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A Schmidt route to 1-azabicyclo[x.y.0]alkanes: a comparison of carbocation stabilizing groups

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Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

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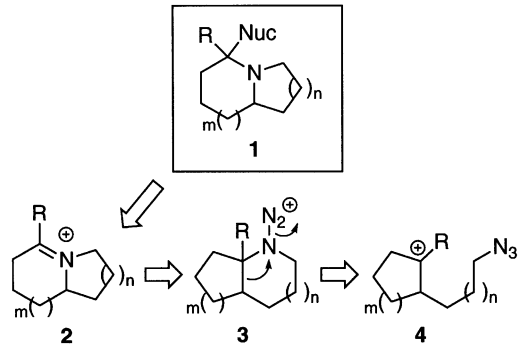
Abstract—The intramolecular Schmidt reactions of tertiary alkyl, tertiary benzylic, tertiary propargylic, and tertiary allylic carbocations with tethered azides are reported. Using product analysis and deuterium labeling studies, the role of cation rearrangement prior to Schmidt reaction is reported.

1. Introduction

As part of our program on the Schmidt reaction of aliphatic azides with carbocations,[1,2] we wished to further explore the use of this chemistry for the generation of indolizidines, quinolizidines, and other 1-azabicyclo[x.y.0]alkanes (**1**). One possible Schmidt route to such heterocycles would be the intramolecular capture of an azide with a carbocation to produce a fused-bicyclic aminodiazonium ion (e.g., **4**→**3**, Scheme 1). Rearrangement of **3** to the iminium ion **2** followed by reaction with a nucleophile should produce the target azabicycles **1**. Several concerns arise. First, how stabilized must the carbocation **4** be to allow this chemistry? Second, will the carbocation rearrange prior to cyclization, perhaps affording other Schmidt products? Third, how does the tether length between the azide and the cation affect the outcome of the cyclization? For example, a longer tether length may slow the initial cyclization enough to allow rearrangement or decomposition of the cation. Herein we report studies on these factors.[3] A key finding is that cation rearrangment prior to cyclization may be expressed to varying degrees depending on the nature of the cation stabilizing group R and the length of the tether between the azide and the cation.



Scheme 1. Target structure and Schmidt strategy.

2. Results and discussion

A representative selection of carbocation precursors **6**–**10**, **16**, and **18** were synthesized as shown in Scheme 2, where the group R was chosen to be alkyl, aryl, alkenyl, and propargyl. Should the initially formed cation cyclize successfully with the pendant azide, a six-membered ring aminodiazonium ion would result in each case except for **16**, which was designed to test for the ability to form a seven-membered ring aminodiazonium ion intermediate. The addition of organomagnesium and organolithium reagents to the azido ketones **5**[3] and **17** was best accomplished with the assistance of $CeCl_3$.[4] The addition of phenylmagnesium bromide to the azido ketone **15** did not require the cerium method. The azido alcohols **6**, **7**, **10**, **16**, and **18** were obtained as single diastereomers, whereas **8** and **9** were each accompanied by a minor diastereomer, presumably involving addition of the organometallic from the face of the carbonyl group *syn* to the azidoalkyl side chain.

The Schmidt reactions of the carbocation precursors **6**–**10**, **16**, **18**, and the alkene **19**, derived from elimination of **7**, are shown in Table 1. Ionization of the alcohols to the carbocations was performed with either stannic chloride or triflic acid, whereas cation formation from the alkene **19** required

Keywords: Schmidt reaction; carbocation; azide; aminodiazonium ion; indolizidine; quinolizidine.

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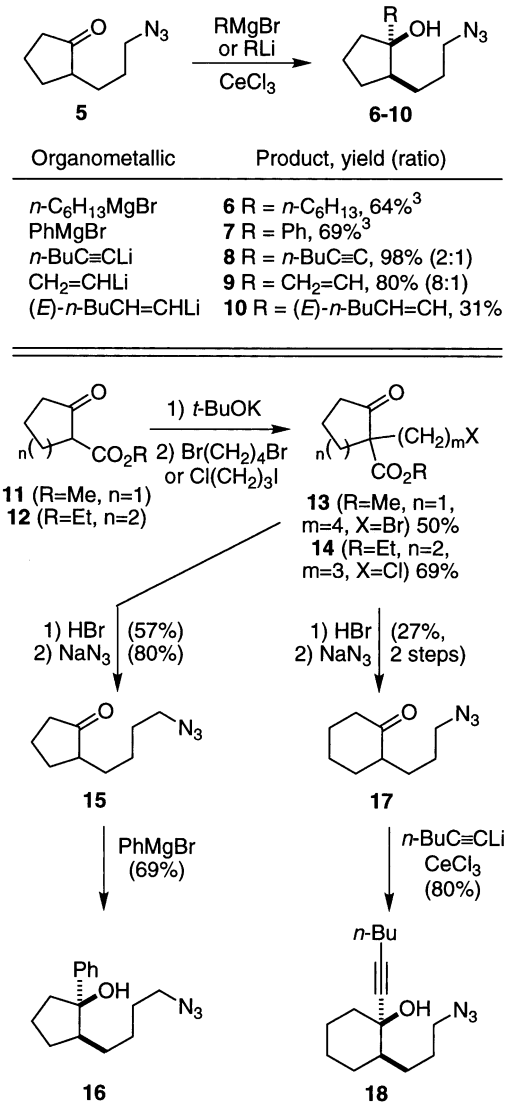


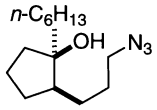
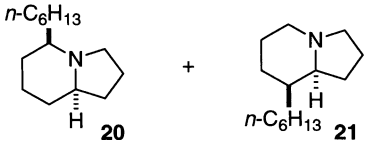
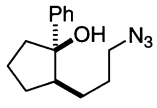
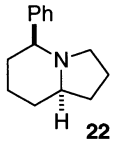
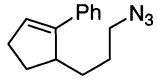
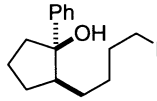
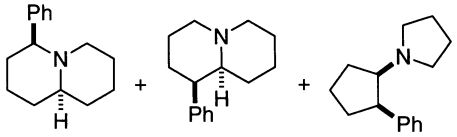
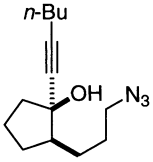
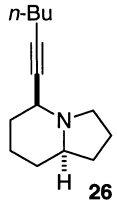
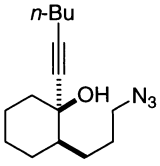
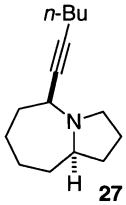
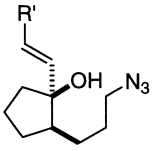
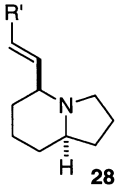
Scheme 2. Synthesis of cation precursors.

protic acid. In all cases, the resultant iminium ions (see **2** in Scheme 1) were reduced with a hydride reagent ($NaBH_4$ or $BH_3{\cdot}Me_2S$) to afford the heterocycles shown. Successful Schmidt reactions were observed where alkyl, aryl, and propargyl groups were present at the site of carbocation generation, whereas only decomposition was observed in attempted Schmidt reactions of the alkenyl systems **9** and **10** (entry 7). The failure of the alkenyl systems may be a result of intramolecular cycloaddition of the azides onto the allylic cation intermediates.[5] In general, the cation stabilizing group R was found adjacent to the bridgehead nitrogen atom in the 1-azabicyclo[x.y.0]alkane products, as expected (Scheme 1). However, the products shown in entries 1 and 4 included azabicycles that did not have this connectivity (i.e., **21**, **24**, and **25**).

