JOC Article

Epoxide-Initiated Cationic Cyclization of Azides: A Novel Method for the Stereoselective Construction of 5-Hydroxymethyl Azabicyclic Compounds and Application in the Stereo- and Enantioselective Total Synthesis of (+)- and (−)-Indolizidine 167B and 209D†

P. Ganapati Reddy and Sundarababu Baskaran*

Department of Chemistry, Indian Institute of Technology, Madras, Chennai-600036, India

sbhaskar@iitm.ac.in

Received August 28, 2003

A novel and general method has been developed for the stereoselective construction of 5-hydroxymethyl azabicyclic ring skeletons based on epoxide-initiated cationic cyclization of azides. The key cyclization reaction was systematically studied with the model compound, 3-(1-oxa-spiro[2.4]hept-4-yl)propyl azide **3a**, and $EtAlCl_2$ was found to be an ideal choice as the catalyst. The generality of this transformation was further tested with different ring sizes, where six- and seven-membered epoxyazides **3b**,**c** underwent smooth cyclization to give 5-hydroxymethyl azepine **4b** and 5-hydroxymethyl azocine **4c**, respectively, as a single detectable diastereomer. This novel methodology was elegantly applied in the stereoselective total synthesis of indolizidine alkaloids 167B and 209D. Further, the enantioselective total synthesis of natural and unnatural indolizidine alkaloids 167B and 209D was accomplished by using Sharpless asymmetric dihydroxylation as a key step.

Introduction

Cation-induced cyclization reactions are major resources for the synthesis of fused polycyclic ring systems.[1] The need for stereo- and enantioselective construction of carbocyclic ring systems of biological origin has evoked considerable interest in the design and development of novel chiral initiating species and selective terminators.[2,3] While the cation-induced cyclization terminated by the attack of carbon nucleophiles is used widely for the preparation of carbocyclic ring systems, the termination by heteroatom has become a popular technique for the synthesis of heterocyclic compounds.[1b] Oxygen and nitrogen nucleophiles are extensively studied as heteroatom terminators. Aube and Pearson have developed a novel method for the synthesis of azabicyclic ring systems using azide as a heteroatom terminator and applied in the stereoselective synthesis of nitrogen containing alkaloids.[4,5] Cation-induced inter- and intramolecular electrophilic cyclization of azidoalkenes[4] and azidoketones[5] has been extensively studied with different protic and Lewis acids; however, the synthetic potential of the corresponding epoxide-initiated Schmidt reaction is yet to be explored.

The azabicyclic ring skeleton is an important structural subunit present in numerous biologically active natural products.[6] In this family, indolizidine alkaloids are the most important class of compounds, known for their wide range of pharmaceutical applications (Figure 1).[7] For example, alkylindolizidine alkaloids isolated from the skin secretions of neotrophical amphibians, mostly from frogs belonging to the dendrobatidae family, are found to function as noncompetitive blockers of neuromuscular transmission.[8] The potent biological activity is due to the interaction of basic indolizidine nucleus with the ganglionic nicotinic acetylcholine receptor-ion channels.[7b] The agonist activity on the nicotinic receptors is similar to

† Dedicated to Professor S. Swaminathan on the occasion of his 80th birthday.

(1) (a) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, UK, 1991; Vol. 3, p 341. (b) Bartlett, P. A. In *Asymmetric Synth*esis Morrison, J. D., Ed.; Academic Press: London, UK, 1984; Vol. 3, p 341. (c) Johnson, W. S. *Tetrahedron* **1991**, *47*, No. 41, xi and references cited therein.

(2) (a) Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem*. **1999**, *64*, 9587. (b) Langkopf, E.; Schinzer, D. *Chem. Rev*. **1995**, *95*, 1375. (c) Fish, P. V.; Johnson, W. S.; Jones, G. S.; Tham, F. S.; Kullnig, R. K. *J. Org. Chem*. **1994**, *59*, 6150. (d) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc*. **1987**, *109*, 2517. (e) Johnson, W. S.; Chen, Y.-Q.; Kellog, M. S. *J. Am. Chem. Soc*. **1983**, *105*, 6653. (f) Johnson, W. S.; Lyle, T. A.; Daub, G. W. *J. Org. Chem*. **1982**, *47*, 161.

(3) (a) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 9999. (b) Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc*. **1996**, *118*, 11982. (c) Fish, P. V.; Johnson, W. S. *Tetrahedron Lett*. **1994**, *35*, 1469. (d) Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett*. **1993**, *34*, 7849. (e) Sarkar, T. K.; Ghosh, S. K.; Subba Rao, P. S. V.; Satapathi, T. K.; Mamdapur, V. R. *Tetrahedron* **1992**, *48*, 6897. (f) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett*. **1991**, *32*, 7005.

(4) (a) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **2001**, *57*, 5081. (b) Pearson, W. H.; Hutta, D. A.; Fang, W.-k. *J. Org. Chem*. **2000**, *65*, 8326. (c) Pearson, W. H.; Fang, W.-k. *J. Org. Chem*. **2000**, *65*, 7158. (d) Pearson, W. H.; Fang, W.-k. *J. Org. Chem*. **1995**, *60*, 4960. (e) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.; Blickensdorf, J. D. *J. Am. Chem. Soc*. **1993**, *115*, 10183. (f) Pearson, W. H.; Schkeryantz, J. S. *Tetrahedron Lett*. **1992**, *33*, 5291.

(5) (a) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc*. **2002**, *124*, 9974. (b) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aube, J. *J. Am. Chem. Soc*. **2000**, *122*, 7226. (c) Smith, B. T.; Gracias, V.; Aube, J. *J. Org. Chem*. **2000**, *65*, 3771. (d) Forsee, J. E.; Aube, J. *J. Org. Chem*. **1999**, *64*, 4381. (e) Milligan, G. L.; Mossman, C. J.; Aube. J. *J. Am. Chem. Soc*. **1995**, *117*, 10449. (f) Aube, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141. (g) Aube, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem*. **1992**, *57*, 1635. (h) Aube, J.; Milligan, G. L. *J. Am. Chem. Soc*. **1991**, *113*, 8965.

(6) For a review on these natural products, see: Daly, J. W. *J. Nat. Prod*. **1998**, *61*, 162.

10.1021/jo035258x CCC: $27.50
Published on Web 04/03/2004

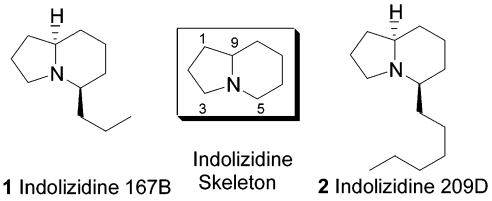


FIGURE 1.

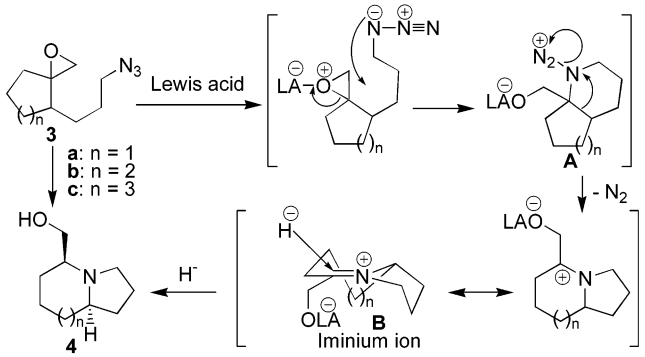
that of phencyclidine, quinacrine, chlorpromazine, and various local anesthetics.[6]

Owing to their wide variety of biological activity, the indolizidine alkaloids have attracted much attention from synthetic chemists. Several total syntheses of indolizidine alkaloids 167B and 209D have been reported in the literature.[9] Indeed, many of the syntheses have utilized naturally occurring chiral starting materials. Stepwise annulations and consecutive amination reactions are the most commonly used strategies for the synthesis of indolizidine alkaloids. Aube and Pearson independently reported an interesting and convergent synthetic method for this class of alkaloids by electrophilic cyclization of azidoketones[5a,b] and azidoalkenes[4b−e] with concurrent intramolecular Schmidt reaction. Recently, we have reported the synthetic potential of the epoxide-initiated electrophilic cyclization of azides in the stereoselective construction of azabicyclic compounds and its application in the stereoselective total synthesis of (±)-indolizidine alkaloids 167B and 209D.[10] In this article, we report a detailed study on epoxide-initiated cationic cyclization of azides and enantioselective total synthesis of both natural and unnatural indolizidine alkaloids 167B and 209D.

