of the various dopamine receptor subtypes.[8-10]



1 Dopamine | **2** Apomorphine (Agonist) | **3** Butaclamol (Antagonist) | **4** Isobutaclamol (Antagonist)

Figure 1. *Some common dopamine analogs with the probable pharmacophore emboldened.*

The structural subunit necessary for dopaminergic activity is not well understood. The basic pharmacophore which elicits dopaminergic activity is believed to be an amine (typically tertiary) held at a certain distance from a π-system (such as an aromatic ring).[5,6,10-16] The majority of dopaminergically active

compounds contain a β-phenethylamine (**5**) in an extended conformation (see emboldened substructures in **2** and **3**), although other compounds which contain an appropriately spaced aromatic group and tertiary amine also exhibit activity (e.g. **4**). In order to explore new types of CNS-active amines, we considered that both α-naphthylmethylamine (**6α**) and β-naphthylmethylamine (**6β**) have a π-surface and an amine situated appropriately to mimic an extended β-phenethylamine (Figure 2). We envisioned that incorporation of the naphthalene π-system into a heterocycle such as an indolizidine (e.g. **7**, m = 1, n = 1) might provide a new class of dopaminergic agents (Figure 3). Naphthalene not only provides a larger π-surface for interaction with the receptor,[17] but will also facilitate the synthesis of these compounds (vide infra). The replacement of the β-phenethylamine substructure with a naphthylmethylamine represents a relatively unexplored strategy for the design of potential dopaminergic agents.[18] Thus, we set out to synthesize 5-(α-naphthyl)indolizidines and 5-(β-naphthyl)indolizidines. Further impetus for the synthesis of these compounds was gained by the recent work of Carson, *et. al*, who found that 5-arylindolizidines and related compounds **8** are a new class of non-opiate antinociceptive agents.[19]

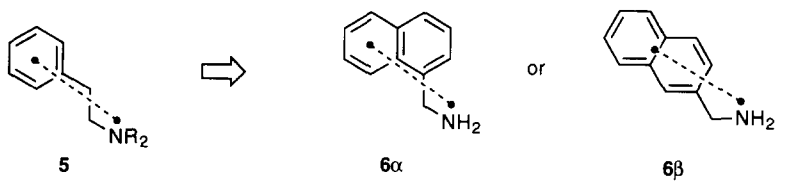


Figure 2. *The distance •-------• between the lone pair and the π-system of β-phenethylamine is also found in α-naphthylmethylamine and β-naphthylmethylamine.*

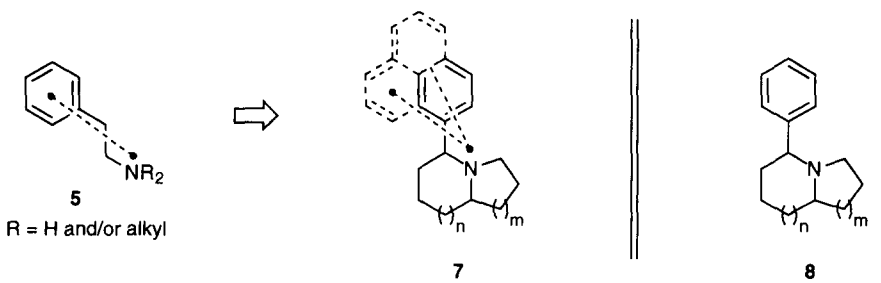
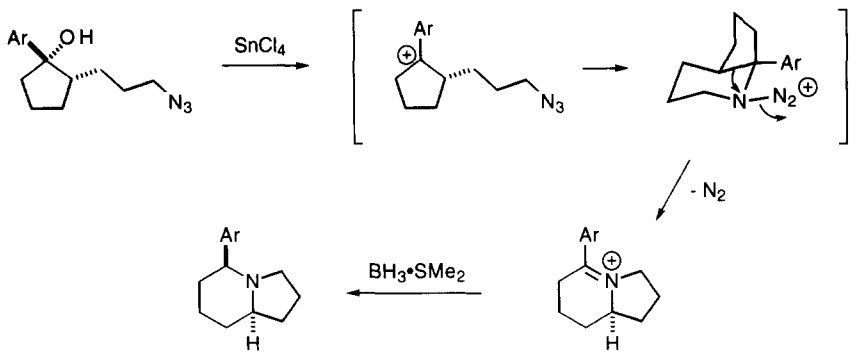