To rationalize the results in Table 1, a mechanistic scheme is proposed in Scheme 3. Formation of the carbocation **4** from the precursors **29** or **30** followed by cyclization should give the fused-bicyclic aminodiazonium ion **3**, as desired. Bond migration as shown should give the iminium ion **2** and thus the azabicycle **1**, where the R group is found adjacent to the bridgehead nitrogen atom. When the nucleophile used is hydride, this pathway would produce the products found in entries 2, 3, 5, and 6 in Table 1, and possibly the heterocycles **20** and **23** in entries 1 and 4, but it would not explain the products **21**, **24**, and **25** found in these last two entries. A likely reason is that rearrangement of the cation **4** to the cation **31** occurs prior to cyclization in some cases. Cyclization of **31** to the spirocyclic aminodiazonium ion **32** followed by rearrangement pathways *a*, *b*, and *c* would produce the iminium ions **33**, **34**, and **35**, respectively, and thus the heterocycles **36**, **37**, and **38** after reduction. A comparison of **1** with **36** reveals that the group R is adjacent to the bridgehead nitrogen atom in both cases, but the position of the nucleophile is different, i.e., the iminium ions **2** and **33** are regioisomeric. When hydride is used to reduce these iminium ions, the same products would be formed, but they would be distinguishable if a different nucleophile were to be used (vide infra). The heterocycle **37** is consistent with the formation of **21** and **24** in entries 1 and 4, and the heterocycle **38** is consistent with the formation of **25** in entry 4, clearly indicating that at least some cation rearrangement occurred in these two entries. The heterocycles **20**, **22**, **23**, **26**, and **27** formed in entries 1–6 could be derived from either the initial cation **4** or the rearranged cation **31**, or a combination of both. For the rearranged cation **31** to be involved in entries 2, 3, 5, and 6, a regioselective migration of bond *a* in **32** would have to be operational, which seems unlikely based on the results of entries 1 and 4, which appear to involve non-regioselective rearrangement. Finally, it is unclear whether the expected heterocycles **20** and **23** in entries 1 and 4 are the result of the non-rearranged pathway (via **3**) or the rearranged pathway (via migration of bond *a* in **32**). To answer these questions, we have examined the use of deuteride rather than hydride in the reduction step, which should allow discrimination of these various pathways.

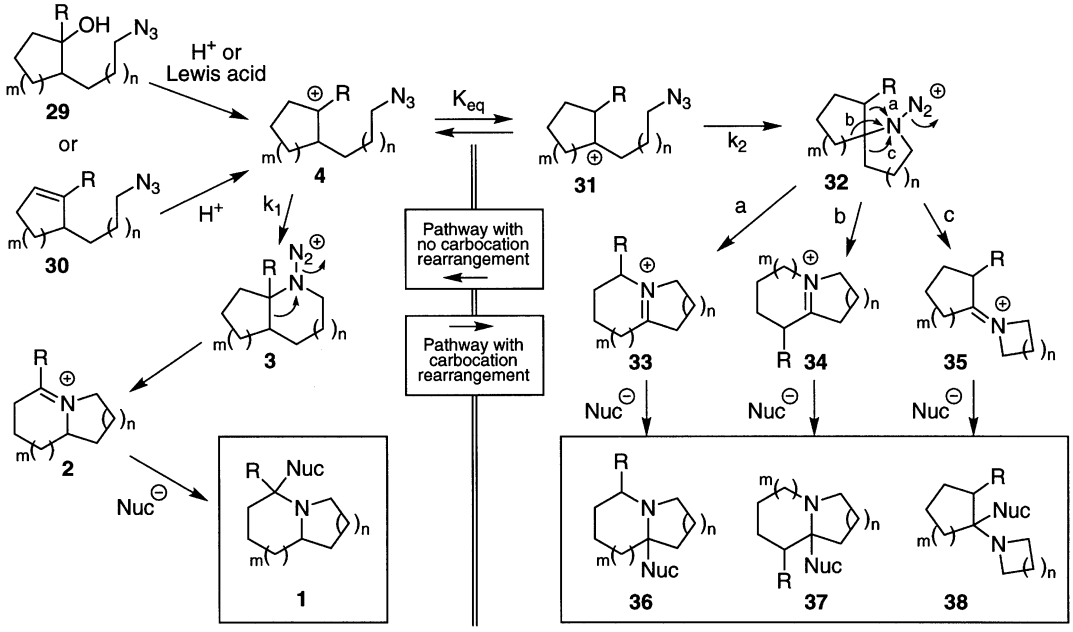
Cation precursors **6**, **7**, and **16** were subjected to Schmidt rearrangement and reduction with sodium borodeuteride (Table 2). Yields were not optimized. Entry 1 produced the deuterated indolizidines **20-*d*** and **21-*d***, each with deuterium at the bridgehead position, clearly a result of cation rearrangement (cf. **4**→→**31**→→**36/37** in Scheme 3). Hence, none of the expected indolizidine **20** is derived from the non-rearranged cation **4**. In contrast, entry 2 shows that the Schmidt reaction of **7** led to **22-*d***, where deuterium was found at the benzylic position only, indicating that this indolizidine was derived solely from the non-rearranged cation **4** (Scheme 3). Thus, the greater stability of the benzylic cation derived from **7** allows cyclization to **3** to compete effectively with rearrangement to **31**. In entry 1, rearrangement of the tertiary cation **4** to the alternative tertiary cation **31** is likely to be fast and reversible, producing roughly equal amounts of these two cations (i.e., K_{eq}=ca. 1), but the relative rate of cyclization of **31** is expected to be faster than that of **4**, since a five-membered ring is formed in the former case versus a six-membered ring in the latter case (i.e., $k_2 > k_1$); hence products from the rearranged cation are formed exclusively. In entry 2, there are two likely scenarios. First, cyclization of **4** to **3** might occur faster than **4** rearranges to **31**. Second, the rearrangement of **4** to **31** may be fast relative to cyclization, but **3** is selectively formed.[15] For this pathway to be operational, k_1

Table 1. Schmidt reactions

Entry	Starting Material	Conditions	Product(s)	Yield (ratio)[a]
1[b]	 **6**	1) $SnCl_4$ 2) BH_3•SMe_2	 **20** + **21**	47% (1.7:1)
2[b,c]	 **7**	1) $SnCl_4$ 2) $NaBH_4$	 **22**	63%
3	 **19**[d]	1) CF_3SO_3H 2) $NaBH_4$	**22**	57%
4	 **16**	1) CF_3SO_3H 2) BH_3•SMe_2	 **23** + **24** + **25**	36%[e] (1.9:1:2.3)
5	 **8**	1) $SnCl_4$ 2) $NaBH_4$	 **26**	60%[f]
6	 **18**	1) $SnCl_4$ 2) $NaBH_4$	 **27**	44%
7	 **9** or **10** (R'=H or *n*-Bu)	*g*	 **28**	0%[g]

[a] Isolated, purified yields unless otherwise noted.
[b] From Ref. 3.
[c] Improved yield over Ref. 3.
[d] From **7** by elimination (MsCl, triethylamine) in 67% yield.
[e] Yield after separation (13% of **22**, 7% of **23**, and 16% of **24**).
[f] Reduced to **20** (indolizidine 209D) with H_2, Pd/C in 80% yield.
[g] Extensive decomposition observed under several protic and Lewis acidic conditions.