Results and Discussion

On the basis of the pioneering work of Aube and Pearson on intramolecular Schmidt reaction of alkyl azides,[4,5] we envisioned that the treatment of epoxyazide **3** with a Lewis acid would lead to cyclization to give aminodiazonium intermediate **A**, followed by intramolecular Schmidt reaction resulting in bicyclic iminium ion

SCHEME 1. Epoxide-Initiated Cationic Cyclization of Azides



B, and in situ reduction[9e] of **B** would give 5-hydroxymethyl azabicyclic compound **4** (Scheme 1). To test the viability of this strategy, a five-membered epoxyazide **3a** was chosen as a model substrate, which was readily synthesized from cyclopentanone as shown in Scheme 2.

Initial trials at the preparation of olefinester **6a** from known ketoester[11] **5a** using Wittig olefination were poor yielding due to the basic conditions. However, by using a modification of the relatively neutral titanium carbene reagent developed by Takai,[12] derived from $Zn/TiCl_4/CH_2X_2$ where CH_2Br_2 has replaced the relatively expensive CH_2I_2, the olefinester **6a** could be isolated in 61% yield after workup and distillation. The olefinester **6a** thus obtained was treated with LAH in THF to furnish the corresponding alcohol **7a** in 95% yield. Alcohol **7a** was converted to the corresponding mesylate in quantitative yield by treatment with CH_3SO_2Cl/Et_3N and the crude mesylate was reacted with excess NaN_3 in dry DMF to furnish azidoolefin **8a** in 98% overall yield. Azidoolefin **8a** on exposure to mCPBA, in the presence of 0.5 M aqueous $NaHCO_3$, in CH_2Cl_2 afforded epoxyazide **3a** as a mixture of cis and trans diastereomers.[13] The mixture was separated by column chromatography to furnish *trans*-**3a** and *cis*-**3a** in 51% and 17% isolated yields, respectively. Similarly, epoxyazides **3b**[14] and **3c** were prepared as shown in Scheme 2, with an overall yield of 41% and 12%, starting from cyclohexanone and cycloheptanone, respectively. Unlike five-membered epoxyazide **3a**, **3b** and **3c** were obtained as an inseparable mixture of cis- and trans-isomers (Scheme 2).

Our earlier efforts on epoxide-initiated cationic cyclization of azide **3a** in THF with a catalytic, as well as a stoichiometric, amount of Lewis acids were not successful and resulted in the isolation of a complex mixture of

(7) (a) Daly, J. W.; Sande, T. F. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1. (b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227. (c) Michael, J. P. In *The Alkaloids*: *Chemistry and Pharmacology*; Cordell, G., Ed.; Academic Press: New York, 2001; Vol. 55, p 91. (d) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719. (e) Lourenco, A. M.; Maximo, P.; Ferreira, L. M.; Pereira, M. M. A. *Stud. Nat. Prod. Chem.* **2002**, *27* (Bioactive Natural Products (part H)), 233. (f) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458.

(8) (a) Daly, J. W. *Prog. Chem. Org. Nat. Prod.* **1982,** *41*, 205. (b) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023. (c) Erspamer, V.; Melchiorri, P. *Trends Pharmacol. Sci.* **1980**, *1*, 391.

(9) For enantioselective total synthesis of indolizidine 167B please see: (a) Chenevert, R.; Ziarani, G. M.; Dasser, M. *Heterocycles* **1999**, *51*, 593. (b) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661. (c) Angel, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549. (d) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151. (e) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. For enantioselective total synthesis of indolizidine 209D please see: (f) Kim, G.; Jung, S.-D.; Kim, W.-J. *Org. Lett.* **2001**, *3*, 2985. (g) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543. (h) Chenevert, R.; Ziarani, G. M.; Morin, M. P.; Dasser, M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3117. (i) Comins, D. L.; Zhang, Y.-m. *J. Am. Chem. Soc.* **1996**, *118*, 12248. (j) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (k) Ahman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747.

(10) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583.

(11) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(12) (a) Hibino, J.-I.; Okazoe, T.; Takai, K.; Nozaki, H.*Tetrahedron Lett.* **1985**, *26*, 5579. (b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417. (c) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. (d) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.

(13) α-Substituted cyclopentanone on treatment with sulfur ylide [(a) Rajan Babu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986] or $Li-CH_2-Cl$ [(b) Gansauer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, 2500] is expected to undergo highly diastereoselective nucleophilic attack from the less hindered side to give *cis*-epoxide. The reported chemical shift values of these epoxy methylene protons are found to be very similar to those of our minor isomer of **3a**. On the basis of the chemical shift values, we concluded that our minor epoxyazide **3a** is cis.

(14) Reddy, P. G.; Pratap, T. V.; Kumar, G. D. K.; Mohanty, S. K.; Baskaran, S. *Eur. J. Org. Chem.* **2002**, 3740.

SCHEME 2. Synthesis of Epoxyazides 3a−c

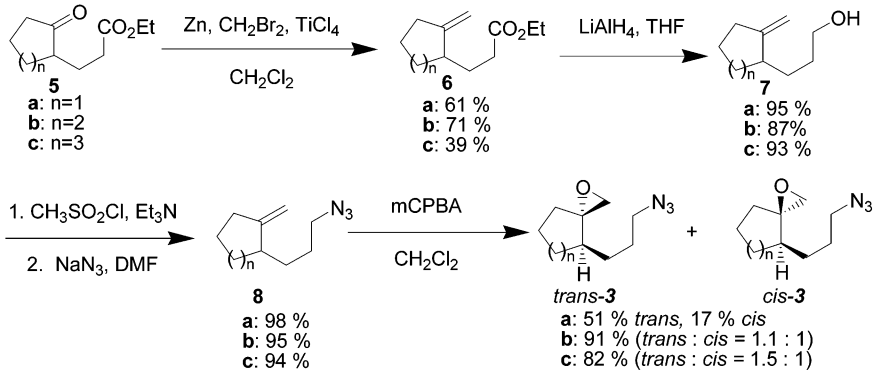
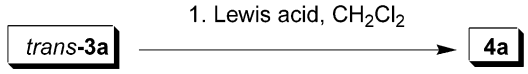


TABLE 1. Epoxide-Initiated Cationic Cyclization of *trans*-Epoxyazide 3a with Different Lewis Acids



entry	Lewis acid[a]	temp (°C)	time[b](min)	yield[c] (%)
1	TfOH	−40	30	25
2	TMSOTf	−78	30	21
3	$BF_3.OEt_2$	−78	45	50
4	$TiCl_4$	−25	30	43
5	$InCl_3$	0	60	25
6	$EtAlCl_2$	−78	45	63

[a] 1.1 equiv was used in all the cases. [b] Lewis acid step. [c] Isolated yields

products along with unreacted starting material. The first successful cyclization reaction was realized when the reaction was carried out in CH_2Cl_2. Treatment of the major *trans*-**3a** with 1.1 equiv of TfOH in CH_2Cl_2 at −40 °C for 30 min followed by the addition of $NaBH_4$ in a 15% aqueous NaOH solution at 0 °C afforded 5-hydroxymethyl indolizidine **4a** in 25% yield as a single detectable diastereoisomer as judged by the ^1H and ^{13}C NMR data (Table 1, entry 1). An extensive investigation was carried out with different Lewis acids to optimize this transformation and the results are summarized in Table 1. Lewis acids such as $InCl_3$, TMSOTf, and TfOH are found to give the cyclized product as a single diastereoisomer, albeit in low yields. Though $BF_3{\cdot}OEt_2$ and $TiCl_4$ are proved to be potential Lewis acid catalysts, $EtAlCl_2$ is found to be an excellent catalyst, in which case the isolated yield is always more than 60%. The high yield with $EtAlCl_2$ could be due to the minimization of side reactions, such as pinacol rearrangement and formation of 1,2-diol or halohydrin, as it would not allow the formation of any protic acid by virtue of its inherent ability to scavenge adventitious protons.[3f,15] Surprisingly, the minor *cis*-epoxyazide **3a** under similar cyclization conditions failed to give any cyclized product.[16]

The relative stereochemistry of the cyclized product was confirmed by NOE experiments on the corresponding acetate **9a**, which was readily prepared from **4a** by using

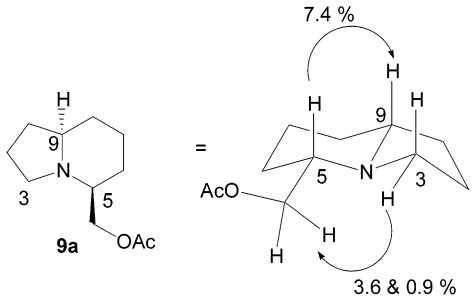


FIGURE 2. NOE experiments to confirm relative stereochemistry at C5 and C9.

standard acylation conditions (Figure 2). Irradiation of the equatorial proton at C3 resulted in the enhancement of intensities of side chain methylene protons by 3.6% and 0.9%. This clearly reveals that the side chain is equatorial. Considerable NOE between the proton at C5 and C9 (7.4%) shows that they are cis to each other. Though significant NOE between C5 and C3 axial hydrogens was observed, the exact magnitude could not be calculated since they are very close to each other.