Figure 3. *The β-phenethylamine mimics α-naphthylamine and β-naphthylamine may be incorporated into a fused-bicyclic amine framework (i.e., 7). Similar aryl-substituted fused-bicyclic amines show antinociceptive activity, e.g. 8.*[19]

Previously, we reported the synthesis of bridged and fused 1-azabicyclic compounds by the intramolecular Schmidt reaction of alkyl azides with carbocations.[20-23] We wish to report the successful application of the intramolecular Schmidt reaction to the synthesis of some new 5-naphthylindolizidines which incorporate the pharmacophore for dopaminergic (and potentially antinociceptive) activity in the form of a naphthylmethylamine (Scheme 1).

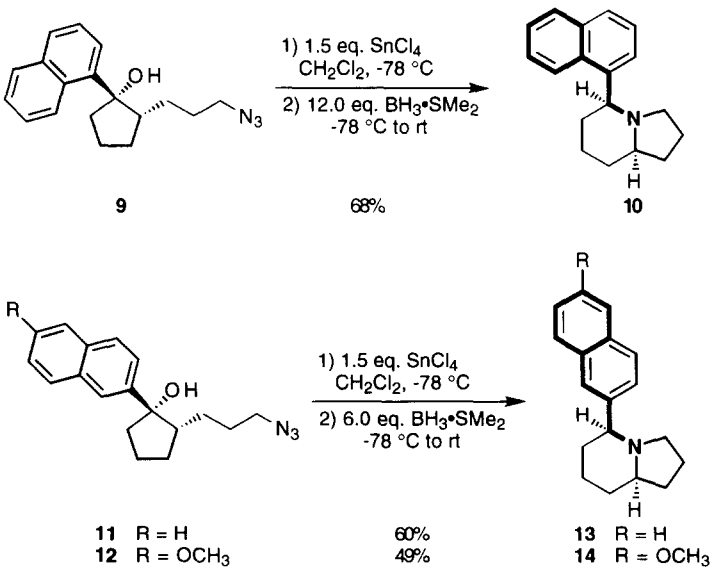


Scheme 1. *The intramolecular Schmidt reaction may be used for the synthesis of 5-arylindolizidines.*

RESULTS AND DISCUSSION

*Synthesis and Conformational Analysis of Analogs **10**, **13**, and **14***

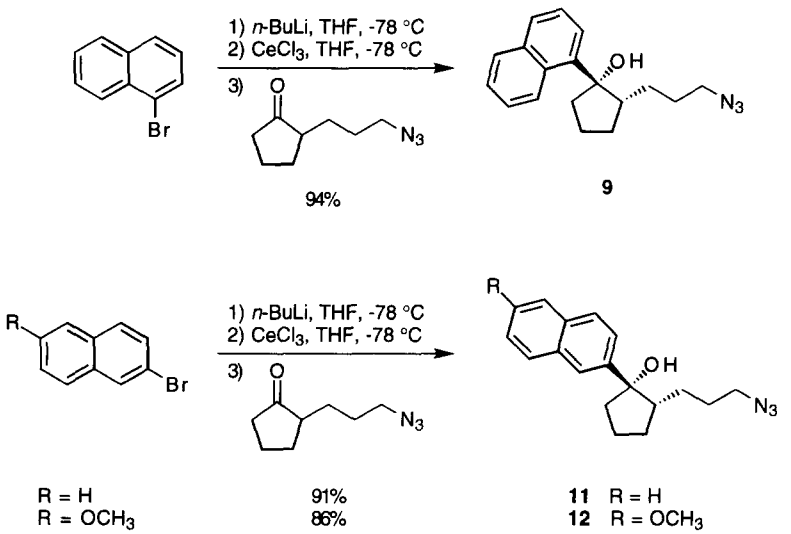
Treatment of azido alcohols **9**, **11**, and **12** with $SnCl_4$ followed by $BH_3{\bullet}SMe_2$[24] gave the 5-naphthylindolizidines **10**, **13**, and **14** (Scheme 2). Intramolecular Schmidt reactions involving benzylic carbocations are particularly facile,[20-22] hence our decision to explore the naphthyl rather than β-phenethylamine substituent. The relative stereochemistries of the racemic indolizidines **10**, **13**, and **14** were based on spectral similarities to known compounds[19,21] and by the presence of Bohlmann bands in their IR