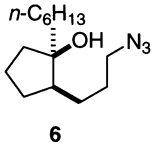
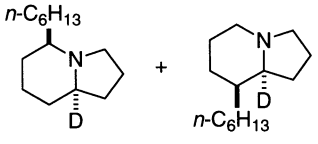
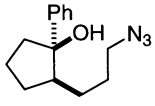
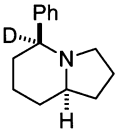
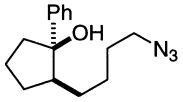
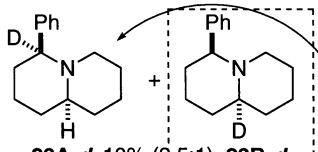
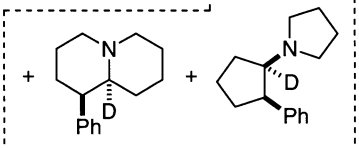
would need to be larger, or at least comparable, to k_2, since K_{eq} is expected to be very small due to the greater stability of **4**. That is, six-membered ring formation would need to be faster or at least comparable in rate to five-membered ring formation, which is possible but not common. To uncover any rearrangement that may be happening when R=Ph in Scheme 3, we studied a longer azide tether, which should slow the cyclization of **4** to **3** because it would involve the formation of a seven-membered ring aminodiazonium ion. Entry 3 shows the results of that study. Cyclization of **16** gave four products, one derived from the non-rearranged pathway (i.e., **23A-*d***), and three derived from rearrangement of the carbocation prior to Schmidt reaction (i.e., **23B-*d***, **24-*d***, and **25-*d***). Products from the rearranged cation pathway predominate by a 69:31 ratio. Hence, adding one methylene group to the tether (cf. **7** vs **16**) slows the rate of Schmidt cyclization enough to allow rearrangement of the tertiary benzylic carbocation **4** (Scheme 3, R=Ph, m=1, n=2) to the less-stabilized cation **31**. A likely scenario is that an equilibrium between **4** and **31** is rapidly achieved,



Scheme 3. Mechanistic rationale.

probably favoring the more stabilized cation **4** (i.e., K_{eq} is small), but the difference in relative rates of cyclization of these two cations (i.e., seven- vs six-membered aminodiazonium ion formation; $k_1 < k_2$) is sufficient to allow a predominance of products derived from the rearranged cation **31**. Overall, entries 1 and 3 in Table 2 are likely to embody the Curtin–Hammett principle, while entry 2 involves a kinetically-controlled cyclization of the initially formed cation. However, it is not possible to rule out a mechanism for entry 2 wherein rearrangement occurs, but an unusually large rate constant k_1 leads to 'unrearranged' products only.[15] Entries 5 and 6 in Table 1, which involve propargyl cations, are presumed to proceed without cation rearrangement, by analogy to the cyclization of the benzylic

Table 2. Deuterium labeling studies

Entry	Starting Material	Conditions	Product(s), (isolated yield)	Cation rearranged prior to cyclization?
1[a]	 **6**	1) CF_3SO_3H 2) $NaBD_4$	 **20-*d*** (14%) + **21-*d*** (11%)	complete rearrangement
2	 **7**	1) CF_3SO_3H 2) $NaBD_4$	 **22-*d*** (50%)	no rearrangement
3	 **16**	1) CF_3SO_3H 2) $NaBD_4$	 **23A-*d*** 10% (3.5:1) **23B-*d***	31% unrearranged 69% rearranged
			 **24-*d*** (5%) **25-*d*** (10%)	

[a] From Ref. 3.
[b] **23A-*d*** and **23B-*d*** could not be separated.

alcohol **7**, but again, rearrangement cannot be ruled out as a non-productive process.

3. Conclusion

Schmidt reactions involving azido cations such as **4** (Schemes 1 and 3, $m=n=1$ or $m=2$, $n=1$) may lead to 1-azabicyclo[5.3.0]decanes or 1-azabicyclo[4.3.0]nonanes (indolizidines) without the formation of products derived from cation rearrangement, as long as the initially-formed carbocation is stabilized at the level of tertiary benzylic or tertiary propargylic. A simple tertiary carbocation is not stabilized enough to prevent the involvement of cation rearrangement, producing regioisomeric indolizidines (e.g., **20/21**, entry 1, Table 1). A longer tether connecting the azide to the carbocation site slows the Schmidt reaction sufficiently that cation rearrangement can occur prior to cyclization, even if the cation is a tertiary benzylic one, allowing a majority of product formation by a rearranged spirocyclic aminodiazonium ion (e.g. **32**, Scheme 3), producing regioisomeric 1-azabicyclo[4.4.0]decanes (quinolizidines; e.g., **23/24**, Tables 1 and 2). These studies provide guidelines for synthetic design when 1-azabicyclo-[x.y.0]alkanes are targeted using this Schmidt reaction variant.

4. Experimental

4.1. (1*R**,2*R**)-1-Hexyl-2-(3-azidopropyl)cyclopentan-1-ol (6) and (1*R**,2*R**)-1-phenyl-2-(3-azidopropyl)cyclopentan-1-ol (7)

See Pearson et al.[3] for the synthesis of these two azido alcohols.

4.2. (1*R**,2*R**)-1-(1-Hexynyl)-2-(3-azidopropyl)cyclopentan-1-ol (8*Z*) and (1*R**,2*S**)-1-(1-hexynyl)-2-(3-azidopropyl)cyclopentan-1-ol (8*E*)

n-Butyllithium (5.0 mL of a 2.0 M solution in hexane, 10.0 mmol) was added to a cold (−30°C) solution of 1-hexyne (0.82 g, 1.2 mL, 10.0 mmol) in THF (14 mL). After 30 min, the solution was cooled to −78°C and transferred via cannula to a cold (−78°C) solution of anhydrous $CeCl_3$ (from 3.73 g of $CeCl_3{\cdot}7H_2O$, 10.0 mmol) in THF (14 mL).[4] After 1 h, a solution of 2-(3-azidopropyl)cyclopentanone (**5**)[3,6] (0.84 g, 5.0 mmol) in THF (8.3 mL) was added. After 2 h, the reaction was quenched by adding 50% aqueous THF. Saturated aqueous KH_2PO_4 was added, and the resulting mixture was extracted 3× with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried (K_2CO_3), and concentrated to provide 1.22 g (98%) of **8*Z*** and **8*E*** as a 2:1 mixture of diastereomers as determined by ^{13}C NMR. Based upon literature precedent,[3,7] the major diastereomer was assigned as **8*Z*** where the hydroxy group is *cis* to the 3-azidopropyl group. For characterization, partial separation of diastereomers was achieved by radial chromatography (5–8% ethyl acetate/hexane gradient). Data for **8*Z***: R_f=0.5 (15% ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 360 MHz) δ 3.28 (t, J=7 Hz, 2 H), 2.24 (t, J=6.8 Hz, 2 H), 1.37–2.15 (m, 16 H), 0.91 (t, J=7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 86.9 (−), 81.3 (−), 78.1 (−), 51.8 (−), 50.4 (+), 42.1 (−), 30.8 (−), 29.2 (−), 28.8 (−), 27.6 (−), 21.9 (−), 20.6 (−), 18.4 (−), 13.5 (+); IR (neat) 3418 (br, m), 2233 (w), 2095 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 267 [$(M+NH_4)^+$, 1.3], 249 [$(M+NH_4-H_2O)^+$, 3.1], 222 (10.9), 204 (100.0); HRMS calcd for $C_{14}H_{23}N_3ONH_4$ 267.2185 [$(M+NH_4)^+$], found 267.2187. Data for **8*E***: R_f=0.4 (15% ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 360 MHz) δ 3.30 (t, J=7 Hz, 2 H), 2.20 (t, J=6.8 Hz, 2 H), 1.41–1.97 (m, 16 H), 0.91 (t, J=7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 84.2 (−), 83.1 (−), 75.5 (−), 51.7 (−), 50.9 (+), 42.4 (−), 30.8 (−), 29.0 (−), 27.7 (−), 25.9 (−), 21.9 (−), 21.2 (−), 18.3 (−), 13.5 (+); IR (neat) 3542 (br, m), 2358 (w), 2095 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 267 [$(M+NH_4)^+$, 3.4], 249 [$(M+NH_4-H_2O)^+$, 4.6], 225 (6.3), 224 (6.2), 222 (13.7), 204 (100.0); HRMS calcd for $C_{14}H_{23}N_3ONH_4$ 267.2185 [$(M+NH_4)^+$], found 267.2182.