Furthermore, the structure and relative stereochemistry of the cyclized product was unambiguously confirmed by single-crystal X-ray analysis. Since the 5-hydroxymethyl indolizidine **4a** is a viscous liquid a crystalline *p*-bromobenzoate hydrochloride salt **11** was prepared and recrystallized from nitromethane to afford good size and quality crystals suitable for X-ray analysis. As revealed in Figure 3, the *p*-bromobenzoate hydrochloride salt **11** possesses the indolizidine basic skeleton and the two hydrogens at C5 and C9 are cis to each other. It is apparent from the X-ray structure that the side chain at C5 is equatorial while six- and five-membered rings are in trans-fused chair and envelop conformations, which are presumed to be stable conformations of the indolizidine skeleton. The remarkable stereochemical outcome of this reaction was rationalized by invoking a similar stereoselective reduction of the intermediate iminium ion in the indolizidine skeleton already reported by several groups.[9e,17] It has been proposed that the high selectivity is a result of stereoelectronic effects and a similar

(15) (a) Snider, B. B. In *Selectivities in Lewis Acid Promoted Reactions*; Schinzer, D., Ed.; Kluwer: Dordrecht, The Netherlands, 1989, Chapter 8. (b) Cartaya-Marin, C. P.; Jackson, A. C.; Snider, B. B. *J. Org. Chem*. **1984**, *49*, 2443. (c) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555. (d) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

(16) The intramolecular opening of Lewis acid-activated epoxide by azide is believed to take place via the S_N2 rather than the S_N1 mechanism leading to amino-diazonium intermediate **A** (Scheme 1). It is clear from the conformational analysis that the *cis*-epoxyazide would resist undergoing cyclization via the S_N2 mechanism due to stereochemical constrains.

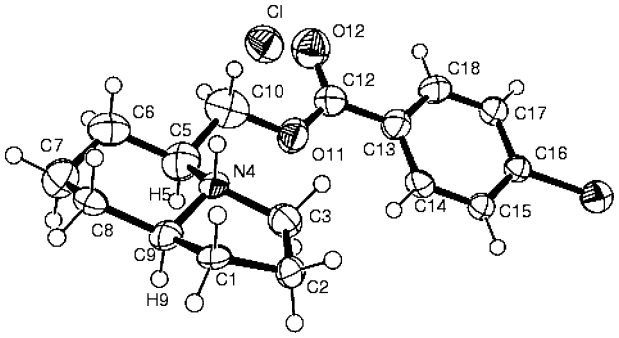
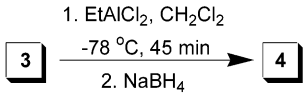


FIGURE 3. ORTEP diagram of the hydrochloride salt of *p*-bromobenzoate **11**.

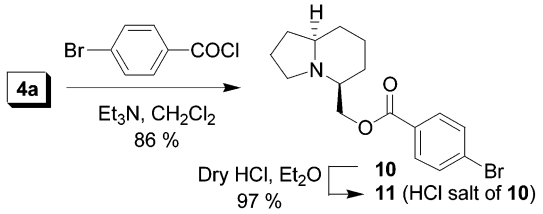
TABLE 2. Epoxide-Initiated Cationic Cyclization of Azides with Different Ring Sizes



n	substrate	product[a]	yield (%)
1	*trans*-**3a**	**4a**	63
2	**3b**[b]	**4b**	42
3	**3c**[b]	**4c**	47

[a] Single diastereomer. [b] Mixture of diastereomers.

SCHEME 3. Synthesis of the Hydrochloride Salt of *p*-Bromobenzoate 11 for X-ray Analysis

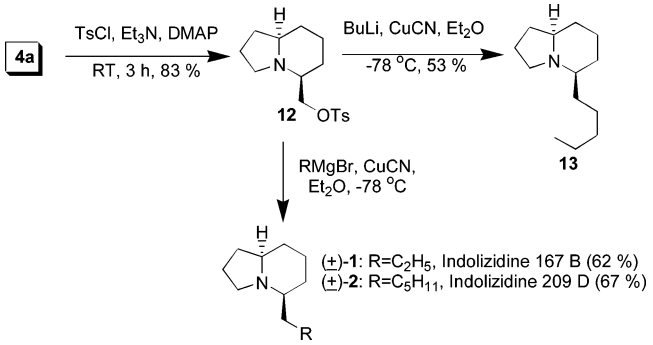


explanation can be given for the reduction of our iminium ion **B** generated from **3a** (Scheme 1).

The generality of this transformation was further tested with different ring sizes. Under standard cyclization conditions as described earlier, the mixture of epoxyazide **3b** afforded 5-hydroxymethyl azepine **4b** as a single diastereomer in 42% yield. Similarly, epoxyazide **3c** furnished a single diastereomer of 5-hydroxymethyl azocine **4c** in 47% yield.[18] The results are summarized in Table 2. The relative stereochemistry of **4b** and **4c** was assigned by NOE experiments.[19]

Stereoselective Synthesis of (±)-Indolizidine Alkaloids 167B and 209D. Interestingly, the 5-hydroxymethyl indolizidine **4a** has similar relative stereochemistry at C5 and C9 of the indolizidine alkaloids such as indolizidine 167B and 209D. Hence, we anticipated that an efficient entry to this class of alkaloids could be achieved readily from 5-hydroxymethyl indolizidine **4a** by simple functional group manipulation of the hydroxy group in the side chain. The 5-hydroxymethyl indolizidine **4a** was converted to the corresponding tosylate **12**, using TsCl and Et_3N in the presence of a catalytic amount of DMAP, in 83% yield.

SCHEME 4. Total Synthesis of Indolizidine Alkaloids



After surveying several solvents and additives with use of $Bu_2Cu(CN)Li_2$ a smooth cuprate displacement of the tosylate was realized when the reaction was carried out in Et_2O medium. Thus, treatment of tosylate **12** with $Bu_2Cu(CN)Li_2$, generated in situ from readily available CuCN and *n*-BuLi, in Et_2O at − 78 °C afforded 5-pentyl indolizidine **13** in 53% yield, which is an analogue of natural indolizidine alkaloids 167B and 209D (Scheme 4). Intriguingly, reaction of the tosylate **12** with $Et_2Cu(CN)MgBr$, in Et_2O medium at −78 °C, afforded indolizidine 167B in 62% yield. Under similar reaction conditions indolizidine 209D was prepared in 67% yield upon treatment of **12** with $(C_5H_{11})_2Cu(CN)MgBr$ (Scheme 4). The spectroscopic data of these two natural products are in complete agreement with the reported data.[9e]

Enantioselective Total Synthesis of (+)- and (−)-Indolizidine Alkaloids 167B and 209D. The successful stereoselective synthesis of indolizidine alkaloids 167B and 209D motivated us to explore the enantioselective synthesis of these alkaloids. Chiral indolizidine 167B and 209D can be achieved readily by our well-established synthetic protocol starting from optically active epoxyazide **3a**. We envisaged the synthesis of optically active epoxyazide **3a** via Sharpless asymmetric dihydroxylation[20] of the racemic azidoolefin **8** as shown in Scheme 5.

