Intramolecular Schmidt Reactions of Azides with Carbocations: Synthesis of Bridged-Bicyclic and Fused-Bicyclic Tertiary Amines

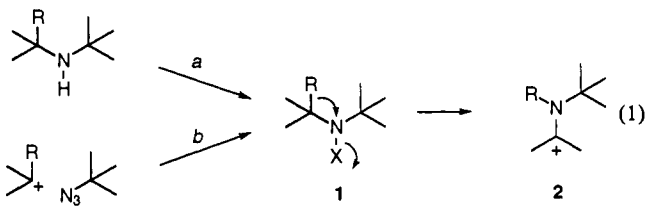
William H. Pearson,* Rajesh Walavalkar, Jeffrey M. Schkeryantz, Wen-kui Fang, and James D. Blickensdorf

Contribution from the Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1055

Received May 28, 1993®

Abstract: Aliphatic azides were captured intramolecularly by carbocations, producing aminodiazonium ion intermediates. Carbon-to-nitrogen rearrangement then occurred, generating bridged- or fused-bicyclic α-amino carbocations or iminium ions, depending on the geometry about the C(+)–N bond. In the bridged systems, rapid elimination of the α-amino carbocations produced twisted enamines with 1-azabicyclo[3.2.2]nonene, 1-azabicyclo[2.2.2]octene, and 1-azabicyclo-[3.2.1]octene skeletons. In the fused systems, the iminium ions were reduced with sodium borohydride to give 1-azabicyclo-[*n*.3.0]alkanes, where *n* = 4 or 5. The carbocations for these intramolecular Schmidt reactions were generated by treatment of alkenes or alcohols with trifluoromethanesulfonic acid. In some cases, carbocation rearrangement was found to be fast relative to capture by the azide. The regioselectivity of the carbon-to-nitrogen shift was proposed to be due to both electronic and stereoelectronic factors. The aminodiazonium ion intermediates were modeled by a combination of molecular mechanics and AM1 semiempirical molecular orbital calculations. Alkaloids indolizidine 167B and indolizidine 209D were synthesized using this methodology.

Placement of a strong electron-withdrawing group on a nitrogen atom is a popular way to promote carbon-to-nitrogen rearrangement reactions, e.g. the Beckman, Curtius, Hoffman, Lossen, Schmidt, and Stieglitz rearrangements.[1] We are interested in the rearrangement of **1** to **2** shown in eq 1.[2] A considerable



amount of research has been carried out by Gassman, Hoffman, and others using rearrangement precursors **1** where X = Cl[3-12] and X = OSO_2Ar,[3,9,13-22] (Stieglitz-type rearrangements), which are prepared from the corresponding amine (path a). As a part of our research on the use of azides in organic synthesis, we became interested in an alternate approach based on the generation and rearrangement of secondary aminodiazonium ion intermediates **1** where X = N_2^+, a version of the Schmidt reaction. An advantage of this method would be a more convergent overall process, since the aminodiazonium ion would be generated *in situ* by the capture of a carbocation with an azide (path b), thus avoiding the synthesis of a secondary amine. We wish to report the first intramolecular examples of such a process.[2]

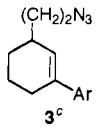
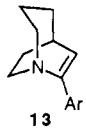
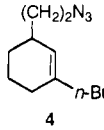
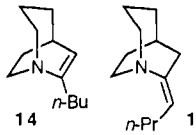
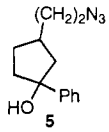
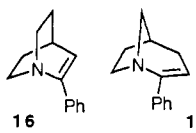
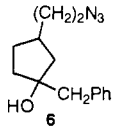
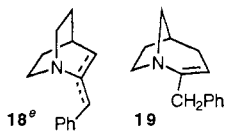
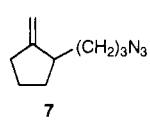
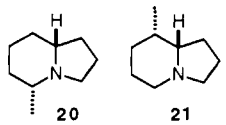
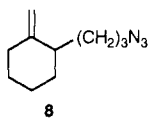
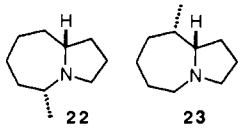
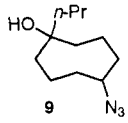
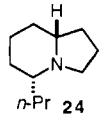
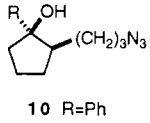
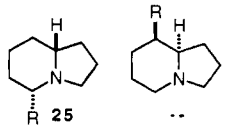
The reaction of hydrazoic acid (HN_3) with carbocations generated from the treatment of alcohols or alkenes with protic acid produces primary aminodiazonium ions, which undergo rearrangement. This variant of the Schmidt reaction[3,23-28] has not seen widespread use. Primary aminodiazonium ions are also produced by protonation of alkyl azides. The more useful and well-known versions of the Schmidt reaction involve the reaction of hydrazoic acid with ketones and carboxylic acids, which undergo

* Abstract published in *Advance ACS Abstracts*, October 1, 1993.

(1) March, J. In *Advanced Organic Chemistry*, 4th ed.; John Wiley and Sons: New York, 1992; pp 1090–1097.
(2) For a preliminary account of this work, see: Pearson, W. H.; Schkeryantz, J. S. *Tetrahedron Lett.* **1992**, *33*, 5291–5294.
(3) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley and Sons: New York, 1963; Vol. 1, pp 457–591.
(4) Gassman, P. G.; Fox, B. L. *J. Am. Chem. Soc.* **1967**, *89*, 338–342.
(5) Gassman, P. G.; Cryberg, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 2047–2052.
(6) Gassman, P. G.; Cryberg, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 5176–5177.
(7) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26–33.
(8) Gassman, P. G.; Carrasquillo, A. *Tetrahedron Lett.* **1971**, 109–112.
(9) Gassman, P. G.; Hartman, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 449–454.
(10) Wasserman, H. H.; Adickes, H. W.; de Ochoa, O. E. *J. Am. Chem. Soc.* **1971**, *93*, 558–559.
(11) (a) Kovacic, P.; Liu, J.-H.; Levi, E. M.; Roskos, P. D. *J. Am. Chem. Soc.* **1971**, *93*, 5801–5805. (b) Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev.* **1970**, *70*, 639.
(12) (a) Schell, F. M.; Ganguly, R. N.; Percell, K. S.; Parker, J. E., III. *Tetrahedron Lett.* **1979**, 4925–4928. (b) Schell, F. M.; Ganguly, R. N. *J. Org. Chem.* **1980**, *45*, 4069–4070. (c) Schell, F. M.; Smith, A. M. *Tetrahedron Lett.* **1983**, *24*, 1883–1884.
(13) Fleury, J.-P.; Biehler, J.-M.; Desbois, M. *Tetrahedron Lett.* **1969**, 4091–4094.
(14) Hoffman, R. V.; Cadena, R.; Poelker, D. J. *Tetrahedron Lett.* **1978**, 203–206.
(15) Hoffman, R. V.; Poelker, D. J. *J. Org. Chem.* **1979**, *44*, 2364–2369.
(16) Hoffman, R. V.; Kumar, A. *J. Org. Chem.* **1985**, *50*, 1859–1863.
(17) Hoffman, R. V.; Kumar, A.; Buntain, G. A. *J. Am. Chem. Soc.* **1985**, *107*, 4731–4736.
(18) Hoffman, R. V.; Buntain, G. A. *J. Org. Chem.* **1988**, *53*, 3316–3321.
(19) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1989**, *30*, 4207–4210.
(20) Hoffman, R. V.; Salvador, J. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1375-1380.
(21) Heesing, A.; Herdering, W. *Chem. Ber.* **1983**, *116*, 1081–1096.
(22) Hoffman, R. V. *Tetrahedron* **1991**, *47*, 1109–1135.
(23) Wolff, H. *Org. React.* **1946**, *3*, 307–336.
(24) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley and Sons: London, 1971; pp 221–329.
(25) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, P., Ed.; John Wiley and Sons: London, 1971; pp 397–440.
(26) Smith, P. A. S. In *Derivatives of Hydrazine and Other Hydronitrogens Having N-N Bonds*; Benjamin/Cummings: London, 1983; pp 263–300.
(27) Kyba, E. P. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, FL, 1984; pp 2–34.
(28) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.

0002-7863/93/1515-10183$04.00/0

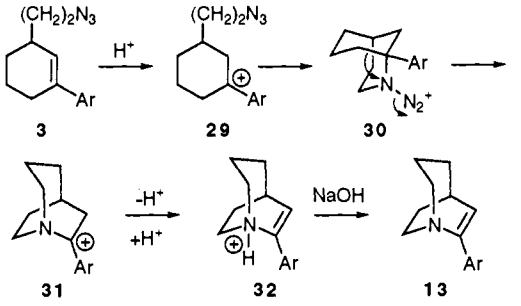
Table I. Schmidt Cyclizations of Azidoalkenes and Azidoalcohols

substrate	conditions[a]	product(s)	% yield (ratio)[b]
 3[c]	A	 13	82
 4	A	 14 15[d]	37 (1:1.1)
 5	B A	 16 17	76 (1.8:1) 53
 6	A	 18[e] 19	21 (4.3:1)
 7	B	 20 21	71 (1:1)[f]
 8	B	 22 23	79 (1:1)[f]
 9	C	 24	47
			
10 R=Ph	B	R 25	--	40 (57)[g]
11 R=*n*-C_3H_7	D	24	26	35 (1.3:1)[h] (1.9:1)[f]
12 R=*n*-C_6H_{11}	B	27	28	25 (1:1.4)[h] (1.3:1)[f]
12 R=*n*-C_6H_{11}	E	27	28	47 (1.7:1)[h]

[a] Conditions. A: TfOH, PhH; NaOH(aq). B: TfOH, PhH; $NaBH_4$, MeOH or EtOH. C: TfOH, Tf_2O, PhH; NaOH(aq). D: TfOH, PhH; BH_3·Me_2S. E: $SnCl_4$, CH_2Cl_2; BH_3·Me_2S. [b] Yields of isolated, purified products unless otherwise indicated. [c] Ar = 3,4-(methylenedioxy)phenyl. [d] Single geometry, presumably *Z*. [e] A 1.5:0.2:1 mixture of alkene isomers. [f] Isomers not separable by chromatography. [g] Yield by GC, using a decane internal standard and calibration. [h] Ratio of isomers before purification determined by GC. [i] Ratio of isomers after purification and separation.

a more predictable rearrangement.[3,23-29] For the transformation shown in eq 1, which proceeds through a *secondary* aminodiazonium ion, an alkyl azide is required rather than hydrazoic acid. However, the use of alkyl azides in any type of Schmidt reaction has long been thought to be unfavorable,[3,23-28] since azides are only weakly nucleophilic. Pritzkow[30] and Wiberg[31] have reported the intermolecular reaction of alkyl azides with trialkyloxonium salts or alkyl halides in the presence of silver perchlorate. Recently, Aubé reported the intermolecular and intramolecular Schmidt reactions of alkyl azides with ketones.[32-36] Another

Scheme I. Proposed Mechanism for the Rearrangement of **3**



closely related process that has been studied by Brown,[37] Evans,[38] and Vaultier[39] is the reaction of azides with boranes, which causes a similar rearrangement involving aminodiazonium ions.[40] We now wish to report the use of an alkyl azide in the intramolecular "carbocation" version of the Schmidt reaction.

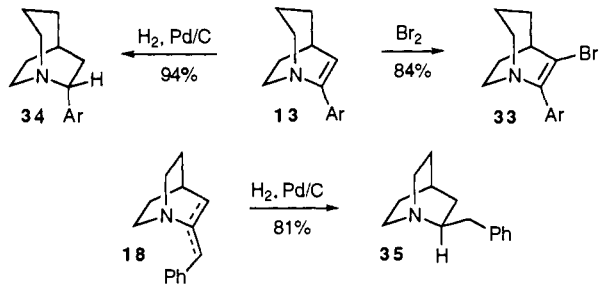
Intramolecular Schmidt Reactions

Treatment of azido alkenes and azido alcohols **3–12** with trifluoromethanesulfonic acid (triflic acid, TfOH) led to gas evolution and the isolation of the rearrangement products **13–28** after workup with base or a hydride reducing agent (Table I). A typical mechanism is illustrated in Scheme I for the cyclization of **3**. Protonation of **3** gives the carbocation **29**, which is trapped intramolecularly by the azide to produce the aminodiazonium ion **30**. A 1,2-migration of a carbon with expulsion of nitrogen gives the cation **31**, whose fate depends on the ability of the neighboring nitrogen atom to donate its electron pair by resonance. An alternative mechanism which is not shown is the loss of nitrogen from the aminodiazonium ion to produce a nitrenium ion, which would undergo a subsequent rearrangement. Nitrenium ions[6,7,41] have been proposed as intermediates in Stieglitz-type reactions studied by Gassman (vide supra). The distinction between these two mechanisms is an important one, since a concerted migration with nitrogen loss as depicted would be expected to have a stereoelectronic preference for rearrangement, while the geometrical requirements for migration to a nitrenium ion should be less stringent. A discussion of this point is presented in the next section.

Although each rearrangement in Table I presumably generates an α-amino carbocation (e.g. **31**), the bridged-bicyclic systems produced from the cyclization of **3–6** do not allow good overlap of the nitrogen lone pair with the carbocation p-orbital. Con-

(29) Shioiri, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 6, pp 795–828.
(30) Pritzkow, W.; Pohl, G. *J. Prakt. Chem.* **1963**, *20*, 132.
(31) Wiberg, N.; Schmid, H. K. *Angew. Chem.* **1964**, 381.
(32) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966.
(33) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635–1637.
(34) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141–1147.
(35) For an application of Aubé's intramolecular Schmidt reaction, see: Le Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933–2935.
(36) For a related reaction, see: Hoffman, R. V.; Salvador, J. M. *J. Org. Chem.* **1992**, *57*, 4487–4490.
(37) (a) Suzuki, A.; Sono, S.; Itoh, M.; Brown, H. C.; Midland, M. M. *J. Am. Chem. Soc.* **1971**, *93*, 4329. (b) Brown, H. C.; Salunkhe, A. M.; Singaram, B. *J. Org. Chem.* **1991**, *56*, 1170–1175. (c) Brown, H. C.; Salunke, A. M. *Tetrahedron Lett.* **1993**, *34*, 1265–1268.
(38) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151–7157.
(39) (a) Carboni, B.; Vaultier, M.; Carrie, R. *Tetrahedron* **1987**, *43*, 1799–810. (b) Carboni, B.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1988**, *29*, 1279–82. (c) Carboni, B.; Vaultier, M.; Courgeon, T.; Carrie, R. *Bull. Soc. Chim. Fr.* **1989**, 844–849. (d) Jego, J. M.; Carboni, B.; Vaultier, M.; Carrie, R. *J. Chem. Soc., Chem. Commun.* **1989**, 142–143. (e) Benalil, A.; Carboni, B.; Vaultier, M. *Tetrahedron* **1991**, *47*, 8177–94. (f) Vaultier, M.; Carboni, B.; Martinez, F. P. *Synth. Commun.* **1992**, *22*, 665–71. (g) Noiret, N.; Youssofi, A.; Carboni, B.; Vaultier, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1105–1107.
(40) For related rearrangements involving azides, see: (a) Szonyi, F.; Cambon, A. *Tetrahedron Lett.* **1992**, *33*, 2339–2343. (b) Tanino, K.; Takahashi, M.; Murayama, K.; Kuwajima, I. *J. Org. Chem.* **1992**, *57*, 7009–7010.
(41) Abramovitch, R. A.; Jeyaraman, R. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: Orlando, FL, 1984; pp 297–357.