4.3. (1*R**,2*R**)-2-(3-Azidopropyl)-1-vinylcyclopentan-1-ol (9*Z*) and (1*R**,2*S**)-2-(3-azidopropyl)-1-vinylcyclopentan-1-ol (9*E*)

Vinyl magnesium bromide (7.5 mL of a 1.0 M solution in THF, 7.5 mmol) was added to a cold (−78°C) solution of anhydrous $CeCl_3$ (from 2.79 g of $CeCl_3{\cdot}7H_2O$, 7.5 mmol)[4] in THF (25 mL). After 1 h, a solution of 2-(3-azidopropyl)-cyclopentanone (**5**) [6] (0.84 g, 5.0 mmol) was added. After 2 h, the reaction was quenched with 10% aqueous acetic acid, and the resulting mixture was extracted 3× with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried (K_2CO_3) and concentrated. Chromatography (3–9% ethyl acetate/hexane gradient) afforded 0.6 g (71%) of **9*Z***, R_f=0.24 (10% ethyl acetate/hexane), and 86 mg (9%) of **157**, R_f=0.19 (10% ethyl acetate/hexane). The relative configuration of the major diastereomer was assigned based on literature precedent.[3,7] Data for **9*Z***: ^1H NMR ($CDCl_3$, 360 MHz) δ 5.87 (dd, J=17, 10.7 Hz, 1 H), 5.28 (dd, J=17, 1.3 Hz, 1 H), 5.10 (dd, J=10.7, 1.3 Hz, 1 H), 3.25 (t, J=6.8 Hz, 2 H), 1.75–2.0 (m, 3 H), 1.40–1.75 (m, 7 H), 1.15–1.25 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 143.8, 112.4, 82.7, 51.7, 48.7, 40.9, 29.7, 27.9, 25.2, 21.4; IR (neat) 3478 (br, m), 2096 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 213 [$(M+NH_4)^+$, 3.2], 195 (9.7), 168 (8.7), 152 (5.5), 151 (26.2), 150 (100.0); HRMS calcd for $C_{10}H_{17}N_3ONH_4$ 213.1715 [$(M+NH_4)^+$], found 213.1727. Data for **9*E***: ^1H NMR ($CDCl_3$, 360 MHz) δ 5.95 (dd, J=17, 10.7 Hz, 1 H), 5.25 (dd, J=17, 1.3 Hz, 1 H), 5.12 (dd, J=10.7, 1.3 Hz, 1 H), 3.22 (m, 2 H), 2.0 (m, 1 H), 1.4–1.9 (m, 9 H), 1.2–1.3 (m, 1 H), 1.0–1.1 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz,) δ 143.8, 112.4, 82.7, 51.7, 48.7, 40.9, 29.7, 27.9, 25.2, 21.4; MS (CI, NH_3) *m/z* (rel. int.) 195 [$(M+NH_4-H_2O)^+$, 7.5], 168 (9.2), 154 (2.4), 152 (8.8), 151 (15.0), 150 (100.0); HRMS calcd for $C_{10}H_{15}N_3NH_4$ 195.1610 [$(M+NH_4-H_2O)^+$], found 195.1608.

4.4. (1*R**,2*R**)-2-(3-Azidopropyl)-1-(1-hexenyl)cyclopentan-1-ol (10)

n-Butyllithium (2.5 mL of a 2.0 M solution in hexane, 5.0 mmol) was added to a cold (−78°C) solution of

1-iodo-1-hexene[3] (1.05 g, 5.0 mmol) in ether (7.5 mL). After 30 min, the solution was transferred via cannula to a cold (−78°C) solution of anhydrous $CeCl_3$ (from 1.86 g of $CeCl_3{\cdot}7H_2O$, 5.0 mmol)[4] in THF (7 mL). After 1 h, a solution of 2-(3-azidopropyl)cyclopentanone (**5**)[3,6] (0.42 g, 2.5 mmol) in THF (4.2 mL) was added. After 2 h, the reaction was quenched by adding 50% aqueous THF. Saturated aqueous KH_2PO_4 was added, and the resulting mixture was extracted 3× with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried (K_2CO_3), and concentrated. Chromatography (0–6% ethyl acetate/hexane gradient) afforded 0.19 g (31%) of the title compound as a colorless oil and as a single diastereomer whose relative configuration was assigned based on literature precedent.[3,7] R_f=0.2 (5% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.68 (td, *J*=15.1, 6.7 Hz, 1 H), 5.48 (d, *J*=15.1 Hz, 1 H), 3.24 (t, *J*=6.9 Hz, 2 H), 2.06 (q, *J*=6.9 Hz, 2 H), 1.10–1.95 (m, 16 H), 0.91 (t, *J*=7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 135.3 (+), 128.7 (+), 82.2 (−), 51.7 (−), 48.9 (+), 41.1 (−), 32.0 (−), 31.6 (−), 29.6 (−), 28.0 (−), 25.3 (−), 22.2 (−), 21.3 (−), 13.9 (+); MS (CI, NH_3) *m/z* (rel. int.) 224 [$(M-N_2+H)^+$, 8.3], 208 (13.2), 207 (28.0), 206 (100.0); HRMS calcd for $C_{14}H_{25}NOH$ 224.2014 [$(M-N_2+H)^+$], found 224.2003.