Scheme 2. *Intramolecular Schmidt reactions produce the desired α- and β-naphthylindolizidines.*

spectra,[25,26] a commonly used method for the determination of stereochemistry in indolizidines and related bicyclic structures.[19,21,27] Analysis of the ^{1}H- and ^{13}C-NMR spectra of **10** was complicated by hindered rotation about the bond between the indolizidine and α-naphthyl rings, necessitating spectral measurements at high temperatures. The estimated barrier to rotation about this bond was calculated by molecular mechanics using the MMX force field to be about 28 kcal/mol.

One of the attractive features of the intramolecular Schmidt reaction is the ease of preparation of the precursors (Scheme 3). Thus, cerium chloride-promoted[28] addition of the appropriate lithionaphthalene to 2-(3-azidopropyl)cyclopentanone[21,23] produced the cyclization precursors in excellent yield.



Scheme 3. *Synthesis of the azido alcohols* ***9****,* ***11****, and* ***12****.*

Indolizidines **10**, **13**, and **14** contain the structural subunit postulated to be the pharmacophore in several known dopamine analogs. Figure 3 shows structural overlays of indolizidine **10** with dopamine (**1**) and butaclamol (**3**), and indolizidine **13** with isobutaclamol (**4**).[29] Compounds **10** and **13** (in the conformations shown) closely resemble dopamine and its analogs in the relative disposition of the amine and the aromatic groups.[4-7,11,12,14,15] Furthermore, the large π-surface of the naphthalene should allow for a better interaction with the receptor. However, the cost of attaining these conformations may detract from their binding affinities (vide infra). The conformations of **10** and **13** which best overlayed with butaclamol and isobutaclamol, and which are shown in Figure 3, are 3.85 and 3.78 kcal/mol, respectively, above their minimum energy conformations. The conformations shown for dopamine (**1**), butaclamol (**3**), and isobutaclamol (**4**) are minimized structures.

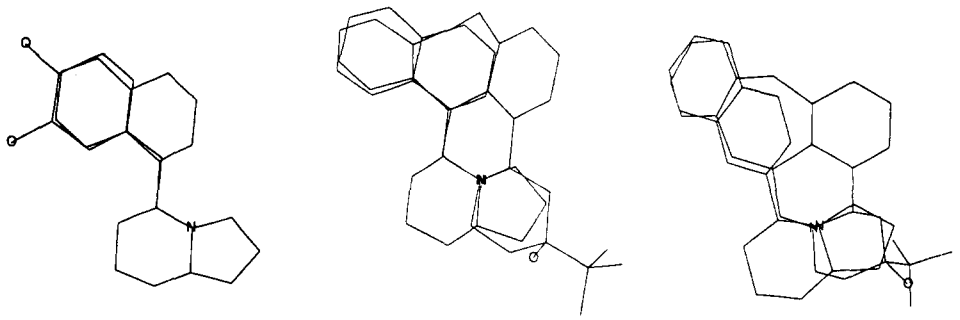


Figure 4. *Structural comparisons[29] of indolizidine 10 with dopamine (1) and butaclamol (3), and indolizidine 13 with isobutaclamol (4).*

Biological Evaluation

The blockage of dopamine and adrenergic receptors has been implicated in the mechanism of action for a number of classes of drugs used for the treatment of both central nervous system and cardiovascular disorders. For example, the ability of antipsychotic drugs to block dopamine D_2 receptors correlates well with their daily efficacious doses. Also, adrenergic drugs have been used in the treatment of hypertension. Many dopaminergic compounds also have significant affinity for adrenergic receptors. Hence, indolizidines **10**, **13** and **14** were evaluated for their ability to bind to dopamine D_2 receptors and to α_1 and α_2 adrenergic receptors. None of these compounds, however, exhibited significant affinity for dopamine D_2 receptors (K_i values > 10μM) as measured by their ability to displace the dopamine antagonist ligand [^{3}H]spiperone from human D_2 receptors expressed in Chinese hamster ovary cells (CHO K1 cells).[30] Similarly, none of the analogs exhibited significant affinity for either α_1 or α_2 adrenergic receptors (K_i values >10 μM) as measured by their ability to displace the α_1 and α_2 adrenergic ligands, [^{3}H]prazosin[31] and [^{3}H]MK912,[32] respectively, from rat cortex.