Scheme II. Transformations of Bridged Bicyclic Enamines



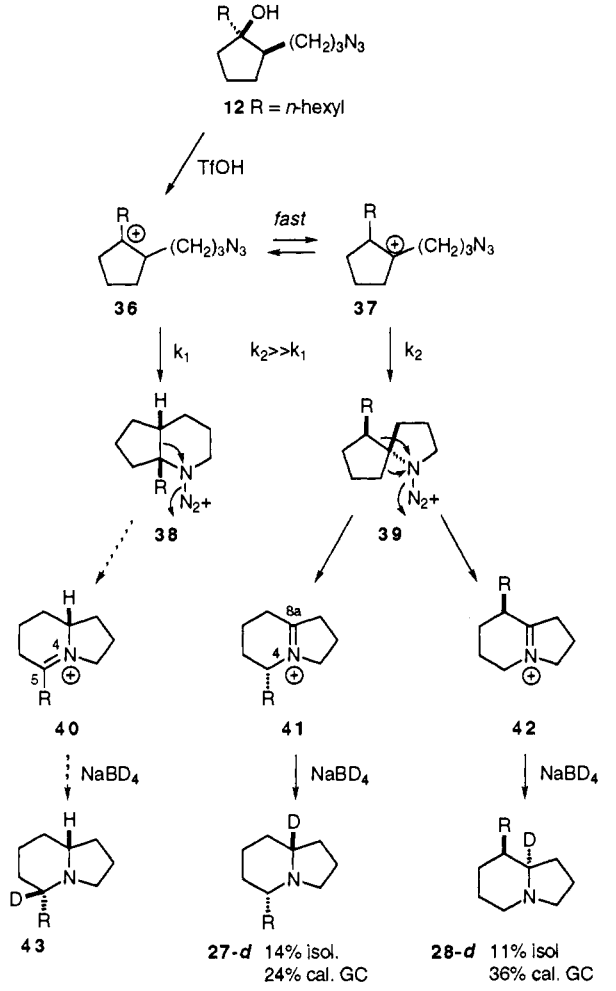
sequently, these cations are probably best considered carbocations rather than iminium ions, and they undergo a rapid deprotonation to produce a twisted enamine which is reprotonated on nitrogen (e.g. **32**). Such an N-protonated enamine **32** was observed by ^{1}H NMR when the cyclization of **3** was carried out in $CDCl_3$. Workup with base affords the twisted enamines **13–19**. Attempted reduction of the rearranged cations with sodium borohydride also led to the enamine products, further verifying that rapid proton transfers had occurred immediately after rearrangement and that **31** had a short lifetime. Cations very similar to **31** have been reported by Grob,[42] Gassman,[4,5,43] and Kovacic,[44] who found that there is some interaction of the nitrogen lone pair with the carbocation, but that the interaction is substantially less than what would be expected in an unrestricted system (i.e., an iminium ion). Calculations have also been carried out on similar cations.[45,46] Twisted enamines related to **13** have also been reported, and their N-protonation has been studied.[47–49]

The regioselectivity of the rearrangement reaction is complete in the cyclization of **3** and **4**, producing only the 1-azabicyclo-[3.2.2]nonene skeleton, although **4** produces two enamines **14** and **15** as a result of a nonselective deprotonation after rearrangement. Molecular modeling predicts that the (*Z*)-isomer of **15** (and **16**, vide infra) is favored over the (*E*)-isomer.[50] In contrast to the selectivity of the above cyclizations, rearrangement of **5** and **6** produces both the 1-azabicyclo[2.2.2]octene (**16** and **18**) and 1-azabicyclo[3.2.1]octene (**17** and **19**) systems. Again, a mixture of enamines is observed for **18** as a result of a nonselective deprotonation step. The regioselectivity of these rearrangements is discussed below.

The synthesis of bridged-bicyclic amines by the intramolecular Schmidt reaction may be useful for the synthesis of alkaloids. For example, the quinuclidines **16** and especially **18** are reminiscent of the Cinchona class of alkaloids. Some transformations of these systems are shown in Scheme II. Bromination of the enamine **13** cleanly produces the β-bromoenamine **33**. Hydrogenation of **13** produces a single stereoisomer of **34**. Reduction of **18** proceeds smoothly, producing the quinuclidine **35**, which has an even closer resemblance to the Cinchona alkaloids.

Cyclization of azides **7–12** followed by workup with sodium borohydride or borane–dimethyl sulfide[51] complex produced the fused-bicyclic amines **20–28**. In this type of cyclization, a true

Scheme III. Rearrangement of Carbocation Prior to Cyclization and Deuterium Labeling Study



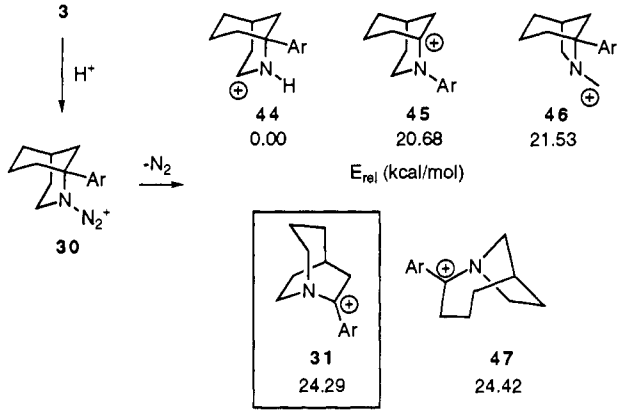
iminium ion is clearly produced, as evidenced by the isolation of amines rather than enamines upon hydride treatment. Triflic acid generally gave the best results, although the cyclization of the azido alcohol **12** was best accomplished with stannic chloride. Alkenes tended to produce higher yields than alcohols (c.f. **7** and **8** vs **9–12**).

This method for the synthesis of fused-bicyclic tertiary amines should be useful for the synthesis of a variety of alkaloids. In fact, the indolizidines **24** (indolizidine 167B) and **27** (indolizidine 209D) are alkaloids isolated in minute quantities from the skin secretions of neotropical frogs[52] and are produced from the cyclizations of **9**, **11**, and **12**. The cyclization of **8** is an efficient entry into the relatively unexplored[32,53] 1-azabicyclo[5.3.0]decane system found in alkaloids such as stenine.[54]

The cyclizations of **7**, **8**, **11**, and **12** were unusual in that an unexpected regioisomer was formed in each case (i.e., compounds **21**, **23**, **26**, and **28**). This was shown to be a result of rearrangement of the initially formed carbocation prior to capture by the azide. Scheme III shows a mechanistic study of the cyclization of **12**. Ionization to the carbocation **36** followed by intramolecular reaction with the azide might be expected to produce the

(42) Grob, C. A.; Sieber, A. *Helv. Chim. Acta* **1967**, *50*, 2531.
(43) Gassman, P. G.; Cryberg, R. L.; Shudo, K. *J. Am. Chem. Soc.* **1972**, *94*, 7600.
(44) (a) Fisher, R. D.; Bogard, T. D.; Kovacic, P. *J. Am. Chem. Soc.* **1972**, *94*, 7599. (b) Fisher, R. D.; Bogard, T. D.; Kovacic, P. *J. Am. Chem. Soc.* **1973**, *95*, 3646.
(45) Nelsen, S. F.; Wang, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7923–7924.
(46) González, J.; Taylor, E. C.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3753–3755.
(47) Grob, C. A.; Kaiser, A.; Renk, E. *Chem. Ind. (London)* **1957**, 598.
(48) Wepster, B. M. *Recl. Trav. Chim. Pays-Bas.* **1952**, *71*, 1171.
(49) Krabbenhoft, H. O.; Wiseman, J. R.; Quinn, C. B. *J. Am. Chem. Soc.* **1974**, *96*, 258.
(50) Minimizations were carried out with BAKMDL on an IBM RS/6000 computer. BAKMDL is the batch mode minimizer sister program of MODEL, by Professor Kosta Steliou, Department of Chemistry, Boston College, Chestnut Hill, MA, 02167. We thank Professor Mark Midland, University of California—Riverside, for the UNIX version of BAKMDL. Calculations were carried out with the statistical search on coordinates option.
(51) Maryanoff, B. E.; McComsey, D. F.; Leo, G. C.; Almond, H. R., Jr. *J. Org. Chem.* **1992**, *57*, 1190–1195.
(52) For recent syntheses of these alkaloids, see: (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688–4693. (b) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393–1405. (c) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513–3518. (d) Fleurant, A.; Célérier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1992**, *3*, 695–696. (e) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119–3122.
(53) Trost, B. M.; Pedregal, C. *J. Am. Chem. Soc.* **1992**, *114*, 7292–7294.
(54) Chen, C.-y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236–6240.

Scheme IV. Possible Rearrangement Products of Aminodiazonium Ion **30** and Their Relative AM1 Energies



aminodiazonium ion **38**, which may rearrange as shown to give the $\Delta^{4,5}$-iminium ion **40**. Alternatively, **36** may undergo a 1,2-hydride shift to give the cation **37**, which is nearly the same energy as the original cation. Cyclization onto the azide would then produce the spirocyclic aminodiazonium ion **39**. Migration of two adjacent bonds would then give the $\Delta^{4,8a}$-iminium ions **41** and **42**. Hydride reduction would produce the observed regioisomeric indolizidines **27** and **28**. To distinguish these pathways, we used sodium borodeuteride in the reduction step. Only indolizidines bearing deuterium at C(8a) were produced, indicating that all of the rearranged products originate from cation **37**. A fast and reversible 1,2-hydride migration is probably taking place, and the rate of cyclization of **37** to produce a five-membered ring aminodiazonium ion is higher than the rate of cyclization of **36** to produce a six-membered ring ion (i.e., $k_2 > k_1$).[55] Another unusual feature of these cyclizations is the low regioselectivity of the migration in the spirocyclic aminodiazonium ions. Normally, one would expect the more substituted group to migrate preferentially, which would produce compounds **20**, **22**, **24**, and **27** as the major products. The observation of nearly equal amounts of the two possible rearrangement products in each case is intriguing, and is the subject of ongoing investigation. Although this low selectivity is undesirable for the synthesis of a particular indolizidine alkaloid such as **24** (indolizidine 167B), the alternative construction using the cyclization of **9** is completely regioselective. An advantage of the intramolecular Schmidt reaction as a route to bicyclic amines is the ability to explore more than one disconnection for the synthesis of a particular system.

Regioselectivity of the Rearrangements

One of the more interesting aspects of the intramolecular Schmidt reactions described above is their regioselectivity. For example, aminodiazonium ion **30** (or the corresponding nitrenium ion) derived from **3** could produce five possible rearrangement products, shown as **31** and **44–47** (Scheme IV). Previous work on a variety of C-to-N rearrangements, including Stieglitz and Schmidt rearrangements, does not provide a consistent picture of the regioselectivity of such migrations.[3,16,18,24–28] In particular, rearrangements of aminodiazonium ions derived from hydrazoic acid additions to carbocations (or by protonation of azides) are not relevant to our work, since free rotation is possible about the C–N bond, therefore masking any stereoelectronic effects. The closest analogies are the Stieglitz-type rearrangements of secondary *N*-chloramines and secondary *N*-sulfonoxyamines, particularly in bridged-bicyclic systems.[4–21,41] The most relevant examples to the current work (generally rigid bicyclo[2.2.1] systems) are thought to rearrange by migration of the group that is antiperiplanar to the N–X bond,[16] although a nitrenium ion mechanism is also proposed.[7,41]

Analysis of our systems is complicated by three factors. First, the stereoelectronic requirement for migration will depend on the mechanism of the reaction: Is it a concerted 1,2-shift with simultaneous expulsion of nitrogen, or is it a two-step mechanism involving nitrenium ion formation followed by 1,2-shift? Although both have been proposed for Stieglitz rearrangements,[41] there is no conclusive evidence for the mechanism of the rearrangement of secondary aminodiazonium ions. Second, if the concerted mechanism is important, what is the structure of the aminodiazonium ion? Is it planar or pyramidal at the internal nitrogen atom? Are the three nitrogen atoms linear or bent? In order to discuss the possibility that an antiperiplanar bond migrates preferentially, the structure of this intermediate must be known. Alternatively, if the mechanism is nitreniumoid, one must also be able to predict the structure of such an intermediate (including the multiplicity of the nitrenium ion) in order to discuss migratory stereoelectronics. Finally, the higher conformational flexibility of our bicyclic systems versus bicyclo[2.2.1] systems in the literature requires conformational analysis of the aminodiazonium ion or nitrenium ion intermediate. Different conformations may place several different groups in the proper position for migration.[16] Superimposed on a discussion of stereoelectronics is the migratory aptitude of various groups and the ability of the migratory origin to stabilize a positive charge.[56] All of these factors may be important, making it difficult to propose a model that will have useful predictive power. Nonetheless, we have attempted to develop a working model, as discussed below.

Before pursuing a regiochemical explanation based on stereoelectronic considerations, we addressed the simplest explanation for the regioselectivity of the Schmidt reaction of **3**, i.e. that rearrangement to the most stable carbocation is observed. Since the stabilization of the carbocation may be strongly influenced by the ability of the nitrogen to donate its lone pair by resonance, we felt that the possible cations **31** and **44–47** might vary widely in their stability. The energies of these cations were calculated by a combination of molecular mechanics[50] and semiempirical molecular orbital (AM1) methods.[57] The AM1 energies of **31** and **44–47** are shown in Scheme IV. Cation **31**, which leads to the observed product **13**, was found to be one of the highest energy molecules. The lowest energy product was **44**, the result of hydrogen migration (or deprotonation/reprotonation). That cation **31** is 24 kcal/mol higher in energy than the alternative cation **44** indicates that product stability does not control the rearrangement. This is reasonable, since rearrangement may initially produce ions that are not in the proper conformation to benefit from resonance stabilization. We then turned to an examination of the proposed aminodiazonium ion intermediate.

The aminodiazonium ions **30**, **39**, and **48–55** proposed in the rearrangement of azides **3–12** are shown in Scheme V. The bonds that are observed to migrate are emboldened. We have no firm evidence that the aminodiazonium ions rearrange in a concerted fashion rather than proceed through a nitrenium ion, but we currently favor the former mechanism for the following reasons.