4.5. 2-(4-Bromobutyl)-2-carbomethoxycyclopentanone (13)

A solution of 2-carbomethoxycyclopentanone (0.71 g, 5.0 mmol) in THF (2.5 mL) was added to a cold (0°C) solution of potassium *tert*-butoxide (0.62 g, 5.25 mmol) in THF (15.7 mL). The mixture was stirred for 30 min, and then 1,4-dibromobutane (1.35 g, 0.75 mL, 6.25 mmol) was added in a dropwise fashion. After 2 h, the mixture was warmed to room temperature for 48 h, and water was added. The resulting mixture was extracted 3× with ethyl acetate, and the combined organic extracts were washed with water and brine, then dried ($MgSO_4$), and concentrated. Chromatography (5–20% ethyl acetate/hexane gradient) afforded 0.69 g (50%) of the title compound as a colorless liquid, R_f=0.7 (33% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.71 (s, 3 H), 3.40 (t, *J*=6.5 Hz, 2 H), 2.30–2.65 (m, 4 H), 1.90–2.09 (m, 4 H), 1.32–1.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.7, 171.3, 60.3, 52.6, 37.9, 33.8, 33.2, 32.7, 32.5, 23.4, 19.6; IR (neat) 1770 (s), 1731 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 277 [$(M+H)^+$, 38.9], 264 (9.7), 263 (9.0), 197 (6.6); HRMS calcd for $C_{11}H_{17}{}^{79}BrO_3H$ 277.0439 [$(M+H)^+$], found 277.0415.

4.6. 2-(3-Chloropropyl)-2-carboethoxycyclohexanone (14)

A solution of 2-carboethoxycyclohexanone (8.51 g, 50.0 mmol) in THF (25 mL) was added to a cold (0°C) solution of potassium *tert*-butoxide (5.90 g, 50.0 mmol) in THF (75 mL). The mixture was stirred for 30 min, and then 1-chloro-3-iodopropane (12.8 g, 62.5 mmol) was added in a dropwise fashion. After 48 h, water was added and the mixture was extracted 3× with ethyl acetate. The combined organic extracts were washed with water and brine, then dried ($MgSO_4$) and concentrated. Chromatography (2% ethyl acetate/hexane) afforded 8.56 g (69%) of the title compound as a colorless liquid, R_f=0.3 (5% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.20 (q, *J*=7 Hz, 2 H), 3.49 (dt, *J*=6.2, 2.1 Hz, 2 H), 2.46 (m, 3 H), 1.90–2.20 (m, 2 H), 1.55–1.85 (m, 6 H), 1.40–1.50 (m, 1 H), 1.25 (t, *J*=7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 207.7 (−), 171.8 (−), 61.3 (−), 60.3 (−), 45.0 (−), 41.0 (−), 36.2 (−), 32.2 (−), 27.6 (−), 27.5 (−), 14.1 (+); IR (neat) 1731 (s), 1707 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 264 [$(M+NH_4)^+$, 33.4], 247 [$(M+H)^+$, 100.0], 218 (5.1), 211 (13.2); HRMS calcd for $C_{12}H_{19}{}^{35}ClO_3H$ 247.1101 [$(M+H)^+$], found 247.1098.

4.7. 2-(4-Bromobutyl)cyclopentanone

Hydrogen bromide (1.13 g, 2.4 mL of a 47–49% aqueous solution, 14.0 mmol) was added to the ketoester **13** (2.77 g, 10.0 mmol) at room temperature, and the resulting mixture was heated at reflux for 4 h, and then cooled to room temperature. Water was added, and the resulting mixture was extracted 3× with ethyl acetate. The combined organic extracts were washed with 10% Na_2CO_3 and brine, then dried ($MgSO_4$), and concentrated. Chromatography (2–10% ethyl acetate/hexane gradient) gave 1.26 g (57%) of the title compound as a pale yellow oil, R_f=0.2 (10% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.35 (t, *J*=6.9 Hz, 2 H), 2.15–2.35 (m, 2 H), 1.90–2.18 (m, 3 H), 1.65–1.85 (m, 4 H), 1.38–1.50 (m, 2 H), 1.15–1.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 220.6, 48.6, 37.8, 33.3, 32.4, 29.3, 28.5, 25.8, 20.4; IR (neat) 1732 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 185 [$(M+NH_4)^+$, 100.0], 221 (1.1), 219 (1.2), 136 (50.2); HRMS calcd for $C_9H_{15}{}^{79}BrONH_4$ 236.0650 [$(M+NH_4)^+$], found 236.0642.

4.8. 2-(4-Azidobutyl)cyclopentanone (15)

Sodium azide (1.40 g, 21.5 mmol) was added to a solution of the 2-(4-bromobutyl)cyclopentanone (1.26 g, 5.4 mmol) in DMSO (10.7 mL). After 12 h, water was added and the resulting mixture was extracted 3× with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (2–13% ethyl acetate/hexane gradient) provided 0.78 g (80%) of the title compound as a colorless oil, R_f=0.4 (10% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.28 (t, *J*=6.5 Hz, 2 H), 2.25–2.45 (m, 2 H), 2.10 (q, *J*=7.7 Hz, 1 H), 1.90–2.1 (m, 2 H), 1.74–1.88 (m, 2 H), 1.45–1.65 (m, 5 H), 1.18–1.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 208.5 (−), 51.1 (−), 48.9 (+), 38.0 (−), 29.4 (−), 29.1 (−), 28.7 (−), 24.6 (−), 20.6 (−); IR (neat) 2094 (s), 1732 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 182 [$(M+H)^+$, 67.8], 154 (100.0), 152 (13.0), 151 (10.3); HRMS calcd for $C_9H_{15}N_3OH$ 182.1293 [$(M+H)^+$], found 182.1293.

4.9. 2-(3-Azidopropyl)cyclohexanone (17)

Hydrogen bromide (2.28 g, 4.8 mL of a 47–49% aqueous solution, 28.2 mmol) was added to the ketoester **14** (4.96 g, 20.1 mmol) at room temperature and the resulting mixture was heated at reflux for 2.5 h and then cooled to room temperature. Water was added, and the resulting mixture was extracted 3× with ethyl acetate. The combined organic extracts were washed with 10% Na_2CO_3 and brine (20 mL), then dried ($MgSO_4$), and concentrated. The residue was

taken up in DMSO (15 mL), and sodium azide (1.71 g, 26.3 mmol) was added. After stirring overnight at 40°C, water was added and the mixture was extracted 3× with ethyl acetate. The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. Chromatography (2–5% ethyl acetate/hexane gradient) gave 0.98 g (27%) of the title compound as a pale yellow liquid, R_f=0.3 (10% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.25 (dt, *J*=6.2, 3.7 Hz, 2 H), 2.25–2.45 (m, 3 H), 2.0–2.2 (m, 2 H), 1.75–1.95 (m, 2 H), 1.50–1.75 (m, 4 H), 1.40 (m, 1 H), 1.20–1.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 212.6 (−), 51.5 (−), 50.2 (+), 42.0 (−), 34.1 (−), 27.9 (−), 26.7 (−), 26.5 (−), 24.9 (−); IR (neat) 2095 (s), 1714 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 199 [$(M+NH_4)^+$, 21.5], 155 (14.7), 154 (100.0); HRMS calcd for $C_9H_{15}N_3ONH_4$ 199.1559 [$(M+NH_4)^+$], found 199.1559.