CONCLUSION

In conclusion, we have synthesized three novel indolizidines that contain the postulated pharmacophore necessary for dopaminergic activity. The synthesis of more refined analogs bearing one or more phenolic groups may provide an extra binding site, although the activity of butaclamol (**3**) and (**4**) seem to indicate that this extra binding is not necessary. The lowered basicity of the benzylic amines of **10**, **13**, and **14** are probably not responsible for reduced binding, since **2-4** are also benzylic amines. The inactivity of these compounds may reflect the difficulty of attaining the conformation required to place the nitrogen and the aromatic ring in the proper orientation.[29] Alternatively, the piperidine ring of **10**, **13**, and **14** may interfere with receptor binding. For example, dopamine, butaclamol, and isobutaclamol (Figure 4) have no atoms in

the area occupied by this piperidine ring. While the current analogs do not show dopaminergic activity, the analgesic activity of **8** is promising precedent for other potential CNS activity of **10**, **13**, and **14**. Testing of these compounds for analgesic activity is underway.

EXPERIMENTAL SECTION

General. Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride under a nitrogen atmosphere. Methanol (MeOH) was distilled from magnesium turnings under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium / benzophenone ketyl under a nitrogen atmosphere. Commercial *n*-butyllithium was purchased from Lithco and titrated, prior to use, versus MeOH using 1,10-phenanthroline as an indicator.[33] All reactions were carried out under an atmosphere of dry nitrogen. Chromatography refers to flash chromatography on silica gel (230-400 mesh). Deactivated silica was prepared by adding 20% by weight of hexamethyldisilazane to a suspension of silica in hexane. After wet-packing the chromatography column, the silica was washed successively with ethyl acetate (EtOAc), 50% EtOAc/hexane, and finally hexane. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 or a Bruker WM-360 spectrometer. J-Modulated Spin Echo Fourier Transform (JMOD) ^{13}C NMR experiments are reported as (+) (for CH_3 and CH) or (-) (for CH_2 and C) and are used as an alternative to off-resonance decoupling experiments. Mass spectral and combustion analyses were performed by the facilities operated by the University of Michigan. Cerium(III) chloride heptahydrate was dried following Imamoto's procedure.[28] Accordingly, freshly ground $CeCl_3 \cdot 7\ H_2O$ was heated (140 °C) with stirring under vacuum overnight, then dry nitrogen was introduced, the flask cooled to 0 °C and THF was added. The resulting suspension was allowed to warm to room temperature and stir overnight before use.

(1*R, 2*R**)-1-(α-Naphthyl)-2-(3-azidopropyl)cyclopentan-1-ol (9).** 1-Bromonaphthalene (0.55 g, 0.37 mL, 2.66 mmol) was dissolved in THF (10 mL), cooled to -78 °C, and *n*-butyllithium (1.1 mL of a 2.4 M solution in hexane, 2.7 mmol) was added. After 30 min, the solution was transferred *via* cannula to a cold (-78 °C) solution of anhydrous $CeCl_3$ (from 1.08 g of $CeCl_3 \cdot 7\ H_2O$, 2.90 mmol) in THF (20 mL). After 30 min, a solution of 2-(3-azidopropyl)cyclopentanone[21,23] (0.30 g, 1.8 mmol) in THF (10 mL) was added in a dropwise fashion *via* syringe over a 20 min period. The resulting solution was stirred for 3 h, then warmed to 0 °C and quenched with saturated aqueous KH_2PO_4 (30 mL). The resulting mixture was extracted with ether (3 x 30 mL), and the combined organic extracts were washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), then dried ($MgSO_4$) and concentrated to give 0.76 g of crude product. Chromatography (5% EtOAc/hexane) gave 0.49 g (94%) of the title compound as a clear, colorless oil, R_f = 0.11 (5% EtOAc/hexane): ^1H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, J = 6.8 Hz, 1 H), 7.78 (d, J = 6.8 Hz, 1 H), 7.70 (d, J = 6.8 Hz, 1 H), 7.30-7.55 (m, 4 H), 3.06-3.22 (m, 2 H, -CH_2-N_3), 2.19-2.60 (m, 3 H), 1.89-2.12 (m, 3 H), 1.42-1.87 (m, 5 H), 1.16-1.40 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 140.76 (-), 134.84 (-), 131.37 (-), 129.00 (+), 128. 32 (+), 126.76 (+), 125.16 (+), 125.08 (+), 124.91 (+), 123.05 (+), 84.61 (-), 51.43 (-), 48.13 (+), 41.79 (-), 29.79 (-), 27.73 (-), 25.82 (-), 21.97 (-); IR ($CDCl_3$) 3599 (s), 3096 (w), 3052 (m), 2944 (s), 2870 (s), 2099 (s), 1598 (m), 1453 (m), 1346 (m), 1262 (s), 1153 (m), 1015 (m) cm^{-1}; MS (EI, 70