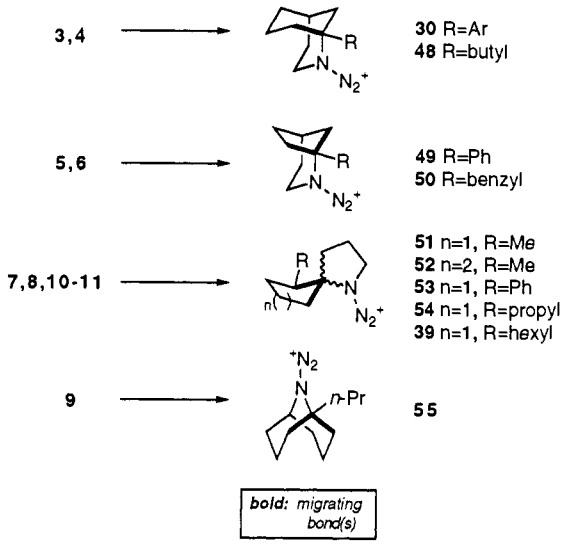
First, a review of the related literature of Stieglitz-type rearrangements provides good evidence that the rearrangement of *N*-(arylsulfonoxy)amines and even *N*-chloramines proceed through a concerted mechanism[16] and that nitrenium ions need not be invoked.[17,41] The analysis made by Hoffman[16,17] for these systems also appears reasonable for aminodiazonium ion rearrangements.

(55) A reviewer suggested an alternative process, where the formation of **38** and **39** is reversible and the products are a result of rearrangement of **39** at a rate faster than that of **38**.

(56) For an excellent discussion of the interplay of stereoelectronics and the electronic character of the migrating group and migrating origin, see ref 16.

(57) Semiempirical AM1 calculations[a] were carried out with MOPAC.[b] (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909. (b) Stewart, J. J. P. Quantum Chemistry Program Exchange No. 455, Version 6.0.

Scheme V. Proposed Aminodiazonium Ion Intermediates



Second, the completely regioselective rearrangement of **3** and **4** (via **30** and **48**) is significant. Examination of structures **30** and **48** in Scheme V does not offer a reasonable explanation for the regioselective migration if a discrete nitrenium ion is formed. Departure of nitrogen would leave an sp^2 hybridized nitrenium ion that is nearly symmetrical. Migration of any one of three neighboring CH_2R groups (but especially one of the two groups attached to the quaternary carbon) could occur without a geometrical problem. If the migration is concerted and if the aminodiazonium ion is pyramidal at the internal nitrogen (vide infra), the departing nitrogen molecule may be preferentially oriented nearly antiperiplanar to one of the neighboring bonds, resulting in regioselective migration.

Finally, aminodiazonium ions have been studied experimentally, whereas firm evidence for the intermediacy of aliphatic nitrenium ions in rearrangement reactions is less straightforward.[17,41] Olah studied the structure of three aminodiazonium ions by NMR spectroscopy.[58] Protonation of HN_3, CH_3N_3, and $CH_3CH_2N_3$ in superacid media gave the aminodiazonium ions which were observable by NMR. Recently, Christe isolated salts of $H_2N_3^+$ that are stable at room temperature and determined their structures by X-ray crystallography.[59] Schmidt had earlier determined the IR spectra of such species.[60] Glaser studied aminodiazonium ions computationally[61-63] and estimated that dissociation to the nitrenium ion is unfavorable (vide infra).[62] While the existence of aminodiazonium ions does not prove that they rearrange in a concerted fashion, the structural data on these compounds may allow the development of mechanistic hypotheses that may be tested experimentally.

It is possible that the regioselectivity of the Schmidt reactions described herein may be explained to a large extent with a stereoelectronic model, where migration of a bond that is approximately antiperiplanar to the departing nitrogen in the aminodiazonium ion is preferred. However, the electronic characteristics of the migrating group and the migrating origin must also be taken into account, since their ability to bear a partial positive charge in the transition state is important.[16] While it is difficult to model the latter electronic effects, the stereoelectronic effects were examined computationally. In order to do so, we must be able to model the aminodiazonium ions, which requires structural information on these species. Olah proposed that aminodiazonium ions are planar species on the basis of NMR studies.[58] This was supported by RHF/3-21G ab initio molecular orbital calculations. Since we require calculations that are reasonably CPU-efficient for our large molecules, we modeled a variety of aminodiazonium ions with semiempirical molecular orbital methods (AM1,[64] PM3,[65] and MNDO[66]) using the MOPAC program[57b] and found that, although the bond lengths agree well with Olah's studies, the internal nitrogen atom was pyramidal in each case. Recent computational studies by Glaser with higher level calculations also showed that $H_2NN_2^+$ is pyramidal at the internal nitrogen.[61-63] The barrier to inversion was also calculated and found to be small (ca. 1 kcal/mol).[61] The dediazoniation energy for the loss of nitrogen from $H_2NN_2^+$ to give the nitrenium ion H_2N^+ was found to be approximately 50–70 kcal/mol, depending on the method used.[62,63] Glaser therefore suggests that aminodiazonium ions are relatively stable toward dediazoniation and are reasonable intermediates for the Schmidt reaction. This is in contrast to earlier studies by Cacace, who has suggested the energy difference is only 1.7 kcal/mol.[67] Most important to our model is Christe's recent isolation and characterization of $H_2NN_2^+$.[59] This stable ion was found to be pyramidal at the internal nitrogen, on the basis of both X-ray crystallographic data and LDF calculations. A comparison of the experimental and the best theoretical structures for $H_2NN_2^+$ with the results from AM1 calculations reveals that the latter calculations (fortuitously, perhaps) produce results that are in agreement with the experimental data (Table II). Especially relevant to this discussion is the degree of pyramidalization of the internal nitrogen atom, as measured by the sum of the three bond angles to this atom (planar = 360°, trigonal bipyramid = 328.5°).

With a reasonable semiempirical method in hand, we turned to modeling the aminodiazonium ion **30**. Molecular mechanics minimization of 1-aryl-2-azabicyclo[3.3.1]nonane was first carried out to generate a set of low-energy conformations for this amine.[50] The N–H bond was then transformed into an $N–N_2^+$ group, and geometry optimizations using AM1 calculations were run on each conformation. The two lowest energy aminodiazonium ions $\mathbf{30_{ax}}$ and $\mathbf{30_{eq}}$ are shown in Figure 1 along with selected dihedral angles. The degree of pyramidalization at the ring nitrogen atom was 342° and 347°, respectively. The conformation with the axial diazonium group was favored over the conformation with the equatorial diazonium group by 2.14 kcal/mol. Examination of the relevant dihedral angles in $\mathbf{30_{ax}}$ shows that the carbon–carbon bond that is experimentally observed to break is indeed approximately antiperiplanar (156.5°) to the departing dinitrogen group. Other C–C bonds in $\mathbf{30_{ax}}$ are not oriented properly for migration with the exception of the $C_3–H_3$ bond, which is approximately antiperiplanar to the leaving group and might also be expected to migrate. However, hydrogen migrations are seldom observed in Schmidt and Stieglitz reactions, perhaps due to the poorer ability of hydrogen versus carbon to bear a partial positive charge in the transition state.[21,41] While the C(9)–C(1) bond of $\mathbf{30_{eq}}$ has a reasonable geometry for migration, this aminodiazonium ion is of higher energy.

The predictive power of the above model has not yet been examined for other systems (e.g., aminodiazonium ions **39** and **49–55**), and a nitrenium ion mechanism cannot be completely ruled out for any of these rearrangements. Further studies to address these issues are underway.

Preparation of Azides

Another attractive feature of the intramolecular Schmidt reactions described herein is the ease by which the cyclization

(58) Mertens, A.; Lammertsma, K.; Arvanaghi, M.; Olah, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 5657–5660.
(59) Christe, K. O.; Wilson, W. W.; Dixon, D. A.; Khan, S. I.; Bau, R.; Metzenthin, T.; Lu, R. *J. Am. Chem. Soc.* **1993**, *115*, 1836–1842.
(60) Schmidt, A. *Chem. Ber.* **1966**, *99*, 2976.
(61) Glaser, R.; Choy, G. S.-C. *J. Chem. Phys.* **1991**, *95*, 7682–7693.
(62) Glaser, R.; Choy, G. S.-C. *J. Org. Chem.* **1992**, *57*, 4976–86.
(63) Glaser, R.; Choy, G. S.-C.; Horan, C. J. *J. Org. Chem.* **1992**, *57*, 995–999.
(64) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
(65) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221.
(66) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.
(67) Cacace, F.; Attina, M.; De Petris, G.; Grandinetti, F.; Speranza, M. *Gazz. Chim. Ital.* **1990**, *120*, 691.

Table II. Comparison of Experimental and Computationally Derived Structures of H(1)H(2)N(1)N(2)N(3)$^+$

	X-ray[a]	AM1[b]	LDF[a]	MP2(full)/6-31G* [c]	RHF/6-31G* [d]
bond lengths (Å)					
N(1)N(2)	1.295	1.321	1.305	1.300	1.28
N(2)N(3)	1.101	1.118	1.126	1.136	1.08
bond angles (deg)					
N(1)N(2)N(3)	175.35	169.65	175.2	174.04	
H(1)N(1)N(2)	107.6	111.82	114.5	113.47	117.2
H(2)N(1)N(2)	107.6	111.82	114.5	113.47	
H(1)N(1)H(2)	118.8	113.79	117.9	118.28	
pyramidalization at N(1) (deg)[e]	332	337	347	345	360

[a] Christe *et al.*[59] [b] This work. [c] Glaser *et al.*[61] [d] Mertens *et al.*[58] [e] Sum of the angles H(1)N(1)N(2), H(2)N(1)N(2), and H(1)N(1)H(2). A planar nitrogen would total 360°, an ideal pyramidal atom would be 328.5°.

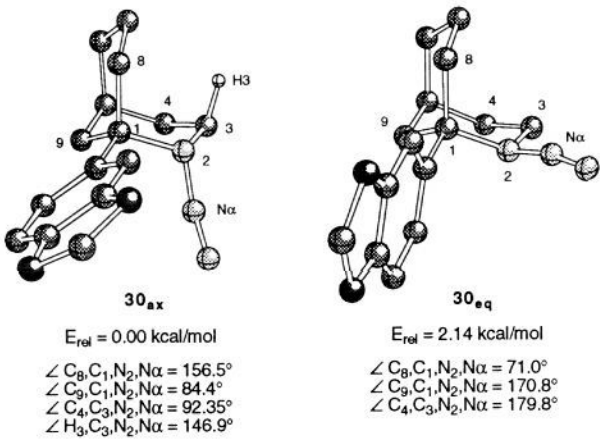


Figure 1. Lowest energy structures of aminodiazonium ions **30** as determined by AM1 calculations.

precursors can be prepared. Scheme VI shows how these compounds were synthesized from known starting materials **56–62**.

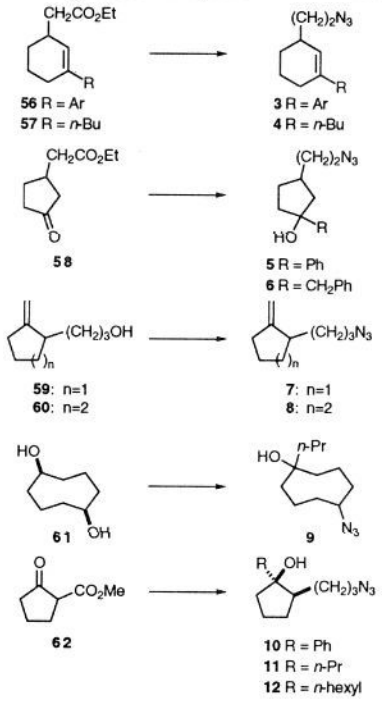
Conclusion

The intramolecular reaction of aliphatic azides with carbocations leads to the formation of cyclic aminodiazonium ions, which rearrange by either a concerted (but perhaps highly asynchronous) or two-step nitreniumoid mechanism. The cyclization substrates are easily prepared. The products from the intramolecular Schmidt reaction are bridged- or fused-bicyclic tertiary amines of the type found in many types of alkaloids. In fact, this method produced the natural indolizidines 167B and 209D with reasonable efficiency. The intramolecular Schmidt reaction with carbocations is complementary to work with ketones by Aubé and with boranes by Brown,[37] Evans,[38] and Vaultier.[39] Studies on other types of carbon electrophiles are underway, as well as applications to other naturally occurring compounds.

Experimental Section

General Procedures. Reagents and starting materials were obtained from commercial suppliers and were used without further purification unless noted. Anhydrous cerium trichloride was prepared by drying cerium trichloride heptahydrate according to the procedure of Imamoto.[68] Trifluoromethanesulfonic acid was distilled prior to use. Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl. Methylene chloride, benzene, and triethylamine were distilled from calcium hydride. Dimethylformamide was distilled from barium oxide at reduced pressure. All reactions were conducted under an atmosphere of dry nitrogen. Chromatography refers to flash column chromatography on silica gel (230–400 mesh) unless otherwise noted. Deactivated silica was prepared by adding 20% by weight of hexamethyldisilazane to a suspension of silica gel in hexane. After cooling, the resulting mixture was used to wet-pack a chromatography column. The column was then washed successively with ethyl acetate, 50% ethyl acetate/hexane, and finally the desired elution solvent before loading the sample. Combustion analyses were performed by Spang Microanalytical Laboratories (Eagle Harbor, MI) or by the microanalytical facility operated by the University of Michigan. The results of 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). Gas chromatographic (GC) analysis was performed on a 530-μ methyl polysiloxane column (3-μm film thickness, 15-m length, flame ionization detector) using a temperature program of 100 °C for 1 min then a 40 °C/min ramp to 200 °C.

Scheme VI. Synthesis of Cyclization Precursors



Transformation	Reagents/Yields
56 → 3	$LiAlH_4$ (89%); MsCl, NEt_3; Bu_4NN_3 (86%)
57 → 4	$LiAlH_4$ (72%); MsCl, NEt_3; NaN_3 (73%)
58 → 5	PhMgBr, $CeCl_3$; $LiAlH_4$ (78%); TsCl, py; NaN_3 (61%)
58 → 6	$PhCH_2MgCl$, $CeCl_3$; $LiAlH_4$ (49%); TsCl, py; NaN_3 (76%)
59 → 7	TsCl, py; NaN_3 (89%)
60 → 8	TsCl, py; NaN_3 (89%)
61 → 9	NaH; TBSCl (94%); MsCl, NEt_3; Bu_4NN_3 (93%); Bu_4NF (90%); PCC/Al_2O_3 (96%); *n*-PrMgBr, $CeCl_3$ (61%)
62 → 10-12	*t*-BuOK; $Cl(CH_2)_3I$ (92%); HBr; NaN_3 (52%); PhMgBr (69%) for **10**, *n*-PrMgBr, $CeCl_3$ (64%) for **11**, *n*-hexylMgBr, $CeCl_3$ (62%) for **12**

7-[3,4-(Methylenedioxy)phenyl]-1-azabicyclo[3.2.2]non-6-ene (13). The azide **3** (0.366 g, 1.35 mmol) in benzene (10 mL) was cooled on an ice–water bath and treated with trifluoromethanesulfonic acid (0.41 g, 0.24 mL, 2.70 mmol). The solution immediately turned red, and gas evolution was observed. After 5 min, 15% NaOH (15 mL) was added and the mixture was stirred vigorously for 10 min. Saturated aqueous NH_4Cl (25 mL) was then added, and the mixture was extracted twice with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (25% EtOAc/hexane) gave 269 mg (82%) of the title compound as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, J = 8.1 Hz, 1 H), 7.18 (s, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.68 (d, J = 7.6 Hz, 1 H), 5.94 (s, 2 H), 3.20

(68) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

(m, 1 H), 2.95 (m, 3 H), 2.57 (m, 1 H), 2.03 (m, 3 H), 1.65 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.84, 147.74, 146.91, 132.40, 125.02, 118.20, 107.90, 105.07, 100.78, 51.29, 48.15, 32.69, 30.47, 30.34, 25.78; IR (neat) 1604 (w), 1502 (m), 1486 (s), 1437 (m), 1245 (s), 1040 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 244 (M^+ + 1, 10.0), 243 (M^+, 61.1), 242 (65.1), 214 (100.0), 186 (2.1), 184 (2.1), 174 (7.2), 156 (4.4), 146 (2.8), 77 (8.0), 41 (10.5). Performing the reaction in dichloromethane at −78 °C for 1 h produced **13** in 80% purified yield.