4.10. (1*R**,2*S**)-1-Phenyl-2-(4-azidobutyl)cyclopentan-1-ol (16)

Phenylmagnesium bromide (5.0 mL, 3.0 M in THF, 15.0 mmol) was added to a solution of the azido ketone **15** (1.81 g, 10.0 mmol) in THF (50 mL) at −78°C. After 20 min, the solution was warmed to 0°C for 30 min, and then to room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted 3× with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (1–5% ethyl acetate/hexane gradient) afforded 1.77 g (69%) of the title compound as a single diastereomer whose relative configuration was assigned as depicted based on literature precedent.[3,7] R_f=0.3 (10% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.46 (d, *J*=7 Hz, 2 H), 7.45 (t, *J*=7 Hz, 2 H), 7.35 (d, *J*=7 Hz, 1 H), 3.16 (t, *J*=6.4 Hz, 2 H), 2.0–2.2 (m, 3 H), 1.7–2.0 (m, 3 H), 1.16–1.70 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 145.9 (−), 128.1 (+), 126.5 (+), 124.9 (+), 84.0 (−), 51.3 (−), 51.0 (+), 43.7 (−), 29.7 (−), 29.0 (−), 27.5 (−), 25.7 (−), 21.7 (−); IR (neat) 3478 (br, m), 2096 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 277 [$(M+NH_4)^+$, 6.5], 259 [$(M+NH_4-H_2O)^+$, 4.8], 242 (5.4), 232 (15.7), 216 (12.0), 215 (85.1), 214 (100.0); HRMS calcd for $C_{15}H_{21}N_3ONH_4$ 277.2028 [$(M+NH_4)^+$], found 277.2019.

4.11. (1*R**,2*R**)-1-(1-Hexynyl)-2-(3-azidopropyl)cyclohexan-1-ol (18)

n-Butyllithium (5.0 mL of a 2.0 M solution in hexane, 10.0 mmol) was added to a cold (−30°C) solution of 1-hexyne (0.82 g, 1.2 mL, 10.0 mmol) in THF (14 mL). After 30 min, the solution was cooled to −78°C and transferred via cannula to a cold (−78°C) solution of anhydrous $CeCl_3$ (from 3.73 g of $CeCl_3{\cdot}7H_2O$, 10.0 mmol)[4] in THF (14 mL). After 1 h, a solution of azido ketone **17** (0.91 g, 5.0 mmol) in THF (8.3 mL) was added. After 2 h, the reaction was quenched by adding 50% aqueous THF. Saturated aqueous KH_2PO_4 was added, and the resulting mixture was extracted 3× with ether. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried (K_2CO_3) and concentrated. Chromatography (2–15% ethyl acetate/hexane gradient) afforded 1.05 g (80%) of the title compound as a single diastereomer, whose relative configuration was assigned based on literature precedent.[3,7] R_f=0.1 (10% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.27 (app q, *J*=6.5 Hz, 2 H), 2.23 (t, *J*=6.8 Hz, 2 H), 1.81–2.01 (m, 3 H), 1.35–1.80 (m, 10 H), 1.10–1.35 (m, 5 H), 0.9 (t, *J*=7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 86.9, 81.2, 72.8, 51.9, 47.7, 41.9, 31.0, 29.5, 27.9, 27.1, 25.6, 24.2, 22.0, 18.4, 13.6; IR (neat) 3426 (br, m), 2095 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 281 [$(M+NH_4)^+$, 1.5], 263 (5.1), 236 (3.9), 220 (6.8), 219 (24.4), 218 (100.0); HRMS calcd for $C_{15}H_{25}N_3ONH_4$ 281.2341 [$(M+NH_4)^+$], found 281.2332.

4.12. 5-(3-Azidopropyl)-1-phenylcyclopent-1-ene (19)

A solution of azido alcohol **7**[3] (1.00 g, 4.1 mmol) in dichloromethane (12 mL) was cooled to −50°C, and triethylamine (0.83 g, 1.1 mL, 8.2 mmol) and methanesulfonyl chloride (0.70 g, 0.47 mL, 6.1 mmol) were added sequentially. After 15 min, the mixture was warmed to 0°C for 2.5 h, and then water (6 mL) was added. The resulting mixture was extracted 3× with dichloromethane and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (0–2% ethyl acetate/hexane gradient) gave 0.62 g (67%) of the title compound as a colorless liquid, R_f=0.8 (5% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.30–7.41 (m, 4 H), 7.22–7.26 (m, 1 H), 6.08 (dd, *J*=4.8, 2.1 Hz, 1 H), 3.21 (m, 2 H), 2.50 (m, 2 H), 2.20 (m, 1 H), 1.75 (m, 1 H), 1.55–1.69 (m, 4 H), 1.3 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 146.1 (−), 136.3 (−), 128.4 (+), 126.9 (+), 126.8 (+), 126.1 (+), 51.6 (−), 44.5 (+), 31.5 (−), 30.5 (−), 29.5 (−), 26.7 (−); IR (neat) 2094 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel. int.) 245 [$(M+NH_4)^+$, 6.2], 228 [$(M+H)^+$, 1.1], 200 (100.0); HRMS calcd for $C_{14}H_{17}N_3H$ 228.1501 [$(M+H)^+$], found 228.1496.

4.13. (5*R**,8a*R**)-5-Hexylindolizidine (indolizidine 209D, 20) and (8*R**,8a*R**)-8-hexylindolizidine (21)

See Pearson et al.[3] for the synthesis of these two indolizidines.

4.14. (5*R**,8a*S**)-5-Phenylindolizidine (22)[3]

From alkene **19**: Trifluoromethanesulfonic acid (0.23 g, 0.13 mL, 1.5 mmol) was added to a cool (15°C) solution of alkene **19** (0.23 g, 1.0 mmol) in benzene (10.0 mL). After 5 min, the mixture was cooled to 0°C, and a cold (0°C) solution of sodium borohydride (0.23 g, 6.0 mmol) in 3 mL of dry methanol was carefully added. After 10 min, the solution was warmed to room temperature for 24 h, then cooled to 0°C, and 15% NaOH was added. The resulting mixture was extracted 3× with ethyl acetate and the combined organic phases were washed with brine, then dried (K_2CO_3) and concentrated. Chromatography (2–25% ethyl acetate/hexane gradient, basic alumina activity I) afforded 0.16 g (57%) of the title compound. All spectral data matched the literature values.[3] *From azido alcohol 7 (improved procedure)*: Repetition of the literature procedure[3] using $SnCl_4$ rather than trifluoromethanesulfonic acid resulted in an improved isolated yield of 63% of the title compound.

4.15. (4*R**,9a*R**)-4-Phenylquinolizidine (23), (1*R**,9a*S**)-1-phenylquinolizidine (24), and (1*R**,2*R**)-2-phenyl-1-(1-pyrrolidino)cyclopentane (25)