eV) *m/z* (rel int) 295 (M^+, 8.3), 196, (2.6), 183 (10.1), 170 (15.5), 155 (36.7), 144 (59.2), 127 (16.9), 115 (36.8), 83 (100), 70 (23.8); HRMS (EI, 70 eV) calcd for $C_{18}H_{21}N_3O$ 295.1685, found 259.1699.

(5*R, 8a*R**)-5-(α-Naphthyl)indolizidine (10).** Stannic chloride (1.0 mL of a 1.0M solution in CH_2Cl_2, 1.0 mmol) was added to a cold (-78 °C) solution of azide **9** (0.20 g, 0.68 mmol) in CH_2Cl_2 (10 mL). After 12 min, BH_3•SMe_2 (4.0 mL of a 2.0M solution in THF, 8.0 mmol) was added in a dropwise fashion. After 2 h, the solution was allowed to warm to room temperature and stirred overnight. Aqueous 15% NaOH (25 mL) was added, resulting in the formation of a dark precipitate. The mixture was filtered through Celite and the filtrate was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with water (25 mL) and brine (25 mL), then dried ($MgSO_4$) and concentrated to give 0.20 g of crude product. Chromatography on deactivated silica (5% EtOAc/hexane) gave 115 mg (68%) of the title compound as a clear, colorless oil, R_f = 0.08 (5% EtOAc/hexane, normal silica): ^{1}H NMR (DMSO-d_6, 360 MHz, 100 °C[34]) δ 8.55 (br d, J = 6.1 Hz, 1 H), 7.89 (m, 1 H), 7.76 (d, J = 8.1 Hz, 1 H), 7.62 (d, J = 6.8 Hz, 1 H), 7.41-7.52 (m, 3 H), 3.81 [dd, J = 10.3, 2.9 Hz, 1 H, -C*H*(Ar)-N], 2.84-3.12 (br s, 1 H, N-CH*H*-), 2.72 [dt, J = 2.4, 8.5 Hz, 1 H, N-C*H*H-], 2.09-2.21 [m, 1 H, CH_2-C*H*(N)-CH_2], 1.25-1.97 (m, 10 H); ^{13}C NMR (DMSO-d_6, 90 MHz, 90-93 °C[34]) δ 139.50, 133.20, 130.34, 128.01, 126.26, 124.93, 124.89, 124.60, 124.20, 122.98, 65.10 [small, broad; -*C*H(Ar)-N], 64.07 [CH_2-*C*H(N)-CH_2], 51.03 (N-*C*H_2-), 33.86, 29.95, 29.84, 24.24, 19.60; IR (neat) 3046 (m), 2930 (s), 2853 (m), 2783 (m), 2737 (w), 1507 (m), 1456 (m), 1437 (m), 1381 (m), 1167 (m), 1128 (m), 1051 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 251 (M^+, 100), 236, (6.2), 222 (30.9), 208 (38.9), 182 (13.2), 167 (22.9), 153 (42.2), 141 (29.6), 124 (80.1), 96 (23.7), 70 (20.4); HRMS (EI, 70 eV) calcd for $C_{18}H_{21}N$ 251.1674, found 251.1663. Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.36; H, 8.51; N, 5.39. The stereochemistry of **10** is supported by the Bohlmann band patterns in the IR spectrum,[25] data which is commonly used to assign the stereochemistry of similar indolizidines.[19,27]