7-Butyl-1-azabicyclo[3.2.2]non-6-ene (14) and (*Z*)-7-(Butylidene)-1-azabicyclo[3.2.2]nonane (15). Trifluoromethanesulfonic acid (0.53 g, 0.31 mL, 3.5 mmol) was added to a cool (15 °C) solution of **4** (0.48 g, 2.3 mmol) in benzene (23 mL). The solution was warmed to room temperature and stirred for 2 h, then quenched with 15% NaOH (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Chromatography (0%–10% EtOAc/hexane gradient, basic alumina, Brockmann I) provided 75 mg (18%) of **14**, R_f= 0.75 (3% EtOAc/hexane, alumina plate) and 81 mg (19%) of **15**, R_f= 0.25 (3% EtOAc/hexane, alumina plate). Data for **14**: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 4.7 (t, *J* = 6.3 Hz, 1 H), 2.8–3.1 (m, 4 H), 1.4–2.2 (m, 11 H), 1.35 (m, 2 H), 0.9 (t, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$,90 MHz) δ 146, 118.1, 57.6, 45.6, 36.1, 31.7, 28.3, 27.7, 25.1, 23.0, 14.02; IR (neat) 2922, 1667, 1453, 1142, 1060 cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 179 (13.4), 150 (33.2), 137 (11.5), 136 (100.0), 122 (21.2), 108 (15.4), 96 (11.7), 94 (10.4), 84 (6.6), 55 (13.3); HRMS calcd for $C_{12}H_{21}N$ 179.1674 ($M + H^+$), found 179.1682. Data for **15**: ^{1}H NMR ($CDCl_3$,360 MHz) δ 5.24 (t, *J* = 6.3 Hz, 1 H), 3.20 (m, 4 H), 2.45 (d, *J* = 17 Hz, 1 H), 2.2 (m, 1 H), 1.9 (q, *J* = 7.4 Hz, 2 H), 1.6 (m, 7 H), 1.40 (m, 2 H), 0.9 (t, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$,90 MHz) δ 146, 120.9, 60.2, 46.3, 33.0, 31.8, 28.6, 27.7, 27.5, 24.5, 22.7, 13.8; IR (neat) 1470, 1381, 912 cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 179 (18.4), 150 (41.7), 136 (100), 122 (21.1), 108 (13.4), 96 (11.2), 94 (8.9), 55 (12.3), 44 (10.3), 42 (12.0), 39 (11.67); HRMS calcd for $C_{12}H_{21}N$ 179.1674 ($M + H^+$), found 179.1686.

2-Phenyl-1-azabicyclo[2.2.2]oct-2-ene (16) and 2-Phenyl-1-azabicyclo-[3.2.1]oct-2-ene (17). A cold (ca. 5 °C) solution of **5** (292 mg, 1.26 mmol) in benzene (8 mL) was added to trifluoromethanesulfonic acid (294 mg, 1.96 mmol). The reaction mixture was warmed to room temperature for 15 min, then a solution of $NaBH_4$ (143 mg, 3.78 mmol) in methanol (8 mL) was added. After 5 min, saturated aqueous $NaHCO_3$ (5 mL) was added. The resulting mixture was extracted with ether (3 × 20 mL), and the combined organic phases were washed with brine (3 x 20 mL), dried ($MgSO_4$), and concentrated to give 0.22 g of crude product, which was found to be a 1.8:1 mixture of **16** and **17** by ^{1}H NMR. Chromatography (1:7 EtOAc/petroleum ether) gave 31 mg (13%) of **17** as a clear oil, R_f = 0.37 (1:7 EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.70–7.67 (m, 2 H), 7.35-7.23 (m, 3 H), 5.79–5.77 (m, 1 H), 3.13–2.91 (m, 4 H), 2.59–2.48 (m, 2 H), 1.96–1.91 (m, 2 H), 1.57–1.53 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 151.73, 138.08, 128.14, 127.43, 125.40, 112.74, 57.79, 57.75, 35.55, 32.17, 31.78; IR (neat) 2949 (m), 2872 (m), 1490 (s), 1446 (s), 768 (s), 736 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 185 (M^+, 46.8), 184 (100), 156 (19.8), 128 (12.7), 91 (12.3); HRMS calcd for $C_{13}H_{15}NH$ 186.1283, found 186.1278. Further elution gave 100 mg (43%) of a mixture of **16** and **17**, followed by 45 mg (19%) of pure **16** as a clear colorless oil, R_f = 0.27 (1:7 EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.71–7.68 (m, 2 H), 7.337–7.25 (m, 3 H), 6.96 (d, *J* = 7.1 Hz, 1 H), 3.10–3.06 (m, 2 H), 2.77–2.64 (m, 3 H), 1.72–1.52 (m, 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 150.57, 136.35, 128.29, 128.12, 127.28, 124.30, 48.85, 28.96, 27.41; IR (neat) 2942 (s), 2864 (s), 1489 (s), 1451 (m), 1344 (s), 1311 (m), 1113 (s), 1060 (s), 1013 (s), 821 (s), 757 (s), 693 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 185 (M^+, 46.8), 184 (100), 156 (19.8), 128 (12.7), 91 (12.3); HRMS calcd for $C_{13}H_{15}$-NH186.1283, found 186.1283. The combined yield of **16** and **17** was 76%. A similar experiment without a sodium borohydride workup (i.e., only aqueous NaOH was used) gave **16** and **17** in 53% yield. Note that the order of combination of reagents is different in these experiments. A combined yield of 54% was obtained when the reaction was carried out by addition of trifluoromethanesulfonic acid to a solution of **3** in benzene, which is usually the preferred order of addition.

2-(Phenylmethyl)-1-azabicyclo[2.2.2]oct-2-ene (18a), 2-Benzylidene-1-azabicyclo[2.2.2]octane (18b), and 2-(Phenylmethyl)-1-azabicyclo[3.2.1]-oct-2-ene (19). A cold (ca. 5 °C) solution of **6** (1.30 g, 5.29 mmol) in benzene (20 mL) was added to triflic acid (1.41 mL, 2.39 g, 15.93 mmol). After 40 min, 15% aqueous NaOH (10 mL) was added. The resultant mixture was extracted with ether (3 × 50 mL), and the combined organic phases were washed with brine (3 × 50 mL), dried ($MgSO_4$), and concentrated. Chromatography (5% MeOH/EtOAc) gave 45 mg (4%) of **19** as a clear oil, R_f = 0.24: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.15 (m, 5 H), 4.86–4.84 (m, 1 H), 3.32 (s, 2 H), 3.13–3.05 (m, 1 H), 2.88–2.68 (m, 3 H), 2.35–2.29 (m, 2 H), 1.94–1.42 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 153.40 (–), 139.31 (–), 129.11 (+), 128.24 (+), 125.96 (+), 113.25 (+), 57.80 (–), 57.37 (–), 42.65 (–), 34.75 (–), 31.80 (+), 31.6 (–); IR (neat) 3026 (s), 2831 (m), 1651 (s), 1494 (s), 1451 (s), 1354 (m), 1149 (s), 1086 (s), 974 (s), 930 (s), 723 (s), 698 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 199 (M^+, 100), 198 (M^+ – 1, 60.4), 170 (19.3), 115 (21.7), 95 (36.2), 91(82.8); HRMS calcd for $C_{14}H_{17}N$ 199.1361, found 199.1357. Further elution gave 181 mg (17%) of an inseparable 1:1.7 mixture of **18a,b** (the latter was a 7.5:1 mixture of *Z* and *E* isomers), R_f = 0.12 (5% MeOH/EtOAc): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.36–7.17 (m, 13.5 H), 6.43–6.42 (m, 1.5 H), 6.38–6.03 (m, 0.2 H), 6.05–6.03 (d, *J* = 6.9 Hz, 1 H), 3.38 (s, 2 H), 3.17–2.96 (m, 7 H), 2.93–2.75 (m, 2.5 H), 2.59 (s, 3 H), 2.53–2.30 (m, 4 H), 2.06–2.02 (m, 1.5 H), 1.96–1.62 (m, 1 H), 1.61–1.41 (m, 9 H), 1.40–1.36 (m, 2.5 H); partial ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 129.19 (+), 128.93 (+), 128.52 (+), 128.37 (+), 128.21 (+), 126.14 (+), 125.98 (+), 121.44(+), 49.52 (–), 48.97 (–), 40.96 (–), 34.74 (–), 29.10 (–), 27.03 (+), 26.33 (–), 23.94 (+); IR (neat) 2940 (s), 2866 (s), 1654 (s), 1453 (m), 1057 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 199 (M^+, 100), 184 (13.1), 170 (45.8), 158 (24.5), 115 (41.8), 91 (47.7), 39 (32.5); HRMS calcd for $C_{14}H_{17}N$ 199.1361, found 199.1356. These compounds were found to be unstable and were reduced immediately to the more stable amine **35** without further manipulation (vide infra).

(5*R,8a*R**)-5-Methylindolizidine (20) and (8*S**,8a*S**)-8-Methylindolizidine (21).** Triflic acid (1.250 g, 8.34 mmol) was added to a cool (5 °C) solution of azide **7** (920 mg, 5.56 mmol) in benzene (55 mL). After 45 min, $NaBH_4$ (631 mg, 16.68 mmol) was added via a pressure equalized solid addition funnel. Methanol (10 mL) was immediately added, and the resulting mixture was stirred for 10 h. Aqueous NaOH (25 mL, 15% w/v) was added, and the resulting mixture was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine (2 × 25 mL) and water (2 × 25 mL), then dried ($MgSO_4$) and concentrated. Chromatography on deactivated silica gel (12% acetone/hexane) afforded 546 mg (71% yield) of a 1:1 mixture of the title compounds as an inseparable mixture as determined by GC analysis, R_f = 0.26: IR (on mixture, neat) 2928 (s), 2779 (s), 2370 (m), 2274 (m), 1457 (m), 1374 (m), 1328 (m) cm^{-1}; ^{1}H NMR (on mixture, $CDCl_3$, 360 MHz) δ 3.15–3.25 (m, 1 H), 2.95–3.1 (m, 2 H), 1.1–2.1 (m, 18 H), 1.09 (s, 1 H), 1.07 (s, 1 H), 0.95 (dd, 1 H), 0.86 (s, 1 H), 0.84 (s, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 70.87, 64.81, 58.94, 54.64, 52.86, 51.78, 36.92, 34.30, 33.47, 31.06, 30.59, 29.13, 25.75, 24.74, 21.13, 20.46, 23.34, 18.87. Data for **20**: MS (EI, 70 eV) *m/z* (rel int) 139 (M^+, 9.19), 138 (13.91), 124 (100), 110 (10.39), 97 (10.53), 96 (39.17), 70 (15.60), 69 (14.73), 68 (12.66), 57 (9.33), 56 (13.71), 55 (14.19), 54 (11.65), 42 (24.68), 41 (46.94), 39 (22.75). GCMS data for **21**: MS (EI, 70 eV) *m/z* (rel int) 139 (M^+, 36.25), 138 (52.24), 124 (20.95), 111 (16.87), 110 (21.19), 97 (66.98), 96 (100), 84 (36.51), 83 (44.31), 82 (22.54), 70 (20.84), 69 (78.02), 68 (30.91), 67 (10.04), 56 (15.32), 55 (27.46), 54 (18.30), 53 (10.94), 43 (16.16), 42 (48.62), 41 (97.96), 40 (10.62), 39 (39.61). The data for **21** matched the literature values.[52a]

(2*R,7*R**)-2-Methyl-1-azabicyclo[5.3.0]decane (22) and (6*S**,7*S**)-6-Methyl-1-azabicyclo[5.3.0]decane (23).** Trifluoromethanesulfonic acid (1.25 g, 8.37 mmol) was added to a cool (5 °C) solution of **8** (750 mg, 4.18 mmol) in benzene (40 mL). After 45 min, $NaBH_4$ (630 mg, 16.7 mmol) was introduced via a pressure equalized solid addition funnel. Methanol (7 mL) was immediately added, and the mixture was stirred at room temperature for 10 h. Sodium hydroxide (15%, 20 mL) was added, and the mixture was extracted with ether (3 × 25 mL). The combined organic phases were washed with brine (2 × 25 mL) and water (2 × 25 mL), dried ($MgSO_4$), and concentrated. Chromatography on deactivated silica gel (30% acetone/hexane) afforded 487 mg (79%) of an inseparable mixture of **22** and **23** (1:1 ratio by GC analysis): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.28 (dt, *J* = 2.1, 9.0 Hz, 1 H), 3.01 (m, 2 H), 2.71 (m, 1 H), 2.60 (q, *J* = 8.9 Hz, 1 H), 2.33 (m, 4 H), 1.65 (m, 23 H), 1.14 (d, *J* = 7.6 Hz, 3 H), 0.89 (d, *J* = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 67.03, 64.09, 61.79, 57.12, 56.57, 54.93, 35.68, 34.98, 34.50, 33.38, 33.15, 29.21, 28.72, 26.14, 24.15, 23.75, 23.32, 22.50, 21.73, 15.56; IR ($CDCl_3$) 1454 (m), 1377 (m), 1251 (m), 1144 (w), 934 (s) cm^{-1}; GCMS of **22** (EI, 70 eV) *m/z* (rel int) 153 (M^+, 17.5), 138 (M^+ – CH_3, 100.0), 124 (48.8), 110 (80.3), 97 (53.5), 96 (37.2), 83 (23.1), 69 (52.3), 41 (90.5); GCMS of **23** (EI, 70 eV) *m/z* (rel int) 153 (M^+, 27.2), 138 (M^+ – CH_3, 5.6), 124 (15.9), 96 (89.0), 83 (100.0), 70 (22.4),

55 (63.8), 41 (73.4); HRMS (EI, 70 eV) calcd for $C_{10}H_{19}N$ 153.1517, found 153.1515.