Asymmetric dihydroxylation (ADH)[21] of the racemic azidoolefin **8** with OsO_4 (0.5 mol %) in the presence of $K_3[Fe(CN)_6]$, $CH_3SO_2NH_2$, and $(DHQD)_2PHAL$ (5 mol %) as a chiral ligand afforded azidodiol **14** as an inseparable mixture of diastereoisomers (cis:trans = 1:1.3, calculated based on NMR data) in 95% yield. Selective mesylation of the primary hydroxyl group of the cis and trans mixture of **14** with CH_3SO_2Cl and Et_3N, followed by treatment with K_2CO_3 afforded epoxyazide **3a** as a

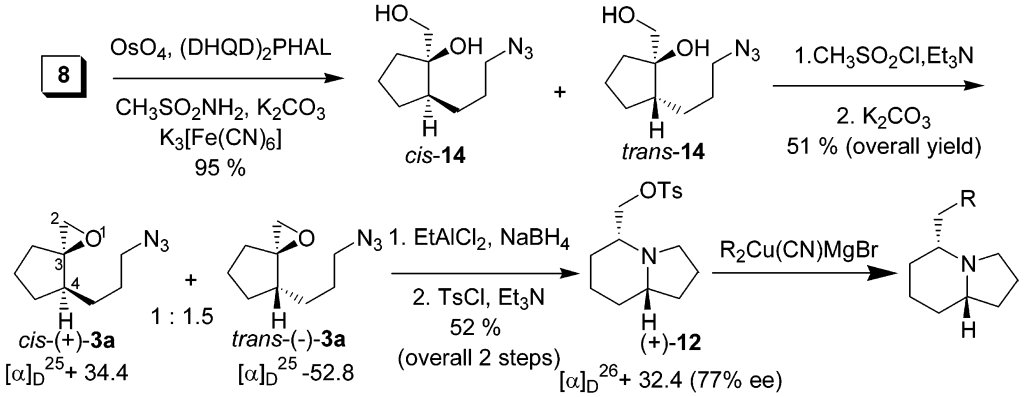
(17) (a) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (c) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868. (d) Satake, A.; Shimizu, I. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1405.

(18) By analogy based on the earlier observation, in the case of epoxyazide **3a**, it is believed that the cyclization products isolated are derived from the corresponding *trans*-epoxyazides.

(19) In the case of the acetate of **4b**, irradiation of equatorial hydrogen at C3 enhanced the signal intensities of side chain methylene hydrogens by 3.1% and 0.4%, indicating that the side chain and C3−H (equatorial) are on the same side of the molecule. Although similar results were not observed in the case of **4c**, however, considerable NOE between the hydrogens at C3 (axial), C5, and C11 upon irradiation of C5−H clearly shows that they are syn to each other.

(20) For reviews please see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993. (c) Sharpless, K. B. *Tetrahedron* **1994**, *50*, 4235.

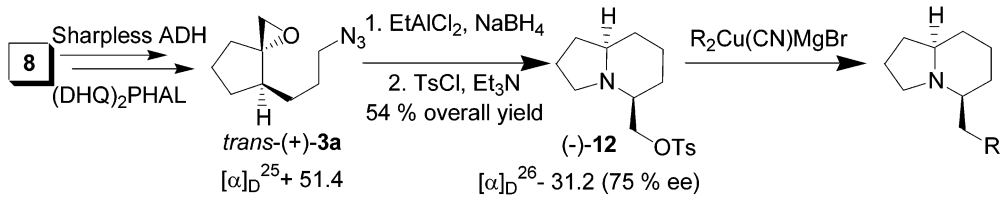
SCHEME 5. Enantioselective Total Synthesis of Unnatural (+)-(5*S*,9*S*)-Indolizidine 167B and 209D



(+)-**1**: R = C_2H_5 (+) - (*5S,9S*)-Indolizidine 167 B, 68 %, $[\alpha]_D^{25}$ + 86.6 (c = 1.3, CH_2Cl_2), 78 % ee

(+)-**2**: R = C_5H_{11} (+) -(*5S,9S*)-Indolizidine 209 D, 74 %, $[\alpha]_D^{25}$ + 59.7 (c = 1.0, CH_2Cl_2), 75 % ee

SCHEME 6. Enantioselective Total Synthesis of Natural (−)-(5*R*,9*R*)-Indolizidine167B and 209D



(-)-**1**: R = C_2H_5 (-) -(*5R,9R*)-Indolizidine 167 B, 68 %, $[\alpha]_D^{25}$ - 83.5 (c = 1.3, CH_2Cl_2), 75 % ee

(-)-**2**: R = C_5H_{11} (-) -(*5R,9R*)-Indolizidine 209 D, 74 %, $[\alpha]_D^{25}$ - 59.5 (c = 1.0, CH_2Cl_2), 74 % ee

separable mixture of *cis*-(+)-**3a** and *trans*-(−)-**3a** in 1:1.5 ratio, respectively (Scheme 5). The major *trans*-(−)-**3a** was subjected to the standard cyclization conditions to give the key intermediate 5-hydroxymethyl indolizidine, which was immediately converted to the corresponding tosylate (+)-**12**. Column chromatography of the crude tosylate (+)-**12** over deactivated silica gel (Et_3N) afforded optically active pure tosylate (+)-**12** in 52% overall yield. The enantiomeric excess (ee) of tosylate (+)-**12** was determined by HPLC analysis, using chiral column (chiralcel OD-H), and found to be 77%. The moderate ee observed for (+)-**12** is due to the poor selectivity in the ADH step of azidoolefin **8**.[21,22] Treatment of the tosylate (+)-**12** with $Et_2Cu(CN)MgBr$ led to the isolation of indolizidine 167B in 68% yield with 78% ee. The spectral data of our synthetic material are found to be in complete agreement with those of the natural (−)-(5*R*,9*R*)-indolizidine 167B except in the sign of rotation. So, the absolute configuration of our synthetic indolizidine 167B was assigned as unnatural (+)-(5*S*,9*S*)-indolizidine 167B. On the basis of this observation, we could unambiguously assign the absolute configuration of the *trans*-(−)-**3a** as (3*R*,4*S*)-4-(3-azidopropyl)-1-oxa-spiro[2.4]heptane, whereas the *cis*-(+)-**3a** is assigned as (3*R*,4*R*)-4-(3-azidopropyl)-1-oxa-spiro[2.4]heptane. Similarly, unnatural (+)-(5*S*,9*S*)-indolizidine 209D was achieved in 74% yield with 75% ee, upon reaction of (+)-tosylate **12** with $(C_5H_{11})_2Cu(CN)$-MgBr (Scheme 5).

As expected, the enantioselective synthesis of *trans*-(+)-epoxyazide **3a** required for the synthesis of natural (−)-(5*R*,9*R*)-indolizidine 167B and 209D was readily achieved by using the chiral ligand $(DHQ)_2PHAL$ instead of $(DHQD)_2PHAL$ in the Sharpless asymmetric dihydroxylation step. Following a similar synthetic sequence as described earlier, the natural (−)-(5*R*,9*R*)-indolizidine 167B was prepared in 75% ee, whereas (−)-(5*R*,9*R*)-indolizidine 209D was achieved with 74% ee starting from *trans*-(+)-(3*S*,4*R*)-**3a** (Scheme 6).

Conclusions

A novel and general method for the stereoselective construction of 5-hydroxymethyl azabicyclic compounds has been developed based on epoxide-initiated cationic cyclization of azides. The cyclization reaction was thoroughly studied with different Lewis acids and ethyl aluminum dichloride was found to be the most efficient Lewis acid catalyst for this novel transformation. The structure and relative stereochemistry of the cyclization product, 5-hydroxymethyl indolizidine, was unambiguously confirmed by NMR and X-ray analysis. The generality of this methodology was further tested with

(21) The 1,1-dialkyl-substituted olefins are known to give moderate ee in the Sharpless asymmetric dihydroxylation reaction. For ADH of 1,1-disubstituted olefins please see: (a) Hale, K. J.; Manaviazar, S.; Peak, S. A. *Tetrahedron Lett*. **1994**, *35*, 425. (b) Crispino, B. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem*. **1993**, *58*, 3785. (c) Wang, Z.-M.; Sharpless, K. B. *Synlett* **1993**, 603. (d) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, A.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768.