(1*R, 2*R**)-1-(β-Naphthyl)-2-(3-azidopropyl)cyclopentan-1-ol (11).** 2-Bromonaphthalene (0.72 g, 3.47 mmol) was dissolved in THF (15 mL), cooled to -78 °C, and *n*-butyllithium (1.4 mL of a 2.4M solution in hexane, 3.4 mmol) was added. After 30 min, the solution was transferred *via* cannula to a cold (-78 °C) solution of anhydrous $CeCl_3$ (from 1.29 g of $CeCl_3$ • 7 H_2O, 3.45 mmol) in THF (30 mL). After 30 min, a solution of 2-(3-azidopropyl)cyclopentanone[21,23] (0.39 g, 2.31 mmol) in THF (10 mL) was added in a dropwise fashion *via* syringe over a 20 min period. The resulting solution was stirred for 2 h, then warmed to 0 °C and quenched with saturated aqueous KH_2PO_4 (40 mL). The mixture was stirred at 0 °C for 10 min, then extracted with ether (3 x 30 mL). The combined organic extracts were washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), then dried ($MgSO_4$) and concentrated to give 0.83 g of crude product. Chromatography (5% EtOAc/hexane) gave 0.62 g (91%) of a single diastereomer of the title compound as a clear, light yellow oil, R_f = 0.03 (5% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ7.97 [d, J = 0.70 Hz, 1 H, C-C*H*=C-C(C)$_2$OH], 7.79-7.88 (m, 3 H), 7.41-7.53 (m, 3 H), 3.05-3.20 (m, 2 H, -C*H*$_2$-N_3), 1.79-2.35 (m, 6 H), 1.48-1.74 (m, 3 H), 1.22-1.48 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 143.27 [(-), *C*-C(C)$_2$-OH], 133.19 (-), 132.26 (-), 128.00 (+), 127.85 (+), 127.40 (+), 126.03 (+), 125.62 (+), 123.48 (+), 123.42 (+), 84.04 [(-), Ar-*C*(C)$_2$-OH], 51.68 [(-), -*C*H_2N_3], 50.86 [(+), (CH_2)$_2$*C*H-C(Ar)OH], 43.92 (-), 30.03 (-), 27.95 (-), 25.48 (-), 21.96 (-); IR ($CDCl_3$) 3600 (s), 3060 (m), 2942 (s), 2870 (s), 2100 (s), 1632 (w), 1601

(w), 1506 (w), 1453 (m), 1350 (s), 1272 (s), 1151 (m), 1019 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 295 (M^+, 8.1), 267 (8.6), 194 (11.6), 183 (19.8), 170 (37.2), 155 (43.4), 144 (100), 127 (30.3), 115 (52.5), 70 (68.8); HRMS (EI, 70 eV) calc for $C_{18}H_{21}N_3O$ 295.1685, found 295.1688.