(5R*,8aR*)-5-Propylindolizidine (Indolizidine 167B) (24). Trifluoromethanesulfonic anhydride (0.21 g, 0.13 mL, 0.76 mmol) and trifluoromethanesulfonic acid (0.11 g, 0.07 mL, 0.76 mmol) were added to a solution of **9** (0.16 g, 0.76 mmol) in benzene (3 mL) at 10 °C. After 1 h, $NaBH_4$ (0.11 g, 3.03 mmol) was added and the suspension was allowed to stir for 2 h. Aqueous NaOH (5 mL of 3 N solution) was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated. Chromatography (deactivated silica gel, 10% EtOAc/hexane) afforded 60.0 mg (47%) of the title compound, R_f = 0.23 (deactivated silica gel, 10% EtOAc/hexane): ^1H NMR ($CDCl_3$, 300 MHz) δ 3.22 (dt, J = 2.2, 9.2 Hz, 1 H), 1.93 (q, J = 9.0 Hz, 1 H), 1.70 (m, 10 H), 1.25 (m, 6 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 65.05 (+), 63.72 (+), 51.53 (–), 37.01 (–), 31.06 (–), 30.96 (–), 30.63 (–), 24.78 (–), 20.49 (–), 19.03 (–), 14.46 (+); IR (neat) 2870 (m), 2780 (m), 2708 (w), 1456 (w), 1380 (w), 1292 (w), 1248 (w), 1178 (w), 1128 (w), 1108 (w) cm^{-1}; MS (EI, 70 eV) 167 (M^+, 2.1), 166 (M^+ – 1, 2.2), 124 (100.0), 96 (17.0), 84 (3.7), 70 (5.5), 55 (5.8), 41 (17.3); HRMS calcd for $C_{11}H_{21}N$ 167.1674, found 167.1669. These spectral data are consistent with those previously reported.[52a]

(5R*,8aR*)-5-Propylindolizidine (Indolizidine 167B) (24) and (8R*,8aR*)-8-Propylindolizidine (26). Trifluoromethanesulfonic acid (0.79 g, 0.47 mL, 5.2 mmol) was added to a cool (15 °C) solution of **11** (0.56 g, 2.6 mmol) in benzene (26 mL). The solution was stirred at 15 °C for 5 min, cooled to 0 °C, and treated with borane–dimethyl sulfide complex (9.2 mL, 2.0 M in THF, 18.5 mmol). After 5 min at 0 °C and 24 h at room temperature, the mixture was cooled to 0 °C and water (10 mL) was added. After 1 h, the mixture was diluted with 15% NaOH (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried (K_2CO_3), and concentrated to provide a 1.3:1 mixture of **24** and **26** as determined by GC analysis (t_R for **24** = 3.15 min, t_R for **26** = 3.22 min). Chromatography on deactivated flash silica gel (0%–10% Et_2O/pentane gradient) afforded 100 mg (23%) of **24** and 53 mg (12%) of **26**. Data for **24**: see above. Data for **26**: ^1H NMR ($CDCl_3$, 360 MHz) δ 3.08 (m, 2 H), 1.0–2.1 (m, 16 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 69.7, 54.6, 52.9, 41.6, 35.7, 30.3, 29.3, 25.7, 20.6, 19.8, 14.3 cm^{-1}; IR (neat) 2930, 2870, 2779; MS (CI, NH_3) m/z (rel int) 168 (MH^+, 100.0), 167 (2.9), 147 (2.9), 136 (37.2), 121 (3.4); HRMS calcd for $C_{11}H_{21}N$ 168.1752 [$(M + H)^+$], found 168.1757.

(5S*,8aR*)-5-Phenylindolizidine (25). Trifluoromethanesulfonic acid (0.22 g, 0.13 mL, 1.5 mmol) was added to a cool (15 °C) solution of **10** (0.18 g, 0.7 mmol) in benzene (7.3 mL). The solution was warmed to room temperature for 1 h and then carefully added to a solution of $NaBH_4$ (0.11 g, 2.9 mmol) in 15 mL of dry methanol at 0 °C. After stirring overnight at room temperature, NaOH (15%, 7 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried (K_2CO_3), and concentrated. The calibrated GC yield versus decane as an internal standard was 57% before purification. Chromatography (2%–25% EtOAc/hexane gradient, basic alumina activity I) afforded 60 mg (40%) of the title compound as an oil, R_f= 0.47 (10% $CH_3OH/CHCl_3$ on SiO_2): ^1H NMR ($CDCl_3$,360 MHz) δ 7.22–7.35 (m, 5 H), 2.93 (dd, J = 11.3, 2.8 Hz, 1 H), 2.74 (td, J = 15, 1.9 Hz, 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 (+), 69.8 (+), 65.1 (+), 52.6 (–), 35.4 (–), 30.8 (–), 30.5 (–), 25.2 (–), 20.3 (–); IR ($CHCl_3$) 2936, 2857, 2790, 1453, 1164, 1059 cm^{-1}; MS (EI, 70 eV) m/z (rel int) 201 (M^+, 34.8), 200 (37.2), 172 (27.0), 159 (14.2), 158 (16.2), 124 (100.0), 104 (54.9), 91 (37.1), 70 (34.4), 41 (27.9); HRMS calcd for $C_{14}H_{19}N$ 201.1517, found 201.1510.

(5R*,8aR*)-5-Hexylindolizidine (Indolizidine 209D) (27) and (8R*,8aR*)-8-Hexylindolizidine (28). With TfOH: Trifluoromethanesulfonic acid (0.60 g, 0.35 mL, 4.0 mmol) was added to a cool (15 °C) solution of **12** (0.51 g, 2.0 mmol) in benzene (20 mL). The solution was stirred for 5 min and cooled to 0 °C, and a cold (0 °C) solution of $NaBH_4$ (0.45 g, 12.0 mmol) in 30 mL of methanol was carefully added. The resulting mixture was stirred for 5 min and then warmed to room temperature for 14 h. Aqueous NaOH (15%, 10 mL) was added, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried (K_2CO_3), and concentrated to provide a mixture of **27** and **28** (1:1.3 by GC, t_R for **27** = 4.6 min, t_R for **28** = 4.8 min). Chromatography on deactivated flash silica gel (1%–10% EtOAc/hexane gradient) afforded 58 mg (14%) of **27**, R_f= 0.7 (25% $CH_3OH/CHCl_3$), and 46 mg (11%) of **28**, R_f= 0.4 (25% $CH_3OH/CHCl_3$). Data for **27**: ^1H NMR ($CDCl_3$, 360 MHz) δ 3.22 (td, J = 9.5, 2 Hz, 1 H), 1.95 (q, J = 9 Hz, 1 H), 1.12–1.87 (m, 22 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 65.0, 63.8, 51.5, 34.6, 31.8, 31.0, 30.8, 30.5, 29.7, 25.8, 24.7, 22.6, 20.3, 14.0; IR (neat) 2929, 2857, 2780 cm^{-1}; MS (CI, NH_3) m/z (rel int) 210 (MH^+, 42.2), 209 (3.2), 208 (6.4), 125 (15.5), 124 (100.0), 96 (10.5); HRMS calcd for $C_{14}H_{27}N$ 210.2222 (M + H^+), found 210.2223. These data matched the literature data.[52a] Data for **28**: ^1H NMR ($CDCl_3$,360 MHz) δ 3.05 (m, 2 H), 2.05 (q, J = 7.7 Hz, 1 H), 1.10–1.95 (m, 21 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 69.7, 54.6, 52.8, 41.7, 33.3, 30.2, 29.6, 29.2, 26.6, 25.6, 22.6, 20.5, 14.1; IR (neat) 2926, 2853, 2779 cm^{-1}; MS (CI, NH_3) m/z (rel int) 210 (MH^+, 100.0), 209 (15.5), 208 (17.7), 138 (17.8), 124 (18.1), 97 (15.8), 96 (15.4), 84 (14.6), 83 (11.3); HRMS calcd for $C_{14}H_{27}N$ 210.2222 [$(M + H)^+$], found 210.2216.

With $SnCl_4$: Stannic chloride (1.5 mL, 1.0 M in CH_2Cl_2, 1.5 mmol) was added to a cold (–78 °C) solution of **12** (0.25 g, 1.0 mmol) in 40 mL of CH_2Cl_2. After 30 min, borane–dimethyl sulfide complex (3.0 mL, 2.0 M in THF, 6.0 mmol) was added and the mixture was warmed to room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (K_2CO_3), and concentrated to provide a 1.7:1 mixture of **27** and **28**. The yield was determined by calibrated GC analysis versus a decane internal standard to be 47%.

(5R*,8aR*)-5-Hexyl-8a-deuterioindolizidine (27-*d*) and (8R*,8aR*)-8-Hexyl-8a-deuterioindolizidine (28-*d*). Trifluoromethanesulfonic acid (0.30 g, 0.17 mL, 2.0 mmol) was added to a cool (15 °C) solution of **12** (0.25 g, 1.0 mmol) in benzene (10 mL). The solution was stirred for 5 min and cooled to 0 °C, and a cold (0 °C) solution of $NaBD_4$ (0.25 g, 6.0 mmol) in 12 mL of methanol-*d*, was added. The resulting mixture was stirred for 5 min and then warmed to room temperature for 14 h. NaOH (15%, 5 mL) was added and the mixture extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (K_2CO_3), and concentrated to provide a mixture of **27**-*d* and **28**-*d* (1:1.5 by GC, yield 60% by calibrated GC analysis versus a decane internal standard). Chromatography on deactivated flash silica gel (1%–10% EtOAc/hexane gradient) afforded 25 mg (14%) of **27**-*d*, R_f= 0.7 (25% $CH_3OH/CHCl_3$), and 30 mg (11%) of **28**-*d*, R_f= 0.4 (25% $CH_3OH/CHCl_3$). Data for **27**-*d*: ^1H NMR ($CDCl_3$, 360 MHz) δ 3.22 (td, J = 9.5, 2 Hz, 1 H), 1.95 (q, J = 9 Hz, 1 H), 1.12–1.87 (m, 21 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 63.8, 51.5, 34.6, 34.4, 31.8, 30.7, 30.4, 30.3, 29.7, 25.8, 24.6, 22.6, 20.3, 14.0; IR (neat) 2929, 2857, 2774 cm^{-1}; MS (CI, NH_3) m/z (rel int) 211 (MH^+, 100.0), 210 (8.1), 137 (4.3), 136 (61.2), 125 (8.3); HRMS calcd for $C_{14}H_{26}DN$ 211.2284 [$(M + H)^+$], found 211.2282. Data for **28**-*d* ^1H NMR ($CDCl_3$,360 MHz) δ 3.05 (m, 2 H), 2.05 (m, 1 H), 1.10–1.95 (m, 20 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 54.5, 52.8, 41.6, 33.3, 31.8, 30.1, 29.7, 29.0, 26.5, 25.5, 22.7, 20.5, 14.1; IR (neat) 2926, 2854, 2776 cm^{-1}; MS (CI, NH_3) m/z (rel int) 211 (MH^+, 100.0), 210 (10.8), 137 (4.2), 136 (59.7); HRMS calcd for $C_{14}H_{26}DN$ 211.2284 (M + H^+), found 211.2288.

7-[3,4-(Methylenedioxy)phenyl]-6-bromo-1-azabicyclo[3.2.2]non-6-ene (33). Bromine was added to a solution of **13** in CH_2Cl_2 (1 mL) until the red color persisted. Water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined and washed with saturated aqueous $Na_2S_2O_3$ (2 × 10 mL), water (15 mL), and brine (15 mL), then dried ($MgSO_4$) and concentrated to give 49.0 mg (84%) of the title compound, which was pure by ^1H NMR, R_f = 0.37 (10% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 7.30 (m, 2 H), 6.78 (d, J = 8.0 Hz, 1 H), 5.95 (s, 2 H), 3.12 (dt, J = 1.8, 7.9 Hz, 2 H), 2.89 (m, 2 H), 2.83 (m, 1 H), 2.39 (m, 1 H), 2.21 (m, 1 H), 2.05 (m, 1 H), 1.91 (m, 1 H), 1.70 (m, 1 H), 1.58 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.12 (–), 147.06 (–), 146.78 (–), 131.59 (–), 122.68 (+), 108.99 (+), 107.52 (+), 100.97 (–), 50.96 (–), 48.02 (–), 44.96 (+), 34.81 (–), 29.06 (–), 25.24 (–); IR (neat) 1605 (w), 1502 (m), 1486 (s), 1435 (m), 1246 (s), 1215 (m), 1040 (s), 938 (m), 794 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 324 (6.58), 323 ($M^{+81}Br$, 37.3), 322 (15.4), 321 ($M^{+79}Br$, 39.0), 295 (24.6), 294 (99.1), 293 (25.5), 292 (100.0), 242 (61.0), 214 (25.9), 212 (35.6), 184 (12.1), 172 (11.1), 155 (12.0), 143 (10.0), 128 (22.2), 115 (23.9), 84 (37.8), 77 (33.1), 49 (38.9), 42 (44.5). The m/z peaks between 324 and 321 match the computed isotopic distribution pattern calculated for $C_{15}H_{16}BrO_2N$. HRMS calcd for $C_{15}H_{16}{}^{79}BrO_2N$ 321.0364, found 321.0371.

(5R*,7R*)-7-[3,4-(Methylenedioxy)phenyl]-1-azabicyclo[3.2.2]-nonane (34). A mixture of **13** (0.27 mg, 1.11 mmol) and 10% Pd/C (ca. 5 mg) in ethanol (2 mL) was shaken at room temperature under an atmosphere of hydrogen (35 psig). After 10 h the solution was filtered

through Celite and concentrated to afforded 260 mg (94%) of the title compound which was found to be pure by ^{1}H NMR analysis, R_f = 0.1 (25% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.99 (s, 1 H), 6.87 (d, J = 8.1 Hz, 1 H), 6.75 (d, J = 8.1 Hz, 1 H), 5.89 (s, 2 H), 3.84, (t, J = 8.7 Hz, 1 H, H(1)), 3.20 (m, 2 H, H(6) and H(7)), 2.72 (m, 2 H, H(4) and H(5)), 2.25 (m, 2 H), 1.91 (t, J = 9.3 Hz, 1 H, H(3)), 1.70 (m, 5 H), 1.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ147.55 (–), 145.79 (–), 137.46 (–) 120.12 (+), 108.30 (+), 107.62 (+), 100.69 (–), 57.94 (+), 49.42 (–), 48.76 (–), 35.15 (–), 33.86 (–), 28.20 (+), 26.67 (–), 24.31 (–); IR (neat) 1502 (s), 1487 (s), 1434 (s), 1235 (s), 1120 (m), 1040 (s), 937 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 246 (M + 1, 24), 245 (M^+, 98), 244 (100), 217 (13), 216 (46), 202 (36), 188 (19), 176 (21), 162 (27), 149 (15), 148 (47), 147 (18), 135 (37), 86 (26), 84 (37), 77 (14), 42 (13), 41 (17); HRMS calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1405. The stereochemistry is that as shown based on a combination of NOESY, COSY, and HETCOR ^{1}H NMR techniques. The key NOE enhancement was between the benzylic methine hydrogen at δ 3.84 and the CH_2N group of the ethano bridge at δ 2.72.