(22) Selective tosylation of the primary hydroxyl group of the cis and trans mixture of **14** using *p*-TsCl and Et_3N afforded a separable mixture of the corresponding monotosylate (please see the Supporting Information). The ee of the monotosylate of *trans*-**14** was found to be 78% by HPLC analysis, using chiral column (Chiralcel OJ-H). In addition, treatment of the monotosylate of *trans*-**14** with K_2CO_3 in MeOH afforded *trans*-(−)-**3a** with optical rotation identical with that of the material obtained via mesylation as described in Scheme 5.

different ring sizes, where six- and seven-membered epoxyazides underwent smooth cyclization to give 5-hydroxymethyl azepine and azocine, respectively. The 5-hydroxymethyl indolizidine has been realized as a potential precursor for the synthesis of biologically important indolizidine alkaloids, such as indolizidine 167B and 209D. Thus, the novel methodology was elegantly applied in the stereoselective total synthesis of indolizidine alkaloids 167B and 209D. Enantioselective total synthesis of both natural and unnatural indolizidine alkaloids 167B and 209D was readily achieved by using Sharpless asymmetric dihydroxylation as a key step.

Experimental Section

General Experimental Procedure for the Preparation of Olefinesters (6a−c). A modified literature procedure[12] was used for the preparation of olefinesters as followed. To a stirred slurry of zinc (16 g, 0.245 mol) in dry THF (300 mL) was added CH_2Br_2 (8.6 mL, 0.122 mol) at room temperature and the resultant mixture was stirred for about 30 min. The reaction mixture was cooled to 0 °C and then treated dropwise with a 1 M solution of $TiCl_4$ (89.7 mL, 89.7 mmol) in CH_2Cl_2. After completion of the addition, the resultant dark brown color solution was allowed to warm to room temperature over a period of 20 min. Ketoester **5a** (15 g, 81.5 mmol) was added to the reaction mixture at room temperature and the solution was allowed to stir for an additional 1 h. The mixture was diluted with EtOAc and then poured in to ice cold 1 M HCl. The mixture was stirred for 15 min and then the layers were separated. The organic layer was washed with a 1 M HCl solution and water and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure and the crude product was distilled under vacuum (bp 70−75 °C at 1 mm) to give pure olefinester **6a** (9.05 g, 61% yield) as a colorless liquid.

Ethyl 3-(2-methylenecyclopentyl)propionate (6a): IR (neat) 1736, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (br s, 1H), 4.81 (br s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.28−2.42 (m, 5H), 1.50−1.99 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 155.7, 105.0, 60.2, 43.4, 33.1, 32.6, 32.5, 29.4, 24.2, 14.3.

Ethyl 3-(2-methylenecyclohexyl)propionate (6b): Purification by column chromatography (gradient elution with 0−5% EtOAc in hexane) on silica gel afforded **6b** in 71% yield (50 mmol scale) as a colorless liquid. IR (neat) 1737, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (br s, 1H), 4.50 (br s, 1H), 4.05 (q, J = 7.1 Hz, 2H), 2.22 (t, J = 7.7 Hz, 2H), 2.10−2.19 (m, 1H), 1.82−2.02 (m, 3H), 1.34−1.70 (m, 6H), 1.19−1.28 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 151.6, 106.4, 60.1, 42.6, 34.2, 33.6, 32.4, 28.6, 27.1, 23.8, 14.2.

Ethyl 3-(2-methylenecycloheptyl)propionate (6c): Purification by column chromatography (gradient elution with 0−5% EtOAc in hexane) on silica gel afforded **6c** in 39% yield (4.72 mmol scale) as a colorless liquid. IR (neat) 1734, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.67 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.17−2.32 (m, 4H), 1.52−1.98 (m, 7H), 1.25 (t, J = 7.1 Hz, 3H), 1.12−1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 153.5, 112.4, 60.0, 45.7, 34.2, 32.9, 32.4, 31.3, 30.8, 30.5, 26.2, 14.2.

General Experimental Procedure for the Preparation of Hydroxyolefins (7a−c). To a stirred suspension of LAH (3.42 g, 90 mmol)) in dry THF (200 mL) was added olefinester **6a** (11 g, 60 mmol) at room temperature and the resultant mixture was stirred at the same temperature for 2 h. The excess LAH was quenched with hydrated Na_2SO_4 (solid) at 0 °C. The white solid separated was filtered through a pad of Celite, and the filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude compound. Column chromatographic purification of the crude compound on silica gel with use of 10% EtOAc in hexane as an eluent afforded pure hydroxyolefin **7a** (8.04 g, 95% yield) as a colorless oil.

3-(2-Methylenecyclopentyl)propan-1-ol (7a): IR (neat) 3331 (broad), 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 (br s, 1H), 4.79 (br s, 1H), 3.65 (t, J = 6.4 Hz, 2H), 2.24−2.33 (m, 3H), 2.08 (br s, 1H), 1.87−1.93 (m, 1H), 1.47−1.76 (m, 5H), 1.16−1.31(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 104.2, 62.9, 43.7, 33.1, 32.7, 30.9, 30.4, 24.1.

3-(2-Methylenecyclohexyl)propan-1-ol (7b): Purification by column chromatography (10% EtOAc in hexane) on silica gel afforded **7b** in 87% yield (31.8 mmol scale) as a colorless liquid. IR (neat) 3342 (broad), 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 1H), 4.49 (s, 1H), 3.55 (t, J = 7.1 Hz, 2H), 2.28 (br s, 1H), 2.11−2.19 (m, 1H), 1.94−1.97 (m, 2H), 1.15−1.73 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 105.6, 63.0, 42.9, 34.6, 33.8, 30.7, 28.8, 28.1, 24.1.

3-(2-Methylenecycloheptyl)propan-1-ol (7c): Purification by column chromatography (10% EtOAc in hexane) on silica gel afforded **7c** in 93% yield (1.81 mmol scale) as a colorless liquid. ^1H NMR (400 Hz, $CDCl_3$) δ 4.79 (br s, 1H), 4.67 (d, J = 1.9 Hz, 1H), 3.59 (t, J = 6.4 Hz, 2H), 1.10−2.24 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 111.6, 62.9, 45.8, 34.3, 33.1, 32.1, 31.2, 30.7, 30.3, 26.3.

General Experimental Procedure for the Preparation of Azidoolefins (8a−c). To a stirred solution of hydroxyolefin **7a** (8.4 g, 60 mmol) in dry CH_2Cl_2 (150 mL) at 0 °C was added Et_3N (17 mL, 0.12 mol) followed by a dropwise addition of CH_3SO_2Cl (5.6 mL, 72 mmol) over a period of 10 min. After being stirred for an additional 15 min at 0 °C, the mixture was diluted with CH_2Cl_2 and the organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the corresponding mesylate as a pale yellow liquid (13.08 g, quantitative yield). The crude mesylate (13.0 g, 59.6 mmol) was redissolved in dry DMF (200 mL) and treated with NaN_3 (7.7 g, 0.119 mol). The resultant mixture was stirred at 50 °C for about 3 h. The reaction mixture was poured into ice-cold water and extracted with hexane, then the combined hexane extracts were washed with water and dried over anhydrous Na_2SO_4. Hexane was removed under reduced pressure to give pure azidoolefin **8a** (9.66 g, 98% yield) as a colorless oil.

3-(2-Methylenecyclopentyl)propyl azide (8a): The physical and spectral data were identical with those previously reported for this compound.[4e] IR (neat) 2095, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (br s, 1H), 4.78 (d, J = 1.47 Hz, 1H), 3.25−3.30 (m, 2H), 2.24−2.33 (m, 3H), 1.87−1.95 (m, 1H), 1.48−1.76 (m, 5H), 1.22−1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 104.3, 51.5, 43.3, 32.9, 32.5, 31.2, 27.0, 24.0; MS (EI) m/z (rel intensity, %) 166 ($M^+ + 1$, 2.5), 124 (100).

3-(2-Methylenecyclohexyl)propyl azide (8b): Under similar reaction conditions azidoolefin **8b** was isolated in 95% yield (33.6 mmol scale). The physical and spectral data were identical with those previously reported for this compound.[4b] IR (neat) 2095, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (br s, 1H), 4.56 (br s, 1H), 3.28(t, J = 6.6 Hz, 2H), 2.17−2.26 (m, 1H), 1.98−2.06 (m, 2H), 1.23−1.80 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 105.9, 51.7, 42.8, 34.5, 33.9, 29.1, 28.8, 26.9, 24.1; MS (EI) m/z (rel intensity, %) 179 ($M^+ - 2$, 2.5), 67 (100).