(5*R, 8a*R**)-5-(β-Naphthyl)indolizidine (13).** Stannic chloride (1.2 mL of a 1.0M solution in CH_2Cl_2, 1.2 mmol) was added to a cold (-78 °C) solution of azide **11** (0.25 g, 0.84 mmol) in CH_2Cl_2 (15 mL). After 15 min, BH_3•SMe_2 (2.5 mL of a 2.0 M solution in THF, 5.0 mmol) was added in a dropwise fashion, stirred 2 h, then allowed to warm to room temperature. After stirring overnight, aqueous 15% NaOH (25 mL) was added, resulting in the formation of a dark precipitate. The mixture was filtered through Celite and the filtrate was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with water (25 mL) and brine (25 mL), then dried ($MgSO_4$) and concentrated to give 0.21 g of crude product. Chromatography on deactivated silica (5% EtOAc/hexane) gave 127 mg (60%) of the title compound as a clear, colorless oil, R_f = 0.07 (5% EtOAc/hexane, normal silica): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74-7.86 (m, 4 H), 7.53 [dd, *J* = 8.5, 1.6 Hz, 1 H, (C)(N)CH-C=C*H*-CH], 7.38-7.49 (m, 2 H), 3.12 [dd, *J* = 10.4, 3.2 Hz, 1 H, -C*H*(Ar)-N], 2.72-2.82 (m, 1 H, N-C*H*H-), 1.97-2.08 [m, 1 H, CH_2-*CH*(N)-CH_2], 1.21-1.96 (m, 11 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 142.29 [(-), *C*-CH(C)N], 133.41 (-), 132.77 (-), 127.74 (+), 127.63 (+), 127.47 (+), 125.82 (+), 125.63 [br, (+)], 125.20 (+), 69.74 [(+), -*C*H(Ar)-N], 65.00 [(+), CH_2-*C*H(N)-CH_2], 52.64 [(-), N-*C*H_2-], 35.41 (-), 30.80 (-), 30.47 (-), 25.13 (-), 20.28 (-); IR ($CDCl_3$) 3059 (m), 2967 (s), 2936 (s), 2859 (m), 2791 (s), 2732 (w), 1601 (w), 1506 (m), 1440 (m), 1356 (m), 1304 (m), 1205 (m), 1164 (m), 1126 (m), 1059 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 251 (M^+, 91.2), 236, (7.9), 222 (39.0), 209 (31.6), 182 (33.7), 167 (27.2), 154 (68.7), 141 (43.5), 124 (100), 96 (31.3), 70 (28.5); HRMS (EI, 70 eV) calcd for $C_{18}H_{21}N$ 251.1674, found 251.1662. The stereochemistry of **13** is supported by the Bohlmann band patterns in the IR spectrum,[25] data which is commonly used to assign the stereochemistry of similar indolizidines.[19,27]

(1*R* *, 2*R)-1-(6-Methoxy-β-naphthyl)-2-(3-azidopropyl)cyclo-pentan-1-ol (12).** 2-Bromo-6-methoxynaphthalene[35] (0.80 g, 3.38 mmol) was dissolved in THF (15 mL), cooled to -78 °C, and *n*-butyllithium (1.3 mL of a 2.4M solution in hexane, 3.2 mmol) was added. After 30 min, the solution was transferred *via* cannula to a cold (-78 °C) solution of anhydrous $CeCl_3$ (from 1.26 g of $CeCl_3$• 7 H_2O, 3.37 mmol) in THF (35 mL). After 30 min, a solution of 2-(3-azidopropyl)cyclopentanone[21,23] (0.38 g, 2.29 mmol) in THF (10 mL) was added in a dropwise fashion *via* syringe over a 20 min period. The resulting solution was stirred for 3.5 h, then warmed to 0 °C and quenched with saturated aqueous KH_2PO_4 (40 mL). The mixture was stirred at 0 °C for 10 min, then extracted with ether (3 x 30 mL). The combined organic extracts were washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), then dried ($MgSO_4$) and concentrated to give 0.92 g of crude product. Chromatography (10% EtOAc/hexane) gave 0.64 g (86%) of a single diastereomer of the title compound as a white solid, R_f = 0.11 (10% EtOAc/hexane): mp = 84-86 °C; ^1H NMR ($CDCl_3$, 360 MHz) 7.88 [d, *J* = 1.6 Hz, 1 H, C-C*H*=C-C(C)$_2$OH], 7.73 (d, *J* = 8.7 Hz, 1 H), 7.71 (d, *J* = 8.5 Hz, 1 H), 7.45 (dd, *J* = 8.7, 1.9 Hz, 1 H), 7.09-7.18 (m, 2 H), 3.91 (s, 3 H, Ar-OC*H*$_3$), 3.03-3.20 (m, 2 H, -C*H*$_2$-N_3), 1.76-2.30 (m, 6 H), 1.45-1.71 (m, 3 H), 1.25-1.44 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 157.56 [(-), CH_3O*C*], 140.90 [(-), *C*-C(C)$_2$-OH], 133.27 [(-), *C*-CH=COCH_3)], 129.51 (+), 128.60 [(-), CH_3OC-CH=CH-*C*], 126.76 (+), 123.96 (+), 123.33 (+), 118.86 [(+), CH_3OC-*C*H=CH-], 105.45