2-(Phenylmethyl)-1-azabicyclo[2.2.2]octane (35). Hydrogenation of a mixture of **18a,b** in methanol (10 mL) with 5% palladium on carbon (200 mg) and a balloon of hydrogen was carried out for 14 h. After filtration of the catalyst, the methanolic solution was concentrated to give 148 mg (81%) of the title compound as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.15 (m, 5 H), 3.14-2.63 (m, 6 H), 1.76–1.14 (m, 7 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.71, 128.93, 128.13, 125.80, 57.37, 49.89, 41.76, 41.64, 33.40, 26.89, 25.53, 21.93; IR (neat) 2934(s), 2858 (s), 1496 (s), 1453 (s), 1322 (m), 1059 (s), 986 (s), 738 (s), 698 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 201 (M^+, 100), 172 (32.7), 160 (40.4), 91(47.3), 82 (36.7), 55 (77); HRMS calcd for $C_{14}H_{19}N$ 201.1517, found 201.1509.

3-(2-Hydroxyethyl)-1-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene. A solution of the ester **56**[69] (7.31 g, 25.4 mmol) in 15 mL of THF was added in a dropwise fashion to a suspension of $LiAlH_4$ (0.96 g, 25.4 mmol) in dry THF (25 mL) at 0 °C. After 1 h, water (25 mL) and 10% HCl (25 mL) were carefully added. The aqueous layer was extracted with EtOAc (3 × 75 mL), and the combined organic phases were washed with H_2O (3 × 50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated. Chromatography (25% EtOAc/hexane) gave 5.53 g (89%) of the title compound as a clear oil,R_f = 0.17 (25% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (d, J = 1.7 Hz, 1 H), 6.85 (dd, J = 1.7, 8.1 Hz, 1 H), 6.75 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.88 (s, 1 H), 3.78 (dt, J = 2.1, 6.6 Hz, 2 H), 2.40 (m, 3 H), 1.88 (m, 2 H), 1.65 (m, 3 H), 1.40 (br s, 1 H), 1.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.69 (–), 146.46 (–), 37.11 (–), 136.48 (–), 128.02 (+), 118.43 (+), 107.93 (+),105.84 (+), 100.87 (–), 60.82 (–), 39.30 (–), 32.66 (+), 28.60 (–), 7.90 (–), 21.88 (–); IR (neat) 3390 (m), 1675 (w), 1500 (s), 1497 (s), 1460 (m), 1230 (s), 1086 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 247 (M^+ + 1, 10.3), 246 (M^+, 53.6), 201 (100.0), 135 (19.3), 128 (8.9), 79 (5.72). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.20; H, 7.37. Found: C, 73.02; H, 7.57.

3-(2-Azidoethyl)-1-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene (3). Methanesulfonyl chloride (2.05 g, 1.38 mL, 17.91 mmol) was added in a dropwise fashion to a solution of the above alcohol (4.00 g, 16.2 mmol) and triethylamine (1.81 g, 2.50 mL, 17.9 mmol) in dry CH_2Cl_2 (20 mL) at –50 °C. The reaction was monitored by TLC (eluting two times with 25% EtOAc/hexane, R_f (mesylate) = 0.35) and was found to be complete in 1 h. Water was added at –50 °C, and the solution was allowed to warm to 23 °C and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated. The resulting oil was dissolved in THF (20 mL), and Bu_4NN_3 (9.24 g, 32.5 mmol) was added. After 9 h, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated. Chromatography (gradient, 0%–5 % EtOAc/hexane) gave 3.80 g (86%) of the title compoundas a pale yellow oil, R_f = 0.60 (25% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.89 (d, J = 1.8 Hz, 1 H), 6.85 (dd, J = 1.8, 8.1 Hz, 1 H), 6.76 (d, J = 8.1 Hz, 1 H), 5.94 (s, 2 H), 5.84 (s, 1 H), 3.39 (dt, J = 1.9, 7.3 Hz, 2 H), 2.37 (m, 3 H), 1.89 (m, 2 H), 1.70 (m, 3 H), 1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.73 (–), 146.60 (–), 137.12 (–), 136.87 (–), 126.96 (+), 118.49 (+), 107.98 (+), 105.84 (+), 100.94 (–), 49.3 (–), 35.18 (–), 33.34 (+), 28.30 (–), 27.87 (–), 21.78 (–); IR (neat) 2098 (s), 1605 (w), 1504 (s), 1487 (s), 1443 (s), 1343 (m), 1248 (s), 1218 (s), 1040 (s), 936 (s), 805 (s) cm^{-1}; MS (CI with NH_3) m/z (rel int) 289 [(M + NH_4)$^+$, 4.38], 265 (8.5), 244 (82.2), 240 (100.0), 223 (8.9), 136 (32.8); HRMS (CI with NH_3) calcd for $C_{15}H_{17}N_3O_2NH_4$ 289.1665, found 289.1668.

1-Butyl-3-(2-hydroxyethyl)cyclohex-1-ene. $LiAlH_4$ (50 mg, 1.4 mmol) was added to a solution of ester **57**[69] (0.31 g, 1.4 mmol) in THF (7 mL) at 0 °C. The mixture was warmed to room temperature for 2 h, then cooled to 0 °C, and 10% HCl (3 mL) was carefully added. The mixture was extracted with ethyl acetate (3 × 7 mL), and the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide 0.18 g (72%) of the title compound as a colorless oil, R_f= 0.3 (10% EtOAc/hexane): ^{1}H NMR ($CDCl_3$,300 MHz) δ 5.27 (bs, 1 H), 3.71 (t, J = 6.8 Hz, 2 H), 2.2 (bs, 1 H), 1.90–1.48 (m, 14 H), 0.9 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 138.4, 124.9, 61.0, 39.5, 37.7, 32.0, 29.9, 29.0, 28.4, 22.4, 21.8, 14.0; IR (neat) 3324, 2926, 1663, 1454 cm^{-1}; MS (EI, 70 eV) m/z (rel int) 182 (7.3), 125 (23.2), 121 (25.1), 107 (62.5), 95 (33.7), 81 (100.0), 79 (68.6), 67 (61.3), 55 (32.9), 41 (56.2); HRMS calcd for $C_{12}H_{22}O$ 182.1671, found 182.1676.

1-Butyl-3-(2-azidoethyl)cyclohex-1-ene (4). A solution of the above alcohol (0.18 g, 1.0 mmol) in CH_2Cl_2 (3 mL) was cooled to –50 °C, and triethylamine (0.20 g, 0.28 mL, 2.0 mmol) and methanesulfonyl chloride (0.17 g, 0.12 mL, 1.5 mmol) were added sequentially. After 2 h, the mixture was diluted with water (3 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), and concentrated. The resulting oil was taken up in DMSO (2.4 mL), and sodium azide (0.26 g, 4.0 mmol) was added. After 2 h at room temperature and 1 h at 45 °C, water (3 mL) was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (1% EtOAc/hexane) gave 150 mg (73%) of the title compound as a pale yellow liquid, R_f= 0.3 (1% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 5.23 (bs, 1 H), 3.32 (t, J = 7.4 Hz, 2 H), 2.2 (bs, 1 H), 1.9–1.1 (m, 14 H), 0.9 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.1, 124.2, 49.5, 37.7, 35.5, 33.0, 30.1, 28.9, 28.5, 22.4, 21.8, 13.9; IR (neat) 2927, 2094, 1665, 1456, 1257 cm^{-1}; MS (CI, NH_3) m/z (rel int) 225 [(M + NH_4)$^+$, 4.5], 181 (22.7), 180 (100.0), 150 (58.8), 137 (47.6), 136 (55.4), 123 (61.3), 122 (51.5), 109 (37.2), 95 (61.2); HRMS calcd for $C_{12}H_{21}N_3$ 225.2079 [(M + NH_4)$^+$], found 225.2078. Anal. Calcd for $C_{12}H_{22}N_3$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.64; H, 10.25; N, 20.11.

3-Hydroxy-3-phenylcyclopentaneethanol. Cerium chloride heptahydrate (2.80 g, 7.50 mmol) was dried at 137 °C in vacuo (<0.1 mmHg) for 3 h. Nitrogen was introduced, the flask was cooled to 0 °C, and cold THF (20 mL, 0 °C) was added. After the resultant suspension was stirred overnight, a solution of ethyl 3-oxocyclopentaneacetate (**58**)[70] (0.85 g, 5.00 mmol) in dry THF (8 mL) was added, and the resulting mixture was stirred 1 h at room temperature and then cooled to 0 °C. Phenylmagnesium chloride (3.80 mL, 2.00 M in THF, 7.60 mmol) was added via syringe. After 30 min at 0 °C, 10% aqueous acetic acid (50 mL) was added. The mixture was extracted with ether (3 × 40 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 × 40 mL) and brine (3 × 30 mL), then dried ($MgSO_4$) and concentrated to afford a 1:1 mixture of ethyl (1R*,3S*)-3-hydroxy-3-phenylcyclopentaneacetate and 1-phenyl-2-oxabicyclo[3.2.1]octan-3-one (vide infra). Without purification or separation, this mixture was dissolved in dry ether (5 mL) and added to a suspension of lithium aluminum hydride (0.285 g, 7.50 mmol) in dry ether (2 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 40 min, then water (1 mL) was carefully added, followed by 15% NaOH (1.5 mL). The mixture was extracted with ether (3 × 50 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated. Chromatography (2:1 EtOAc/hexane) gave 0.80 g (78% overall) of the title compound as a colorless oil, R_f = 0.21 (2:1 EtOAc/hexane), which was found to be a 1:1 mixture of diastereomers by ^{1}H NMR. This mixture was carried on to the next step without separation. In separate experiments, the cerium-promoted Grignard addition and hydride reductions were repeated, except that the products from each reaction were separated and purified in order to allow characterization:

Ethyl (1R,3S*)-3-hydroxy-3-phenylcyclopentaneacetate* (47% from ethyl 3-oxocyclopentaneacetate on a 7.5-mmol scale after separation from the lactone described below by chromatography with 1% EtOAc/hexane), R_f= 0.29 (1:3 EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.49–7.23 (m, 5 H), 4.14 (q, J = 7.1 Hz, 2 H), 2.87–2.80 (m, 1 H), 2.44–1.98

(69) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 2986–2987.

(70) McMurry, J. E.; Andrus, W. A.; Musser, J. H. *Synth. Commun.* **1978**, *8*, 53-57.

(m, 7 H), 1.77–1.47 (m, 3 H), 1.27 (t, J = 12.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 172.93, 146.62, 128.21, 126.89, 124.93, 83.28, 60.21, 48.27, 40.81, 40.45, 34.42, 30.33, 14.22; IR (neat) 3431 (br s), 1732 (s), 1196 (m), 1030 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 248 (M^+, 21.8), 173 (19.2), 161 (50), 142 (32.6), 133 (41.0), 120 (46.0), 105 (100), 91 (17), 77 (30); HRMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1412.

1-Phenyl-2-oxabicyclo[3.2.1]octan-3-one (43% from ethyl 3-oxocyclopentaneacetate on a 7.5-mmol scale, separated from the hydroxyester above by chromatography, total yield for the two compounds = 90%), R_f = 0.20 (1:3 EtOAc/hexane): ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.52–7.48 (m, 2 H), 7.40–7.28 (m, 3 H), 2.80–2.48 (m, 4 H), 2.28–2.10 (m, 4 H), 1.86–1.79 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.30, 140.69, 128.47, 127.96, 125.37, 91.49, 41.58, 40.31, 39.67, 32.51, 30.29; IR (neat) 1727 (s), 1381 (m), 1249 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 202 (M^+, 12.4), 145 (19.4), 120 (52.5), 105 (100), 77 (43.0), 49 (28.8); HRMS calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.1001.

(1R,3S*)-3-Hydroxy-3-phenylcyclopentaneethanol* [75% from ethyl (1R*,3S*)-3-hydroxy-3-phenylcyclopentaneacetate on a 2.34-mmol scale], R_f= 0.32 (ether): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.48–7.46 (m, 2 H), 7.36–7.31 (m, 2 H), 7.26–7.22 (m, 1 H), 3.67 (t, J = 6.7 Hz, 2 H), 2.55–2.46 (m, 1 H), 2.24–2.11 (m, 3 H), 2.04–1.95 (m, 2 H), 1.81–1.61 (m, 4 H), 1.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 146.95, 128.21, 126.84, 124.95, 83.35, 62.05, 48.84, 40.93, 39.12, 34.59, 30.75; IR (neat) 3347 (br s), 1446 (s), 1055 (m), 760 (s), 699 (s) cm^{-1}; MS (CI, NH_3) m/z (rel int) 224 [$(M + NH_4)^+$, 4.4], 206 [$(M + NH_4 - H_2O)^+$, 84.8], 189 (100), 171 (4.7), 143 (7.7), 105 (5.2); HRMS (CI, NH_3) calcd for $C_{13}H_{16}ONH_4$ 206.1545, found 206.1532.

(1R,3R*)-3-Hydroxy-3-phenylcyclopentaneethanol* (95% from 1-phenyl-2-oxabicyclo[3.2.1]octan-3-one on a 1.73-mmol scale): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.19 (m, 5 H), 3.64 (dt, J = 1.7, 6.8 Hz, 2 H), 2.40–2.25 (m, 4 H), 2.03–1.95 (m, 3 H), 1.78–1.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.49, 128.11, 126.67, 124.90, 83.13, 61.72, 48.08, 42.38, 39.59, 35.42, 31.36; IR (neat) 3356 (br s), 1600 (s), 1493 (s), 1446 (s), 1012 (m), 763 (m), 700 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 206 (M^+, 11.5), 177 (15.3), 161 (31.8), 133 (72.6), 120 (47.1), 105 (100), 77 (33.6), 55 (27); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1310.

3-(Azidoethyl)-1-phenylcyclopentan-1-ol (5). Pyridine (0.51 mL, 6.59 mmol) and tosyl chloride (0.80 g, 4.20 mmol) were added to the diastereomeric diols from above (0.44 g, 2.13 mmol) in dry chloroform (5 mL) at 0 °C. After 4 h at 0 °C, ether (150 mL) and water (30 mL) were added. The water layer was extracted with ether (2 × 50 mL), and the combined organic phases were washed with 10% aqueous acetic acid (30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and water (2 × 30 mL), then dried ($MgSO_4$) and concentrated to give the crude tosylates, which were dissolved in DMSO (6 mL) and treated with sodium azide (0.53 g, 8.15 mmol). After stirring overnight, water (40 mL) was added, and the mixture was extracted with ether (3 × 50 mL). The combined organic phases were washed with water (3 x 30 mL), then dried ($MgSO_4$) and concentrated. Chromatography (1:3.5 EtOAc/petroleum ether) gave 0.30 g (61%) of azide **5** as a clear oil which was found to be a 1:1 mixture of diastereomers by ^{1}H NMR. These were not separated and were characterized as a mixture, R_f = 0.29 (1:4 EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.47–7.44 (m, 2 H), 7.40–7.31 (m, 2 H), 7.27–7.22 (m, 1 H), 3.29 (t, J = 7.0 Hz, 2 H), 2.51–2.46 (m, 0.5 H), 2.33–2.29 (m, 0.5 H), 2.20–2.11 (m, 2 H), 2.02–1.98 (m, 2 H), 1.83–1.63 (m, 4.5 H), 1.47–1.42 (m, 0.5 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 147.23, 146.65, 128.23, 126.93, 126.85, 124.89, 124.85, 83.25, 83.04, 50.55, 50.49, 48.53, 47.94, 42.28, 40.71, 36.13, 35.99, 35.41, 35.05, 31.30, 30.45; IR (neat) 3415 (br s), 2096 (s), 1494 (s), 1446 (s), 1260 (m), 1002 (m), 763 (s), 700 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 231 (M^+, 5.1), 202 (16), 174 (37.1), 133 (26.8), 120 (35.4), 105 (100), 91 (39.7), 77 (50.2), 43 (30.4); HRMS calcd for $C_{13}H_{17}N_3O$ 231.1372, found 231.1357.