3-(2-Methylenecycloheptyl)propyl azide (8c): Under similar reaction conditions azidoolefin **8c** was isolated in 94% yield (1.63 mmol scale). The physical and spectral data were identical with those previously reported for this compound.[4b] IR (neat) 2095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.81 (br s, 1H), 4.68 (br s, 1H), 3.25 (t, J = 6.9 Hz, 2H), 2.16−2.22 (m, 2H), 1.85−2.15 (m, 1H), 1.80−1.84 (m, 2H), 1.48−1.68 (m, 4H), 1.08−1.46 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 111.8, 51.5, 45.7, 34.4, 33.0, 32.1, 31.1, 30.1, 26.9, 26.4.

General Experimental Procedure for the Preparation of Epoxyazides (3a−c). To a solution of 3-(2-methylene cyclopentyl)propyl azide **8a** (2.2 g, 13.3 mmol) in CH_2Cl_2 (30

mL) was added 0.5 M aqueous $NaHCO_3$ solution (30 mL). The resultant two-phase mixture was cooled to 0 °C and mCPBA (50% suspension, 5.0 g, 14.5 mmol) was added portion-wise. The mixture was stirred at the same temperature for about 2 h and then diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude compound as a mixture of diastereomers. The mixture was separated by column chromatography over deactivated (Et_3N) silica gel by using 5% EtOAc in hexane as an eluent to afford pure *cis*-epoxyazide **3a** (410 mg, 17% yield) and *trans*-epoxyazide **3a** (1.24 g, 51% yield) as colorless liquids.

3-(1-Oxa-spiro[2.4]hept-4-yl)propyl azide (3a): Major diastereomer (*trans*-3a): IR (neat) 2095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.26 (m, 2H), 2.90 (d, J = 4.4 Hz, 1H), 2.71 (d, J = 4.9 Hz, 1H), 1.16−2.17 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.8, 51.5, 50.3, 42.5, 32.2, 31.1, 28.7, 27.2, 22.6; MS (EI) *m*/*z* (rel intensity, %) 153 (M^+ − 28, 1.5), 95 (100). Anal. Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 60.01; H, 8.14; N, 23.25. **Minor diastereomer (*cis*-3a):** IR (neat) 2095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (t, J = 7.3 Hz, 2H), 2.81 (d, J = 4.9 Hz, 1H), 2.71 (d, J = 4.9 Hz, 1H), 1.16−2.03 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.4, 51.3, 50.1, 40.5, 32.2, 31.4, 27.1, 25.6, 22.3.

3-(1-Oxa-spiro[2.5]oct-4-yl) propyl azide (3b): Purification by column chromatography on silica gel (deactivated with Et_3N) with 5% EtOAc in hexane as an eluent afforded pure title compound **3b** in 91% yield (2.5 g scale) as a colorless liquid (inseparable mixture of diastereomers). IR (neat) 2095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.26 (m, 2H), 2.67 (t, J = 6.6 Hz, 1H), 2.52 (t, J = 5.8 Hz, 1H), 1.06−1.95 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.1, 53.5, 51.6, 51.4, 40.8, 40.1, 32.8, 31.7, 30.1, 29.4, 26.9, 26.8, 26.4, 25.6, 25.0, 23.1, 22.1; MS (EI) *m*/*z* (rel intensity, %) 196 (M^+ − 1, 1.5), 79 (100). Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.75; H, 8.44; N, 21.85.

3-(1-Oxa-spiro[2.6]non-4-yl)propyl azide (3c): Purification by column chromatography on silica gel (deactivated with Et_3N) with 5% EtOAc in hexane as an eluent afforded pure title compound **3c** in 82% yield (1.5 mmol scale) as a colorless liquid (inseparable mixture of diastereomers). IR (neat) 2093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.27 (m, 2H), 2.59 (m, 2H), 1.20−2.04 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.9, 62.7, 55.2, 54.1, 52.0, 51.9, 44.2, 43.7, 33.2, 32.8, 31.8, 31.6, 30.1, 29.5, 29.4, 29.3, 27.3, 27.2, 25.9, 25.3, 25.1, 24.6. Anal. Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.24; H, 9.21; N, 20.50.

General Experimental Procedure for the Preparation of 5-Hydroxymethyl Azabicyclic Compounds (4a−c). To a stirred solution of *trans*-(±)-**3a** (181 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) at − 78 °C was added $EtAlCl_2$ (1.8 M solution in toluene, 0.611 mL, 1.1 mmol) dropwise. The resultant mixture was stirred for 45 min at −78 °C and then allowed to warm to room temperature. After being stirred for additional 5 min at room temperature, the mixture was cooled to 0 °C and treated with a solution of $NaBH_4$ (266 mg, 7 mmol) in 15% aqueous NaOH (3 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude compound that was purified by column chromatography on basic alumina (gradient elution with 0−10% EtOAc in hexane) to afford pure 5-hydroxymethyl indolizidine **4a** (97 mg, 63% yield) as a colorless syrup.

5-(Hyroxymethyl)indolizidine (4a): IR (neat) 3362 (broad), 2788, 2358 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.65 (dd, J = 4.4, 10.7 Hz, 1H), 3.47 (dd, J = 2.9, 10.7 Hz, 1H), 3.15 (dt, J = 2.2, 8.8 Hz, 1H), 2.90 (br s, 1H), 1.04−2.0 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.9, 64.8, 64.5, 51.5, 30.8, 30.4, 28.4, 24.5, 20.8; MS (EI) *m*/*z* (rel intensity, %) 155 (M^+, 2.5), 124 (100). Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.72; H, 11.09; N, 9.32.

5-(Hydroxymethyl)octahydropyrrolo[1,2-*a*]azepine (4b): Purification by column chromatography (gradient elution with 0−15% EtOAc in hexane) over basic alumina afforded pure compound **17b** in 42% yield (2 mmol scale) as a colorless syrup. IR (neat) 3268 (broad), 2831, 2735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (dd, J = 5.4, 10.3 Hz, 1H), 3.46 (dd, J = 4.2, 10.3 Hz, 1H), 3.40−3.58 (br s, 1H), 3.14−3.22 (m, 1H), 2.94 (dq, J = 2.0, 8.0 Hz, 1H), 2.61−2.66 (m, 1H), 2.45 (ca. q, J = 8.0 Hz, 1H), 1.34−2.01 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.7, 63.6, 61.4, 52.9, 35.9, 33.4, 30.6, 26.8, 24.7, 23.1; MS (EI) *m*/*z* (rel intensity, %) 169 (M^+, 1.6), 138 (100). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 8.28; N, 8.28. Found: C, 71.04; H, 11.62; N, 8.54.

5-(Hydroxymethyl)decahydropyrrolo[1,2-*a*]azocine (4c): Purification by column chromatography (gradient elution with 0−20% EtOAc in hexane) over basic alumina afforded pure compound **17c** in 47% yield (1 mmol scale) as a colorless syrup. ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (dd, J = 5.4, 10.4 Hz, 1H), 3.46 (dd, J = 5.3, 10.4 Hz, 1H), 3.25−3.19 (m, 1H), 3.17−3.05 (m, 1H), 2.97−3.33 (br s, 1H), 2.81−2.86 (m, 1H), 2.52 (ca. q, J = 8.3 Hz, 1H), 1.40−1.97 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.7, 61.8, 61.1, 50.7, 35.8, 32.6, 29.1, 26.7, 24.3, 24.2, 23.9; MS (EI) *m*/*z* (rel intensity, %) 183 (M^+, 5.5), 152 (100). Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.38; H, 11.64; N, 7.84.

5-(Acetoxymethyl)indolizidine (9a): To a stirred solution of alcohol **4a** (1.4 g, 9.03 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (2.5 mL, 18.06 mmol) followed by Ac_2O (1 mL, 10.84 mmol) and the resultant mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude compound. Column chromatographic purification of the crude compound (gradient elution with 0−2.5% EtOAc in hexane) on basic alumina furnished pure acetate **9a** (1.62 g, 91% yield) as a colorless oil. IR (neat) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (dd, J = 4.9, 11.2 Hz, 1H), 4.04 (dd, J = 5.4, 11.2 Hz, 1H), 3.24 (dt, J = 2.4, 8.8 Hz, 1H), 2.21−2.27 (m, 1H), 2.05−2.14 (m, 1H), 2.07 (s, 3H), 1.63−1.95 (m, 7H), 1.16−1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 67.6, 65.3, 62.4, 52.1, 30.8, 30.2, 29.1, 24.4, 21.3, 20.9; MS (EI) *m*/*z* (rel intensity, %) 197 (M^+, 0.5), 124 (100). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.03; H, 9.41; N, 7.42.