Trifluoromethanesulfonic acid (0.29 g, 170 μL, 2.0 mmol) was added to a cool (15°C) solution of alcohol **16** (0.25 g, 1.0 mmol) in benzene (10 mL). After 5 min, the solution was cooled to 0°C, and treated with borane–dimethyl sulfide complex (3.0 mL of a 2.0 M solution in THF, 6.0 mmol). After 5 min at 0°C and 14 h at room temperature, the mixture was cooled to 0°C and water was added. After 1 h, the mixture was diluted with 15% NaOH and extracted 3× with ethyl acetate. The combined organic extracts were washed with brine, dried (K_2CO_3), and concentrated. Chromatography on deactivated silica gel[9] (0–10% ethyl acetate/hexane gradient) gave 28 mg (13%) of **23** whose spectral properties matched those reported in the literature,[10] R_f=0.7 (5% ethyl acetate/hexane, deactivated silica plate), 15 mg (7%) of **24**, R_f=0.3 (5% ethyl acetate/hexane, deactivated silica plate), and 33 mg (16%) of **25**, R_f=0.1 (5% ethyl acetate/hexane, deactivated silica plate). The relative configuration of **24** was assigned by analogy to C(8)-substituted indolizidines (cf. **21**).[3] The relative configuration of **25** was assigned by comparison to reduction products of analogous iminium ions.[11,12] Data for **23**: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.30 (m, 5 H), 2.89 (dd, *J*=11, 3 Hz, 1 H), 2.62 (d, *J*=11 Hz, 1 H), 1.91 (t, *J*=9.7 Hz, 1 H), 1.46–1.85 (m, 7 H), 1.25–1.45 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 145.6 (−), 128.2 (+), 127.5 (+), 126.6 (+), 70.5 (+), 63.4 (+), 53.7 (−), 36.6 (−), 33.9 (−), 33.8 (−), 26.2 (−), 24.9 (−), 24.8 (−); IR (neat) 2785 (s), 2750 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 215 (M^+, 34.8), 214 (37.9), 172 (28.0), 138 (100.0); HRMS calcd for $C_{15}H_{21}N$ 215.1674, found 215.1665. Data for **24**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10–7.40 (m, 5 H), 3.22 (dt, *J*=7.9, 3.7 Hz, 1 H), 2.64 (q, *J*=7.9 Hz, 1 H), 2.35 (m, 4 H), 2.15 (m, 1 H), 1.4–2.0 (m, 9 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 145.6 (−), 129.0 (+), 127.7 (+), 125.6 (+), 71.3 (+), 53.8 (−), 48.8 (+), 36.6 (−), 33.2 (−), 30.8 (−), 29.7 (−), 23.4 (−), 22.4 (−); IR ($CDCl_3$) 2785 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 215 (M^+, 15.6), 115 (5.2), 111 (12.7), 110 (100.0); HRMS calcd for $C_{15}H_{21}N$ 215.1674, found 215.1665. Data for **25**: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.60 (d, *J*=6.9 Hz, 2 H), 7.27 (t, *J*=6.9 Hz, 2 H), 7.18 (t, *J*=6.9 Hz, 1 H), 2.8–3.0 (m, 2 H), 2.2–2.3 (bs, 1 H), 2.1 (m, 2 H), 1.05–1.95 (m, 11 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 144.4, 130.0, 127.6, 125.6, 65.0, 57.3, 45.6, 29.7, 25.08, 25.07, 21.3; IR (neat) 2934 (s), 2756 (m), 1491 (m), 1443 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 215 (M^+, 33.7), 214 (14.9), 123 (20.1), 111 (57.9), 110 (23.8), 104 (17.3), 98 (70.5), 91 (19.0), 83 (100.0); HRMS calcd for $C_{15}H_{21}N$ 215.1674, found 215.1669.

4.16. (5*R**,8a*S**)-5-(1-Hexynyl)indolizidine (26)

Stannic chloride (1.5 mL, 1.0 M in dichloromethane, 1.5 mmol) was added to a cold (−78°C) solution of **8*Z*** and **8*E*** (0.25 g, 1.0 mmol, 2:1 mixture of diastereomers) in dichloromethane (40 mL). After 10 min, a cold (0°C) solution of sodium borohydride (0.23 g, 6.0 mmol) in methanol (4 mL) was added, and the mixture was warmed to room temperature for 20 h. It was then cooled to 0°C, and quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted 3× with dichloromethane and the combined organic extracts were washed with brine, dried (K_2CO_3), and concentrated. Chromatography (2–10% ethyl acetate/hexane gradient) provided 0.12 g (60%) of the title compound as a colorless oil and as a single diastereomer, R_f=0.3 (10% ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.44 (t, *J*=8.6 Hz, 1 H), 2.73 (bd, *J*=10.7 Hz, 1 H), 2.16 (m, 2 H), 2.05 (m, 1 H), 1.25–1.89 (m, 15 H), 0.89 (t, *J*=7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 82.9, 80.6, 64.1, 54.9, 53.2, 33.3, 31.3, 30.9, 29.7, 24.3, 22.7, 20.1, 18.4, 14.8; IR (neat) 2933 (s), 2930 (s), 2857 (s), 2782 (m), 2361 (w), 1456 (m), 1378 (m), 1362 (m), 1304 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 206 [$(M+H)^+$, 20.1], 205 (M^+, 69.2), 204 (79.5), 176 (70.2), 163 (74.5), 162 (100.0), 154 (84.2), 124 (44.3), 120 (59.8), 41 (57.3); HRMS calcd for $C_{14}H_{23}NH$ 206.1909 [$(M+H)^+$], found 206.1913. Catalytic hydrogenation (hydrogen, Pd/C) gave indolizidine 209D (**20**)[3] in 80% yield.

4.17. (2*R**,7*S**)-2-(1-Hexynyl)-1-azabicyclo[5.3.0]-decane (27)

Stannic chloride (0.8 mL of a 1.0 M solution in dichloromethane, 0.8 mmol) was added to a cold (−78°C) solution of **18** (0.14 g, 0.5 mmol) in dichloromethane (22 mL). After 10 min, a cold (0°C) solution of sodium borohydride (0.12 g, 3.2 mmol) in methanol (3 mL) was added. After 5 min, the reaction mixture was warmed to 0°C for 30 min, and then to room temperature for 20 h. It was then cooled to 0°C, and quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted 3× with dichloromethane, and the combined organic extracts were washed with brine, then dried (K_2CO_3) and concentrated. Chromatography (3–15% ethyl acetate/hexane gradient) provided 53 mg (44%) of the title compound as a colorless oil, as a single diasteromer. The relative configuration was assigned based on the stereoelectronic model proposed for reduction of analogous iminium ions.[10,13,14] R_f=0.3 (15% ethyl acetate/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.49 (dt, *J*=9.7, 3.2 Hz, 1 H), 3.11 (bs, 1 H), 2.58 (q, *J*=8 Hz, 1 H), 2.49 (q, *J*=8 Hz, 1 H), 2.18 (t, *J*=6.4 Hz, 2 H), 1.3–2.0 (m, 6 H), 0.9 (t, *J*=7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 82.7 (−), 82.5 (−), 61.9 (+), 57.1 (+), 56.9 (−), 36.1 (−), 35.1 (−), 34.0 (−), 30.9 (−), 26.7 (−), 24.1 (−), 22.8 (−), 22.0 (−), 18.5 (−), 13.6 (+); IR (neat) 2780 (m), 2244 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 219 (M^+, 55.1), 190 (51.8), 177 (25.9), 176 (100.0); HRMS calcd for $C_{15}H_{25}N$ 219.1987, found 219.1982.