In a separate experiment, a single diastereomeric diol from above, (1R*,3R*)-3-hydroxy-3-phenylcyclopentaneethanol, was converted to (1R*,3R*)-3-(azidoethyl)-1-phenylcyclopentan-1-ol in 66% overall yield on a 0.52-mmol scale for the purpose of characterization, R_f = 0.29 (1:4 EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.21 (m, 5 H), 3.29 (t, J = 7.0 Hz, 2 H), 2.36–1.99 (m, 5 H), 1.84–1.20 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.21, 128.24, 126.86, 124.87, 83.07, 50.49, 47.95, 42.28, 36.11, 36.01, 31.32; IR (neat) 3419 (br s), 2096 (s), 1494 (s), 1446 (m), 1259 (m), 1004 (m), 764 (s), 700 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 231 (M^+, 4.0), 202 (23.2), 174 (59.0), 105 (100), 91 (25.3), 77 (47.1), 43 (31.3); HRMS calcd for $C_{13}H_{17}N_3O$ 231.1372, found 231.1381.

3-Hydroxy-3-(phenylmethyl)cyclopentaneethanol. Cerium chloride heptahydrate (5.60 g, 15.00 mmol) was dried at 137 °C in vacuo (<0.1 mmHg) for 2 h. Nitrogen was introduced, the flask was cooled to 0 °C, and cold (0 °C) THF (40 mL) was added. After the resultant suspension was stirred overnight, a solution of ethyl 3-oxocyclopentaneacetate[70] (1.70 g, 10.00 mmol) in dry THF (12 mL) was added, and the resulting mixture was stirred 1 h at room temperature and then cooled to 0 °C. Benzylmagnesium chloride (7.5 mL, 2.0 M in THF, 15 mmol) was added via syringe, and the mixture was stirred at 0 °C for 30 min, then 10% aqueous acetic acid (100 mL) was added. The resulting mixture was extracted with ether (3 × 60 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (3 × 60 mL) and brine (3 × 50 mL), then dried ($MgSO_4$) and concentrated to give a mixture of ethyl (1R*,3S*)-3-hydroxy-3-(phenylmethyl)cyclopentaneacetate and 1-(phenylmethyl)-2-oxabicyclo[3.2.1]octan-3-one. These were dissolved in dry THF (8 mL) and added to a suspension of lithium aluminum hydride (0.57 g, 15 mmol) in dry THF (2 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h, then water (1 mL) was carefully added, followed by 15% aqueous NaOH (1.5 mL). The resulting mixture was extracted with ether (3 × 50 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. Chromatography (2:1 EtOAc/petroleum ether) gave 1.08 g (49%) of a mixture of two diastereomeric diols as a colorless oil, R_f = 0.20 (2:1 EtOAc/hexane). These were not separated but were taken on to the next step. Characterization of the mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.21 (m, 5 H), 3.64 –3.59 (m, 2 H), 2.89–2.79 (m, 2 H), 2.31–1.97 (m, 4 H), 1.87–1.48 (m, 6 H), 1.35–1.28 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.16, 138.08, 130.15, 130.10, 128.21, 126.43, 81.97, 81.75, 62.00, 61.84, 47.73, 47.63, 46.86, 45.643, 40.00, 87, 39.24, 38.79, 35.21, 34.52, 30.92, 30.65; IR (neat) 3354 (br s), 1452 (m), 1050 (m), 702 (s) cm^{-1}; MS (CI, NH_3) m/z (rel int) 238 [$(M + NH_4)^+$, 24.6], 220 (100), 203 (25.3), 136 (81.8); HRMS (CI, NH_3) calcd for $C_{14}H_{20}O_2NH_4$ 238.1807, found 238.1798. In separate experiments, the hydroxyester and lactone were prepared again and separated, then reduced to give pure samples of each diastereomeric diol:

1-(Phenylmethyl)-2-oxabicyclo[3.2.1]octan-3-one, R_f = 0.38: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.33–7.23 (m, 5 H), 3.07 (AB q, J_{AB} = 13.9 Hz, 2 H), 2.63-2.43 (m, 3 H), 2.09–1.60 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 171.24, 136.62, 130.31, 128.18, 126.69, 91.59, 43.33, 40.08, 39.09, 36.28, 31.76, 29.84; IR (neat) 1731 (s), 1350 (s), 1230 (m), 952 (s), 702 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 216 (M^+, 14.69), 125 (100), 97 (30.6), 91 (63.7), 82 (33.3), 69 (50), 55 (40), 41 (28.3); HRMS calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1154. This was separated from ethyl (1R*,3S*)-3-hydroxy-3-(phenylmethyl)cyclopentaneacetate by chromatography with 3% EtOAc/hexane. Unfortunately, this hydroxyester could not be obtained in pure form and was thus reduced without further characterization.

(1R,3R*)-3-Hydroxy-3-(phenylmethyl)cyclopentaneethanol* (from the above lactone by hydride reduction in 94% yield on a 0.90-mmol scale), R_f = 0.20 (2:1 EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.22 (m, 5 H), 3.64 (t, J = 6.7 Hz, 2 H), 2.85 (AB q, J = 13.3 Hz, 2 H), 2.13–1.99 (m, 2 H); 1.87–1.45 (m, 9 H), 1.36–1.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.96, 130.12, 128.15, 126.35, 81.71, 61.56, 47.38, 45.22, 39.73, 39.48, 34.87, 30.72; IR (neat) 3355 (br s), 1495 (s), 1453 (m), 1047 (m), 702 (s) cm^{-1}; MS (CI, NH_3) m/z (rel int) 238 [$(M + NH_4)^+$, 10.3], 220 [$(M + NH_4 - H_2O)^+$, 88.7], 203 (100), 198 (10.5), 185 (17.3), 157 (4.9), 148 (4.5), 108 (5.3), 91 (5.3); HRMS (CI, NH_3) calcd for $C_{14}H_{18}ONH_4$ 220.1701, found 220.1686.

(1R,3S*)-3-Hydroxy-3-(phenylmethyl)cyclopentaneethanol* (from the above hydroxyester by hydride reduction), R_f = 0.20 (1:1 EtOAc/petroleum ether): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.21 (m, 5 H), 3.58 (t, J = 6.9 Hz, 2 H), 2.85(t, J = 14 Hz, 2 H), 2.33–2.22 (m, 1 H), 2.05–1.93 (m, 1 H), 1.87–1.54 (m, 7 H), 1.32–1.19 (m, 2 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 138.40, 130.20, 128.29, 126.51, 82.03, 62.01, 47.77, 46.88, 39.26, 38.82, 34.55, 30.67; IR (neat) 3345 (br s), 1494 (m), 1052 (m), 701 (m) cm^{-1}; MS (CI, NH_3) m/z (rel int) 238 [$(M + NH_4)^+$, 15.6], 220 [$(M + NH_4 - H_2O)^+$, 100], 203 (98.4), 189 (26.7), 185 (45.8), 147 (23.6), 138 (15.7), 129 (37.7), 111 (16.5), 91 (34.1); HRMS (CI, NH_3) calcd for $C_{14}H_{18}ONH_4$ 220.1701, found 220.1690.

3-(Azidoethyl)-1-(phenylmethyl)cyclopentan-1-ol (6). Pyridine (0.50 mL, 6.12 mmol) and tosyl chloride (0.74 g, 3.88 mmol) were added to a mixture of the diastereomeric diols from above (0.43 g, 1.94 mmol) in dry chloroform (5 mL) at 0 °C. After 4 h, ether (150 mL) and water (30 mL) were added. The water layer was extracted with ether (2 × 50 mL), and the combined ether phases were washed with 10% aqueous acetic acid (30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and water

(2 × 30 mL), then dried ($MgSO_4$) and concentrated to give the crude tosylates, which were dissolved in DMSO (6 mL) and treated with sodium azide (0.48 g, 7.31 mmol). After stirring overnight, water (40 mL) was added and the mixture was extracted with ether (3 x 50 mL). The combined ether phases were washed with water (3 x 30 mL), dried ($MgSO_4$) and concentrated. Chromatography (1:3.5 EtOAc/petroleum ether) gave 0.36 g (76%) of a mixture of diastereomeric azides **6** as a light yellow oil, R_f = 0.29 (1:4 EtOAc/hexane). These were not separated and were characterized as a mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.14 (m, 5 H), 3.27–3.21 (m, 2 H), 2.91–2.80 (m, 2 H), 2.32–1.91 (m, 2 H), 1.89–1.76 (m, 1 H), 1.73–1.43 (m, 5 H), 1.37–1.21 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.11, 138.03, 130.24, 130.19, 128.45, 126.68, 81.98, 81.71, 50.65, 47.75, 47.68, 45.53, 40.07, 38.80, 35.97, 35.89, 35.42, 35.16, 20.86, 30.46; IR (neat) 3438 (br m), 2095 (s), 1453 (m), 1261 (m), 703 (s) cm^{-1}; MS (CI, NH_3) *m/z* (rel int) 263 [$(M + NH_4)^+$, 10.1], 200 (81.4), 136 (100); HRMS (CI, NH_3) calcd for $C_{14}H_{19}N_3ONH_4$ 263.1872, found 263.1880.

In a separate experiment, pure (1*R**,3*R**)-3-hydroxy-3-(phenylmethyl)cyclopentaneethanol from above was converted into *(1R*,3R*)-3-(azidoethyl)-1-(phenylmethyl)cyclopentan-1-ol* in 67% overall yield on a 0.79-mmol scale by the above synthetic sequence for the purpose of characterization, R_f = 0.29 (1:4 EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.22 (m, 5 H), 3.26 (t, J = 7.0 Hz, 2 H), 2.85 (AB q, J = 13.3 Hz, 2 H), 2.08–1.85 (m, 3 H), 1.74–1.49 (m, 5 H), 1.35–1.27 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.81, 130.12, 128.34, 126.56, 81.58, 50.48, 47.46, 45.23, 39.92, 35.79, 35.69, 30.73; IR (neat) 3448 (br s), 2095 (s), 1453 (m), 1262 (m), 703 (m) cm^{-1}; MS (CI, NH_3) *m/z* (rel int) 263 [$(M + NH_4)^+$, 8.1], 218 (5.3), 200 (100), 136 (53.7); HRMS (CI, NH_3) calcd for $C_{14}H_{19}N_3ONH_4$ 263.1872, found 263.1870.

2-(3-Azidopropyl)methylenecyclopentane (7). Pyridine (3.74 mL, 46.3 mmol) was added to a cooled (–5 °C) solution of 2-(3-hydroxypropyl)-methylenecyclopentane (**59**)[71] (2.95 g, 21 mmol) in dichloromethane (50 mL). After 20 min, tosyl chloride (8.81 g, 46.2 mmol) was added and the mixture was stirred at –5 °C for 3 h. Aqueous acetic acid (20 mL, 10%) was added, and the resulting mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (2 × 25 mL) and water (2 × 25 mL), then dried ($MgSO_4$) and concentrated. Sodium azide (4.88 g, 75 mmol) was added to a solution of the crude tosylate in DMSO (50 mL), and the mixture was stirred for 34 h at room temperature. Aqueous NaOH (20 mL, 10% w/v) was added, and the mixture was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL) and water (2 × 25 mL), then dried ($MgSO_4$) and concentrated. Chromatography (15% ethyl acetate/hexane) afforded 3.08 g (89% yield over two steps) of the title compound as a colorless oil, R_f = 0.85. IR (neat) 3070 (m), 2949 (s), 2095 (s), 1653 (m), 1451 (br), 1350 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.89 (br s, 1 H), 4.78 (br d, J = 2 Hz, 1 H), 3.27 (t, J = 7 Hz, 2 H), 2.22–2.45 (m, 3 H), 1.18–1.97 (m, 8 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 156.20, 104.50, 51.77, 43.53, 33.08, 32.62, 31.486, 27.22, 24.08; MS (CI, NH_3) *m/z* (rel int) 183 ($M + NH_4^+$, 2), 139 (18), 138 (100), 137 (13), 136 (65), 123 (6), 122 (36), 110 (14), 109 (64), 108 (36), 96 (13), 95 (9), 94 (15), 93 (7), 83 (10), 82 (8), 81 (26), 80 (9); HRMS calcd for $C_9H_{15}N_3NH_4^+$ 183.1610, found 183.1607.

2-(3-Azidopropyl)methylenecyclohexane (8). Pyridine (11.59 mL, 143.5 mmol) was added to a cooled (–5 °C) solution of 2-(3-hydroxypropyl)methylenecyclohexane (**60**)[72] (6.92 g, 44.8 mmol) in chloroform (100 mL). After 20 min, tosyl chloride (17.10 g, 89.7 mmol) was added and the mixture was stirred at –5 °C for 3 h. Aqueous acetic acid (50 mL, 10%) was added, and the resulting mixture was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL) and water (2 × 25 mL), then dried ($MgSO_4$) and concentrated. Sodium azide (8.66 g, 134.5 mmol) was added to a solution of the crude tosylate in DMSO (90 mL), and the mixture was stirred for 6 h at room temperature. Aqueous NaOH (30 mL, 10% w/v) was added, and the mixture was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL) and water (2 × 25 mL), then dried ($MgSO_4$) and concentrated. Chromatography (5% ethyl acetate/hexane) afforded 7.18 g (89% overall) of the title compound as a colorless oil, R_f = 0.85: IR (neat) 2931 (s), 2856 (m), 2095 (s), 1645 (m), 1446 (m), 1349 (m), 1258 (br, m), 891 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.68 (br s, 1 H), 4.57 (br d, J = 2 Hz, 1 H), 3.25 (t, J = 7 Hz, 2 H), 1.23–2.32 (m, 13 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 152.14, 105.92, 51.70, 42.86, 34.45, 33.84, 29.13, 28.71, 26.89, 23.98; MS (CI, NH_3) *m/e* (rel int) 197 ($M + NH_4^+$, 20), 154 (7), 153 (16), 152 (100), 150 (11), 136 (10), 123 (22), 122 (11), 108 (5); HRMS calcd for $C_9H_{15}N_3NH_4^+$ 197.1766, found 197.1758.