4-Bromo(indolizidin-5-ylmethyl)benzoate (10): To a stirred solution of alcohol **4a** (155 mg, 1 mmol) in CH_2Cl_2 was added Et_3N (0.278 mL, 2 mmol) followed by *p*-bromobenzoyl chloride (241 mg, 1.1 mmol) at room temperature. The resultant mixture was stirred for about 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$ solution, then the organic layer was dried over anhydrous $MgSO_4$. Solvent was removed under reduced pressure and the crude compound was purified by column chromatography over silica gel (deactivated with Et_3N), using 15% EtOAc in hexane as an eluent, to afford pure title compound **10** (289 mg, 86% yield) as a colorless low-melting solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 4.43 (dd, J = 5.9, 11.2 Hz, 1H), 4.29 (dd, J = 5.4, 11.2 Hz, 1H), 3.30 (dt, J = 1.96, 8.8 Hz, 1H), 2.39 (m, 1H), 2.18 (ca. q, J = 8.8, 9.3 Hz, 1H), 1.67−1.95 (m, 7H), 1.23−1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 131.6, 130.9, 128.9, 127.9, 68.4, 64.8, 61.9, 52.0, 30.5, 29.8, 28.9, 24.0, 20.6. Anal. Calcd for $C_{16}H_{20}BrNO_2$: C, 56.82; H, 5.96; N, 4.14. Found: C, 56.98; H, 6.04; N, 4.52.

Hydrochloride salt of 4-bromo(indolizidin-5-ylmethyl)benzoate (11): Dry HCl gas was passed through a solution of 4-bromo(indolizidin-5-ylmethyl)benzoate **10** (100 mg, 0.296 mmol) in dry Et_2O (10 mL) at 0 °C for 2 min. The white solid that separated was filtered and washed with Et_2O (10 mL). The solid was azeotropically dried with toluene (2 × 5 mL)

under high vacuum at room temperature to give pure title compound **11** as a white solid (108 mg, 97% yield). Recrystallization of **11** from nitromethane (50 mg/10 mL) by slow evaporation technique at room temperature afforded good size and quality crystals (colorless needles) suitable for X-ray diffraction studies (please see the Supporting Information for X-ray crystallographic data).

2-(3-Azidopropyl)-1-hydroxymethylcyclopentanol (14): To a stirred solution of olefinazide **8** (825 mg, 5 mmol) in a 1:1 mixture of *t*-BuOH−water (30 mL) were added sequentially $K_3[Fe(CN)_6]$ (4.94 g, 15 mmol), K_2CO_3 (2.07 g, 15 mmol), $(DHQD)_2PHAL$ (195 mg, 0.25 mmol), $CH_3SO_2NH_2$ (475 mg, 5 mmol), and OsO_4 (0.250 mL of a 0.1 M solution in *t*-BuOH, 0.025 mmol). The resulting mixture was stirred at 6 °C for 3.5 h. $Na_2S_2O_5$ (30 mg) was added to the reaction mixture and stirred for an additional 45 min at room temperature. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite and the filter cake was thoroughly washed with EtOAc. The combined filtrates were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica gel with us eof 20−40% EtOAc in hexane solvent gradient to afford a diastereomeric mixture of azidodiols **14** (945 mg, 95% yield) as a colorless syrup. IR (neat) 3408 (broad), 2112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.62 (dd, J = 11.2, 17.2 Hz, 1H), 3.48 (ca. t, J = 11.2, 12.4 Hz, 1H), 3.28−3.30 (m, 2H), 2.78 (br s, 1H), 2.39 (br s, 1H), 1.13−2.06 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) d 83.2, 82.1, 69.0, 65.5, 51.7, 51.6, 48.4, 45.6, 37.6, 35.6, 30.7, 29.5, 27.9, 27.8, 26.9, 26.6, 21.6, 20.9. Anal. Calcd for $C_9H_{17}N_3O_2$: C, 54.25; H, 8.60; N, 21.09. Found: C, 54.25; H, 8.48; N, 21.29.

General Procedure for the Preparation of Optically Active 4-(3-Azidopropyl)-1-oxa-spiro[2.4]heptane (3a). To a stirred solution of a diastereomeric mixture of azidodiol **14** (597 mg, 3 mmol, prepared by the Sharpless ADH reaction of azidoolefin **8** with $(DHQD)_2PHAL$ as a chiral ligand) in dry CH_2Cl_2 (15 mL) was added Et_3N (0.835 mL, 6 mmol) followed by CH_3SO_2Cl (0.285 mL, 3.6 mmol) at 0 °C. The mixture was stirred for 1 h at the same temperature and then it was diluted with CH_2Cl_2. The organic layer was washed with water and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give crude compound. The crude monomesylate was redissolved in methanol (15 mL) and treated with K_2CO_3 (828 mg, 6 mmol) at room temperature and the resultant mixture was stirred for 45 min. Solvent was removed under reduced pressure and the residue was diluted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude epoxyazide **3a** as a mixture of diastereomers. The mixture was separated by column chromatography over silica gel with use of 0−2.5% EtOAc in hexane solvent gradient as eluent to give pure *trans*-(−)-**3a** (168 mg, 31% yield) and *cis*-(+)-**3a** (114 mg, 21% yield).

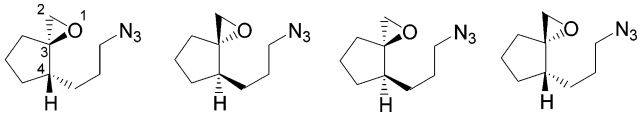
Under similar reaction conditions, *trans*-(+)-**3a** and *cis*-(−)-**3a** were obtained in 23% and 30% yield, respectively (total 53% yield, 3.52 mmol scale), from the azidodiol **14**, which in turn was prepared by the Sharpless ADH reaction of racemic olefinazide **8** with $(DHQ)_2PHAL$ as a chiral ligand. ^1H and ^{13}C NMR data for *trans*-(+)-**3a** and (−)-**3a** are in complete agreement with those of *trans*-(±)-**3a** obtained by mCPBA oxidation of olefinazide **8**. Similarly, spectral data for *cis*-(+)-**3a** and (−)-**3a** are comparable with those of *cis*-(±)-**3a**.

5-(*p*-Toluenesulfonyloxymethyl)indolizidine (12): *trans*-**3a** (1.81 g, 10 mmol) was subjected to standard cyclization conditions to afford pure 5-hydroxymethylindolizidine **4a** (1.0 g, 63% yield) as a colorless syrup. To a stirred solution of alcohol **4a** (1.0 g, 6.45 mmol) in dry CH_2Cl_2 (20 mL) at room temperature were added Et_3N (1.8 mL, 12.9 mmol) and TsCl (1.35 g, 7.1 mmol) followed by a catalytic amount of DMAP. The mixture was allowed to stir for 3 h and then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and water, and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the crude compound was purified over deactivated silica gel (Et_3N) with 25% EtOAc in hexane as eluent to give pure tosylate **12** (1.65 g, 83% yield) as a colorless oil. IR (neat) 2861, 2791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 4.09 (dd, J = 5.4, 9.8 Hz, 1H), 3.89 (dd, J = 5.4, 9.8 Hz, 1H), 3.04 (dt, J = 2.4, 8.5 Hz, 1H), 2.44 (s, 3H), 2.23−2.28 (m, 1H), 2.04 (q, J = 9.0 Hz, 1H), 1.61−1.87 (m, 7 H), 1.07−1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 132.6, 129.7, 127.8, 72.9, 64.6, 61.5, 51.6, 30.3, 29.8, 28.5, 23.7, 21.5, 20.5; MS (EI) *m*/*z* (rel intensity, %) 309 (M^+, 1.7), 124 (100). Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 62.32; H, 7.56; N, 4.73.