[(+), C-*C*H-COCH$_3$], 83.97 [(-), Ar-*C*(C)$_2$-OH], 55.29 [(+), -O*C*H$_3$], 51.59 [(-), -*C*H$_2$N$_3$], 50.69 [(+), (CH$_2$)$_2$*C*H-C(Ar)OH)] 43.71 [(-), -*C*H$_2$-C(Ar)OH], 29.80 (-), 27.86 (-), 25.33 (-), 21.74 (-); IR ($CDCl_3$) 3600 (s), 3061 (m), 3006 (m), 2940 (s), 2869 (s), 2096 (s), 1635 (m), 1606 (m), 1505 (m), 1486 (m), 1439 (w), 1268 (s), 1206 (s), 1033 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 325 (M$^+$, 48.8), 297 (8.1), 278 (20.7), 213 (52.4), 200 (91.3), 185 (100), 174 (30.8), 157 (35.1), 115 (20.0), 91 (30.5), 70 (57.2); HRMS (EI, 70 eV) calc for $C_{19}H_{23}N_3O_2$ 325.1790, found 325.1795. Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.70; H, 7.29; N, 12.71.

(5*R, 8a*S**)-5-(6-Methoxy-β-naphthyl)indolizidine (14).** Stannic chloride (1.4 mL of a 1.0 M solution in CH_2Cl_2, 1.4 mmol) was added to a cold (-78 °C) solution of azide **12** (0.31 g, 0.94 mmol) in CH_2Cl_2 (25 mL). After 10 min, BH_3·• SMe_2 (2.8 mL of a 2.0 M solution in THF, 5.6 mmol) was added in a dropwise fashion, stirred 2 h, then allowed to warm to room temperature. After stirring overnight at room temperature, aqueous 15% NaOH (25 mL) was added, resulting in the formation of a dark precipitate. The mixture was filtered through Celite and the filtrate was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with water (25 mL) and brine (25 mL), then dried ($MgSO_4$) and concentrated to give 0.23 g of crude product. Chromatography on deactivated silica (5% EtOAc/hexane) gave 131 mg (49%) of the title compound as colorless crystals, R_f = 0.03 (5% EtOAc/hexane, regular silica): mp = 123-125 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.65-7.73 (m, 3 H), 7.49 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.08-7.14 (m, 2 H), 3.90 (s, 3 H, Ar-OC*H*$_3$), 3.07 (dd, *J* = 10.5, 3.2 Hz, 1 H, -C*H*Ar-N), 2.70-2.79 (m, 1 H, N-C*H*H-), 1.94-2.05 [m, 1 H, CH$_2$-C*H*(N)-CH$_2$], 1.09-1.93 (m, 11 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 157.31 [(-), CH$_3$O*C*], 140.06 [(-), *C*-CH(C)N], 133.83 [(-), *C*-CH=COCH$_3$], 129.21 (+), 128.89 [(-), CH$_3$OC-CH=*C*H-*C*], 126.68 (+), 126.47 (+), 125.58 (+), 118.54 [(+), CH$_3$OC-*C*H=CH-], 105.58 [(+), C-*C*H-COCH$_3$], 69.77 [(+), -*C*H(Ar)-N], 65.19 [(+), CH$_2$-*C*H(N)-CH$_2$], 55.27 [(+), -O*C*H$_3$], 52.76 [(-), N-*C*H$_2$-], 35.38 (-), 30.90 (-), 30.52 (-), 25.22 (-), 20.30 (-); IR ($CDCl_3$) 3060 (m), 3005 (m), 2938 (s), 2858 (s), 2791 (s), 2727 (m), 2705 (m), 1635 (s), 1607 (s), 1506 (s), 1484 (s), 1464 (s), 1390 (s), 1303 (s), 1265 (s), 1218 (s), 1174 (s), 1121 (s), 1033 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 281 (M$^+$, 100), 266 (12.8), 252 (44.7), 239 (43.0), 212 (34.2), 198 (33.5), 184 (80.6), 171 (51.6), 141 (34.4), 124 (79.1), 96 (33.5); HRMS (EI, 70 eV) calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1774. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.62; H, 8.31; N, 4.99. The stereochemistry of **14** is supported by the Bohlmann band patterns in the IR spectrum,[25] data which is commonly used to assign the stereochemistry of similar indolizidines.[19,27]

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