4.18. (5*R**,8a*S**)-5-Phenyl-5-deuterioindolizidine (22-*d*)

Trifluoromethanesulfonic acid (1.13 g, 0.67 mL, 7.5 mmol) was added to a cool (15°C) solution of **7**[3] (0.73 g, 3.0 mmol) in benzene (30.0 mL). After 5 min, the mixture was cooled to 0°C, and a cold (0°C) solution of $NaBD_4$ (0.75 g, 18.0 mmol) in methanol-*d* (9.0 mL) was carefully added. After 10 min, the solution was warmed to room temperature for 24 h, then cooled to 0°C, and 15% NaOH was added. The resulting mixture was extracted 3× with ethyl acetate and the combined organic phases were washed with brine, then dried (K_2CO_3), and concentrated. Chromatography (2–25% ethyl acetate/hexane gradient, basic alumina activity I) afforded 0.30 g (50%) of the title compound as an oil. The

position of the deuterium label was determined by ^{13}C NMR spectroscopy, wherein the signal at δ 69.8 for the benzylic carbon at the C-5 position was completely absent. Data for **22-*d***: R_f=0.47 (10% methanol/chloroform on silica gel); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.22–7.35 (m, 5 H), 2.74 (bs, 1 H), 1.3–2.0 (m, 12 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 144.7 (−), 128.1 (+), 127.4 (+), 126.8 (+), 65.1 (+), 52.6 (−), 35.4 (−), 30.8 (−), 30.5 (−), 25.2 (−), 20.3 (−); IR (neat) 2781 (s), cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 202 (M^+, 68.6), 201 (59.7), 200 (27.8), 125 (100.0); HRMS calcd. for $C_{14}H_{18}DN$ 202.1580, found 202.1580.

4.19. (4*S**,9a*S**)-4-Phenyl-4-deuterioquinolizidine (23A-*d*), (4*S**,9a*S**)-4-phenyl-9a-deuterioquinolizidine (23B-*d*), (1*R**,10*S**)-1-phenyl-10-deuterioquinolizidine (24-*d*), and (1*R**,2*R**)-2-phenyl-1-(1-pyrrolidino)-1-deuteriocyclopentane (25-*d*)

Trifluoromethanesulfonic acid (0.36 g, 0.2 mL, 2.4 mmol) was added to a cool (15°C) solution of alcohol **25** (0.31 g, 1.2 mmol) in benzene (12 mL). After 5 min, the reaction mixture was cooled to 0°C, and a cold solution of $NaBD_4$ (0.30 g, 7.2 mmol) in methanol-*d* (3.5 mL) was added. After 10 min at 0°C and 24 h at room temperature, the mixture was cooled to 0°C, and 15% NaOH was added. The resulting mixture was extracted 3× with ethyl acetate, and the combined organic extracts were washed with brine, then dried (K_2CO_3), and concentrated. Chromatography on deactivated silica gel[9] (0–10% ethyl acetate/hexane gradient) afforded 24 mg (10%) of a 3.5:1 mixture [^2H NMR: ($CDCl_3$ external standard, 360 MHz) δ 2.89 (bs, 0.99 D), 1.90 (bs, 0.28 D)] of **23A-*d*** and **23B-*d***, R_f=0.7 (5% ethyl acetate/hexane, deactivated silica plate), 12 mg (5%) of **24-*d***, R_f=0.3 (5% ethyl acetate/hexane, deactivated silica plate), and 25 mg (10%) of **25-*d***, R_f=0.1 (5% ethyl acetate/hexane, deactivated silica plate). The % deuterium incorporation was estimated to be 90% by comparision of the mass spectra of **23** and **23-*d***. The position of the deuterium label for the mixture of **23A-*d*** and **23B-*d*** was determined by deuterium (^2H) NMR. The signal at δ 2.89 (bs, 1.01 D) corresponds to the deuterium label at the benzylic carbon and the signal at δ 1.90 (bs, 0.27 D) corresponds to the deuterium label at the bridgehead position. The position of the deuterium label for **24-*d*** and **25-*d*** was assigned spectroscopically: In the ^{13}C NMR spectrum of **24-*d*** the signal at δ 71.3 for the bridgehead carbon was completely absent and in the ^{13}C NMR spectrum of **25-*d*** the signal at δ 65.0 for the carbon next to nitrogen was completely absent. Data for **23A-*d*** and **23B-*d***: ^1H NMR ($CDCl_3$, 360 MHz) δ 7.20–7.40 (m, 5 H), 2.89 (dd, *J*=11, 3 Hz, 0.2 H), 2.62 (d, *J*=11 Hz, 1 H), 1.91 (t, *J*=9.7 Hz, 1 H), 1.46–1.85 (m, 7 H), 1.25–1.45 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 145.6 (−), 128.2 (+), 127.5 (+), 126.6 (+), 70.5 (+), 63.4 (+), 53.7 (−), 36.6 (−), 33.9 (−), 33.8 (−), 26.2 (−), 24.9 (−), 24.8 (−); IR (neat) 2779 (s), 1445 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 216 (M^+, 60.7), 215 (48.3), 139 (100.0); HRMS calcd for $C_{15}H_{20}DN$ 216.1737, found 215.1741. Data for **24-*d***: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10–7.40 (m, 5 H), 3.22 (bs, 1 H), 2.2–2.4 (m, 4 H), 2.15 (m, 1 H), 1.4–1.9 (m, 9 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 145.6, 129.0, 127.7, 125.6, 53.7, 48.7, 36.6, 33.2, 30.8, 29.7, 23.4, 22.4; IR (neat) 2773 (m), 1493 (m), 1452 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 216 (M^+, 47.4), 215 (10.4), 117 (12.1), 112 (24.0), 111 (100.0); HRMS calcd for $C_{15}H_{20}DN$ 216.1737, found 216.1742. Data for **25-*d***: ^1H NMR ($CDCl_3$, 360 MHz) δ 7.58 (d, *J*=6.9 Hz, 2 H), 7.27 (t, *J*=6.9 Hz, 2 H), 7.18 (t, *J*=6.9 Hz, 1 H), 2.8–3.0 (m, 2 H), 2.1–2.2 (bs, 1 H), 1.1–1.9 (m, 12 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 144.4, 130.0, 127.6, 125.6, 57.3, 45.6, 29.7, 25.08, 25.07, 21.3; IR ($CDCl_3$) 1601 (m), 1418 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel. int.) 216 (M^+, 100.0), 215 (36.9), 112 (71.4), 111 (32.5), 41 (28.6); HRMS calcd for $C_{15}H_{20}DN$ 216.1737, found 216.1732.

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References

1. (a) Pearson, W. H. *J. Heterocyclic Chem.* **1996**, *33*, 1489–1496 (recent papers). (b) Pearson, W. H.; Fang, W.-k. *Isr. J. Chem.* **1997**, *37*, 39–46. (c) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **2000**, *65*, 7158–7174. (d) Pearson, W. H.; Hutta, D. A.; Fang, W.-k. *J. Org. Chem.* **2000**, *65*, 8326–8332.
2. Aubé has shown that aliphatic azides may participate in Schmidt reactions with ketones and related electrophiles. See: (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966. Selected recent references: (b) Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771–3774. (c) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232. (d) Iyengar, R.; Schildknegt, K.; Aubé, J. *Organic Lett.* **2000**, *2*, 1625–1627.
3. For preliminary examples related to this work, see: Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194.
4. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.
5. Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682–2684.
6. Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966.
7. Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662–4672.
8. Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753–2754.
9. Deactivated silica gel was prepared by adding 20% by weight of hexamethyldisilazane to a suspension of flash silica gel in hexane. After wet-packing the chromatography column, the silica gel was washed successively with ethyl acetate, 50% ethyl acetate/hexane, and hexane.
10. Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157–2167.
11. Smith, M. B.; Shroff, H. N. *Heterocycles* **1985**, 2229–2235.
12. Bohlmann, F.; Schumann, D.; Arndt, C. *Tetrahedron Lett.* **1965**, 2705–2711.
13. Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296.
14. Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688–4693.
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