Preparation of (+)-(5*R*,9*S*)- and (−)-(5*S*,9*R*)-5-(*p*-toluenesulfonyloxymethyl)indolizidine (12). Under similar reaction conditions as described above *trans*-(−)-epoxyazide **16a** was converted to the corresponding (+)-(5*R*,9*S*)-5-(*p*-toluenesulfonyloxymethyl)indolizidine (**12**) {$[\alpha]^{26}_D$ +32.4 (*c* 1.0, CH_2Cl_2)} in 52% overall yield with 77% ee (determined by HPLC analysis on a chiral column). Similarly, *trans*-(+)-epoxyazide **3a** was converted to the corresponding (−)-(5*S*,9*R*)-5-(*p*-toluenesulfonyloxymethyl)indolizidine (**12**) {$[\alpha]^{26}_D$ −31.2 (*c* 1.0, CH_2Cl_2)} in 53% overall yield with 75% ee (determined by HPLC analysis on a chiral column). Spectral data for (+)- and (−)-tosylate **12** were found to be identical in all respects with those of the racemic tosylate **12**. HPLC (chiral) column: Chiralcel OD-H (0.46 × 25 cm^2); λ = 222 nm. Mobile phase: 0.5% isopropyl alcohol in hexane at 0.5 mL/min flow rate. Retention times: 32.64 min [(+)-(5*R*,9*S*)-**12**], 35.05 min [(−)-(5*S*,9*R*)- **12**].

Preparation of 5-Pentylindolizidine with $Bu_2Cu(CN)Li_2$ in Et_2O (13). CuCN (119 mg, 1.33 mmol) was placed in a dry two-neck round-bottom flask and azeotropically dried with toluene (2 × 5 mL) at room temperature under vacuum. The powder was placed under argon and dry Et_2O (5 mL) was introduced. The slurry was cooled to − 78 °C and then *n*-BuLi (2.5 mL of 1.1 M solution in hexane, 2.65 mmol) was added dropwise. The heterogeneous mixture was allowed to warm to 0 °C to give a homogeneous solution and then recooled to − 78 °C. A solution of tosylate **12** (82 mg, 0.265 mmol) in dry Et_2O (2 mL) was added dropwise and the resultant mixture was allowed to stir for 2 h at − 78 °C. Aqueous ammonia solution (10 mL, 25%) was added to the reaction mixture and extracted with EtOAc. Combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude compound was purified by column chromatography (gradient elution with 0−10% EtOAc in hexane) over silica gel (deactivated with Et_3N) to afford pure 5-pentyl indolizidine **13** (27 mg, 53% yield) as a colorless liquid. IR (neat) 2928, 2864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.27 (dt, J = 2.0, 8.8 Hz, 1H), 1.98 (q, J = 8.8 Hz, 1H), 1.61−1.92 (m, 9H), 1.11−1.50 (m, 11H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.0, 63.9, 51.5, 34.6, 32.3, 30.9, 30.8, 30.5, 25.5, 24.7, 22.6, 20.4, 14.0; MS (EI) *m*/*z* (rel intensity, %) 195 (M^+, 12.5), 124 (100).

TABLE 3. Optical Rotations and Absolute Configurations for 4-(3-Azidopropyl)-1-oxa-spiro[2.4]heptanes



trans-(-)-**3a** *trans*-(+)-**3a** *cis*-(+)-**3a** *cis*-(-)-**3a**

S. No.	ligand used in ADH reaction of azidoolefin **8**	isolated epoxyazide (abs config) trans	isolated epoxyazide (abs config) cis	obsd optical rotation (c 1.0, CH_2Cl_2) trans	obsd optical rotation (c 1.0, CH_2Cl_2) cis
1	$(DHQD)_2PHAL$	(−)-**3a** (3*R*,4*S*)	(+)-**3a** (3*R*,4*R*)	−52.8	+34.4
2	$(DHQ)_2PHAL$	(+)-**3a** (3*S*,4*R*)	(−)-**3a** (3*S*,4*S*)	+51.4	−32.3

General Procedure for the Preparation of Indolizidine Alkaloids 167B and 209D (1, 2) with Magnesium Cuprates. To a slurry of azeotropically dried CuCN (671 mg, 7.5 mmol) in dry Et_2O (5 mL) was added a solution of EtMgBr (15 mmol, generated from 360 mg of magnesium and 1.12 mL of ethyl bromide) in 10 mL of dry Et_2O. The heterogeneous mixture was allowed to warm to −10 °C (a dark yellow color suspension was observed) at which temperature it was stirred for about 10 min and then recooled to −78 °C. A solution of tosylate **12** (309 mg, 1 mmol) in dry Et_2O (5 mL) was added and the resultant mixture was allowed to warm to 0 °C over a period of 2 h. Quenching of the reaction mixture with saturated aqueous NH_4Cl (20 mL) followed by standard workup and purification, as described for 5-pentylindolizidine **13**, furnished pure (±)-indolizidine alkaloid 167B **1** (104 mg, 62%) as a colorless liquid. The physical and spectral data were identical with those previously reported for this compound.[9e] IR (neat) 2870, 2780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.28 (dt, J = 2.4, 8.8 Hz, 1H), 1.99 (q, J = 9.0 Hz, 1H), 1.62−1.92 (m, 9H), 1.14−1.49 (m, 7H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.0, 63.7, 51.4, 36.8, 30.9, 30.7, 30.4, 24.6, 20.3, 19.0, 14.4; MS (EI) *m*/*z* (rel intensity, %) 167 (M^+, 14.5), 124 (100). Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 78.59; H, 12.86; N, 8.39.

Enantioselective Synthesis of (+)-(5*S*,9*S*)- and (−)-(5*R*,9*R*)-Indolizidine Alkaloid 167B (1). Under similar reaction conditions as described above, (+)-(5*R*,9*S*)-tosylate **12** was converted to the corresponding unnatural (+)-(5*S*,9*S*)-indolizidine 167B {$[\alpha]^{26}_D$ +86.6 (*c* 1.3, CH_2Cl_2), 78% ee)} in 68% yield. Similarly, (−)-(5*S*,9*R*)-tosylate **12** was converted to the corresponding natural (−)-(5*R*,9*R*)-indolizidine 167B {$[\alpha]^{26}_D$ −83.5 (*c* 1.3, CH_2Cl_2; lit.[9e] $[\alpha]^{26}_D$ −111.3 (*c* 1.3, CH_2Cl_2), 75% ee)} in 68% yield. Spectral data of unnatural and natural indolizidine alkaloid 167B were found to be identical in all respect with those of the racemic indolizidine alkaloid 167B **1**.

(±)-Indolizidine-209D (2): Under similar conditions (±)-indolizidine 209D was prepared with $C_5H_{11}MgBr$. Purification by column chromatography (gradient elution with 0−25% EtOAc in hexane) on deactivated silica gel (Et_3N) afforded pure title compound as a colorless liquid in 67% yield (500 mg scale). IR (neat) 2857, 2780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (dt, J = 2.0, 8.8 Hz, 1H), 1.96 (q, J = 9.0 Hz, 1H), 1.61−1.90 (m, 10H), 1.09−1.49 (m, 12H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.3, 64.1, 51.8, 34.8, 32.1, 31.2, 31.1, 30.8, 30.0, 26.0, 24.9, 22.9, 20.6, 14.3; MS (EI) *m*/*z* (rel intensity, %) 209 (M^+, 8.5), 124 (100). Anal. Calcd for $C_9H_{15}N_3O$: C, 80.31; H, 13.00; N, 6.69. Found: C, 80.70; H, 12.94; N, 6.85.

Enantioselective Synthesis of (+)-(5*S*,9*S*)- and (−)-(5*R*,9*R*)-Indolizidine Alkaloid 209D (2). Under similar reaction conditions as described above (+)-(5*R*,9*S*)-tosylate **12** was converted to the corresponding unnatural (+)-(5*S*,9*S*)-indolizidine 209D {$[\alpha]^{26}_D$ +59.7 (*c* 1.0, CH_2Cl_2, 75% ee)} in 74% yield. Similarly, (−)-(5*S*,9*R*)-tosylate **12** was converted to the corresponding natural (−)-(5*R*,9*R*)-indolizidine 209D {$[\alpha]^{26}_D$ −59.5 (*c* 1.0, CH_2Cl_2); lit.[9e] $[\alpha]^{26}_D$ −80.4 (*c* 1.0, CH_2Cl_2), 74% ee)} in 74% yield. Spectral data of unnatural and natural indolizidine alkaloid 209D were found to be identical in all respects with those of the racemic indolizidine alkaloid 209D.

Acknowledgment. We thank DST, New Delhi and DRDO, New Delhi for financial support and P.G.R. thanks CSIR, New Delhi and IIT Madras for research fellowships. We are grateful to RSIC, IIT Madras, for spectral data.

Supporting Information Available: General experimental methods, representative ^1H and ^{13}C NMR spectra for all the new compounds, chiral HPLC reports of **12**, monotosylate of *trans*-**14,** and X-ray crystallographic data for **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035258X