***trans*-5-Azido-1-[(*tert*-butyldimethylsilyl)oxy]cyclooctane.** Sodium hydride (1.40 g, 34.7 mmol, 60% dispersion in mineral oil) was added to a solution of *cis*-1,5-cyclooctanediol (**61**) (5.00 g, 34.7 mmol) in THF (70 mL). After 2 h, *tert*-butyldimethylsilyl chloride (5.23 g, 34.7 mmol) was added and the solution was stirred for 2 h. Water (100 mL) was added, and the mixture was extracted with ether (3 × 50 mL). The organic phases were combined and washed with water (2 × 50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated to give 8.41 g (94 %) of *cis*-5-[(tert-butyldimethylsilyl)oxy]cyclooctan-1-ol, which was not purified further but taken on to the next step, R_f = 0.12 (10% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (m, 2 H), 1.83 (m, 4 H), 1.64 (m, 6 H), 1.44 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

Methanesulfonyl chloride (2.92 g, 1.97 mL, 25.5 mmol) was added in a dropwise fashion to a solution of the above alcohol (4.95 g, 19.2 mmol) and triethylamine (2.58 g, 3.58 mL, 25.5 mmol) in CH_2Cl_2 (25 mL) at –50 °C. The reaction was monitored by TLC (10% EtOAc/hexane, R_f(mesylate) = 0.19) and was found to be complete in 1 h. Water was added at –50 °C, and the solution was allowed to warm to 23 °C. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated. The resulting oil was dissolved in THF (25 mL), and Bu_4NN_3 (10.9 g, 38.3 mmol) was added. After 3 h, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated. Chromatography (gradient, 2.5%–5% EtOAc/hexane) gave 5.02 g (93%) of the title compound as a pale yellow oil, R_f = 0.60 (25% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (m, 1 H), 3.58 (m, 1 H), 1.88 (m, 2 H), 1.63 (m, 10 H), 0.75 (s, 9 H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.30, 61.58, 35.78, 35.37, 25.91, 19.39, 18.16, –4.73; IR (neat) 2089 (s), 1471 (s), 1447 (m), 1360 (m), 1252 (s), 1073 (s), 1018 (s), 938 (m), 836 (s), 774 (s) cm^{-1}; MS (CI with NH_3) 256 ($(M - N_2 - H)^+$, 9.6), 180 (3.1), 136 (81.1), 124 (100.0), 94 (2.8); HRMS calcd for $C_{14}H_{29}NOSiH$ 256.2097, found 256.2088.

***trans*-5-Azidocyclooctanol.** Tetrabutylammonium fluoride (47.7 mL, 47.7 mmol, 1 M in THF) was added to a solution of the above azide (4.50 g, 15.8 mmol) in THF (5 mL). After 48 h, water was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated. Chromatography (25% EtOAc/hexane) afforded 2.20 g (90%) of the title compound as a colorless oil, R_f = 0.20 (25% EtOAc/hexane, visualization with 5% $KMnO_4/H_2O$): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (m, 1 H), 3.51 (m, 1 H), 1.89 (m, 4 H), 1.63 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 71.09 (+), 61.10 (+), 35.37 (–), 32.05 (–), 19.47 (–); IR (neat) 3367 (br, s), 2091 (s), 1252 (s), 987 (s) cm^{-1}.

5-Azidocyclooctanone. A solution of the above alcohol (1.89 g, 12.3 mmol) in CH_2Cl_2 (10 mL) was added to a solution of pyridinium chlorochromate (3.99 g, 18.5 mmol) and alumina (11.96 g) in CH_2Cl_2 (20 mL) at 0 °C. After 2.5 h, the solution was filtered through a bed of silica gel (10 g) topped with Celite (5 g). The filter cake was then washed with 5% ether/petroleum ether (75 mL). The filtrate was concentrated to afford 1.81 g (96%) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.24 (tt, J = 3.1, 9.1 Hz, 1 H), 2.55 (m, 2 H), 2.28 (m, 2 H), 2.03 (m, 2 H), 1.75 (m, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 215.72, 60.18, 41.77, 32.95, 22.80; IR (neat) 2092 (s), 1699 (s), 1558 (m), 1466 (m), 1448 (s), 1335 (s), 1248 (s), 1202 (s), 1176 (m), 1099 (m), 842 (m) cm^{-1}; MS (CI with NH_3) 168 (M^+, 0.3), 140 ($M - N_2 + H)^+$, 100.0), 136 (85.6), 122 (1.6), 94 (2.5); HRMS calcd for $C_8H_{13}NOH$ 140.1075 [$(M - N_2 + H)^+$], found 140.1083.

5-Azido-1-propylcyclooctan-1-ol (9). Tetrahydrofuran (35 mL) was added to cerium trichloride (dried at 140 °C at 0.1 Torr, from 3.34 g (8.97 mmol) of heptahydrate), and the suspension was stirred for 24 h. The above azidoketone (418 mg, 2.50 mmol) was added, and the solution was stirred for 2 h. Propylmagnesium bromide, generated from propyl bromide (1.10 g, 0.82 mL, 8.97 mmol) and magnesium (0.23 g, 9.57 mmol) in THF (5 mL), was transferred into the $CeCl_3$/ketone mixture at 0 °C via cannula. After 15 min, water (25 mL) was added and the mixture was extracted with ether (3 × 25 mL). The combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated. Chromatography (gradient, 5%–10 % EtOAc/hexane) afforded 0.32 g (61%) of a mixture of diastereomers, R_f(diastereomer 1) = 0.49, R_f(diastereomer 2) = 0.39 (25% EtOAc/hexane). Less polar compo-

(71) Gream, G. E.; Serelis, A. K.; Stoneman, T. I. *Aust. J. Chem.* **1974**, *27*, 1711-1729.

(72) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 3461–2464.

nent: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.51 (t, J = 10.3 Hz, 1 H), 1.90 (m, 4 H), 1.65 (m, 6 H), 1.38 (m, 7 H), 0.87 (t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 73.87, 60.24, 45.91, 36.28, 33.57, 18.96, 16.39, 14.56; IR (neat) 3314 (br, s), 2088 (s), 1452 (s), 1377 (m), 1251 (s), 1135 (m), 914 (m) cm^{-1}; MS (CI with NH_3) (rel int) 212 (MH^+, 0.9), 186 (12.2), 184 (21.5), 166 (100.0), 140 (23.3), 122 (6.4), 96 (4.1); HRMS calcd for $C_{11}H_{21}N_3OH$ 212.1763, found 212.1763. More polar component: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.41 (m, 1 H), 1.98 (m, 2 H), 1.60 (m, 10 H), 1.35 (m, 5 H), 0.91 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 74.32, 61.38, 43.41, 36.37, 33.97, 20.06, 16.01, 14.54; IR (neat) 3414 (m), 2088 (s), 1452 (s), 1252 (s), 1135 (m), 914 (m) cm^{-1}; MS (CI with NH_3) 184 ($(M - N_2 + H)^+$, 47.4), 166 (100.0), 140 (8.3), 138 (9.7), 124 (6.3), 110 (3.7), 96 (5.6); HRMS calcd for $C_{11}H_{21}N_3OH - N_2$ 184.1701, found 184.1706.

Methyl 1-(3-Chloropropyl)-2-oxocyclopentanecarboxylate. A solution of methyl 2-oxocyclopentanecarboxylate (**62**) (7.10 g, 50.0 mmol) in THF (25 mL) was added to a solution of potassium *tert*-butoxide (5.90 g, 50.0 mmol) in 75 mL of dry THF. The mixture was stirred for 30 min and then 1-chloro-3-iodopropane (12.77 g, 62.5 mmol) was added dropwise. After 48 h, water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated. Chromatography (3% EtOAc/hex) afforded 10.0 g (92%) of the title compound as a colorless liquid, R_f= 0.12 (3% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (s, 3 H), 3.44 (t, J = 6 Hz, 2 H), 2.3–2.5 (m, 2 H), 2.2 (m, 1 H), 1.70–2.0 (m, 5 H), 1.66 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.7, 171.4, 59.7, 52.3, 44.7, 37.7, 33.2, 31.3, 28.2, 19.4; IR (neat) 1752, 1726, 1678, 1641, 1630, 1444, 1258, 1233, 1163 cm^{-1}; MS (EI, 70 eV) m/z (rel int) 218 (M^+, 0.8), 190 (32.4), 187 (11.8), 175 (10.3), 155 (16.9), 128 (15.7), 123 (43.3), 110 (24.0), 96 (35.1), 67 (100.0), 41 (62.7); HRMS calcd for $C_{10}H_{15}ClO_3$ 218.0709, found 218.0714.

2-(3-Azidopropyl)cyclopentanone.[32] Hydrogen bromide (4.56 g, 9.7 mL of a 47%–49% solution, 56.3 mmol) was added to the above ketoester (8.77 g, 40.2 mmol) at room temperature, and the resulting mixture was heated at reflux for 2.5 h and then cooled to room temperature. Water (10 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with 10% Na_2CO_3 (40 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated to provide a mixture of 2-(3-chloropropyl)cyclopentanone[73] and 2-(3-bromopropyl)cyclopentanone[74] [2:1 by ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.50 (m, 2 H, CH_2Cl), 3.38 (m, 1 H, CH_2Br)]. This mixture was taken up in DMSO (56 mL), and sodium azide (7.28 g, 112.0 mmol) was added. After stirring overnight at 40 °C, water (50 mL) was added and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. Chromatography (2% EtOAc/hexane) gave 3.5 g (52%) of the title compound as a pale yellow liquid, R_f= 0.3 (5% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.28 (t, J = 6.6 Hz, 2 H), 2.2 (m, 2 H), 2.04 (m, 3 H), 1.8 (m, 2 H), 1.67 (m, 2 H), 1.57 (m, 1 H), 1.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 219.9, 51.6, 48.5, 37.9, 29.7, 27.1, 27.0, 20.7; IR (neat) 2095, 1736, 1453, 1405, 1255, 1155 cm^{-1}; MS (CI, NH_3) m/z (rel int) 185 [$(M + NH_4)^+$, 15.23], 168 (MH^+, 5.5), 140 (100.0), 136 (29.0), 96 (4.7), 79 (3.2); HRMS calcd for $C_8H_{14}N_3O$ 168.1137 [$(M + H)^+$], found 168.1137. Anal. Calcd for $C_8H_{14}N_3O$: C, 57.47; H, 7.84; N, 25.13. Found: C, 57.34; H, 8.21; N, 25.16.

(1*R,2*R**)-1-Phenyl-2-(3-azidopropyl)cyclopentan-1-ol (10).** Phenyl magnesium bromide (0.66 mL, 3.0 M THF, 1.98 mmol) was added to a solution of 2-(3-azidopropyl)cyclopentanone (0.22 g, 1.3 mmol) in THF (6.6 mL) at −78 °C. The solution was stirred at −78 °C for 20 min, warmed to 0 °C for 30 min, and then warmed to room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (1%–15% EtOAc/hexane gradient) afforded 0.22 g (69%) of the title compound as asingle diastereomer, R_f= 0.3 (15% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.45 (d, J = 7 Hz, 2 H), 7.32 (t, J = 7 Hz, 2 H), 7.2 (d, J = 7 Hz, 1 H), 3.15 (t, J = 6.3 Hz, 3 H), 2.05 (m, 3 H), 1.75–1.95 (m, 3 H), 1.45–1.65 (m, 3 H), 1.2-1.4 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 145.8, 128.2, 126.6, 124.9, 83.9, 51.6, 50.8, 43.9, 29.8, 27.9, 25.3, 21.7; IR (neat) 3478, 2095, 1493, 1446, 1351, 1258, 1031 cm^{-1}; MS (CI, NH_3) m/z (rel int) 263 [$(M + NH_4)^+$, 33.1], 245 (25.5), 218 (20.4), 202 (16.6), 201 (100.0), 200 (100.0), 172 (31.2), 105 (29.3), 97 (16.1); HRMS calcd for $C_{14}H_{19}N_3O$ 263.1872 [$(M + NH_4)^+$], found 263.1868.

(1*R,2*R**)-1-Propyl-2-(3-azidopropyl)cyclopentan-1-ol (11).** To a solution of $CeCl_3$ (from 1.12 g of $CeCl_3 \cdot 7H_2O$, dried as described previously, 3.0 mmol) in THF (10 mL) was added 2-(3-azidopropyl)-cyclopentanone (0.33 g, 2.0 mmol). After 1 h at room temperature, the mixture was cooled to 0 °C and propylmagnesium bromide (3.8 mL, 0.78 M in ether, 3.0 mmol) was added. After 30 min, the reaction was quenched with 10% aqueous acetic acid (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (30 mL), then dried ($MgSO_4$) and concentrated. Chromatography (1%–10% EtOAc/hexane gradient) provided 0.27 g (64%) of the title compoundas asingle diastereomer, R_f= 0.2 (5% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.27 (t, J = 6.7 Hz, 2 H), 1.38–1.68 (m, 16 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 82.4, 52.0, 48.2, 42.3, 39.1, 30.2, 28.1, 26.1, 21.2, 17.9, 14.7; IR (neat) 3478, 2096, 1466, 1455, 1350, 1258, 1144 cm^{-1}; MS (CI, NH_3) m/z (rel int) 229 [$(M + NH_4)^+$, 1.6], 167 (20.1), 166 (100.0), 140 (8.2), 136 (75.3); HRMS calcd for $C_{11}H_{21}N_3O$ 229.2028 [$(M + NH_4)^+$], found 229.2022.

(1*R,2*R**)-1-Hexyl-2-(3-azidopropyl)cyclopentan-1-ol (12).** To a solution of $CeCl_3$ (from 2.79 g of $CeCl_3 \cdot 7H_2O$, dried as described previously, 7.5 mmol) in THF (10 mL) was added 2-(3-azidopropyl)-cyclopentanone (0.83 g, 5.0 mmol). After 1 h at room temperature, the mixture was cooled to 0 °C and hexylmagnesium bromide (8.0 mL, 0.93 M in ether, 7.5 mmol) was added. After 30 min, the reaction was quenched with 10% aqueous acetic acid (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (40 mL), then dried ($MgSO_4$) and concentrated. Chromatography (1%–5% EtOAc/hexane gradient) provided 0.81 g (64%) of the title compound as asingle diastereomer, R_f= 0.3 (5% EtOAc/hexane): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 3.27 (t, J = 6.7 Hz, 2 H), 1.1–1.9 (m, 22 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 82.4, 51.8, 48.0, 39.5, 38.7, 31.8, 29.9, 29.8, 28.0, 25.8, 24.6, 22.6, 21.0, 14.1; IR (neat) 3473, 2095, 1456, 1378, 1349, 1257, 1140 cm^{-1}; MS (CI, NH_3) m/z (rel int) 271 [$(M + NH_4)^+$, 1.0], 228 (11.0), 209 (18.0), 208 (82.9), 140 (60.2), 136 (100.0); HRMS calcd for $C_{14}H_{27}N_3O$ 271.2498 [$(M + NH_4)^+$], found 271.2487.

Acknowledgment. We thank the National Institutes of Health (GM-35572) for support of this research.

(73) Fang, C.; Suganuma, K.; Suemune, H.; Sakai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1549–1554.

(74) (a) Dombrovskii, V. A.; Fonskii, D. Yu.; Filippova, T. M.; Mironov, V. A. *Zh. Org. Khim.* **1986**, *22*, 1636–1646. (b) Crandall, J. K.; Magaha, H. S.; Henderson, M. A.; Widener, R. K.; Tharp, G. A. *J. Org. Chem.* **1982**, *47*, 5372–5380. (c) White, J. D.; Lodwig, S. N.; Tramell, G. L.; Fleming, M. P. *Tetrahedron Lett.* **1974**, 3263.